–Chapter 1–

Introduction

1.1 AIDS

The disease now known as Acquired Immunodeficiency Syndrome (AIDS) was first described in 1981 and soon after, in 1984, the etiological agent of the disease was identified as the Human Immunodeficiency Virus (HIV). Since then, AIDS and HIV infection have escalated dramatically. It is estimated that 39.5 million people worldwide are currently living with HIV[1] and that during 2006, 4.3 million people contracted the virus and 2.9 million lost their lives due to AIDS and associated complications.[1]

More than two decades have passed since AIDS was first observed and there still exists neither a cure nor a vaccine for its treatment and consequently this illness remains a serious global health problem.[2] AIDS and HIV infection pose both a major medical challenge to humankind, and a complex scientific puzzle which has stimulated some remarkable research. Scientific and therapeutic progress in the fight against HIV/AIDS has been extraordinary. Within six years of the first observation of AIDS, the pathogenic virus, HIV, had been identified, sensitive tests to detect infected patients had been developed and the first rationally designed anti-HIV drug, zidovudine (AZT), had been released as a therapy. Today the prognosis for patients that have full access to an effective regimen of antiretrovirals has changed completely since the first cases of AIDS were reported. The median survival rate now exceeds 8 years, compared to 6 months before AZT was released, largely due to the development of effective therapies and to early detection of HIV-positive individuals. Whilst it is undeniable that there has been immense progress made in the HIV/AIDS treatment arena, mutations to the HIV-1 genome have rendered viral strains resistant to the currently available drugs.[3,4] The development of new drugs, particularly those with novel modes of action, is therefore essential for continued effective therapy.[5]

1.1.1 HIV and its Effects

HIV belongs to a group of RNA-viruses called retroviruses. RNA-viruses use RNA as their hereditary material but unlike other RNA-viruses that use their RNA to transcribe and replicate directly, retroviruses do so *via* a DNA intermediate.[6] In the absence of a host organism, viruses are unable to replicate since this process is accomplished using the biochemical machinery present in the host organism. HIV primarily infects $CD4^+$ T lymphocytes, an integral component of the body's immune response. This severely compromises an infected individual's immune system thus increasing their vulnerability to opportunistic infections. A person is clinically diagnosed as having AIDS when the titer of T lymphocytes drops below 200 cells per mm^3, from a healthy 800 cells per mm^3, and if one or more of the following are present: pulmonary tuberculosis, recurrent pneumonia, and for women, invasive cervical cancer.[6]

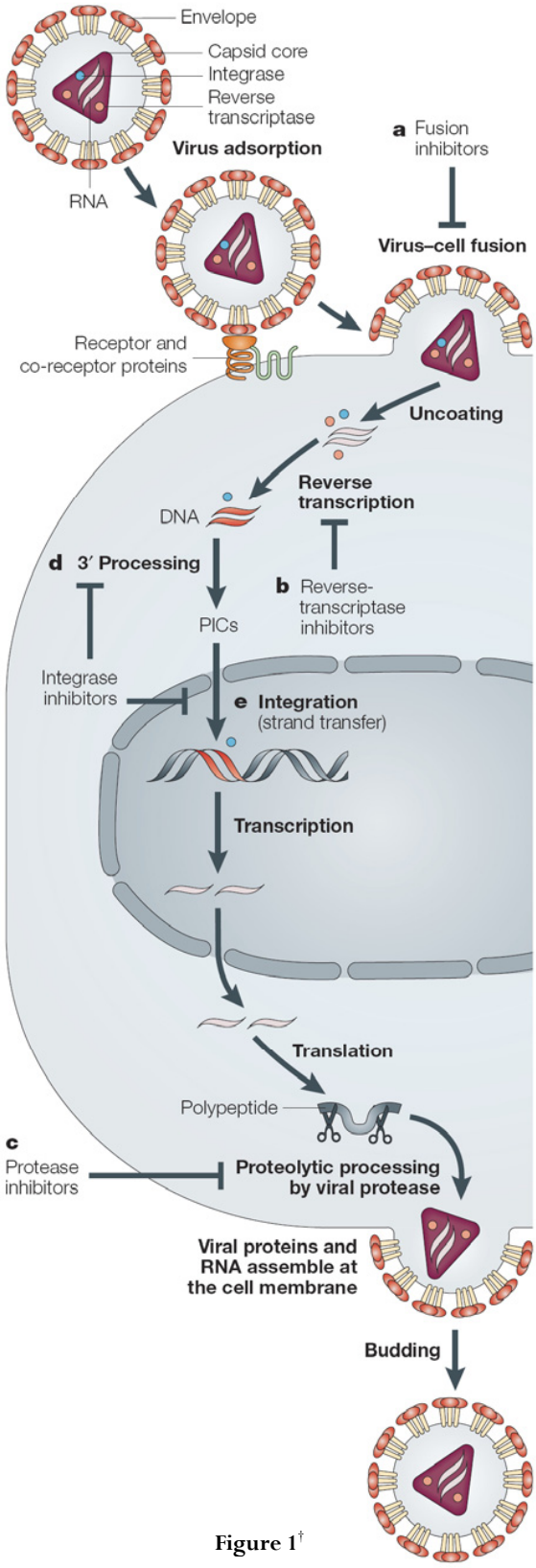


Figure 1[†]

1.1.2 The HIV Lifecycle

The HIV lifecycle (**Figure 1**[†]) begins with the viral particle binding to the CD4 glycoprotein receptor on the surface of the host cell in a process known as virus adsorption. This triggers a cascade of biochemical events which allows for the viral envelope to merge with the cell membrane, known as fusion, which results in the expulsion of the capsid core into the cytoplasm of the host cell. The capsid core is then uncoated, releasing viral RNA, enzymes and proteins into the cytoplasm of the host cell. The viral RNA is then reverse transcribed using the viral enzyme reverse transcriptase to give a double stranded DNA copy that is now ready for integration into the host genome. Integration requires two consecutive steps that are catalysed by the viral enzyme integrase (IN). Firstly, IN performs 3' end processing, a procedure that prepares the 3' end of the viral DNA for insertion into the host cell DNA. The processed DNA remains bound to integrase, and along with other viral and cellular proteins, forms the pre integration complex (PIC). The PIC is actively transported into the nucleus of the cell, whereupon the second function of integrase, strand transfer, is conducted. The strand transfer reaction is an intricate process that ultimately results in the viral DNA being completely embedded within the host cell DNA. With the viral DNA now completely inserted into the host cell genome, the virus has now effectively 'hijacked' the host cell, and uses the biochemical machinery present in the host to

[†] Image reproduced with permission from review by Pommier *et al.*[7]

replicate and manufacture progeny viral particles. This involves direct transcription to give viral RNA, as well as translation to give to assorted polypeptides (proteins). In the cytoplasm of the cell, the viral enzyme protease is responsible for the proteolytic processing of these proteins into functional viral proteins and enzymes necessary for viral propagation. Protease also helps to package these together and expel them from the cell wall in a process known as budding. These viral particles then mature and can go on to infect other previously healthy cells, thus completing the viral life cycle.

1.1.3 Current Treatments

There currently exist five major classes of HIV/AIDS medications: Entry and Fusion Inhibitors, Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), and very recently, Integrase Inhibitors. Most currently available anti-retroviral medications fall into either the NRTI or PI class of drugs, however, the other classes still play an important role in conventional treatment regimes. There are currently 29 anti-retroviral medications approved by the United States Food and Drug Administration (USFDA) for the treatment of HIV/AIDS, including 4 formulations composed of mixtures of drugs and all of these are listed in **Table 1**.

Table 1[†]

FDA Approval	Brand Name	Generic Name(s)	Manufacturer
Fusion and Entry Inhibitors			
2003	Fuzeon	Enfuvirtide (T-20)	Hoffmann-La Roche & Trimeris
2007	Selzentry	Maraviroc	Pfizer
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
1987	Retrovir	Zidovudine (AZT)	GlaxoSmithKline
1991	Videx	Didanosine (ddI)	Bristol Myers-Squibb
1992	Hivid	Zalcitabine (ddC)	Hoffmann-La Roche
1994	Zerit	Stavudine (d4T)	Bristol Myers-Squibb
1995	Epivir	Lamivudine (3TC)	GlaxoSmithKline
1997	Combivir	Lamivudine+Zidovudine	GlaxoSmithKline
1998	Ziagen	Abacavir	GlaxoSmithKline
2000	Trizivir	Abacavir+Zidovudine+Lamivudine	GlaxoSmithKline
2000	Videx EC	Didanosine, enteric coated (ddI EC)	Bristol Myers-Squibb
2001	Viread	Tenofovir disoproxil (TDF)	Gilead Sciences
2003	Emtriva	Emtricitabine (FTC)	Gilead Sciences
2004	Epzicom	Abacavir+Lamivudine	GlaxoSmithKline
2004	Truvada	Tenofovir disoproxil+Emtricitabine	Gilead Sciences, Inc.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
1996	Viramune	Nevirapine (NVP)	Boehringer Ingelheim
1997	Rescriptor	Delavirdine (DLV)	Pfizer
1998	Sustiva	Efavirenz (EFV)	Bristol Myers-Squibb
Protease Inhibitors (PIs)			
1995	Invirase	Saquinavir Mesylate (SQV)	Hoffmann-La Roche
1996	Crixivan	Indinavir (IDV)	Merck
1996	Norvir	Ritonavir (RTV)	Abbott Laboratories
1997	Fortovase	Saquinavir (no longer marketed)	Hoffmann-La Roche
1997	Viracept	Nelfinavir (NFV)	Agouron Pharmaceuticals
1999	Agenerase	Amprenavir (APV)	GlaxoSmithKline
2000	Kaletra	Lopinavir+Ritonavir (LPV+RTV)	Abbott Laboratories
2003	Lexiva	Fosamprenavir	GlaxoSmithKline
2003	Reyataz	Atazanavir (ATV)	Bristol-Myers Squibb
2005	Aptivus	Tipranavir (TPV)	Boehringer Ingelheim
2006	Prezista	Darunavir	Tibotec, Inc.
Integrase Inhibitor			
2007	Isentress	Raltegravir	Merck and Co., Inc.

Enfuvirtide is considered a fusion inhibitor and is the only drug to inhibit the viral particles from binding to the CD4 glycoprotein receptor of lymphocyte cells. In a related vein, the newly developed drug Maraviroc (a CCR5 co-receptor antagonist) acts to prevent the biochemical cascade that results in viral entry to the host cell. NRTIs and NNRTIs invoke their antiviral activity by inhibiting the function of the viral enzyme reverse transcriptase, although they differ in the way this is accomplished. NRTIs are synthetic nucleoside and nucleotide mimics which basically serve as alternative DNA building blocks to the viral enzyme reverse transcriptase. When viral RNA is reverse transcribed to viral DNA, these alternate substrates are incorporated and act as chain terminators,[9] halting reverse transcription. In a natural nucleoside, a hydroxyl group is located at the 3' position of the ribose, however, most NRTIs typically contain other functional groups at the 3' position to disrupt the crucial 3',5'-phosphate linkage that is created in a DNA strand. A representative structure (**1**, AZT) is shown in **Figure 2**, with the non-natural component shown in red. NNRTIs by contrast, bind to an allosteric (i.e., non-endogenous substrate binding) site of reverse transcriptase, triggering a conformational change of the enzyme which

[†] Table created from data obtained from the USFDA.[8]

then prevents access of substrates to the active site of the enzyme, thus rendering the enzyme ineffective. NNRTIs are varied in their structure so no representative structure is shown here.

An alternative target of currently available medication is the viral enzyme protease. All PIs that have been licensed by the USFDA (except tipranavir) are peptidomimetic and consequently act on protease in the same manner and share a similar structural scaffold (coloured red, **2**, **Figure 2**). Instead of containing a normal peptide bond, PIs contain a hydroxyethylene group which serves as a non-scissible peptide bond isostere for protease.[10]

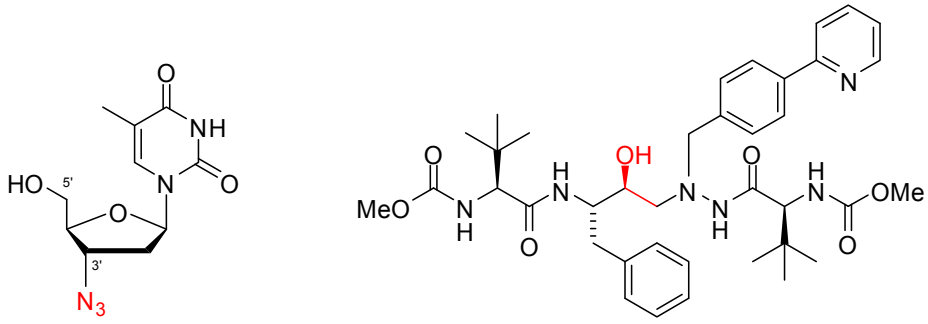


Figure 2

Due to the rapidly mutating nature of the human immunodeficiency virus, drug resistant viral strains are constantly emerging. In an effort to combat this, multiple drugs from various classes are administered and it has been shown that by using specific cocktails of drugs, it is possible to restore the sensitivity of the virus to drugs it was once previously resistant to. Of particular importance is Highly Active Antiretroviral Treatment (HAART), a therapeutic regime that consists of a PI or an NNRTI in combination with two NRTIs, which has now become the routine form of treatment for patients with access to these medications. Since the introduction of HAART, HIV/AIDS has become a manageable chronic illness rather than the life threatening disease it once was. The lifespan of an infected individual has improved dramatically from 6 months when AIDS was first observed, to in excess of 8 years (the data here are limited by the fact that HAART has only been in effect for about 11 years). When antiretroviral drugs were first introduced, risks and toxicities were tolerated in the face of imminent death. With increasing survival periods and the disappearance of the common symptoms of underlying HIV disease, adverse complications of antiretroviral drugs (side effects and associated toxicities of the drugs) are now being identified and characterised.[11] Despite the monumental successes of HAART, some factors have limited the success of this therapy. HAART requires compliance, is expensive and is often not well tolerated by patients due to the toxicity of the drugs.[12] The effectiveness of HAART is also starting to decline due to the emergence of viral strains displaying multi-drug resistance.[3,4] These factors highlight the urgent need for novel therapeutic approaches for the treatment of HIV/AIDS. The

development of new chemotherapeutic agents that target different stages of the viral life cycle should have an enormous impact on current treatment regimes.

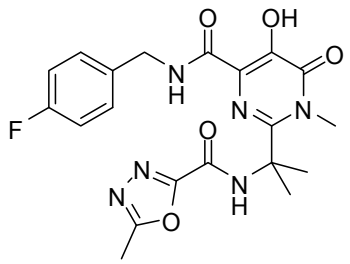
1.1.4 HIV-1 Integrase as a Therapeutic Target

The therapeutic rationale for targeting HIV-1 integrase has long been clear. HIV-1 IN inhibitors have received a great deal of attention over the past decade and until very recently, integrase remained clinically unexploited, despite the impressive potential for such therapies.

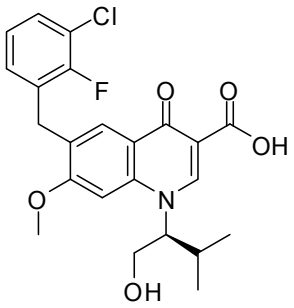
There is no known counterpart to integrase found in human cells and as a consequence, specific and potent integrase inhibitors should be accessible. It is also expected that the addition of integrase inhibitors to combination therapies will circumvent multi-drug resistance.[5] Multiple mutations of the viral genome would be required to overcome drug resistance, however, this is detrimental to viral replication and growth, and would lead to non-viable viral strains.[13,14] There are also other foreseeable advantages to adding integrase inhibitors to combination therapies. The dosage of each of the constituent drugs could potentially be lowered, thus minimising unwanted side effects and the impact of toxicity.

Recent work with integrase inhibitors has demonstrated that selective inhibition of integrase alone can successfully halt viral replication in whole cells.[15] Integrase inhibitors have also been shown to suppress retroviral replication in animal models,[16] thereby validating integrase as a target for anti-HIV chemotherapeutics.

This area of research is entering an exciting period with the recent release of the first USFDA approved IN inhibitor, raltegravir (isentress, MK-0518) (**3**, **Figure 3**). Developed by Merck, raltegravir has completed all clinical trials and recently gained approval by the USFDA for use by "treatment experienced" patients.[8,17] Gilead Science's elvitegravir (JTK-303, GS-9137) (**4**, **Figure 3**), has also passed phase II clinical trials with good results,[18,19] further substantiating the influential role of integrase inhibitors for future therapies.



raltegravir (isentress, MK-0518)
(Merck)
3



elvitegravir (JTK-303, GS-9137)
(Gilead Sciences)
4

Figure 3

1.1.5 Function of HIV-1 Integrase

The first function of HIV-1 integrase, 3' end processing, is a process whereby the two terminal nucleic acids from each 3' end of viral DNA are cleaved to leave reactive 3' hydroxyl DNA ends. These hydroxyl groups are the reactive sites required for the second function of integrase, strand transfer, which occurs within the nucleus. At a chemical level, this is a transesterification reaction whereby the hydroxyl groups (on the 3' end of the viral DNA) participate in nucleophilic attack on the host DNA phosphodiester moiety.[20] This is followed by DNA repair, presumably by cellular repair enzymes, which render the fully functional and fully integrated DNA. Once integrated into the host chromosome the proviral DNA is replicated and transmitted as part of the cellular genome,[14] as well as directly producing progeny viral particles as discussed in **Section 1.1.2**.

1.1.6 Structure of HIV-1 Integrase

HIV-1 Integrase is a 32 kDa enzyme comprising a 288 amino acid sequence and can be divided into three structural domains: residues 1–50 form the N-terminal domain (NTD), residues 50–212 form the catalytic core domain (CCD), and residues 213–288 form the carboxy-terminal domain (CTD).[21] The atomic structures of each of these domains have been determined separately by X-ray diffraction (albeit in dimeric form), and solution NMR.[7,22] Structures have also been determined for the CCD joined to the NTD, and the CCD with the CTD, however, at present there exist neither structures for complete integrase nor integrase complexed with a DNA substrate.[21]

It is known that all three domains are required for catalytic activity and that each domain possesses specific attributes.[21,23] The NTD is known to contain an HHCC motif (where H is hystidine and C is cysteine) that binds a zinc cation[24] whilst the CTD is known to bind DNA strongly but in a non-specific manner.[21,25] The CCD contains a triad of carboxylate containing residues which create the so called

D,D-35E motif believed to be the active site of the enzyme.[21,23] This motif is highly conserved among retroviral integrases and in the case of HIV integrase, this catalytic triad consists of D64, D116 and E152 (where D is aspartic acid and E is glutamic acid). Modification of any of these residues renders the enzyme inactive. Integrase also requires a divalent metal for activity, most likely Mg^{2+}, but Mn^{2+} cannot be precluded. The function of integrase in the presence of inhibitors can be highly metal dependant.[26,20,27] There is still some ambiguity as to whether there are one or two divalent metals at the active site and it has been postulated that the second metal is introduced with the entering DNA. It is widely accepted, and supported by X-ray crystallographic data,[28] that the D64 and D116 residues form a coordination complex with Mg^{2+} (**Figure 4**) but the second divalent metal may complex between D116 and E152.[28]

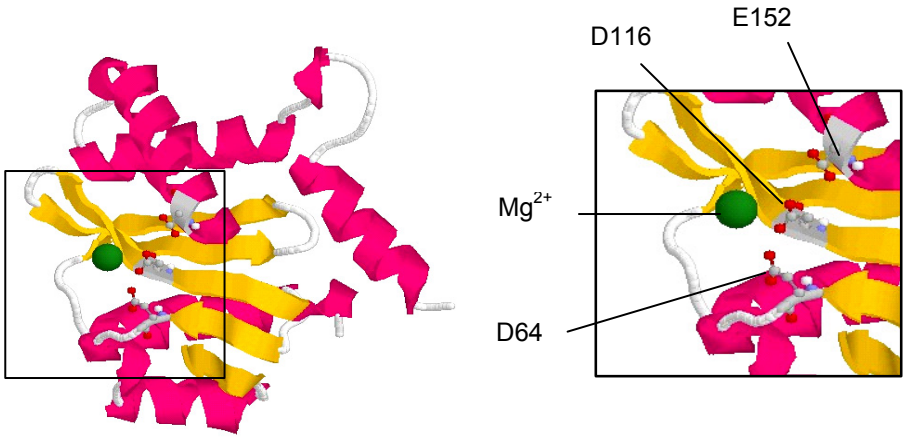


Figure 4[†]

Despite the considerable structural database generated for HIV-1 integrase, there is still little known about the actual solution conformation of the active enzyme. Crystal structure data suggest a dimeric CCD, however, the spatial arrangement of the active site in conjunction with NMR data suggests a higher-order complex and in particular, tetramers and/or octamers have been proposed as the active species.[7,23] The CCD is highly flexible and a coherent picture as to the solution conformation of the active complex with DNA substrate bound is still lacking. For these reasons, rational drug design of HIV-1 integrase inhibitors has proven difficult.

[†] Image courtesy of Kaitlin Beare, generated from data published by Goldgur *et al*.[29]

1.2 Inhibitors of HIV-1 Integrase

The pursuit of IN inhibitors has been a highly active research area, resulting in the disclosure of a large number of chemical structures with reported IN inhibitory activity. Despite the large number of IN inhibitors being identified, progress of these entities through to clinical trials has been slow. The slow progress seems to be, at least in part, due to difficulties in the identification of genuine lead compounds.[30,31] Although many compounds have been reported as IN inhibitors, most of these lack selectivity and tend to inhibit many other enzymes as well, complicating the elucidation of the genuine mode of action. Furthermore, the *in vitro* activity of many compounds has not translated to antiviral activity in cells, further hampering efforts.[15]

The discovery of IN inhibitors has primarily relied on the results of simple *in vitro* assays that use recombinant integrase and short oligonucleotide substrates that mimic the viral DNA ends.[32] This style of assay has been used extensively in high throughput screening, resulting in the identification of several classes of IN inhibitors being recognised. The most promising of these are the hydroxylated aromatics (or catechols) and the diketo acids (DKAs). Other, less well recognised classes include the sulfones, sulfonamides, and sulfonates; peptides and proteins; nucleotides; and DNA binding agents. For a more detailed account of these latter inhibitors, consult the review by Makhija and references cited therein.[33]

1.2.1 Hydroxylated Aromatic Inhibitors (Catechols)

The hydroxylated aromatics were among the first IN inhibitors discovered[34] and currently represent the largest class of IN inhibitors.[30] This class encompasses both natural and synthetic compounds. A disadvantage that plagues many members of this class is the potential for collateral toxicity due to inhibition of multiple enzyme systems.[35] Whilst this is true for many hydroxylated aromatics, a number have been found to be devoid of any toxicity and some are regularly consumed in particular diets.

One of the first group of hydroxylated aromatics studied was the flavonoids, such as quercetagetin (**5**), largely due to the availability of derivatives and diverse biological effects.[22,34] Unfortunately, these diverse biological effects precluded them from being good lead compounds, but nonetheless *in vitro* IN inhibition was displayed. **Figure 5** also illustrates several other significant hydroxylated aromatics.

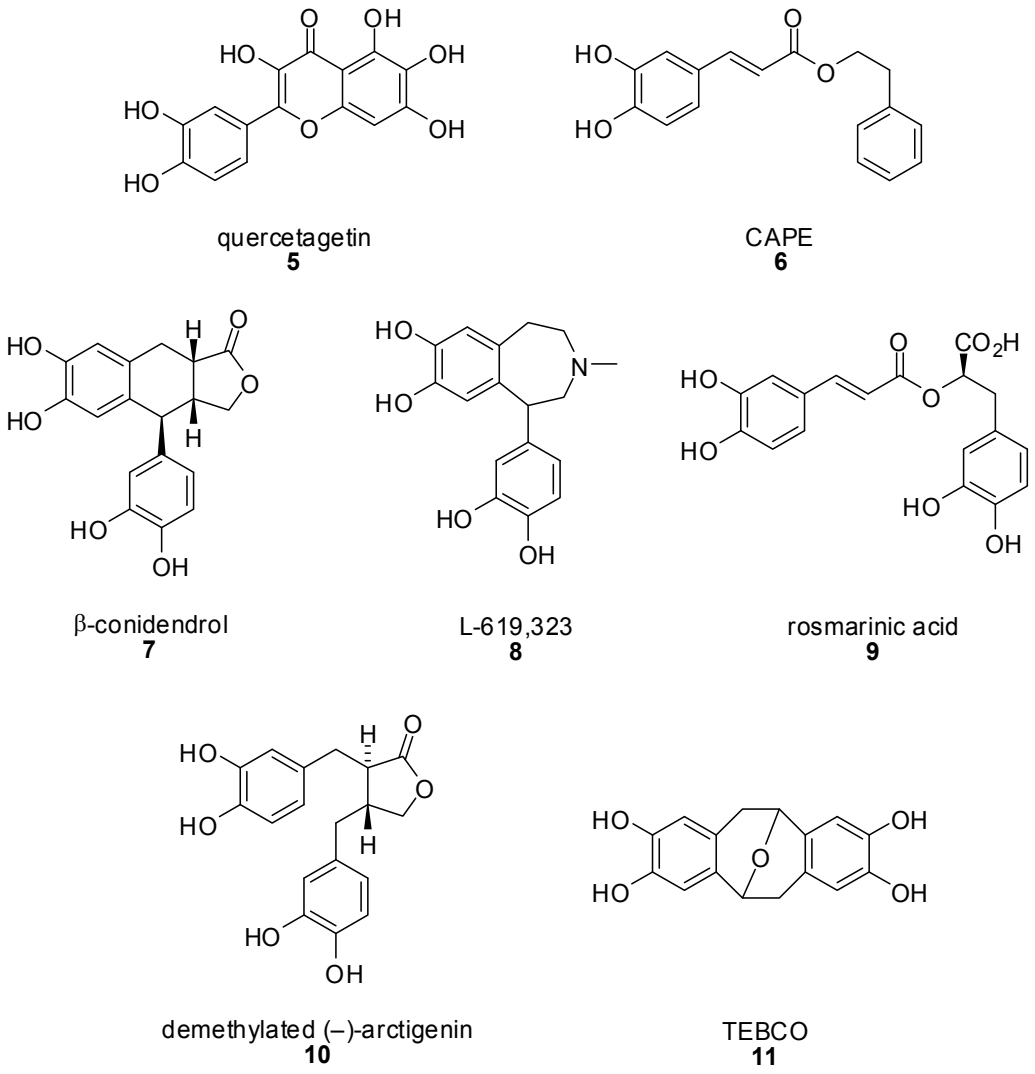
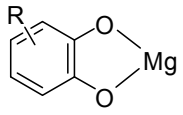


Figure 5

Caffeic acid phenylethyl ester (CAPE) (**6**) formed the prototype for an array of studies into structure activity relationships and was the first strand transfer inhibitor to be noted.[34] This example is somewhat atypical as CAPE represents the only compound active against IN that does not possess a bis-catechol motif. The first patent in the field covered β-conidendrol (**7**), which was reported as an effective IN inhibitor. Unfortunately, *in vitro* enzyme inhibition did not translate into antiviral activity in cell cultures.[36] Other bis-catechols include the natural product rosmarinic acid (**9**), compound **10**, derived from the natural product arctigenin, and the totally synthetic TEBCO (**11**). From various studies, it has been concluded that the bis-catechol is crucial for IN inhibitory activity.[36,37,38] It has also been determined that the nature of the linker between the two catechol groups is not subject to stringent requirements. This linker may be composed of an amide, aliphatic or aromatic groups, flexible or constrained and still have IN inhibitory activity. From structural considerations, it appears likely that the mode of action is *via* metal chelation (**12**, **Figure 6**). It has, however, also been proposed that the

catechol may be oxidized to reactive *ortho*-quinones, may be engaged in redox reactions (eg. with cysteine residues) or may intercalate in DNA,[22] and these hypotheses cannot be ruled out.

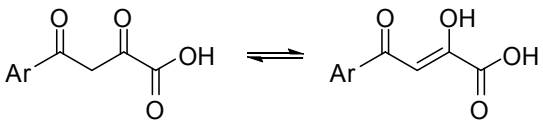


12

Figure 6

1.2.2 Diketo Acid Inhibitors

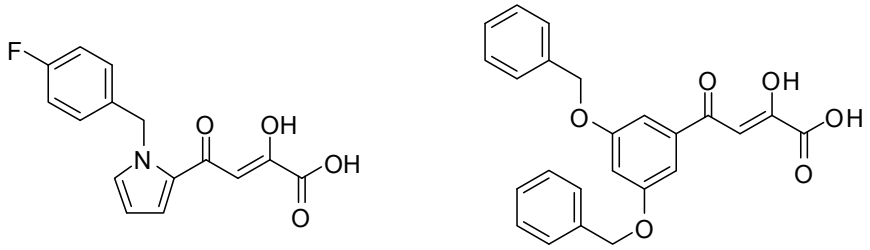
Diketo acids as inhibitors of IN were first reported by Merck in 2000. In a modified screening procedure developed by Merck, over 250,000 compounds were assessed, and a variety of IN inhibitor classes were identified.[15] The most potent and specific of these classes comprised synthetic compounds with a unified structural motif, the diketo acid moiety (**13**, **Figure 7**), giving rise to their name. Keto-enol tautomerism is likely to occur, rendering **14** as the more abundant tautomer, and either form is commonly accepted and used.[39] The diketo acid functionality is an intrinsic feature of these compounds, however, the presence of this moiety alone is not sufficient for activity.



13 **14**

Figure 7

L-731,988 (**15**) and L-708,906 (**16**) (**Figure 8**) were two of the most active DKAs identified from this study.[15] A trademark signature of the DKAs is their ability to inhibit the strand transfer reaction at nanomolar concentrations. DKAs also inhibit the 3' processing step, albeit at 30–70-fold higher concentrations.[26,15] The discovery of this class of compounds represented a breakthrough, not only because of their potent antiviral activity, but also because it was the first well-characterised selective targeting of integrase in HIV-infected cells. DKAs have also been shown to exhibit their antiviral activity exclusively by inhibition of IN, as they show no inhibition of the other steps in the viral lifecycle, making them the first truly authentic IN inhibitors. As mentioned previously in brief, the Merck research unambiguously provided the proof of concept that IN inhibition alone can successfully halt viral propagation in both HIV-infected cells and in animal models.[15,16]

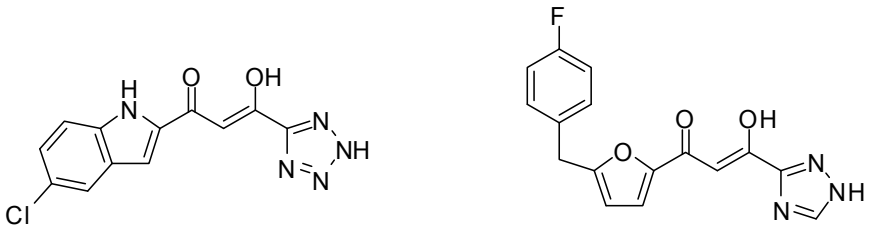


L–731,988 (Merck)
15

L–708,906 (Merck)
16

Figure 8

Independently, and at roughly the same time, scientists at Shionogi and Co. discovered a similar structural motif that could be functionally classified as a DKA. There exists some overlap in the patents filed by each of these companies. The Shionogi & Co. compounds, typified by 5-CITEP (**17**) and S-1360 (**18**), focused largely on indole and other heteroaromatics for the aromatic portion and also replaced the carboxylate with other known bioisosteres such as triazoles and tetrazoles (**Figure 9**).

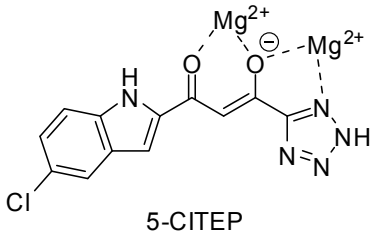


5-CITEP (Shionogi & Co.)
17

S-1360 (Shionogi & Co.)
18

Figure 9

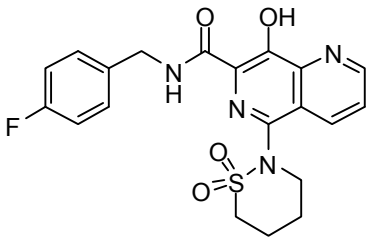
5-CITEP was a breakthrough because it was co-crystallised with the CCD of integrase, the first co-crystal of this type, and found to be in close proximity to the DDE motif, confirming previous speculation that this is the catalytically active site of the enzyme.[40] A proposed binding model is shown in **Figure 10**. S-1360 advanced into phase II clinical trials but was withdrawn due to poor pharmacokinetic data. The company has a back-up candidate, currently called RSC-1838 whose structure is reportedly similar to S-1360 but as yet remains undisclosed.



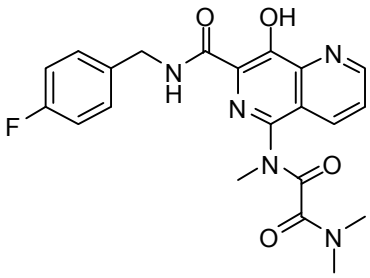
5-CITEP
17

Figure 10

Unfortunately, a problem that plagues many of the DKAs is their unsuitability as therapeutic agents, largely due to toxicity. Further optimisation efforts on the DKA motif by the Merck group have led to analogues, namely the 8-hydroxy-[1,6]napthyridine-7-carboxamides, typified by L-870,810 (**19**) and L-870,812 (**20**) with IN inhibition in the nanomolar range. Compound L-870,810 proved very promising in early stages of testing, but during phase II clinical trials was withdrawn due to liver and kidney toxicity observed in dogs.[41] More analogues of these systems were developed by Merck, ultimately leading to raltegravir (**3**, **Figure 3**), recently approved by the USFDA.[8]



L–870,810 (Merck)
19



L–870,812 (Merck)
20

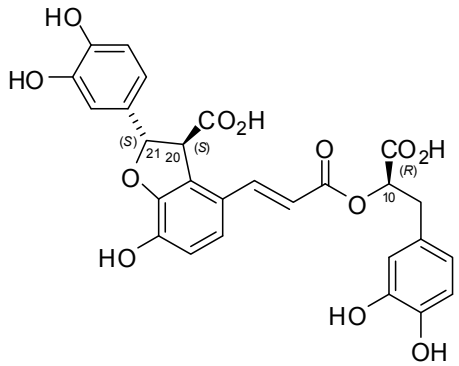
Figure 11

The DKA motif is not wholly restricted to the totally synthetic compounds that spawned the theme. Some natural products contain motifs that can be considered as DKAs. Merck are also working on natural products as lead compounds and from this approach, Integramycin (**47**) has been identified as a potent IN inhibitor that could be considered to be from the DKA class of IN inhibitors. This will be discussed in more detail in **Section 1.4**.

1.3 Lithospermic Acid

1.3.1 A Historical Account

The first notable report of the compound known as lithospermic acid dates back to 1963, when it was isolated by Johnson *et al*. as the principal polyphenolic present in the aqueous extracts of the roots of the plant *Lithospermum ruderale* (**Figure 12**).[42] At this point in time, interest in the chemical constituents of *Lithospermum ruderale* stemmed largely from reports that certain native Nevadan Indians had used the plant to brew a contraceptive tea.[43] Lithospermic acid has also been reported as being biologically inactive, and that on oxidation it formed a polymer that displayed anti-ovulatory activity in some animals.[44] Partial characterisation of lithospermic acid led to the identification of some of the structural elements present, but a complete structure was unable to be determined. A number of years later in 1975, lithospermic acid was isolated by Wagner *et al*.[45] from *Lithospermum officinale* and Kelley *et al*.[43] from *Lithospermum ruderale* Dougl. ex Lehm, both plants from the *Boraginaceae* family. Both groups independently established the structure of lithospermic acid as **21** (**Figure 12**), although the absolute configuration remained unassigned. Kelley *et al*. concluded a *trans* relationship of the C20/C21 substituents by comparison of ^{1}H NMR coupling constants with similar compounds.



(+)-lithospermic acid
21

Figure 12

Interestingly, lithospermic acid has also more recently been isolated from *Salvia miltiorrhiza*, a plant of the *Lamiaceae* family. Danshen, the dried roots of *Salvia miltiorrhiza*, is one of the most popular herbs in traditional Chinese medicine and has been used to treat an extensive array of ailments for centuries. Most notably, it is widely used in China, and to a lesser extent in Japan, the United States and a number

of European countries, to treat cardiovascular and cerebrovascular diseases.[46] Early studies into danshen focused on the lipophilic components, revealing more than 30 diterpenes. More recently, focus has shifted to the hydrophilic components with caffeic acid derivatives occurring as the major isolates, known as salvianolic acids and lithospermic acids. Twenty-five caffeic acid derivatives have been isolated and identified, many with known biological activities. Many of these are monomers or higher oligomers of caffeic acid, some examples of which are shown in **Figure 13**.

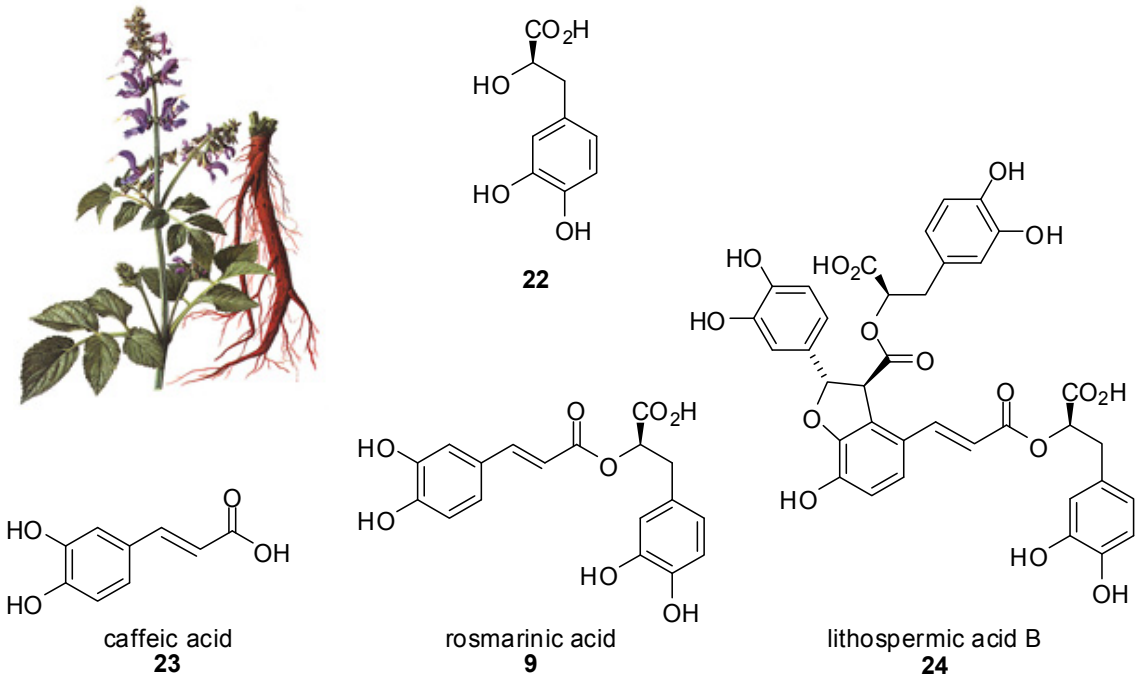


Figure 13

Lithospermic acid (**21**) has also been isolated from many other plants, including: *Lycopus europaeus*, *Lycopus virginicus*, *Symphytum officinale*, *Anchusa officinalis*, and *Echium vulgare*.[42] The isolated yields of lithospermic acid from the natural sources are dependant on the species as well as the location on the plant.

1.3.2 Lithospermic Acid as an Integrase Inhibitor

Reports pertaining to lithospermic acid (**21**) were infrequent during the period from its discovery through until 2002, well after the onset of the HIV/AIDS epidemic. At this time an influential finding by Abd-Elazem *et al*. sparked a great deal of interest in the lithospermic acids as they were reported to display potent inhibition of HIV integrase with minimal toxicity.[47]

Lithospermic acid (**21**) and lithospermic acid B (**24**) were isolated from the methanolic extracts of the roots of *Salvia miltiorrhiza*. Following size exclusion chromatography and HPLC using 3' processing activity guided fractionation, **21** and **24** were isolated in 0.018% and 0.038% yield respectively. The

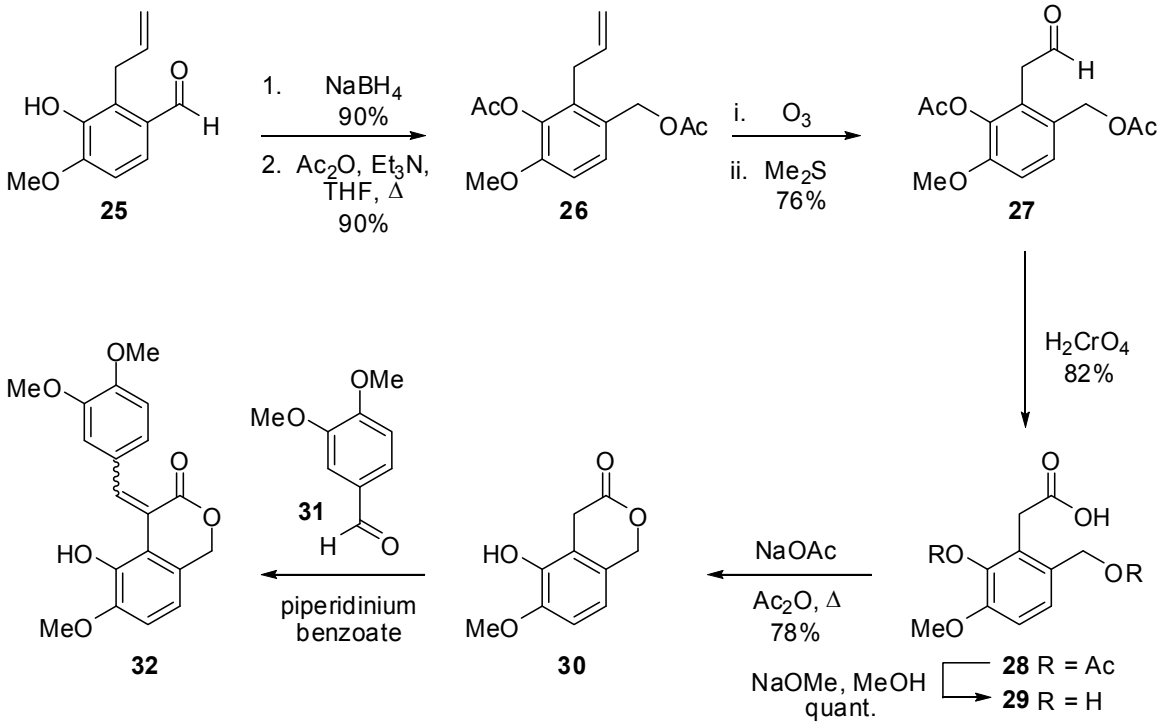
identities of these compounds were confirmed by comparison with previous literature. Both isolates were then subjected to a range of assays which revealed that **21** showed no cytotoxicity to H9 cells even at high concentrations (CC_{100}>297μM) and the IC_{50}s for 3' processing and the strand transfer reaction were found to be 0.83 μM and 0.48 μM, respectively. Most importantly, when applied to a cell based assay, this activity was transferred and **21** was shown to strongly suppress acute HIV-1 infection in infected H9 cells with an IC_{50} value of 2.0 μM. Furthermore, **21** was shown to have no effect on the function of reverse transcriptase and was also shown to not prevent HIV entry in H9 cells.[47] These attributes are important in establishing an authentic integrase inhibitor.

Lithospermic acid (**21**) clearly falls into the category of the hydroxylated aromatic HIV integrase inhibitors and more specifically, it shares the classic structural motif of the other well known IN inhibitors, the bis-catechols.

1.3.3 Previous Synthetic Efforts

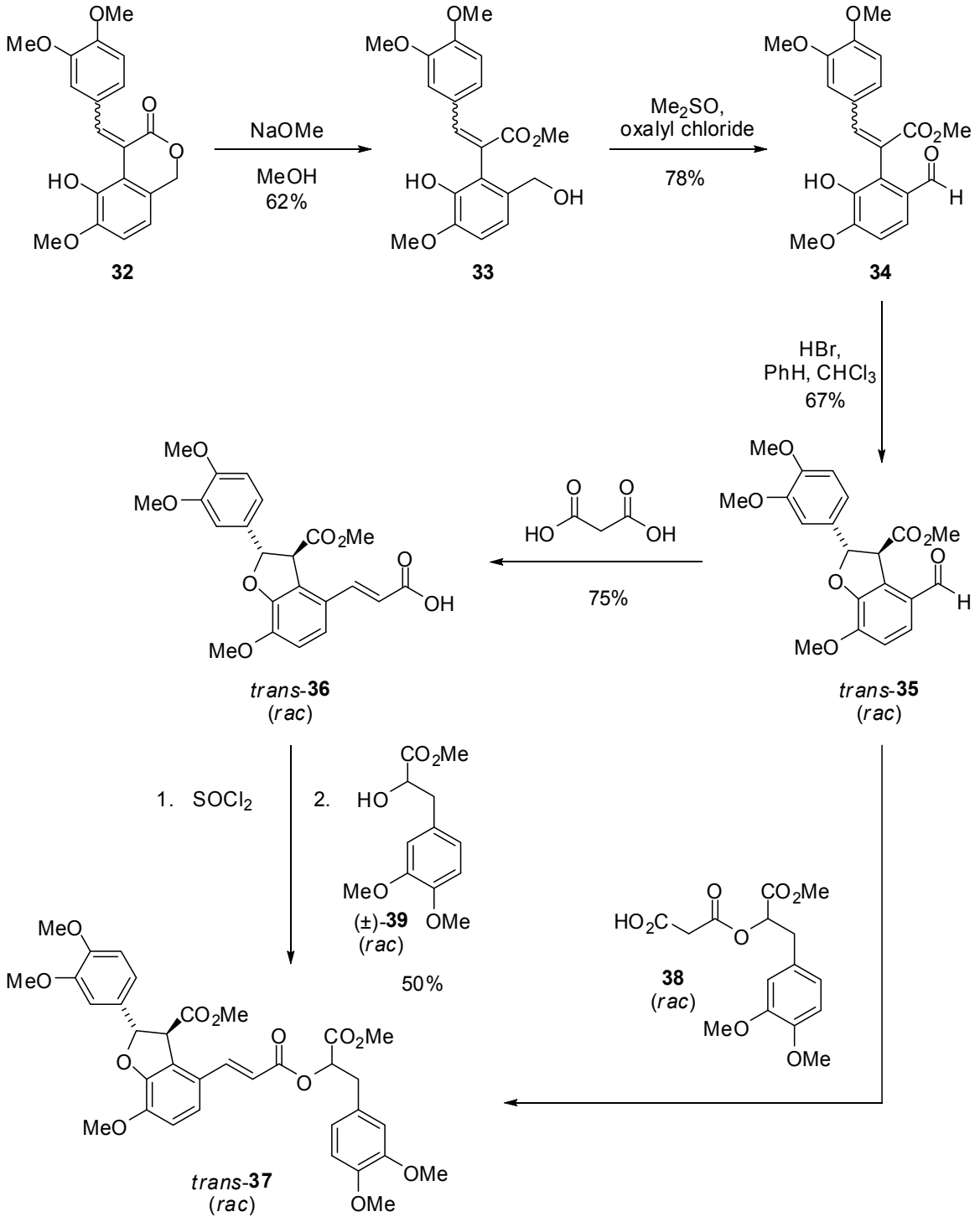
Prior to our commencing this work, the first, and to the best of our knowledge, only attempted synthesis of lithospermic acid (**21**) was carried out by Jacobson and Raths[48] in 1979 and is presented in **Scheme 1** and **Scheme 2**.

This approach commenced with the formation of 2-allylisovanillin (**25**) from isovanillin. Reduction of **25** with sodium borohydride, followed by bis-acetylation gave **26**. Ozonolysis followed by reduction with dimethyl sulfide afforded aldehyde **27**, which was oxidized with Jones' reagent to give acid **28**. Acetate cleavage was accomplished with methanolyic sodium methoxide and treatment of the generated diol **29** with sodium acetate in refluxing acetic anhydride gave benzopyranone **30**. Piperidinium benzoate catalysed condensation of **30** with methylvanillin (**31**) afforded the aldol condensation product **32** as a mixture of *E* and *Z* isomers.



Scheme 1

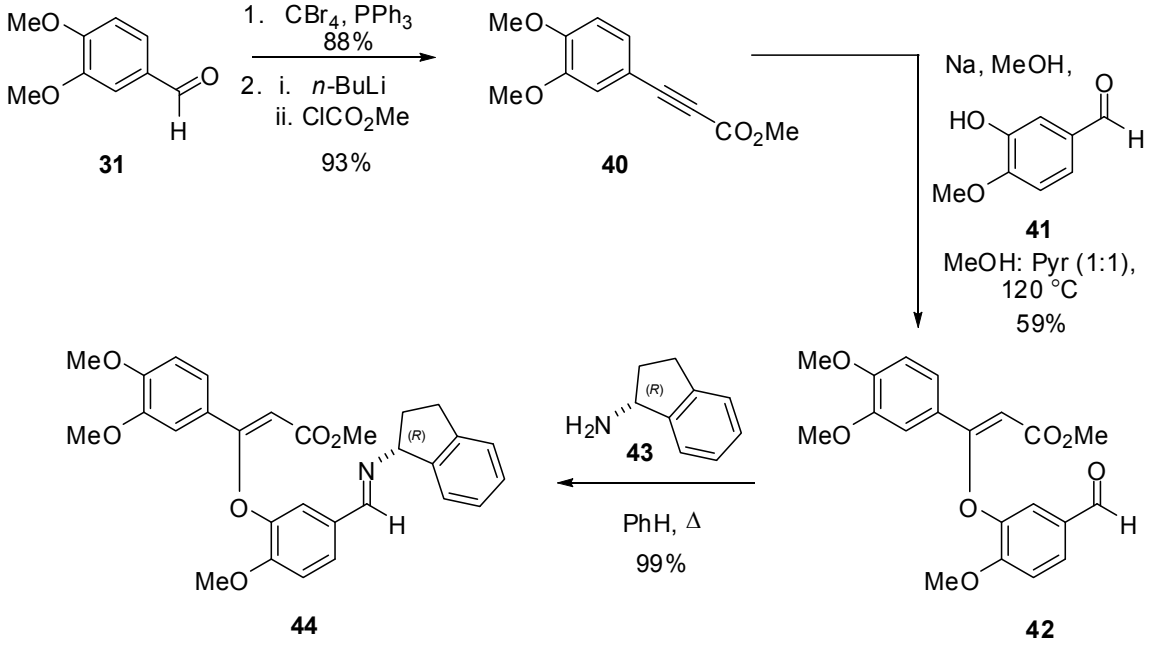
Lactone **32** was opened with methanolic sodium methoxide to give benzyl alcohol **33** (**Scheme 2**), which underwent Swern oxidation to afford benzaldehyde **34**. Hydrogen bromide promoted cyclisation of **34** gave the *trans* 2,3-dihydrobenzofuran *trans*-**35**. Conversion to heptamethyl lithospermate could be realised by two alternate strategies. Direct Knövenagel condensation with **38** furnished racemic heptamethyl lithospermate (**37**) in a modest yield. A more efficient strategy followed a two step procedure. Firstly, Knövenagel condensation of aldehyde *trans*-**35** with malonic acid gave cinnamic acid *trans*-**36**, which, proceeding *via* its corresponding acid chloride, was esterified with alcohol **39**. This alternate procedure gave heptamethyl lithospermate (**37**) in a more respectable yield (50%). The reported synthesis concluded at this point, leaving one to assume that the methyl protecting groups proved too stable to demethylation, or the conditions available at the time lead to decomposition. In particular, the dihydrobenzofuran and ester moieties would be expected to be labile to the typically harsh conditions needed for demethylation.


NaOMe
MeOH
62%
Me2SO,
oxalyl chloride
78%
HBr,
PhH, CHCl3
67%
75%
1. SOCl2
2.
50%
32
33
34
trans-36
(rac)
trans-35
(rac)
(±)-39
(rac)
38
(rac)
trans-37
(rac)

Scheme 2

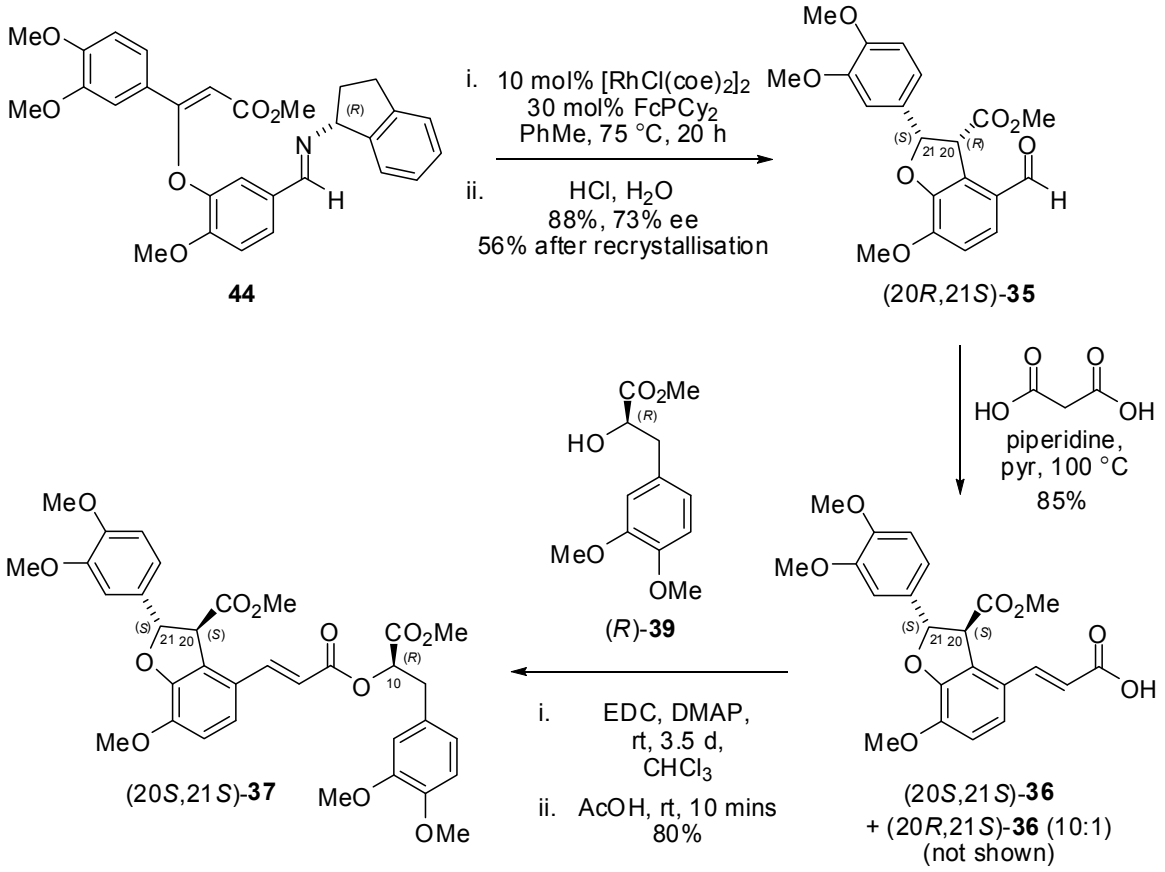
An alternate and elegant strategy was reported more recently in 2005 by Ellman and co-workers.[49] This synthesis was published during the course of this work and the impact of this publication will become apparent in **Chapter 4**.

The Ellman synthesis starts with a Corey–Fuchs olefination of methylvanillin (**31**), followed by conversion to the 1-lithio alkyne and subsequent trapping with methyl chloroformate, to give alkyne **40**. Conjugate addition with isovanillin (**41**) furnished the enol ether as a 3.2:1 mixture of *Z*:*E* isomers that were separated by chromatography and crystallisation to give the *Z* isomer (**42**) in 59% isolated yield.



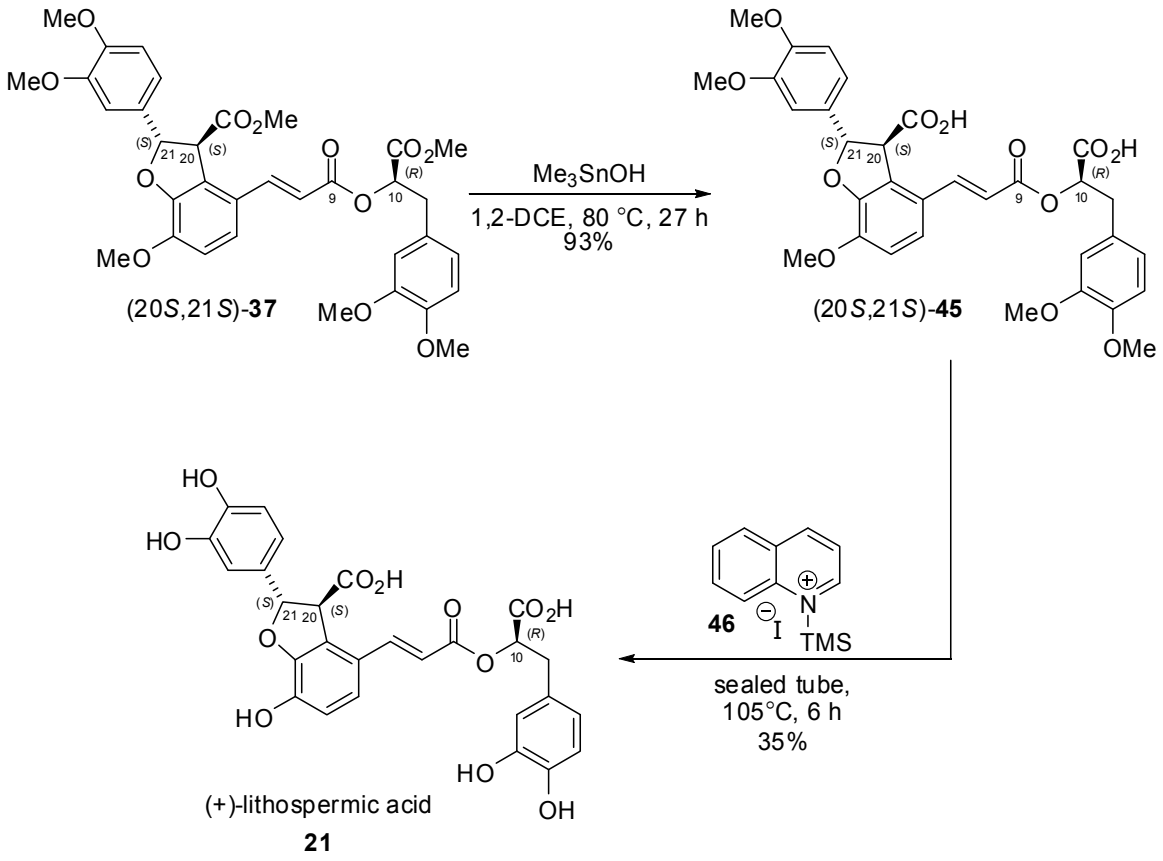
Scheme 3

The key step in the synthesis, an enantioselective intramolecular alkylation, showcased the rhodium-catalysed C–H bond activation methodology recently developed within the Ellman group. After a wide range of chiral catalysts had failed to deliver the requisite dihydrobenzofuran (20*R*,21*S*)-**35**, alternate approaches were sought. Chiral imines were investigated as a tactic to introduce a chiral auxiliary. The desired chiral imine **44** was prepared by condensation of aldehyde **42** with the chiral amine (*R*)-aminoindane (**43**).



Scheme 4

The *cis*-dihydrobenzofuran (20*R*,21*S*)-**35** was generated in good yield (88%) with a modest 73% *ee* after examination of a range of catalysts. Subsequent recrystallisation of this product afforded the single enantiomer (20*R*,21*S*)-**35**, in 56% yield (99% *ee*). In the subsequent step, Knövenagel condensation with malonic acid, epimerisation took place to give predominantly the more thermodynamically stable *trans* isomer. This gave a *ca*. 10:1 mixture of *trans*:*cis* isomers, that were separable by column chromatography to provide the requisite (20*S*,21*S*)-**36** in 85% yield. Esterification of (20*S*,21*S*)-**36** with alcohol (*R*)-**39** gave a single isomer of heptamethyl lithospermate ((20*S*,21*S*)-**37**) in good yield.



Scheme 5

The final global deprotection of (20*S*,21*S*)-**37** to give lithospermic acid (**21**) had proven an insurmountable obstacle for Jacobsen and Raths, however, this was overcome in the Ellman synthesis. Conditions for demethylation were investigated and optimised using the conversion of permethylated rosmarinic acid back to rosmarinic acid as a model. This gave rise to the use of Brossi's conditions,[50] in which preformed trimethylsilylquinolinium iodide (**46**) was the reagent of choice for this transformation. Unfortunately, these conditions did not prove directly transferable to (20*S*,21*S*)-**37**. Ring opening of the dihydrobenzofuran through β-elimination of the C21 phenoxy group proved to be the major decomposition pathway. A two-step sequence was then employed to minimise this degradation pathway. Using trimethyltin hydroxide, the methyl esters were cleaved selectively in preference to the internal C9 ester linkage, to give diacid (20*S*,21*S*)-**45**. Subjecting (20*S*,21*S*)-**45** to Brossi's trimethylsilylquinolinium iodide conditions then delivered (+)-lithospermic acid (**21**), thus completing the first total synthesis of this natural product and confirming the assigned absolute configuration.

This efficient, asymmetric synthesis of (+)-lithospermic acid was achieved in 10 steps and an impressive 5.9% overall yield from methylvanillin (**31**). Importantly, the final deprotection of the permethylated lithospermic acid was accomplished, however, a number of steps suffered from low yields and the asymmetric induction achieved in the key step was only modest. The rhodium-catalysed step would also

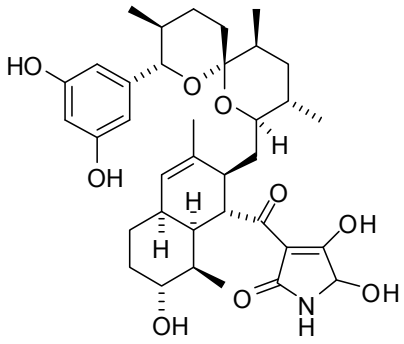
be sensitive to substrate composition and would likely limit the choice of protecting groups and functionality that would be tolerated by this approach. Overall, this approach is elegant, efficient and sets a high standard to try to surpass.

1.4 Integramycin

The Merck research laboratories perform routine screening of microbial extracts in the search for natural product HIV-1 IN inhibitors, and this has resulted in the identification of several active microbial extracts. The bioassay guided separation of these extracts has proven to be a successful technique to discover natural product IN inhibitors. This technique has resulted in the isolation and identification of several IN inhibitory compounds including equisetin,[51] integric acid,[52] and complestatin.[53] In 2002, this process unveiled the novel compound integramycin (**47**).[54]

Size exclusion chromatography of the methyl ethyl ketone extract of *Actinoplanes* sp. (ATCC202188, grown on liquid media), followed by reverse phase High Performance Liquid Chromatography (HPLC) gave integramycin (200 mgL^{-1}) as a colourless powder.

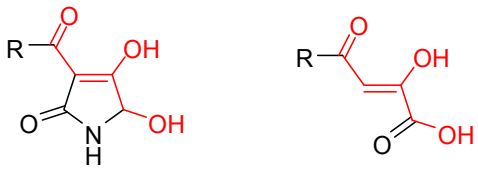
High-resolution ESIMS provided a molecular formula for integramycin. UV and IR spectra in conjunction with the ^{1}H and ^{13}C NMR spectra, were used to assign a possible structure for integramycin. NMR data were recorded in several solvents to circumvent problems associated with tautomeric equilibria and to achieve optimal separation of overlapping signals. A range of NMR experiments were conducted, including 2D COSY, 2D TOCSY, 1D TOCSY, HMQC and HMBC, identifying three contiguous spin systems which were further substantiated by ESIMS data. Relative configuration was deciphered using a combination of vicinal coupling constants, NOESY correlations, ChemDraw three-dimensional modelling and inspection of Dreiding models. The absolute configuration is yet to be confirmed. Ultimately, the structure of integramycin has been deduced as that shown in **Figure 14**.



Integramycin (**47**)

Figure 14

Integramycin (**47**) inhibited the strand transfer reaction of HIV-1 integrase with an IC_{50} value of 4 μM and also showed no cytotoxicity in a DNAase assay up to 100 μM.[54] These desirable biological properties, combined with the unique hexacyclic structure, render integramycin a worthwhile target for further synthetic study.



48 **49**

Figure 15

Little is known about the mode of action of integramycin on integrase, however, it is possible that the tetramic acid subunit may be functioning as a bioisostere of the well known DKA motif. **Figure 15** shows the structural similarities displayed between the tetramic acid and a representative DKA. This is an intriguing prospect since integramycin displays a structurally novel unit that may mimic the DKA motif. This mimicking of the DKA motif is a trend that has been seen previously with drugs such as **17**, **18**, **19** and **20**, all of which display a DKA mimicking motif and have progressed through to phase II clinical trials.

Integramycin represents both a potential drug lead and a formidable challenge to the synthetic chemist. This has attracted at least two other research groups from the synthetic organic chemistry community. Wang and Floreancig have developed a route to the aryl spiroacetal subunit of integramycin[55] whilst Dineen and Roush[56] have developed methodology to furnish the *cis*-decalin subunit. However, no reports of synthetic efforts towards the tetramic acid segment, the focus of this work, have appeared in the literature to date.

1.5 Project Aims

The overall aims of this project were to:

(i) Complete an efficient total synthesis of lithospermic acid *via* a flexible, convergent, modular route that would allow ready access to analogues, for future SAR studies, and

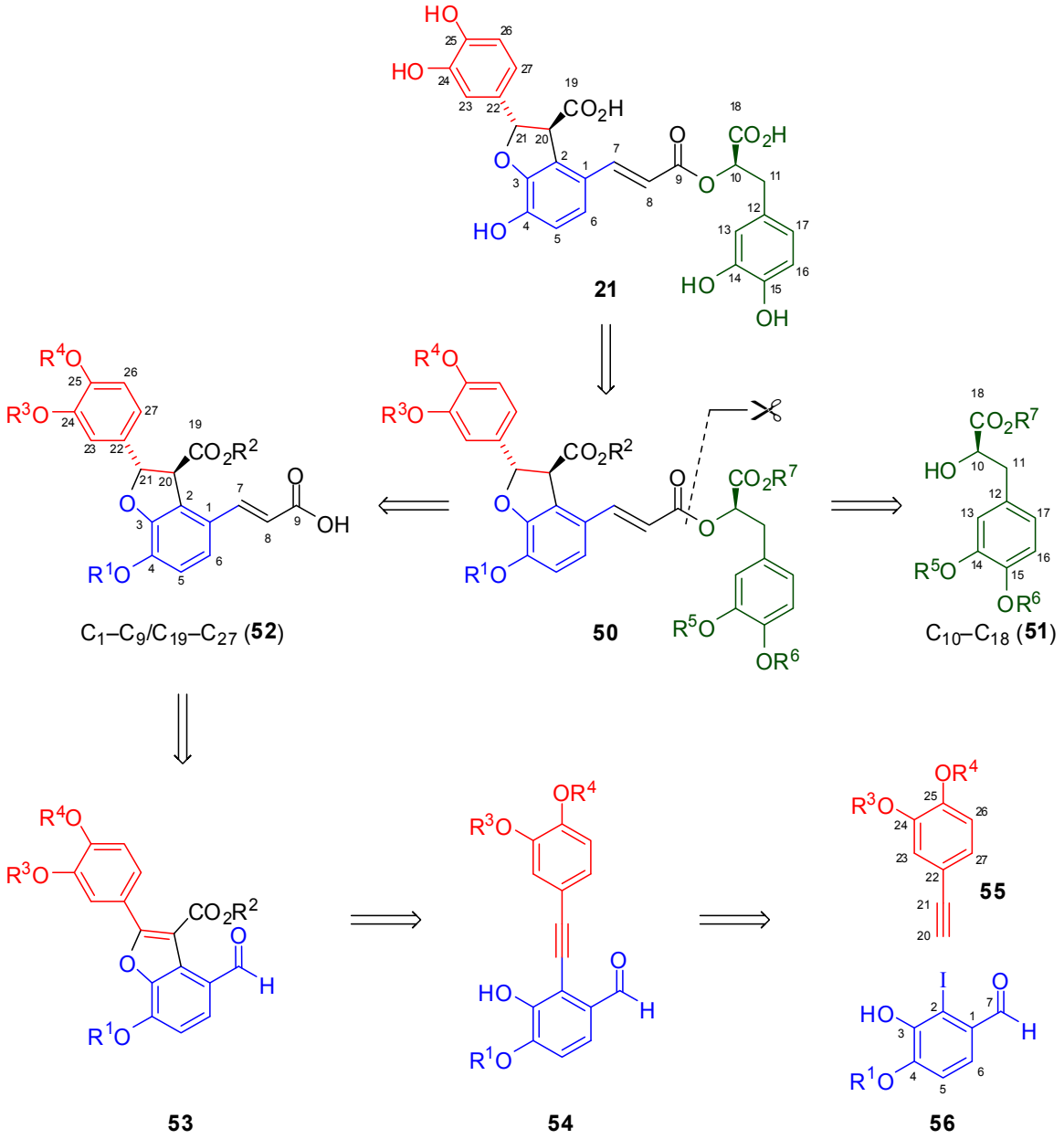
(ii) Explore synthetic strategies towards the tetramic acid subunit of integramycin.

–Chapter 2–

Model System Studies of Lithospermic Acid and Initial Investigations Into Protecting Group Strategy

2.1 Retrosynthetic Analysis of Lithospermic Acid

With the objective of accessing lithospermic acid (**21**) and various derivatives, a modular, flexible and convergent synthetic approach was desirable. **Scheme 6** below illustrates the retrosynthetic analysis employed to meet these objectives.



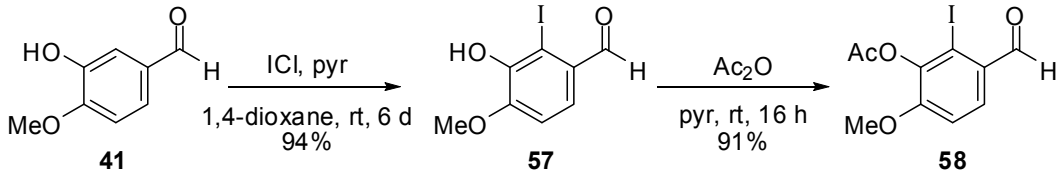
Scheme 6

In this strategy, the target natural product lithospermic acid (**21**) would originate from the global deprotection of a suitably protected precursor (**50**) that could, in turn, be obtained from fragments **51** and **52** *via* esterification. This occurs at a late stage in the synthesis conferring convergence and

modularity to this strategy. The specific example of fragment **51** where R^5= R^6= R^7= Me (**39**), is a known compound[49] and there also exist other examples of differing R^5, R^6 and R^7 groups[57-60] which leaves the focus on the C_1–C_9/C_{19}–C_{27} fragment **52**. This could be accessed by the reduction of benzofuran **53**, followed by condensation of the aldehyde with malonic acid to give the desired **52**. Benzofuran **53** would originate from *ortho*-hydroxydiarylalkyne **54** in the key step of the synthesis, a palladium-mediated carbonylative annulation reaction. The diarylalkyne precursors **54** could be assembled *via* the Sonogashira coupling of appropriately functionalised arylalkynes (**55**) and aryl iodides (**56**). It is envisaged that this carbonylative annulation/reduction sequence may provide a potentially novel, general route to 2,3-dihydrobenzofurans bearing ester functionality at the 3-position.

2.2 Synthesis of the C_1–C_7 Aryl Iodide

The protected iodoisovanillin **58** was prepared according to **Scheme 7**.



Scheme 7

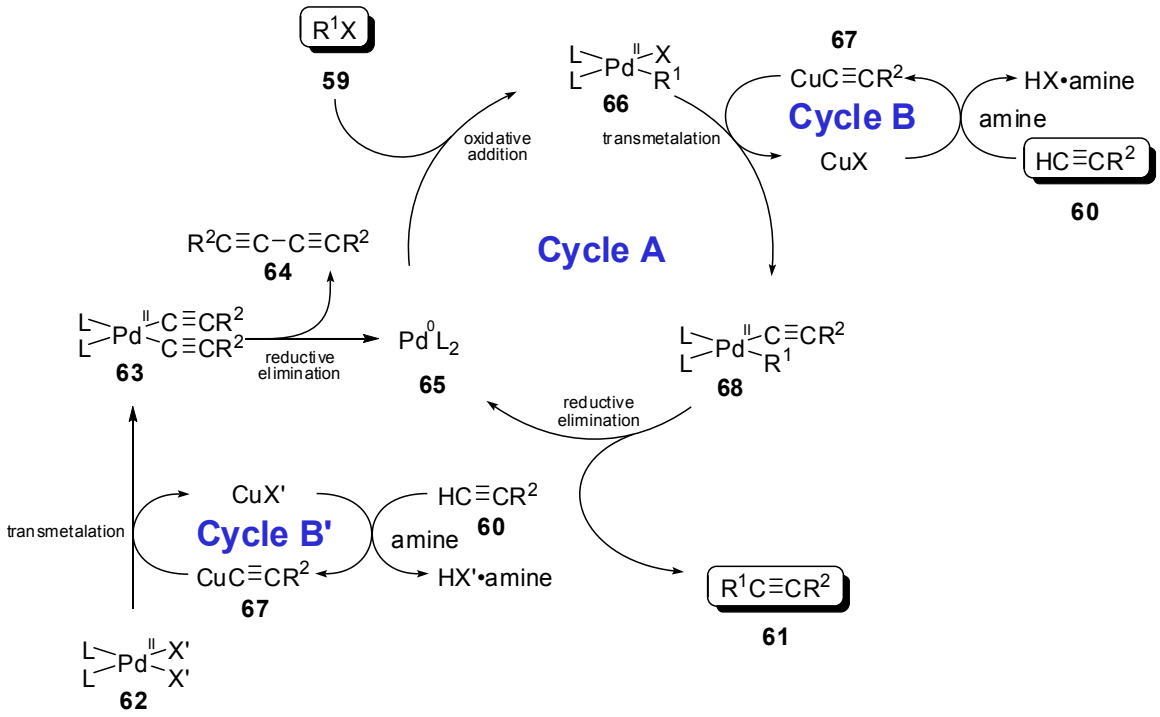
Isovanillin **41**, was regioselectively iodinated using iodine monochloride in the presence of pyridine according to a procedure by Markovich *et al.*[61] to yield iodoisovanillin **57**. Pyridine was employed to generate the phenoxide of **41** so as to have a stronger *ortho*-directing effect than the parent compound to increase regioselectivity. Phenol **57** was then protected as the acetate **58** in high yield. These reactions were carried out on large scale (*ca.* 28 g) as **58** was required as an early stage intermediate for all following work.

2.3 Synthetic Studies on a Model System

To examine the viability of our planned route to the benzofuran compounds **53**, a model system study was undertaken. In this series, commercially available phenylacetylene (**69**) was used as the non-oxygenated C_{20}–C_{27} fragment (**55**).

2.3.1 Sonogashira Coupling

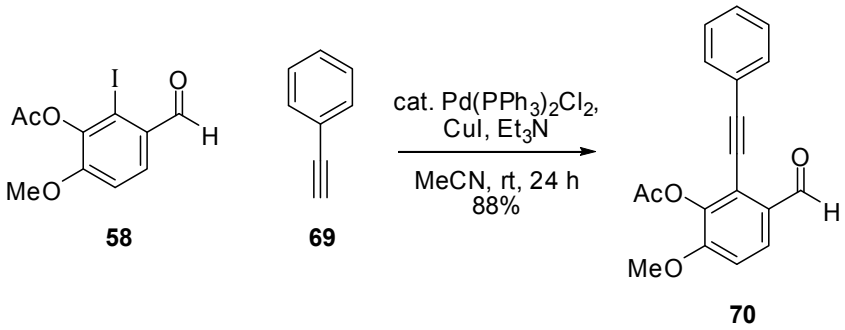
In order to access the requisite diarylalkynes (**54**), Sonogashira coupling chemistry was utilised. The origins of the Sonogashira coupling are based on an observation in 1963 by Stephens and Castro,[62] that the coupling of aryl iodides with copper(I) acetylides occurred in refluxing pyridine. Considering the valuable potential of this cross coupling reaction between sp- and sp^2-hybridised carbon atoms, there was much impetus to find milder reaction conditions. In 1975, Sonogashira and co-workers reported just such a facile and mild process.[63] The reaction now known as the Sonogashira coupling, is a process whereby a terminal alkyne is coupled to an aryl or vinyl halide or triflate, under palladium catalysis, usually in the presence of catalytic copper(I). The presumed catalytic cycle, uniting aryl halide **59** with alkyne **60** to generate arylalkyne **61**, is presented in **Scheme 8**.[64,65]



Scheme 8

Palladium(0) (**65**), the putative active catalyst, is conceivably generated *in situ* by the reduction of a palladium(II) source (**62**), often bis(triphenylphosphine)palladium(II) dichloride. Terminal alkyne **60** is converted to copper(I) acetylide **67** which can then undergo transmetalation/ligand exchange with **62** (2 × Cycle B') to form bis-acetylide **63** and regenerate the copper(I) halide. The bis-acetylide **63** then reductively eliminates to generate the homocoupled by-product **64**, and also furnishes the active catalyst **65**. The highly coordinatively unsaturated 14-electron palladium(0) complex **65** participates in an oxidative addition reaction with **59** to give the 16-electron palladium(II) complex **66**. Transmetalation/ligand exchange with copper acetylide **67** furnishes the aryl alkynyl palladium(II)

complex **68** and regenerates the copper(I) halide to continue in Cycle B. The palladium(II) complex **68** then undergoes reductive elimination to reveal the desired alkyne **61** and regenerate the active palladium(0) **65**, which can further participate in the catalytic process (Cycle A).

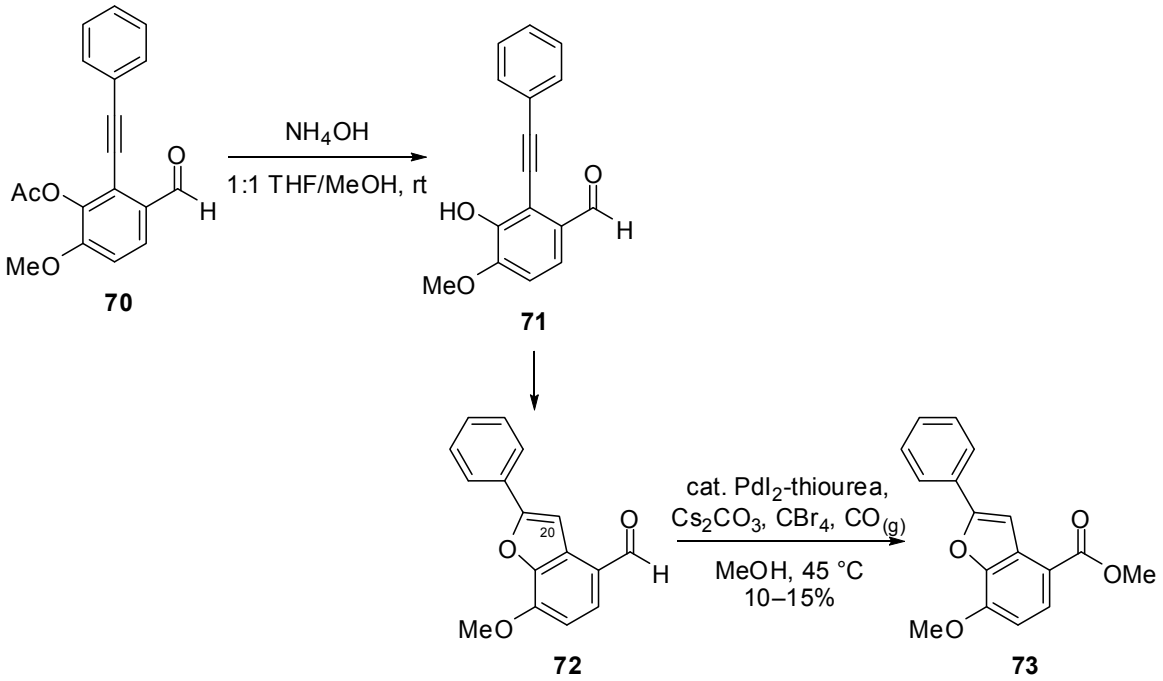


Scheme 9

The standard conditions prescribed for the Sonogashira coupling reaction were applied to our model system. The newly generated aryl iodide **58** was successfully coupled with phenylacetylene **69** to give the desired diarylalkyne **70** in good yield (88%). With **70** in hand, the deprotection of the acetate could now be investigated to prepare the requisite *ortho*-hydroxydiarylalkyne **71**.

2.3.2 A Troublesome Deprotection

The conditions for the de-acetylation of the phenolic acetate were adapted from the work of Yang and co-workers.[66] Initially, when performed on small scale (*ca*. 100 mg), the desired *ortho*-hydroxydiarylalkyne **71** was obtained in a modest 70% yield after 50 min, as a white solid (**Scheme 10**).



Scheme 10

When repeated on larger scale (*ca*. 650 mg), however, the reaction provided **72**, which was initially misidentified as **71** due to the similarity of appearance, yields and their respective ^{1}H NMR spectra. Benzofuran **72** was isolated as an off-white solid in 82% yield after 2 h. It was noted that the peak in the ^{1}H NMR at δ 6.17 had shifted to δ 7.78, however, this was mistakenly attributed to an NMR concentration effect. It was later established that the peak at δ 7.78 was in fact due to the C20-H proton of **72**, and not the phenolic proton of **71**. Prior to the realisation of the misidentification, a sample of **72** from the large scale reaction was subjected to the carbonylative annulation conditions, which gave rise to ester **73** (10–15%). The ^{1}H NMR of **73** was similar to **72**, but lacked the aldehyde singlet at δ 10.04, and possessed a three proton singlet at δ 3.88. The identity of **73** was further confirmed by electrospray mass spectrometric analysis (m/z 282). Ester **73** was likely formed by disproportionation in a process analogous to the Cannizzaro reaction.[67] This reaction is likely to have been promoted by the methoxide generated *in situ* from cesium carbonate and methanol.

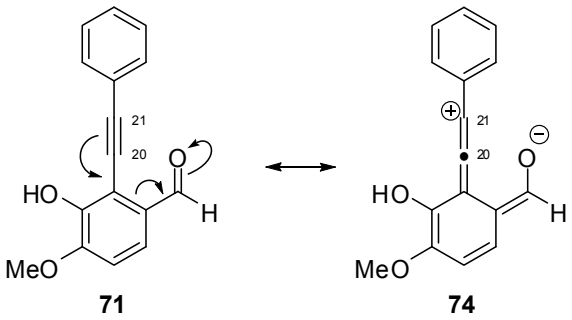
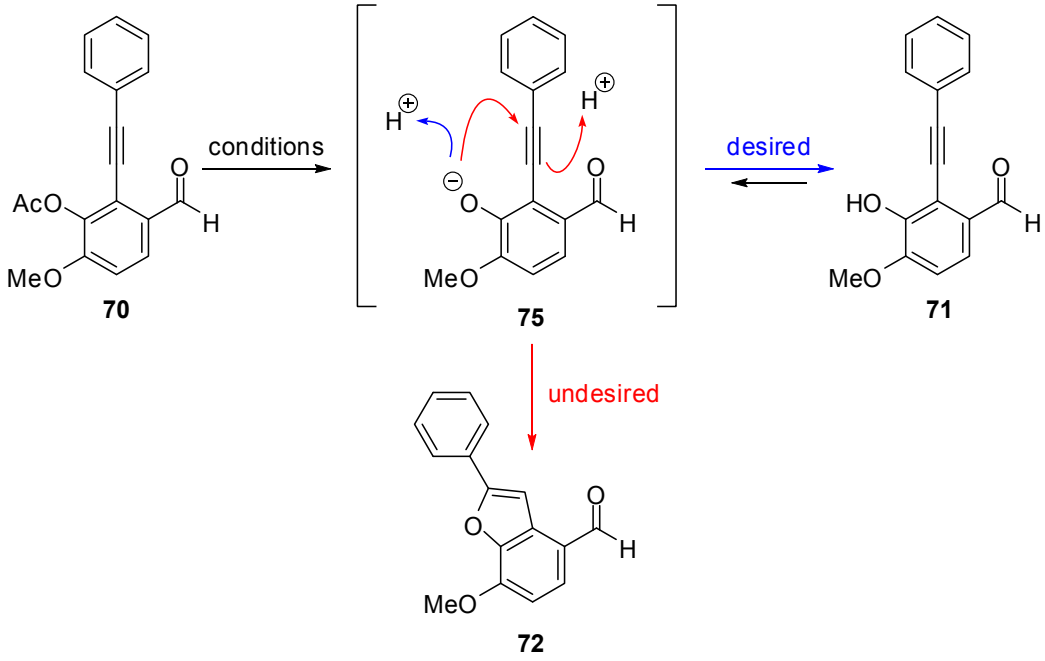


Figure 16

After re-examining the evidence, this misassignment was corrected and the de-acetylation step was again investigated. It is expected that the *ortho*-aldehyde may well activate the alkyne at the C21 position towards nucleophilic attack as is illustrated by the resonance contributor **74**, shown in **Figure 16**. This would have an unfavourable effect in that it would promote the formation of the unwanted by-product **72**. Efforts were now focused on developing conditions that could deliver **71**, selectively and reliably, without the formation of **72**.



Scheme 11

Under the basic hydrolysis of ester **70** (**Scheme 11**), the phenoxide **75** is generated *in situ* and the desired fate of this phenoxide is simple protonation, presumably a reversible process involving protic solvent, to deliver **71**. However, the phenoxide can also spontaneously attack the alkyne at the electrophilic C21 position, in a favourable 5-*endo-dig* cyclisation event to give rise to the undesired benzofuran **72**.

An investigation was subsequently conducted to establish an effective and reliable procedure to produce the desired phenol **71** whilst minimising the competitive formation of the undesired benzofuran **72**. The results of this investigation are summarised in **Table 2**.

Table 2

Entry	conditions	Temp	Time	Product ratio[†]				
				70	:	**71**	:	**72**
1	Cs_2CO_3 (1.2 equiv.), MeOH	40 °C	15 min	0	:	8	:	92
2	Amberlyst-15, MeOH	rt	4 d	49	:	49	:	2
3	$H_2NNH_2.1H_2O$, THF	rt	2 h	–		–		–[‡]
4	$NH_4OH_{(aq)}$ (3 equiv.), THF/MeOH	rt	3.75 h	16	:	61	:	23
5	$NH_4OH_{(aq)}$ (3 equiv.), THF/MeOH	rt	7 h	7	:	51	:	42
6	$NH_4OH_{(aq)}$ (4.5 equiv.), THF/MeOH	rt	1 h	36	:	58	:	5
7	$NH_4OH_{(aq)}$ (9 equiv.), THF/MeOH	rt	1 h	8	:	77	:	15
8	$NH_4OH_{(aq)}$ (9 equiv.), THF/MeOH	0 °C	1.25 h	9	:	87	:	4
9	$NH_4OH_{(aq)}$ (9 equiv.), THF/MeOH	0 °C	16 h	0	:	70	:	30
10	$NH_4OH_{(aq)}$ (12 equiv.), THF/MeOH	-10 °C	3 h	7	:	90	:	3

[†] Ratios determined by integration of the methoxy signal in the ^{1}H NMR spectra of the crude product.

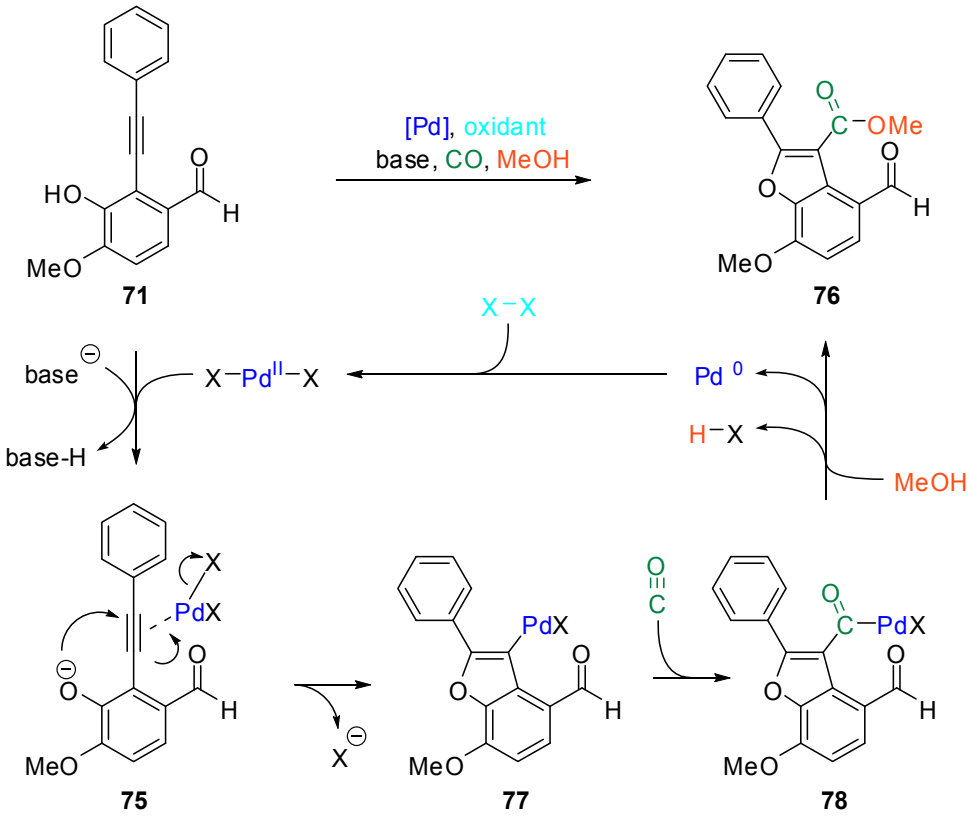
[‡] Decomposition of starting material observed.

The use of cesium carbonate (**Entry 1**, **Table 2**) was based on the work of Zaugg,[68] who had reported the use of alkali carbonates (specifically cesium carbonate in refluxing THF) as a reagent combination for the deacetylation of phenolic esters. In this case, these conditions did not give satisfactory results, instead leading to a preponderance of the undesired, protio-cyclised benzofuran **72**. A recent publication by Das *et al.*[69] reported that phenolic acetates could be selectively removed using Amberlyst-15 in MeOH at rt, however, as shown in **Entry 2**, it proved sluggish and the product isolated (after removal of the amberlyst resin by filtration) contained a polymeric contaminant from the amberlyst resin. The use of hydrazine hydrate in THF (**Entry 3**) had proven successful for Yang,[70] but unfortunately attempted application of these conditions to the deacetylation of **70** led solely to decomposition, presumably *via* reaction at the aldehyde functional group. The original procedures of using aqueous ammonium hydroxide were revisited (**Entries 4–10**) and by lowering the temperature, the formation of **72** was retarded, however, the reactions became much slower, thereby necessitating the use of larger quantities of aqueous ammonium hydroxide. Ultimately, the best results were obtained using the conditions of **Entry 10**, in which it was possible to obtain, after chromatographic separation, the desired

product **71** in an isolated yield of 81%. This gave sufficient material to investigate the key step in this synthesis – the carbonylative annulation.

2.3.3 The Carbonylative Annulation

The carbonylative annulation is a palladium-mediated reaction involving the cyclisation of an *ortho*-hydroxydiarylalkyne, such as **71** (**Scheme 12**), with concomitant methoxycarbonylation to deliver the 3-substituted benzofuran ring system, such as **76**. The first transformation of this kind was reported by Sakamoto and co-workers in 1989,[71] in the formation of both indole and benzofuran ring systems. There are many reagents involved in this reaction, and numerous variations have since been reported in the literature.[66, 70, 72-80] All these reported conditions exploit related reagent sets: a palladium source, an oxidant, a base, carbon monoxide and an alcohol. The mechanism for this reaction, as postulated by Sakamoto and co-workers,[71, 77] is shown in **Scheme 12**.

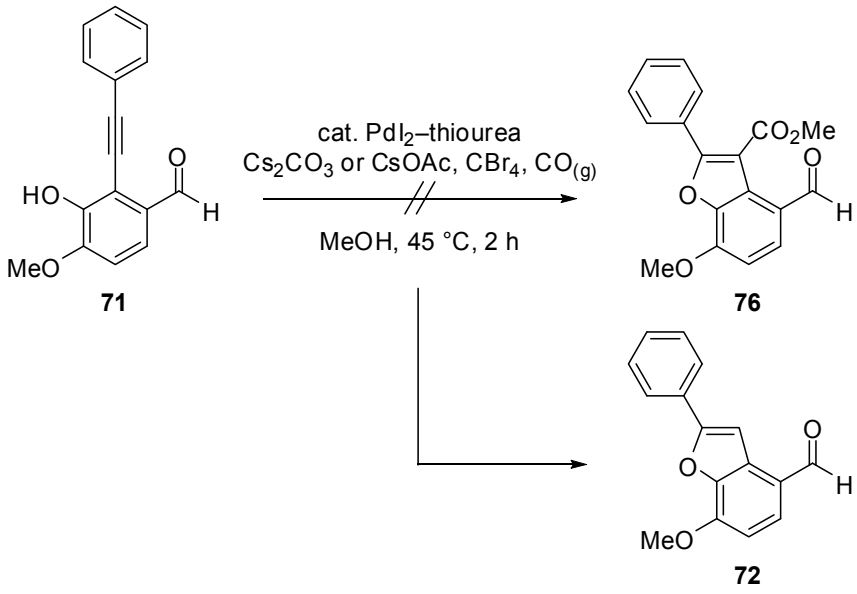


Scheme 12

The reaction is instigated by deprotonation of the phenol by the base, and coordination of palladium (II) to the alkyne (**75**). This activates the alkyne to palladative 5-*endo-dig* cyclisation to give **77**. Carbon monoxide then inserts into the palladium-carbon bond to form the acylpalladium species **78**. Methanol intercepts the acylpalladium species **78**, and reductive elimination ensues to provide both the product

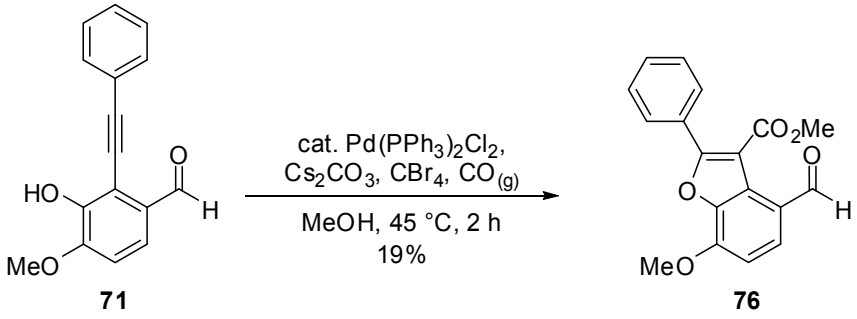
methyl ester **76**, and palladium (0). The palladium (0) is then oxidised to palladium (II) by the oxidant in order to complete the catalytic cycle. Due to the complexity of this reaction, judicious choice of reagents is necessary to avoid unwanted side-reactions, eg. protio-cyclisation.

After surveying numerous reported reagent sets for this transformation documented in the literature, the conditions of Yang and co-workers (PdI_2–thiourea, Cs_2CO_3, CBr_4, MeOH, $CO_{(g)}$)[66] were chosen. These conditions were reported to be a highly effective co-catalysis system for carbonylative annulation of both electron rich and electron deficient *ortho*-hydroxydiarylalkynes. Also of considerable appeal, was the reported functional group tolerance, as *tert*-butyldimethylsilyl ethers had been shown to be stable under these conditions.



Scheme 13

Unfortunately when the Yang conditions were applied to this substrate, none of the desired product **76** was observed. This situation was not improved by changing the base from cesium carbonate to cesium acetate. ^{1}H NMR of the crude products showed *ca*. 3:1 ratio of **71**:**72** for the case using cesium carbonate, and *ca*. 1:3 ratio **71**:**72** for cesium acetate.

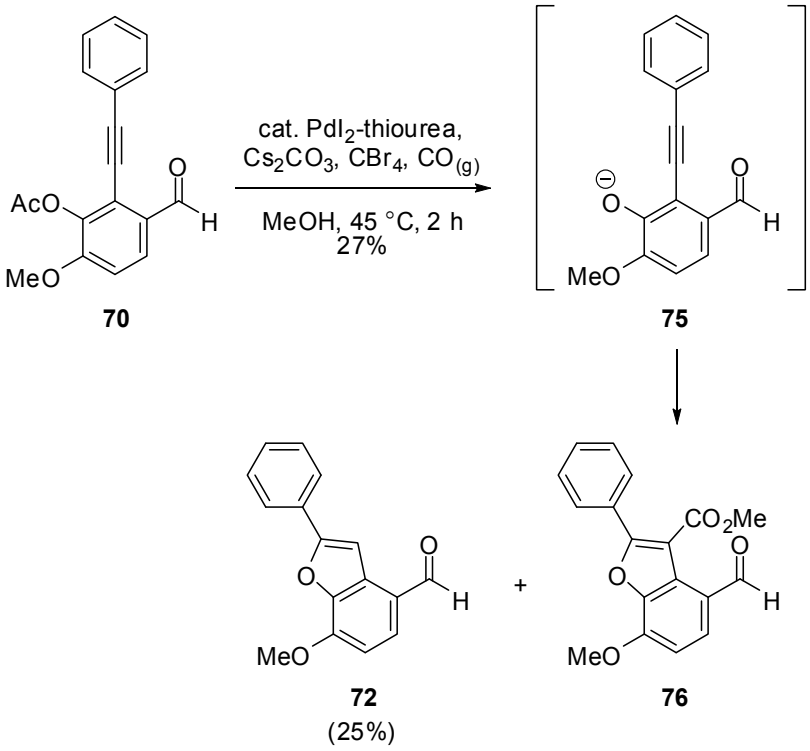


Scheme 14

The desired product **76** could be obtained by changing the palladium source to dichlorobistriphenylphosphine palladium and using cesium carbonate as the base, although **76** was only afforded in a low isolated yield of 19%.[†]

2.3.4 Tandem Deprotection and Carbonylative Annulation

In order to combat this facile and undesired protio-cyclisation pathway, an alternative tandem approach was trialed (**Scheme 15**). It was anticipated that by carrying out the deprotection *in situ* during the carbonylative annulation reaction, that the formation of **72** could be impeded and give better yields of the desired tetrasubstituted benzofuran **76**. This concept is based on the aforementioned precedent of using alkali carbonates in the deprotection of phenolic acetates[68] and the fortuitous use of cesium carbonate as the preferred base in the carbonylative annulation reaction. This approach does not completely circumvent the possibility of phenoxide **75** following the non-palladium-mediated pathway to give the undesired protio-cyclised benzofuran **72**, however, it was anticipated that this approach would minimise the concentration of phenoxide **75** relative to palladium (as the phenoxide would be generated over time) and thus enhance the likelihood of the palladium-mediated pathway.



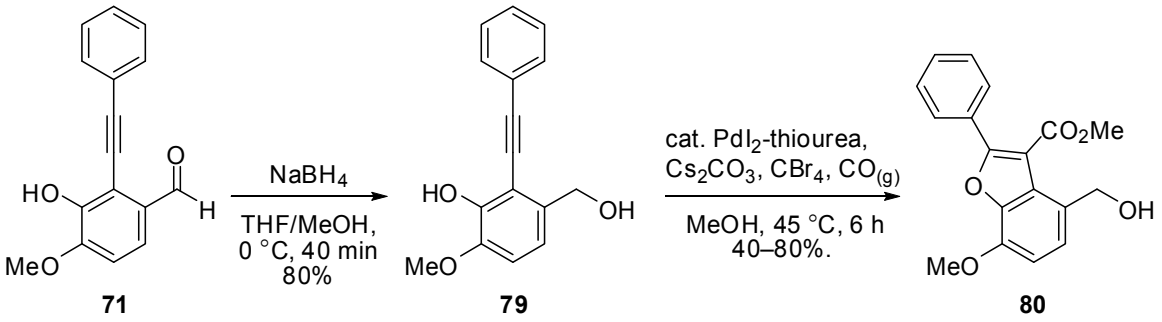
Scheme 15

[†] Reaction conducted by Dr M. J. Coster

In the first step of this reaction the acetate is cleaved to give phenoxide **75**, which should undergo the palladium-mediated pathway as discussed previously (**Scheme 12**, structure **75** onwards) to generate the desired benzofuran **76**. This reaction proved to be cleaner and a little more effective in forming **76**, however, the reaction gave the desired benzofuran in only a modest yield of 27% which was accompanied by the undesired by-product **72** in a similar amount (25%). This approach was not pursued further, as it was suspected that the aldehyde functional group may have been responsible for the unimpressive yields.

2.3.5 Masking the Aldehyde

It was speculated that the aldehyde functional group was largely responsible for the unacceptably low yields in the carbonylative annulation reaction due to the promotion of side-reactions such as proti-cyclisation and disproportionation. To test this hypothesis, the aldehyde was reduced to the benzyl alcohol, thereby altering the electronics of the system and preventing side-reactions associated with benzaldehydes.



71 **79** **80**

Scheme 16

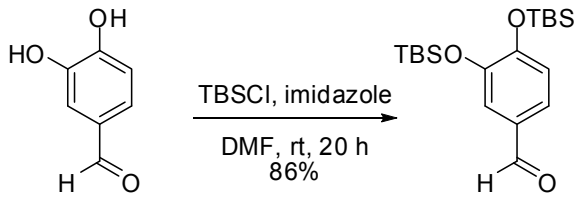
Sodium borohydride reduction of the benzaldehyde **71** proceeded smoothly to afford the corresponding benzyl alcohol **79** in high yield. Owing to the poor solubility of **71** in MeOH, THF was introduced as a co-solvent. The *ortho*-hydroxydiarylalkyne **79** was then trialed in the carbonylative annulation reaction using the conditions of Yang,[66] this time yielding the desired tetrasubstituted benzofuran **80** in a respectable, although somewhat variable yield (40–80%). Use of $Pd(PPh_3)_2Cl_2$-dppp as catalyst was also effective, providing **80** in 38% yield. These examples supported the hypothesis that the aldehyde functional group was at fault in the previously low yielding carbonylative annulation reaction. With this encouraging result in hand, efforts were focused on applying this methodology to substrates bearing the requisite C24 and C25 oxygenation corresponding to lithospermic acid (**21**).

2.4 Towards a System Possessing the Oxygenation of the Natural Product

Owing to the perceived problem of removing methyl ether protecting groups at the final step of the synthesis of lithospermic acid, as experienced by Jacobsen *et al.*,[48] we chose to utilise the F^-/acid labile *tert*-butyldimethylsilyl (TBS) protecting groups at the C24 and C25 hydroxyl groups.

2.4.1 Synthesis of an Oxygenated C_{20}–C_{27} Arylalkyne

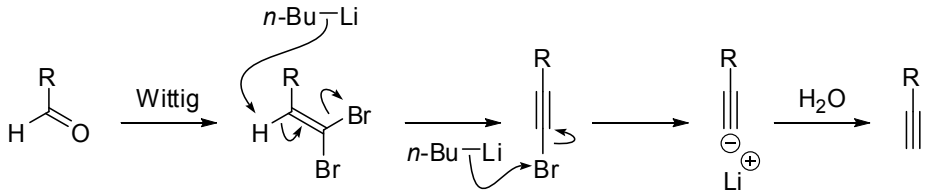
The desired arylalkyne **90**, was synthesised from 3,4-dihydroxybenzaldehyde (**81**) by a synthetic sequence involving firstly protection of the catechol, then Corey–Fuchs conversion of the aldehyde to the corresponding alkyne. **Scheme 17** shows the first of these steps.



81 **82**

Scheme 17

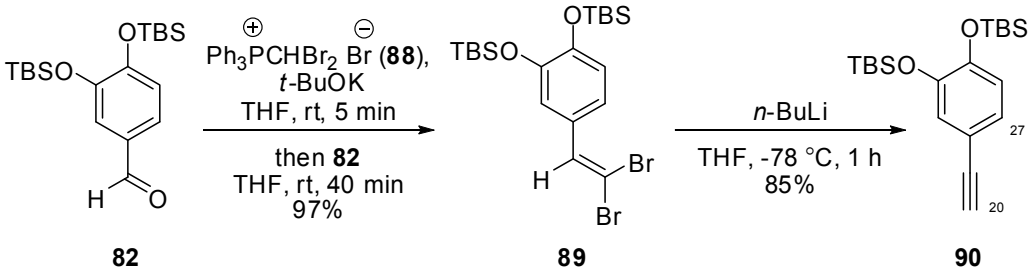
3,4-Dihydroxybenzaldehyde (**81**) was protected as the corresponding bis-*tert*-butyldimethylsilyl ether **82** using standard conditions.[81, 82] The aldehyde then needed to be converted into the corresponding alkyne, typically achieved using the Corey–Fuchs protocol,[83] a very general and mild procedure used to convert aldehydes to their corresponding alkynes. The general mechanism is shown in **Scheme 18**.



83 **84** **85** **86** **87**

Scheme 18

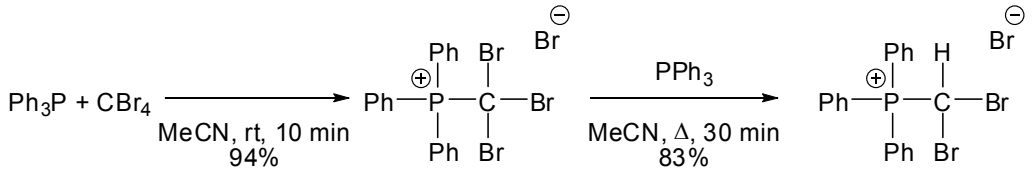
The first step entails a Wittig olefination[84] with CBr_4/PPh_3 to give the *gem*-dibromoalkene **84**. This is then treated with 2 equivalents of *n*-butyllithium. The first equivalent abstracts the olefinic proton, forming bromoalkyne **85**. The second equivalent undertakes lithium–halogen exchange to form the lithiated species **86** and quenching of this species with an aqueous work-up furnishes the desired terminal alkyne **87**. It is worth noting that **86** may also be quenched with alternative electrophiles, giving access to disubstituted alkynes.



82 **89** **90**

Scheme 19

The first step of the Corey–Fuchs reaction ordinarily utilises CBr_4/PPh_3 directly, however, due to the availability of reagent **88**,[†] and the superior results reported by some laboratories, a modified Corey–Fuchs procedure, developed by Michel *et al.*,[85] was investigated for this transformation. This modified procedure was reportedly a superior reaction in terms of cleanliness, functional group tolerance and overall efficiency.[85] Dibromomethyltriphenylphosphonium bromide (**88**) was treated with potassium *tert*-butoxide to form the ylide which was subsequently treated with aldehyde **82**. Gratifyingly, this procedure gave the desired dibromoalkene **89** cleanly and in excellent yield (97%), which was used as soon as possible in the next step. *gem*-Dibromoalkene **89** was converted to the desired arylalkyne **90** in high yield by utilising the same chemistry as that used in the traditional Cory–Fuchs procedure.[83] With the success of this two-step protocol, a large quantity of dibromomethyltriphenylphosphonium bromide (**88**), was prepared according to **Scheme 20**.



91 **88**

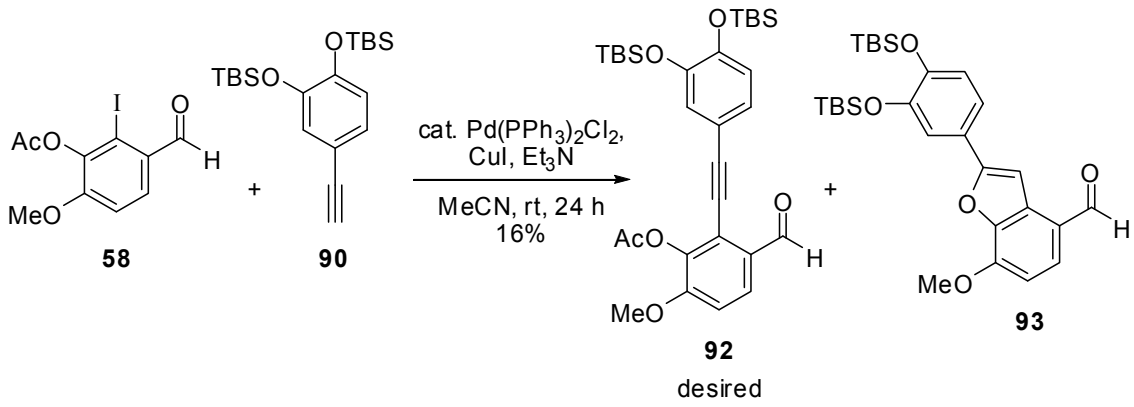
Scheme 20

The phosphonium salt **88** was initially made on a test size scale according to the method of Wolkoff[86] as shown in **Scheme 20**. Surprisingly, the melting point of **88** from this batch (213–215 °C) did not match the literature value (144–147 °C), although this may have been due to the literature value corresponding to recrystallised material (from acetonitrile) whereas material we obtained was not recrystallised prior to melting point determination. Regardless, the purity and activity was assessed by using **88** to affect conversion of **82** to **89** on small scale. The successful dibromoolefination proved that **88** was active, regardless of the discrepancies in melting point. Since the synthesis of **88** had been successful, a large quantity (*ca.* 50 g) of **88** was prepared. Accordingly, this was tested for activity in the same manner before use in preparing a large quantity of the dibromoalkene **89**.

[†] Material kindly donated by Dr D. Wong

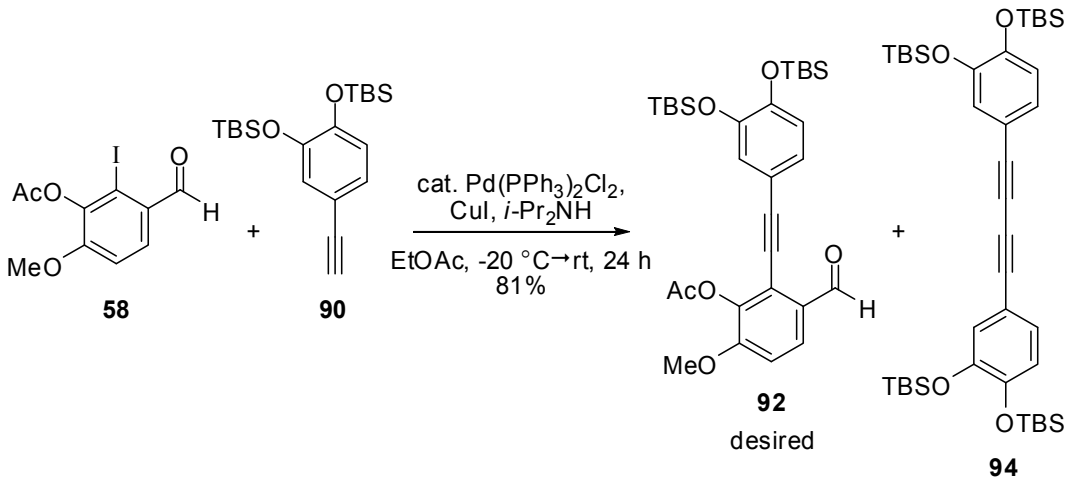
With a scalable, efficient route established, large quantities of the arylalkyne **90** (*ca*. 3.5 g) were prepared which allowed for an investigation of the Sonogashira coupling.

2.4.2 Sonogashira Coupling



Scheme 21

The first attempt at the Sonogashira coupling employed the same conditions as in the model study (**Scheme 9**). Unfortunately, this resulted in poor yields of the desired product **92** (16%), as well as the undesired protio-cyclised by-product **93** (14%). In an effort to optimise this transformation, a modified protocol developed by Andrus *et al*.[87] was examined, described below in **Scheme 22**.

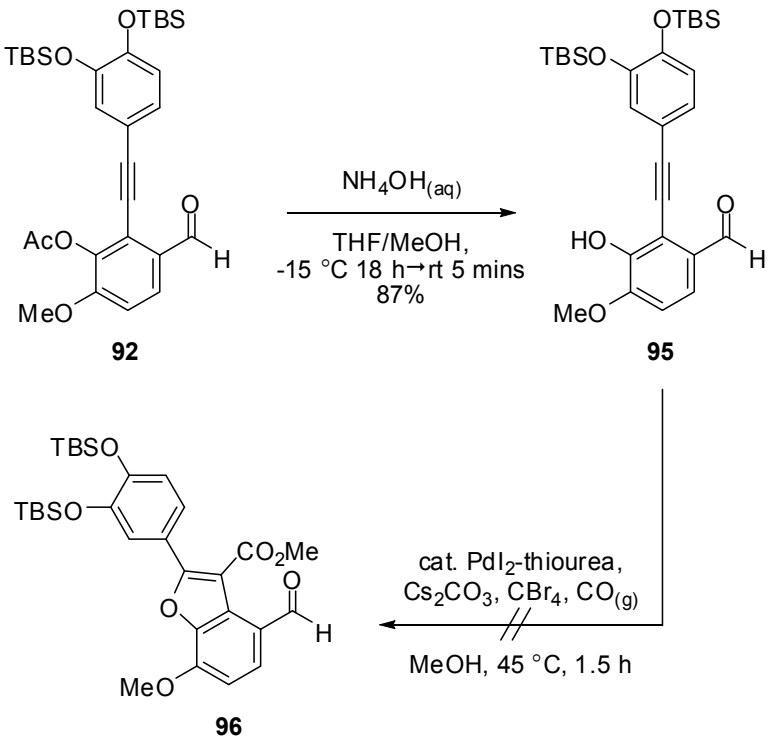


Scheme 22

Under these modified conditions, using *i*-Pr_2NH as base and ethyl acetate as solvent, the yield of **92** rose to 56%, however, this was accompanied by the formation of the homocoupled by-product **94** (25%). The identity of **94** was confirmed by both ^1H NMR and mass spectroscopy. The ^1H NMR spectrum strongly resembled that of **90**, except that it lacked the alkyne proton resonance at δ 2.96 and the mass spectrum indicated a peak at m/z 722, consistent with the presence of **94**. The formation of **94** indicates that the palladium is being oxidised during the reaction. When palladium is oxidised to palladium(II), by

conditions such as oxygen dissolved in the solvent, it must undergo reduction once more to get back to the active palladium(0) (**65**, **Scheme 8**). This consumes more of the arylalkyne **90** in the process and delivers the observed homocoupled by-product **94** (analogous to **64**, **Scheme 8**, Cycle B').[65] It is expected that the homocoupled by-product **94** should be observed in the same molar quantities as the palladium(II) catalyst loading, however, the formation of **94** in quantities greater than this is indicative of oxidation during the reaction. In an effort to minimise the formation of **94**, the solvent was degassed. Two alternative methods were investigated, (i) the bubbling of argon gas through the solvent prior to use in the reaction and (ii), the use of three freeze-pump-thaw cycles. Both of these methods proved effective, resulting in an improved yield of **92** (81%) with less of **94** being isolated (16%).

2.4.3 De-acetylation and Carbonylative Annulation

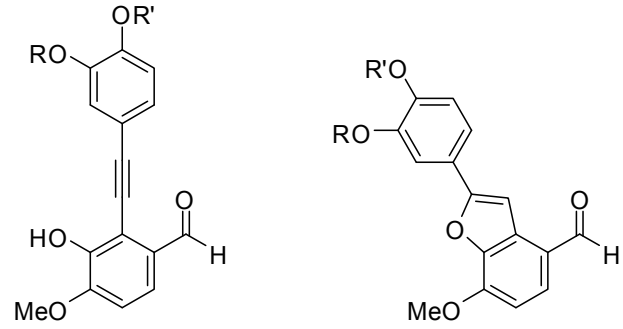


Scheme 23

The deprotection proceeded well using the optimised procedures developed in the model study—12 equivalents of ammonium hydroxide in THF/MeOH at -15 °C—to yield the desired phenol **95** in high yield (87%), with no observed autocyclised by-product **93**. With *ortho*-hydroxyarylacetylene **95** in hand, the carbonylative annulation could be attempted.

Despite several attempts, the desired benzofuran **96** was not afforded in any of these trial reactions. Instead, a black solution was produced from which very little material was isolated. Decomposition was evidenced by the disappearance of signals in the ^{1}H NMR spectrum corresponding to the starting material, and the appearance of an abundance of unassignable peaks. A small amount (*ca.* 5%) of impure

material was isolated by column chromatography which, by ^{1}H NMR and mass spectroscopy, appeared to contain one of the compounds shown in **Figure 17**.

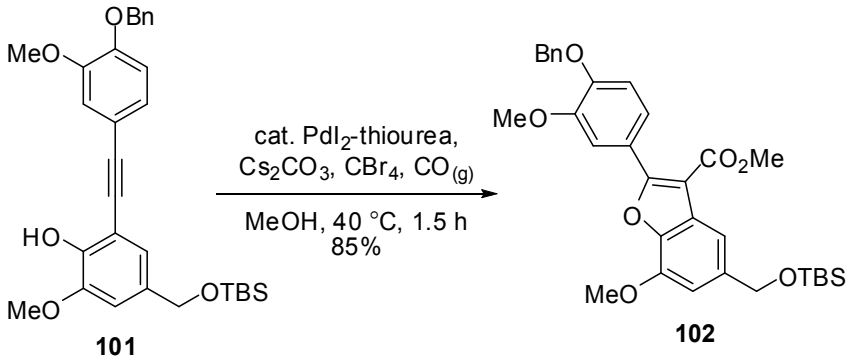


97 R = H, R' = TBS
98 R = TBS, R' = H

99 R = H, R' = TBS
100 R = TBS, R' = H

Figure 17

With this result, it was believed that the *tert*-butyldimethylsilyl ether protecting groups on this specific system were too labile under the reaction conditions. Upon closer inspection of the work of Yang and co-workers,[66] and comparison of the specific reported example possessing a *tert*-butyldimethylsilyl ether, it is evident that the nature of these ethers are different, giving rise to their difference in stability.

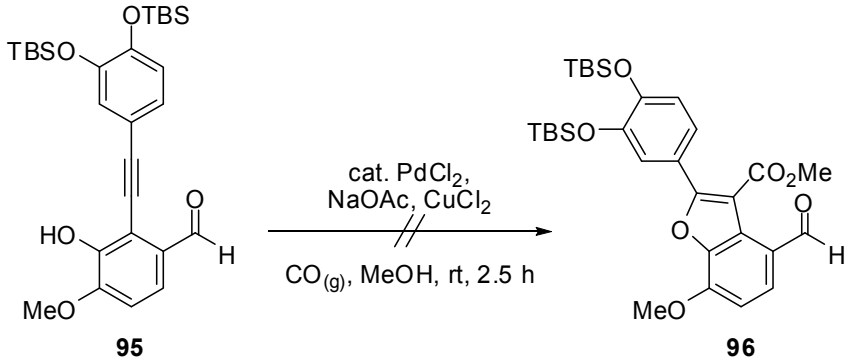


101 **102**

Scheme 24[66]

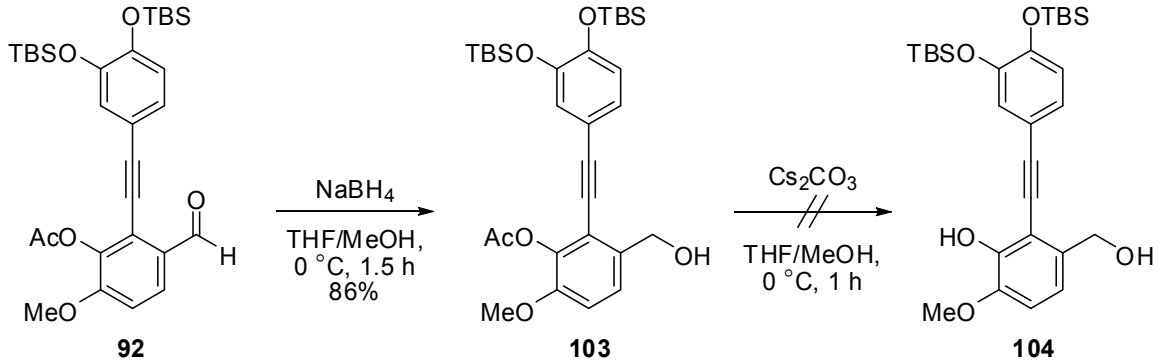
The silyl ether of the benzyl alcohol (**101**) in Yangs would be expectedly more stable than the silyl ether derived from the phenol in our case, due to the greater stability of phenoxides versus alkoxides (i.e. better leaving group).

Owing to the fickle nature of the palladium iodide–thiourea reagent combination experienced thus far, further inspection of the literature pertaining to the carbonylative annulation was conducted. This led us to a publication by Scammells and co-workers[80] who had examined cases more aligned with our system. They had found the conditions of Kondo *et al.*[71,77] to be particularly proficient on systems that possessed an electron donating substituent *ortho* to the phenol, such as the methoxy group in our example. In light of this, it was considered sensible to explore this reagent combination (**Scheme 25**), but unfortunately the product **96** was not observed, instead, degradation to a complex mixture of products was observed.



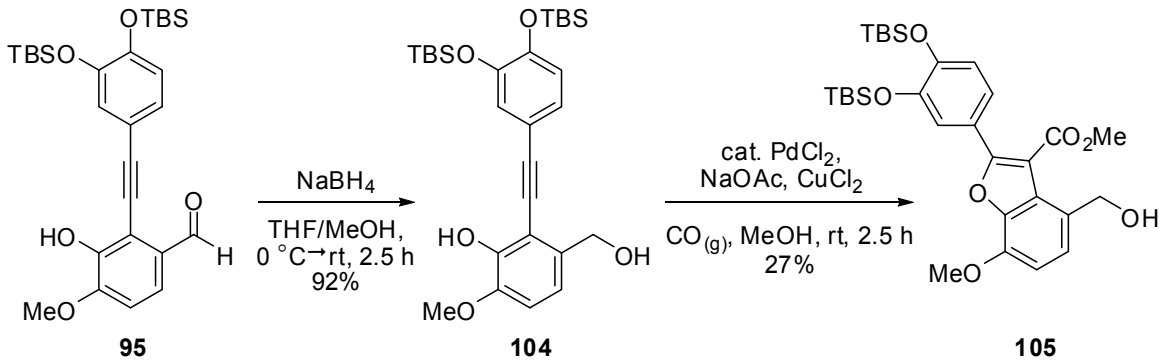
Scheme 25

As was performed in the model studies, a non-aldehyde containing system was also briefly investigated. Starting from the Sonogashira coupling product **92**, reduction with sodium borohydride afforded **103** in 86% yield without optimisation. De-acetylation of **103** with cesium carbonate in THF/MeOH (a reagent system that had proven successful on a related system being investigated simultaneously) proved inadequate. The desired **104** was not forthcoming and instead, products displaying TBS group cleavage were observed, providing further supporting evidence that cesium carbonate in THF/MeOH are incompatible with these TBS ethers.



Scheme 26

The benzyl alcohol **104** could be accessed *via* an alternate route (**Scheme 27**) by reduction of aldehyde **95** with sodium borohydride to give **104** in excellent yield (92%). Unfortunately, this substrate gave a disappointing yield for the carbonylative annulation, and **105** was isolated in only 27% yield.

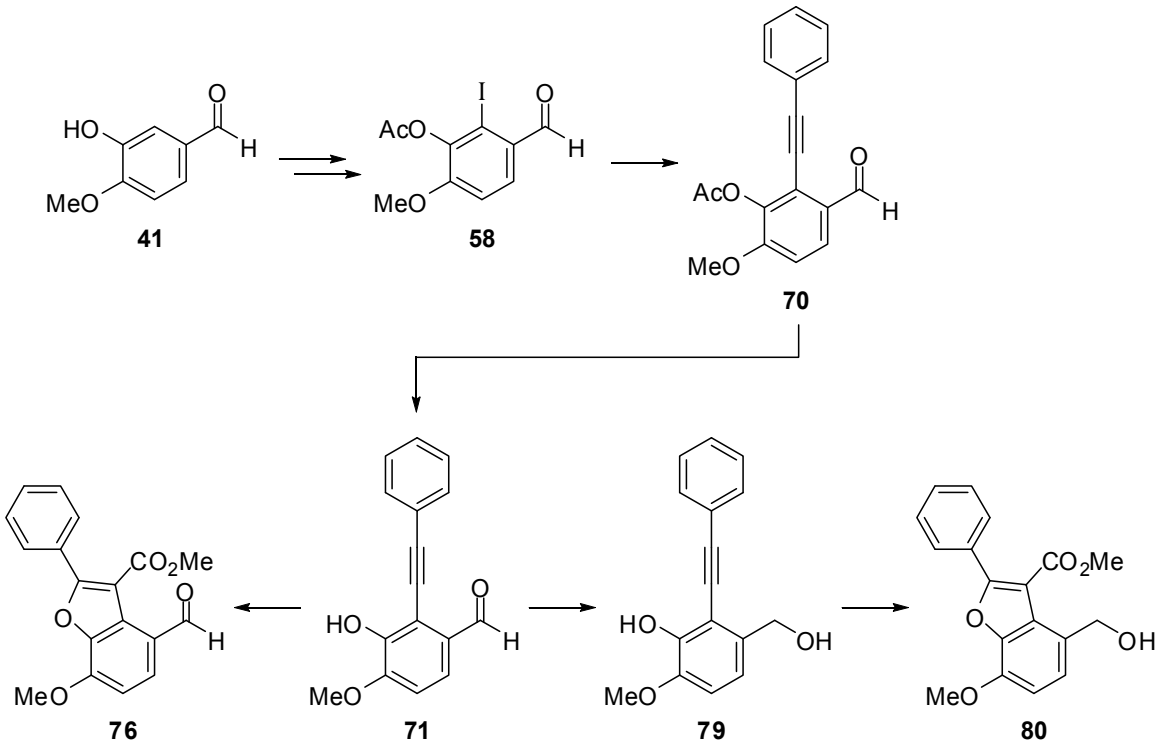


Scheme 27

Given the instability of the phenolic TBS ethers encountered thus far, and the disappointingly low yield for the key step, we conceded that this line of investigation was not viable and thus the focus shifted towards the investigation of an alternative protecting group strategy.

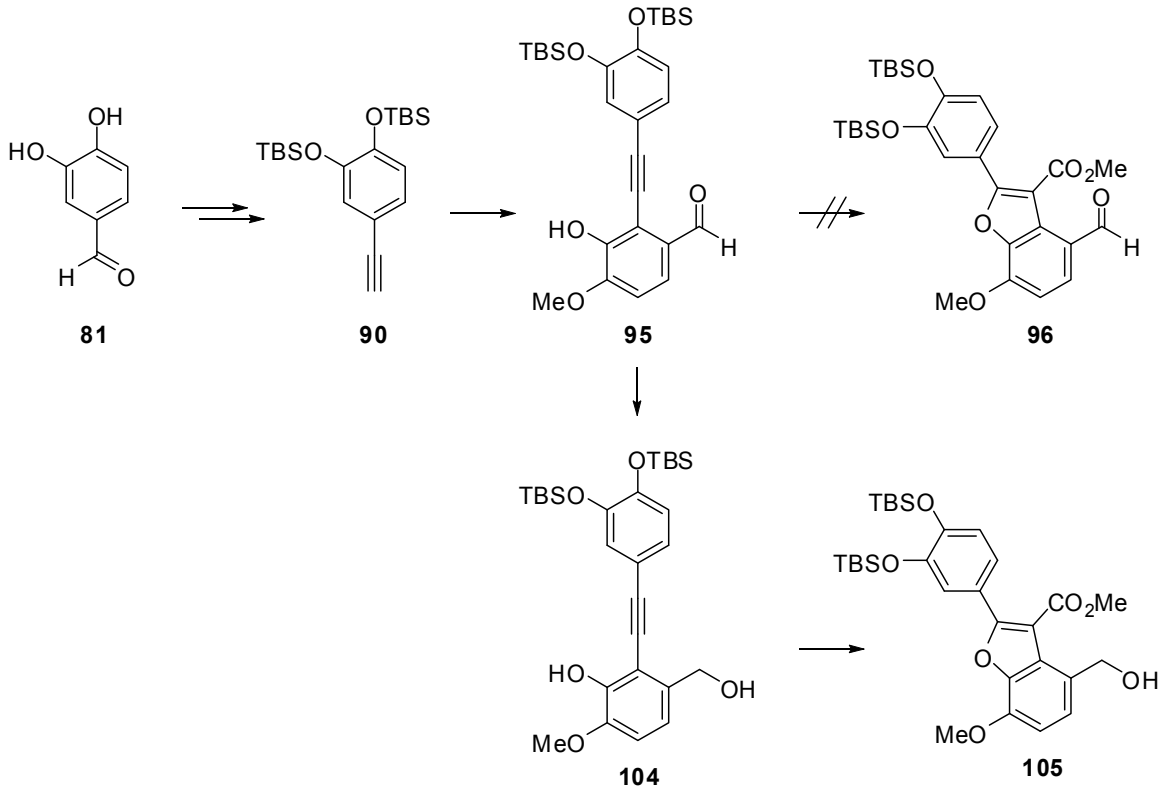
2.5 Summary

Isovanillin (**41**) was functionalised to form the aryl iodide **58**, that formed the basis of all future investigations in this area. Using phenylacetylene (**69**) as the coupling partner in the Sonogashira reaction, diarylacetylene **70** was afforded and provided the platform for model system studies. De-acetylation conditions were optimised to give *ortho*-hydroxydiarylalkyne **71** as a substrate for the carbonylative annulation reaction. This transformation proved fickle, however, the capricious nature of the reaction was alleviated by masking the aldehyde as the corresponding benzyl alcohol (**Scheme 28**).



Scheme 28

With these positive results obtained, our investigation progressed to a system that possessed the relevant C24/C25 oxygen bearing functionality. Bis-TBS protection of 3,4-dihydroxybenzaldehyde (**81**) followed by a modified Corey–Fuchs transformation furnished the requisite arylacetylene **90**, which was coupled to **58**, then de-acetylated to give *ortho*-hydroxydiarylalkyne **95**. Complications arose in the carbonylative annulation primarily due to the lability of the phenolic TBS ethers and problems with the aldehyde functional group. By avoiding the use of cesium carbonate, and masking the aldehyde as the benzyl alcohol, the desired tetrasubstituted benzofuran **105** could be accessed, although in low yield (**Scheme 29**).



Scheme 29

–Chapter 3–

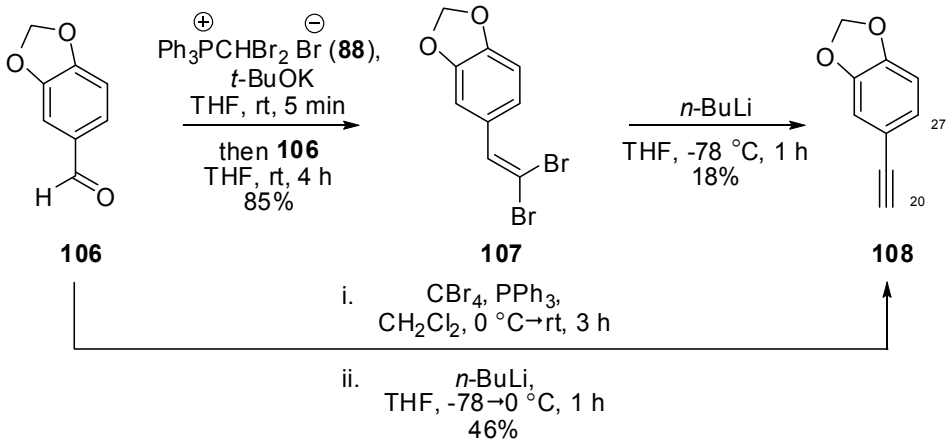
Synthesis of the C_1–C_9 / C_{19}–C_{27} Fragment of Lithospermic Acid

3.1 An Alternative Protecting Group Strategy

Considering the pressing evidence that silyl ether instability was almost certainly to blame for the undoing of the first synthetic approach, it was considered prudent to investigate an alternative protecting group strategy. There are many alternatives known for the protection of the catechol moiety and after careful consideration, the methylene acetal was chosen for the following reasons: it should confer more stability than the silyl ether, and further to this, it should be easier to remove than the bis-methyl ether, as this protecting group strategy had proven impossible to remove in the hands of Jacobson and Raths.[48] The methylene acetal protected catechol would also form a novel lithospermic acid (**21**) analogue as this functional group is common in bioactive natural products. Additional advantages of this choice are that the starting material, piperonal (**106**), is cheap and readily available. The protecting group is also already incorporated, thus minimising the number of synthetic manipulations and improving the overall efficiency of the synthesis.

3.1.1 Synthesis of the C_{20}–C_{27} Arylalkyne

Whilst the appropriately functionalised arylalkyne **108** is commercially available, the sources are limited. Instead, **108** was prepared by two alternate procedures and these are outlined in **Scheme 30**.



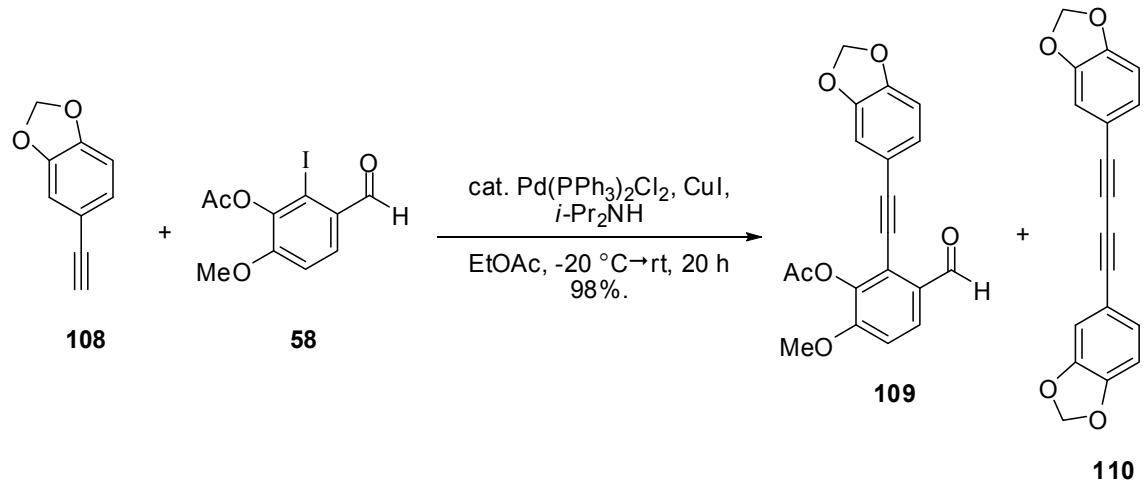
Scheme 30

In the initial approach, the requisite arylalkyne **108** was prepared from piperonal (**106**) in a two step sequence. The first step involved the modified Corey–Fuchs procedure used in the previous series (**Scheme 19**). This protocol proved once more to be clean and efficient, delivering a very respectable yield of dibromoalkene **107** (85%) that was subsequently treated with *n*-butyllithium to generate the desired terminal arylalkyne **108**, albeit in a disappointing yield (18%). The low yield of this step was attributed to the volatility of the product, a property that was only discovered after the low yield had

been noted. The more conventional Corey–Fuchs procedures, utilised previously by Bridges *et al.*[88] were also trialed, as we felt that the exotic conditions of dibromoalkene formation were not strictly necessary on this rather robust substrate. This route proved to be quite effective, although purification was more difficult. Separating out the large amounts of triphenylphosphine oxide generated when this reaction was performed on a large scale was an arduous task. Nonetheless, a large stock (*ca.* 4.5 g) of the requisite arylalkyne **108** was prepared for use in the following synthetic sequence.

3.1.2 Sonogashira Coupling

With the newly formed arylalkyne **108** in hand, it was possible to investigate the Sonogashira coupling with aryl iodide **58** (**Scheme 31**).

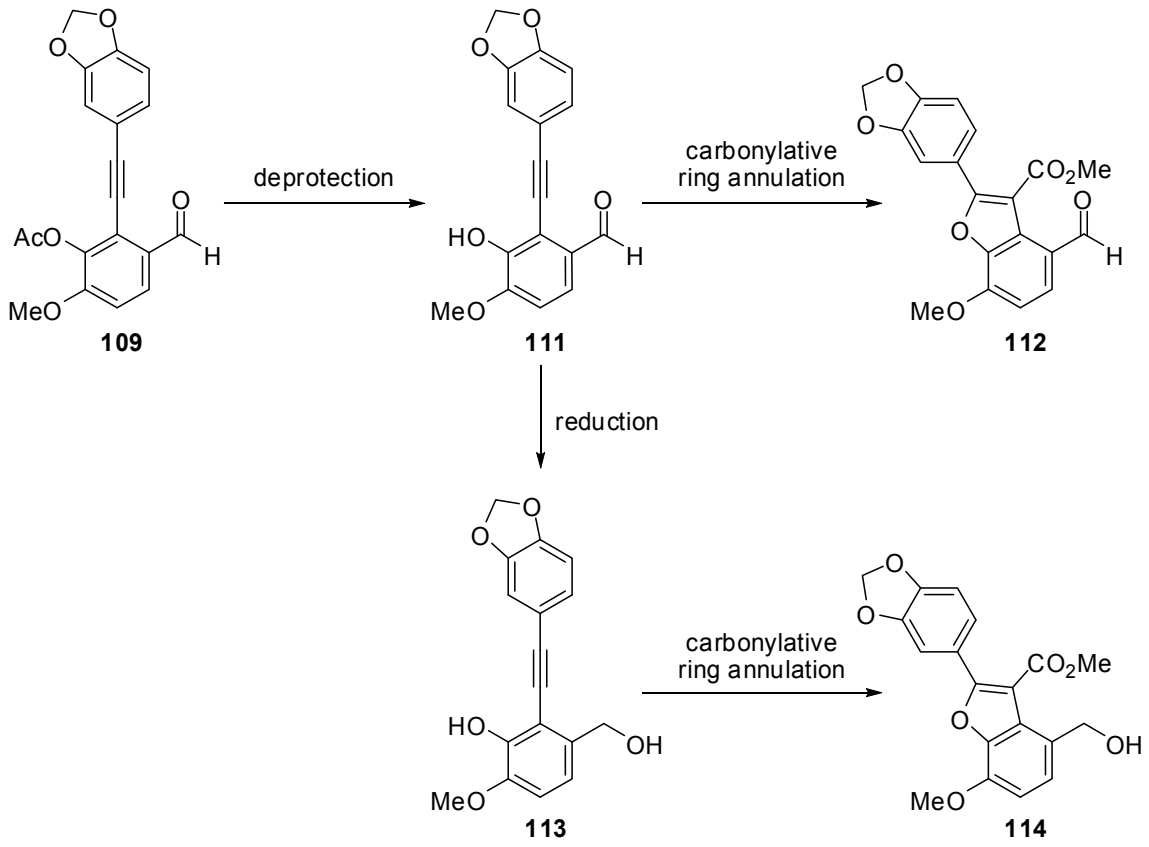


Scheme 31

Once more, the modified Sonogashira coupling conditions (**Section 2.4.2**) were used to carry out this coupling, using a slight excess (1.1 equiv.) of the arylalkyne **108**. Initial attempts gave the desired product **109** in isolated yields of *ca.* 60–70%, accompanied by the homocoupled by-product **110** (*ca.* 20%) and starting material **58** (*ca.* 30–40%), which were readily separable by column chromatography. As had been conducted previously (**Section 2.4.2**), the solvent was degassed to remove trace oxygen and with this precaution, the desired diarylalkyne **109** could be isolated in 98% yield on *ca.* 5 g scale.

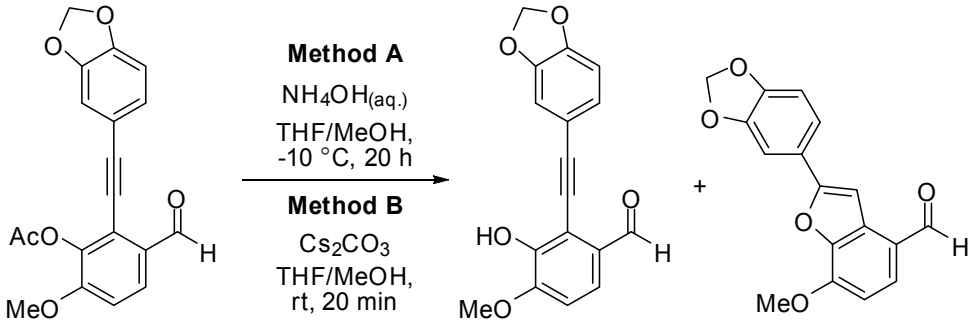
3.1.3 Synthesis of the *ortho*-hydroxydiarylalkyne

In the previous chapter it was noted that the aldehyde appeared to be incompatible with the conditions for the carbonylative annulation, although this was not definitive. To put this beyond doubt, we decided to embark on a synthetic route that would lend itself to testing this observation further. By following the route outlined in **Scheme 32**, both the aldehyde and the alcohol bearing substrates, **111** and **113** respectively, could be examined in the carbonylative annulation. This strategy would permit a direct comparison between the systems and would allow us to see the effects the aldehyde had on this step.



Scheme 32

Initially, the deprotection was conducted on the aldehyde bearing system using ammonium hydroxide in THF/MeOH (**Scheme 33**). Unfortunately, these conditions proved unsatisfactory for this system and complications associated with the solubility of substrate **109** were encountered. This resulted in sluggish reactions which extended the reaction times and increased the amount of the undesired protio-cyclised benzofuran **115** being formed.



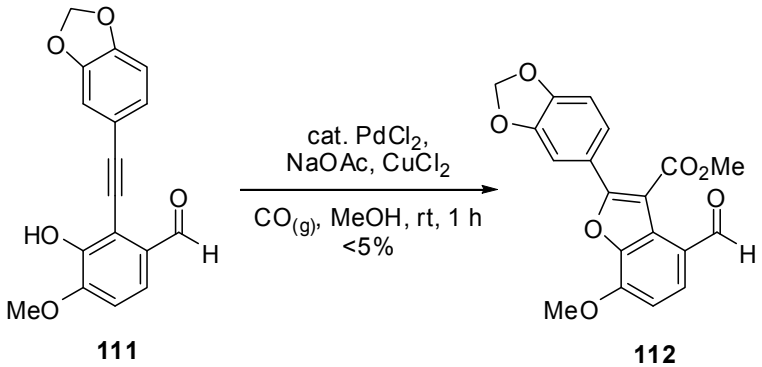
109 **111** **115**

Method A: 61% 25%

Method B: 78% –

Scheme 33

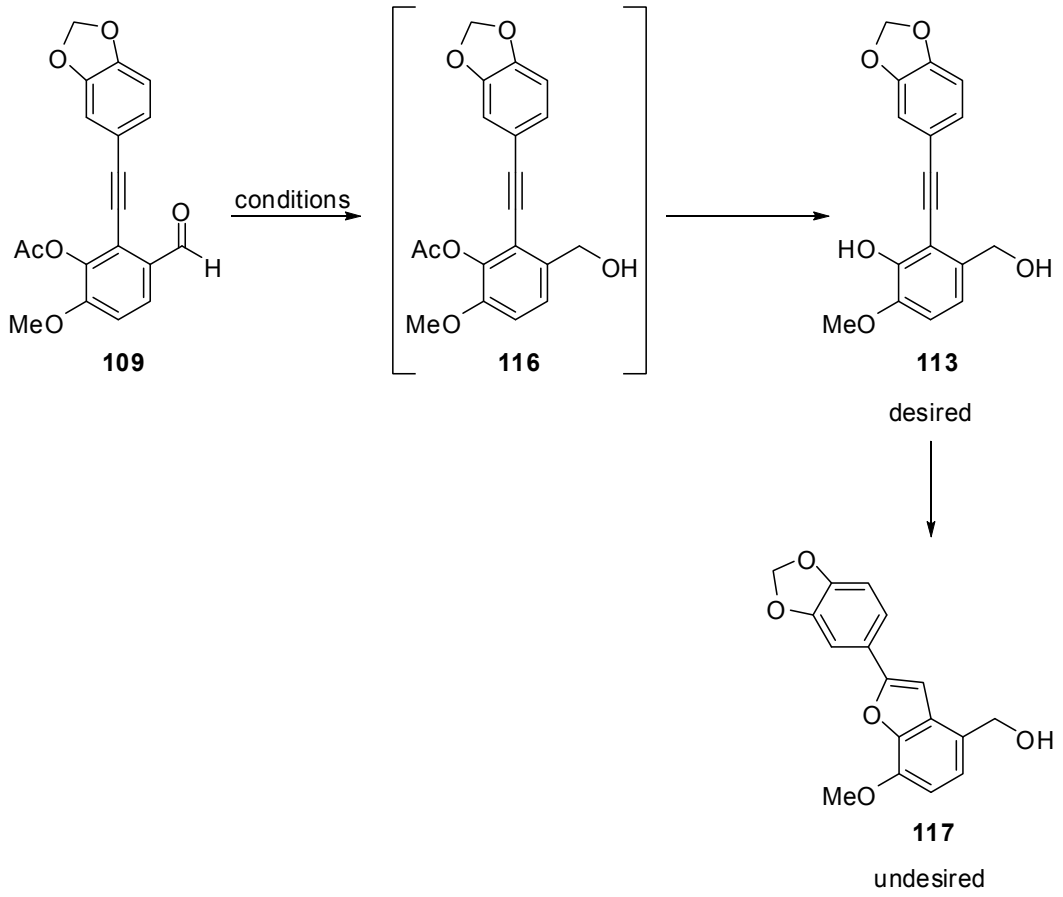
To combat the solubility issues, the reaction was diluted whilst maintaining the concentration of ammonium hydroxide. The desired *ortho*-hydroxydiarylalkyne **111** was isolated in a modest yield of 61% using this procedure, with the mass balance being dominated by the undesired **115** (25%). Examination of other bases found that sodium acetate in THF/MeOH proved unsuitable, resulting in the isolation of the starting material **109**. Alternatively, cesium carbonate in THF/MeOH gave the desired *ortho*-hydroxydiarylalkyne **111** rapidly and in 78% yield on small scale. Whilst this branch of work was not completely optimised, it gave sufficient quantities of material to investigate the carbonylative annulation on the aldehyde system, shown in **Scheme 34**.



111 **112**

Scheme 34

Unfortunately, when subjecting *ortho*-hydroxydiarylalkyne **111** to the carbonylative annulation conditions, the reaction proved unclean, generating a complex mixture of products that proved difficult to separate and identify. Although some peaks in the crude ^{1}H NMR spectrum could be reconciled with the desired product (**112**), it was concluded that this would not be a high yielding or synthetically viable approach and we concluded that the aldehyde was indeed incompatible with the carbonylative annulation reaction. With this result, the focus shifted back to the benzyl alcohol bearing system.



Scheme 35

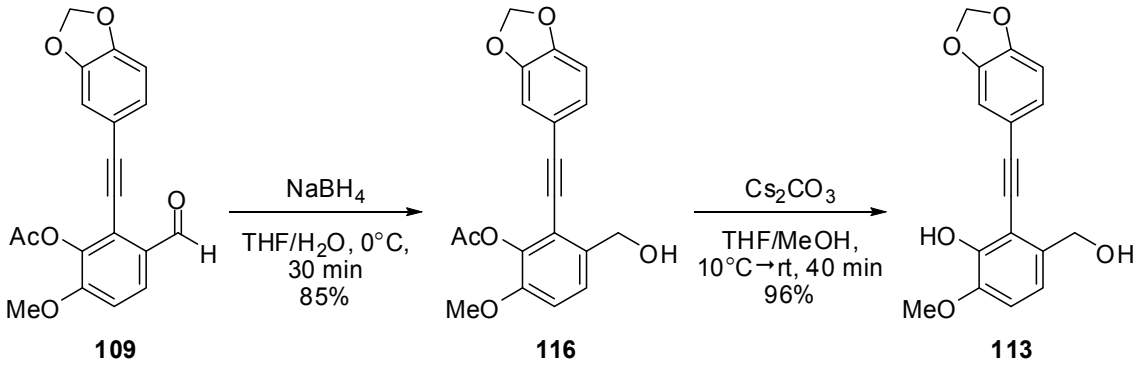
It was anticipated that the desired reduced *ortho*-hydroxydiarylalkyne **113** could be furnished in a single step from **109** *via* a tandem reduction and deprotection sequence. A range of conditions were explored to affect this transformation and these are summarised in **Table 3**.

Table 3

Entry	conditions	result
1	$NaBH_4$ (3.0 equiv.), THF/H_2O, 0 °C, 2 h.	**116** isolated (83%)
2	$LiBH_4$ (3.0 equiv.), THF, -78 °C, 3 h.	**116** isolated (86%)
3	$LiAlH_4$ (3.0 equiv.), THF, 0 °C, 5 h.	**116** isolated (73%)
4	DIBAL-H (8.0 equiv.), CH_2Cl_2, -78 °C, 1 h.	**113** formed, difficult to purify
5	DIBAL-H (8.0 equiv.), CH_2Cl_2, -78 °C→0 °C, 3 h.	**117** isolated (51%)

Sodium borohydride (**Table 3**, **Entry 1**) proved to be a very effective reagent for the reduction of the aldehyde to give **116**, however, progression to the desired phenol **113** did not ensue as intended. Similar results were obtained with lithium borohydride (**Entry 2**) and lithium aluminium hydride (**Entry 3**). Upon using diisobutylaluminium hydride (**Entry 4**), the desired *ortho*-hydroxydiarylalkyne **113** was formed, however, isolation proved difficult. The products **113** and **116** have almost identical R_f values in all of the solvent systems trialed, rendering their separation by column chromatography virtually impossible. Indeed, a clean sample of **113** was not obtained by this method and an accurate yield cannot be quoted, but it is estimated to be in the order of 50%. In order to rectify this problem, the reaction was conducted under more forcing conditions to completely consume both **109** and **116**, thus obviating the need for separation. Unfortunately this proved incompatible with this system and only the undesired protio-cyclised benzofuran **117** was isolated in 51% yield. Armed with these results and due to time constraints, we decided to follow the simpler approach of a two step procedure involving reduction of the aldehyde followed by de-acetylation.

3.1.4 Two step Reduction then De-acetylation

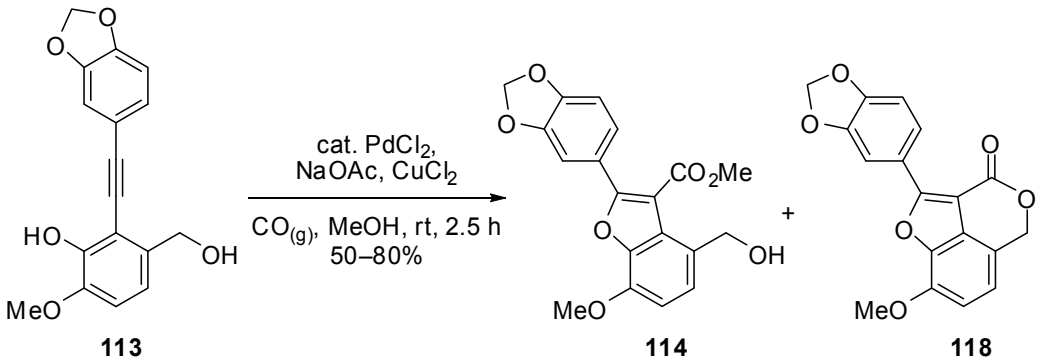


Scheme 36

Given the success of sodium borohydride as an agent for reducing the benzaldehyde **109** to the benzyl alcohol **116**, it seemed fitting to use this reagent as a starting point. With very little effort in

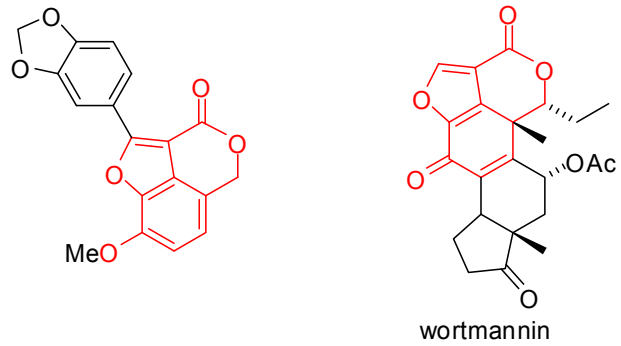
optimisation, the desired benzyl alcohol **116** was obtained in a respectable 85% yield. The conditions developed for the de-acetylation on the model system—ammonium hydroxide in THF/MeOH—were initially used, but this proved to be rather sluggish. Considering the success of the cesium carbonate mediated de-acetylation on the aldehyde bearing system (**Scheme 33**, Method B), these conditions were revisited for the current benzyl alcohol system. Pleasingly, this combination gave the desired *ortho*-hydroxydiarylalkyne **113** cleanly, rapidly and in excellent yield (96%).

3.1.5 The Carbonylative Annulation



Scheme 37

With the desired *ortho*-hydroxydiarylalkyne **113** in hand, we were set to investigate the carbonylative annulation once more. Gratifyingly, using the conditions of Scammells and co-workers[80] the desired tetrasubstituted benzofuran **114** was generated in high, yet variable, yield (50–80%). The yields obtained from batch to batch seemed to have little dependence on any variable that was monitored. There was some indication, however, that the quality of the palladium (eg. source, age, etc.) may be responsible for the erratic yields, but this was not extensively examined and could therefore not be confirmed. Interestingly, the lactone by-product **118** was also isolated in varying yields, typically in the order of 10–22%. This by-product was not unexpected, however, the lactone thus formed is still an intriguing revelation as this ring system is present in other natural products such as wortmannin (**119**, **Figure 18**). This could prove to be an interesting new synthetic approach to these types of ring systems.

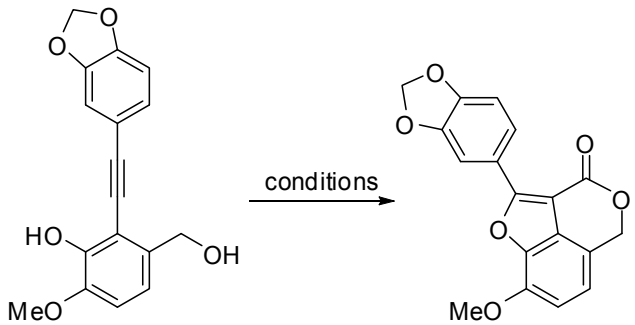


118 **119**

Figure 18

3.1.6 Exclusive Formation of the Lactone

Given the interesting nature of the ring system in the lactone by-product, we decided to investigate strategies to optimise the formation of **118** (**Scheme 38**).



113 **118**

Scheme 38

Reaction conditions were examined in an attempt to form lactone **118** exclusively. The variables examined included solvent, reaction temperature and palladium source. The results of this investigation are summarised in **Table 4**.

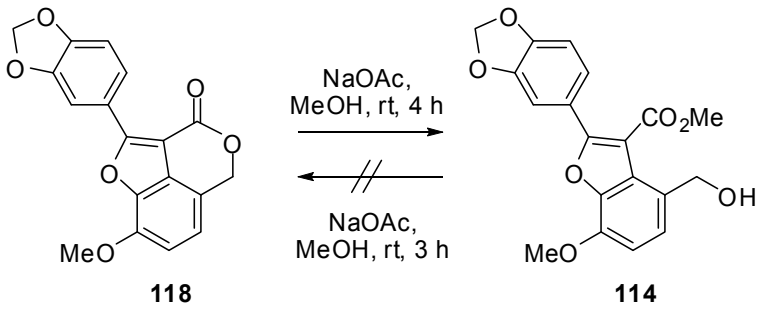
Table 4

Entry	conditions	result
1	$PdCl_2$, NaOAc, $CuCl_2$, $CO_{(g)}$, MeOH, rt, 7 h.	**118** (22%), **114** (56%)
2	$PdCl_2$, NaOAc, $CuCl_2$, $CO_{(g)}$, THF, rt, 3 h.	**118** (21%), **113** (41%)
3	$PdCl_2$, NaOAc, $CuCl_2$, $CO_{(g)}$, MeCN, rt, 3 h.	**118** (11%)
4	$PdCl_2$, NaOAc, $CuCl_2$, $CO_{(g)}$, MeOH, 0 °C, 1 h.	**118** (13%), **114**(18%), **113**(20%)
5	PdI_2–thiourea, Cs_2CO_3, CBr_4, $CO_{(g)}$, MeOH, 45 °C, 1.5 h	**118** not formed

Upon examination of **Table 4**, it is apparent that the yield of the lactone by-product **118** was not improved upon. In an effort to completely prohibit the formation of benzofuran **114**, the solvent was changed from MeOH to a solvent that could not take part in the reaction. The first in this series was to use THF in the place of MeOH (**Entry 2**), since THF had been used with success as a co-solvent in work by Yang and co-workers in their total synthesis of wedelolactone.[78] Unfortunately, the reaction was slower and the formation of an unknown by-product led to the reaction being quenched before the starting material was completely consumed, accounting for the observed low yields of **118**. Alternatively, MeCN, which had also been used with success in carbonylative annulation reactions as either a solvent or a co-solvent,[74, 75, 79] was trialed in this reaction (**Entry 3**). Unfortunately this solvent choice gave rise to a complex reaction mixture that proved difficult to separate and purify, whilst only delivering minor quantities of the desired lactone **118**. It is speculated that this low yield could be attributed to the precipitation of palladium black from solution due to a lack of stabilising ligands on the palladium, thus removing it from the catalytic cycle and halting the reaction. It had been noted previously in the formation of benzofuran **114** (**Scheme 37**) that by tlc it appeared lactone **118** was forming faster than **114**. This indicated that **118** may be rapidly formed, then more slowly methanolysed to **114**. Under this logic, the reaction was carried out at lower temperature (**Entry 4**) to limit the formation of **114**. The implementation of lower temperatures improved the ratio of lactone **118** to benzofuran **114** but unfortunately also retarded the conversion from **113**, and hence there was no improvement in the isolated yield of **118** (13%). Interestingly, the use of the palladium iodide–thiourea catalyst system (**Entry 5**) never provided **118** as a by-product. It is believed that in this case, the higher temperature and stronger base (cesium carbonate) would instigate methanolysis of the lactone (if it is indeed formed at all) which would happen rapidly, and faster than the palladative cyclisation. In effect, even if lactone **118** was formed, it would not be able to be observed or isolated under these conditions.

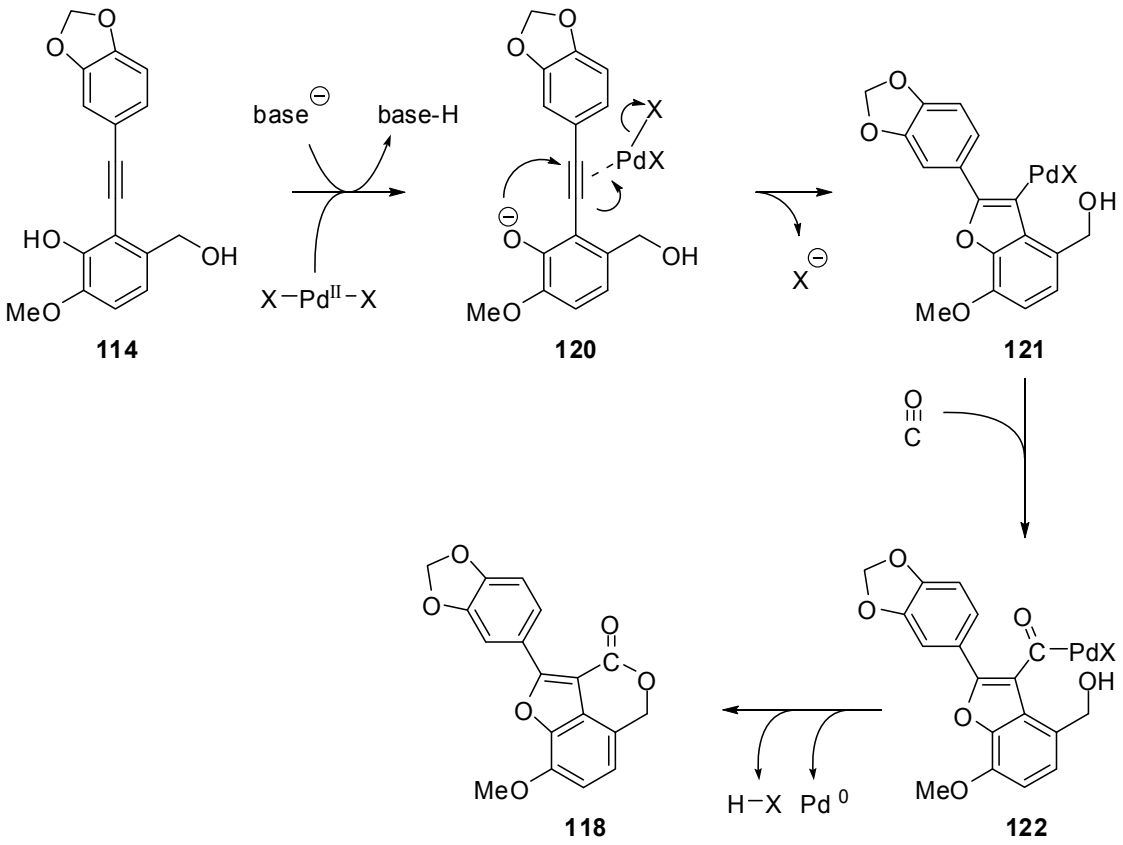
3.1.7 Probing the Formation of the Lactone

As mentioned previously, the lactone appeared to form faster than the benzofuran during the reaction, and it was believed that **118** may be forming first, then subsequently methanolising *in situ* to give the ring opened benzofuran **114**.



Scheme 39

By subjecting **118** to NaOAc in MeOH, conditions analogous to the carbonylative annulation reaction, it was discerned that the lactone could be methanolysed under these conditions, giving rise to the desired benzofuran in a *ca*. 40:60 ratio of **118**:**114** after 4 h, as determined by ^{1}H NMR. This is consistent with the tlc observation that suggested lactone **118** was formed rapidly but then tended to decline in the later stages of the reaction. Alternatively, subjecting benzofuran **114** to these conditions did not lead to the formation of the lactone **118**. This excludes the possibility of a route to the lactone which proceeds *via* benzofuran formation, followed by *in situ* lactonisation. Further evidence to support this is presented later in this manuscript (**Section 6.2**), in which efforts to react at the methyl ester in an analogous system proved difficult, thus highlighting the stability of this methyl ester. This evidence leads us to propose that the lactone is formed *via* a palladium-mediated pathway, and this can be rationalised by the mechanism shown in **Scheme 40**, which is closely aligned to the mechanism for the carbonylative annulation proposed by Kondo and co-workers (**Scheme 12**).[71]

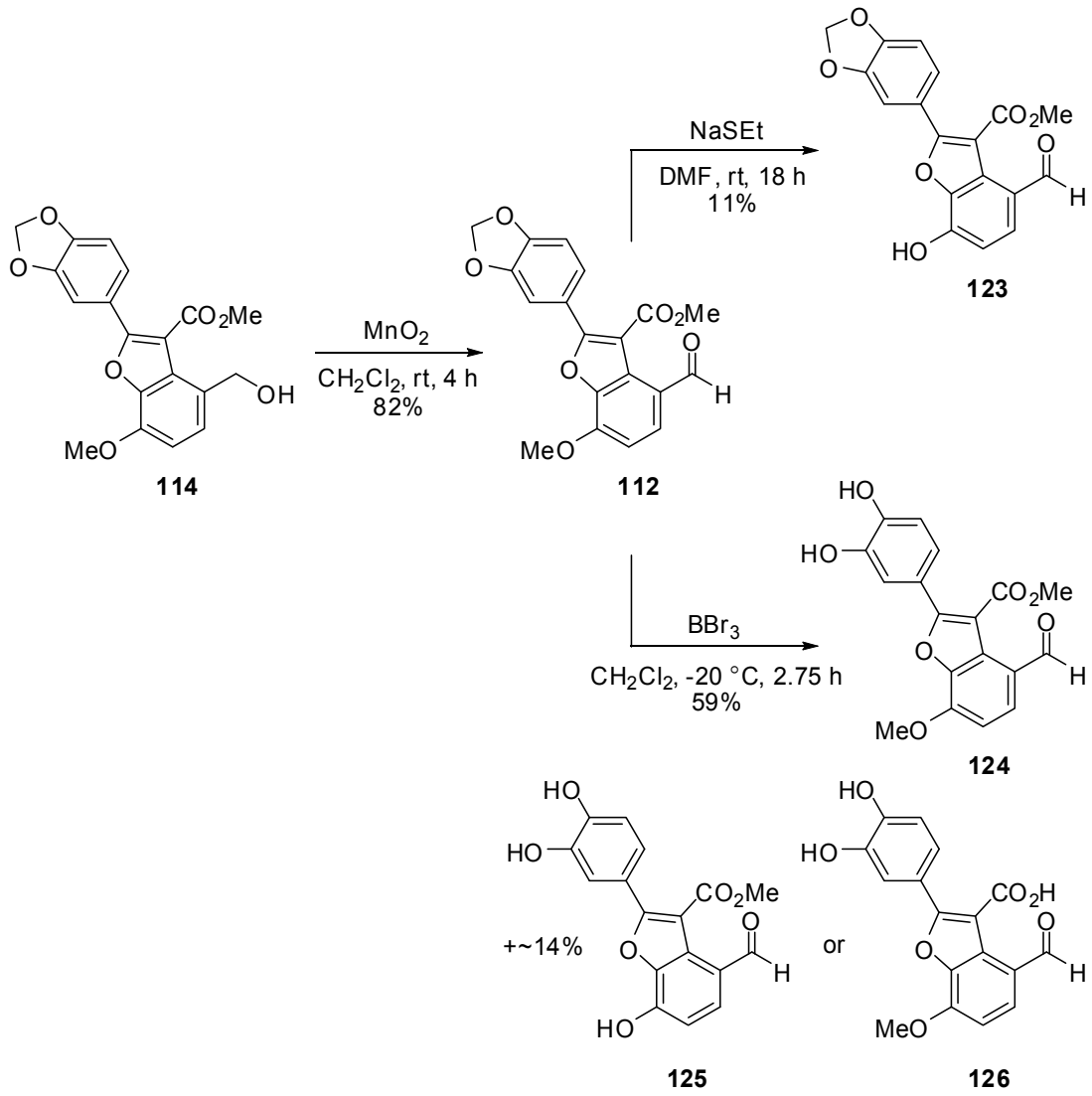


Scheme 40

Initially, the reaction follows the same pathway for formation of **122** as presented in **Scheme 12**, with phenolic proton removal, palladium-mediated cyclisation to give species **121**, followed by carbon monoxide insertion to give **122**. The mechanism diverts from **Scheme 12** at this point, whereby instead of intermolecular attack of the solvent methanol hydroxyl group, there is intramolecular attack of the benzylic alcohol, followed by expulsion of palladium *via* reductive elimination, giving rise to the observed lactone **118**.

3.2 Selective Deprotection Studies

It was anticipated that the unmasking of selected protecting groups at this stage should deliver interesting fragments for biological evaluation. This strategy is conveyed in **Scheme 41**.

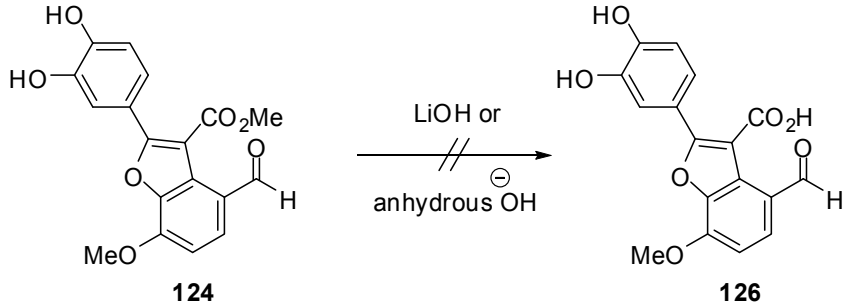


Scheme 41

The conversion of the benzyl alcohol functional group to the aldehyde serves two purposes. Firstly, this should avoid side reactions *via* the formation of the corresponding benzylic cation, and secondly, the presence of the aldehyde should activate the *para*-methoxy substituent towards demethylation.[89]

The benzyl alcohol **114** was smoothly oxidized to the corresponding benzaldehyde **112** by manganese dioxide.[90] After the reaction was deemed complete, removal of the manganese dioxide by filtration delivered the aldehyde cleanly, without the need for purification. Treatment with a soft nucleophile, such as the thiolate anion, should displace the methyl group in an S_N2 sense, generating a phenoxide as

the leaving group. This phenoxide leaving group would be stabilised by the presence of the aldehyde in the *para* position. Accordingly, treatment with sodium ethanethiolate[91,92] successfully led to selective deprotection of the methyl ether to give the desired phenol **123**. Alternatively, selective cleavage of the methylenedioxy group could be achieved by treatment of **112** with the Lewis acid boron tribromide,[93,94,95,96] to give catechol **124**. At -78 °C, complete conversion was not achieved and **124** was formed in low yield (*ca*. 40%). Additional boron tribromide was therefore used (10 equiv.) and the temperature was increased to affect complete consumption of the starting material. Whilst this did have the effect of increasing the yield of **124** to 59%, it also produced a small amount of overreacted material (~14%) possessing only one methyl group as determined by ^{1}H NMR and this by-product was tentatively assigned as **125** or **126**. The exact methyl group that remained was partially investigated.



Scheme 42

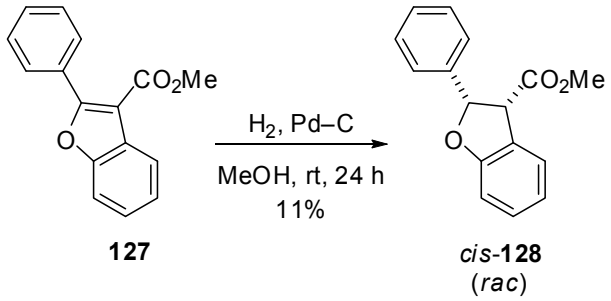
It was anticipated that saponification of ester **124** with lithium hydroxide would give acid **126** selectively, since lithium hydroxide is selective for ester cleavage and would not promote ether cleavage. This would give an authentic sample of **126** to compare with the overreacted material previously obtained and enable us to identify which of the methyl groups were cleaved in the overreacted product. Unfortunately, treatment with lithium hydroxide had no effect and the use of anhydrous hydroxide[97] led to decomposition. Considering the small amount of the overreacted material generated in the previous step and the fact that both target compounds **123** and **124** had been successfully obtained, this was considered low priority and this line of investigation was abandoned.

In addition to these demethylation conditions, treatment of **112** with aqueous HBr;[98,99] aqueous HBr with AcOH; and molten pyridinium hydrochloride[100,101] were also conducted. In all of these cases, there was no evidence for demethylation.

The two compounds, **123** and **124**, were screened for anti HIV-1 integrase activity, the results of which are discussed in **Section 3.4**.

3.3 Reduction of the Benzofuran Ring system

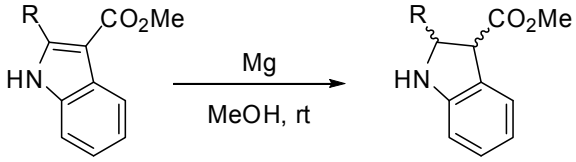
Within the literature there are many examples of reductions of tetrasubstituted double bonds, so too are the reduction of benzofurans to 2,3-dihydrobenzofurans. However, literature on the reduction of the tetrasubstituted double bond embedded within 2,3-disubstituted benzofurans is much more limited, and to date there exists only one example (**Scheme 43**).[102]



127 *cis*-**128** (*rac*)

Scheme 43

In this example, a 2,3-disubstituted benzofuran is reduced using hydrogen over catalytic palladium on charcoal, albeit in low yield (11%). There are limited examples of the reduction of indoles to the corresponding indolines, the most notable of which is the magnesium–methanol reduction reported by Youn *et al*.[103] The use of magnesium as a single electron source in a protic solvent is used to provide a reducing environment. It is mentioned, however, that this is a non-straightforward transformation for 2-carboxylate appended systems, and that of all other reagent combinations, the magnesium–methanol system is unique.

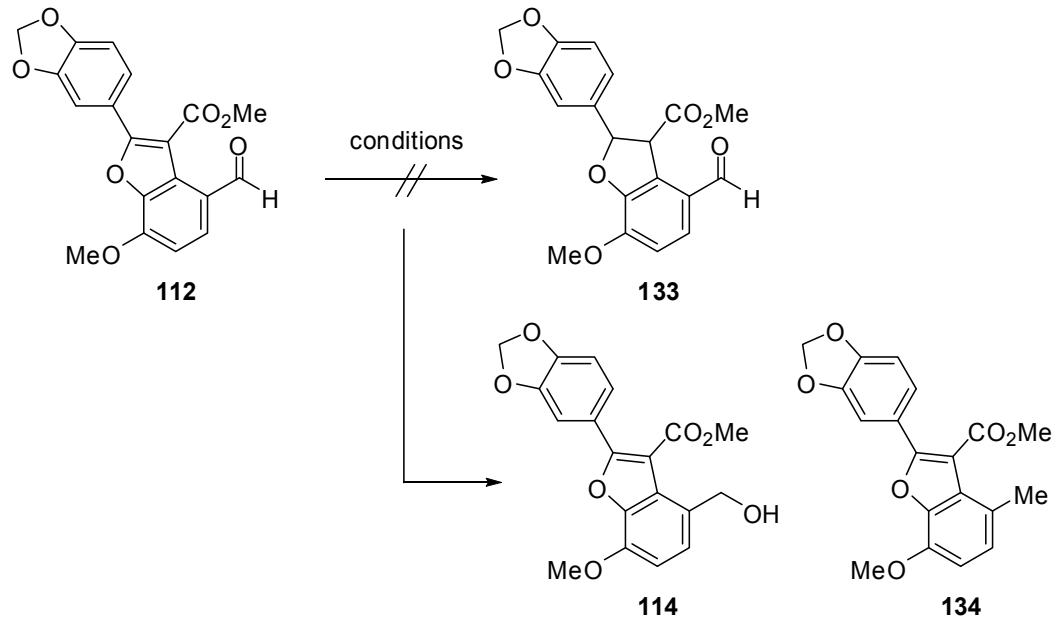


R = H, **129** **130** (96%)

R = CH_3, **131** **132** (98%)

Scheme 44

The success of our approach to lithospermic acid hinged on this transformation being accomplished, and given the scant precedent for this transformation, this was a formidable task.



Scheme 45

Several reaction conditions were trialed to achieve the transformation shown in **Scheme 45** and these are summarised in **Table 5**.

Table 5

Entry	conditions	result
1	H_2, Pd–C, MeOH, rt, 30 min	**114** (72%)
2	Mg, MeOH, rt → 45 °C, 5 h	complex mixture
3	(*R*)-*p*-tolBINAP, $CuCl_2$, *t*-BuONa, PMHS, *t*-AmOH, pentane, toluene, 0 °C → rt, 48 h	**112** recovered (7%), **114** (33%)

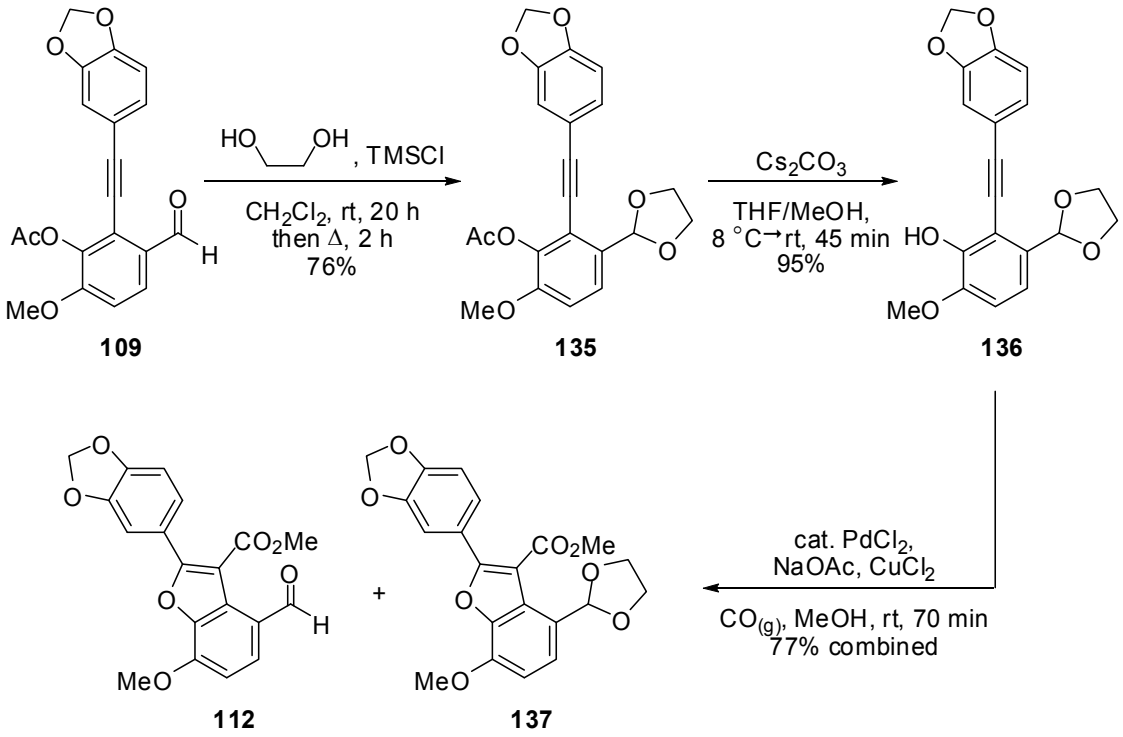
Initially it was envisaged that this transformation could be conducted according to the conditions of Juhász *et al.*[102] where hydrogenation over palladium–charcoal had been used successfully on an unfunctionalised benzofuran system (**Scheme 43**). Not unexpectedly, the only reaction was the reduction of the aldehyde to give the benzyl alcohol **114** (72%) (**Entry 1**, **Table 5**). It was decided to resubject **114** to the same conditions but for a longer time period (3.5 d) in an effort promote the desired transformation. Unfortunately, this led to a complex mixture of products, with the only identifiable compound being **134** (23%), where the alcohol had been completely reduced to the methyl group. Unfortunately, the conditions of Youn *et al.*[103] (**Entry 2**) proved unsuccessful on this system, leading instead to a complex mixture of products. Of this mixture, no peaks in the ^{1}H NMR spectrum could be reconciled with the desired product **133**, nor any other related compounds. In an attempt to perform the reduction in an asymmetric sense, the conditions developed by the Buchwald group[104-108] for

conjugate reduction of α,β-unsaturated carbonyl compounds, were investigated. These conditions (**Entry 3**), involving *in situ* formation of a chiral Cu(I) hydride species, did not give the desired 2,3-dihydrobenzofuran **133**, but simply reduced the aldehyde to the corresponding alcohol **114**.

These results indicate that neither the benzaldehyde nor the benzyl alcohol functional groups are compatible with the reduction process.

3.3.1 Aldehyde Protection as the Dioxolane

It was anticipated that both the variable yields in the carbonylative annulation reaction step and the problems encountered in the reduction step, could be addressed by installing an alternate protecting group, such as the dioxolane, prior to the carbonylative annulation. For these reasons, we went back to the Sonogashira coupling product **109** to circumvent these issues by carrying forward a protected form with minimal synthetic steps and maximum efficiency, as shown in **Scheme 46**.



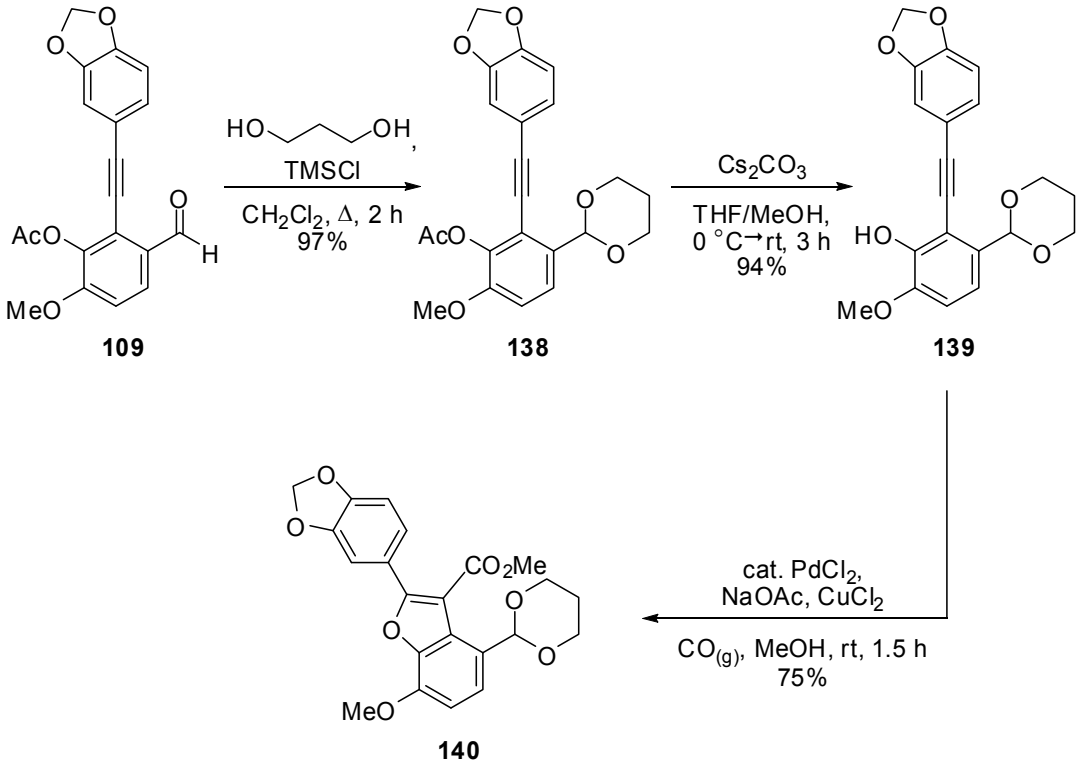
Scheme 46

Commencing with the Sonogashira coupling product **109**, the aldehyde was protected as the corresponding 5-membered cyclic acetal (dioxolane) using ethylene glycol.[109] In this reaction, the trimethylsilyl chloride serves two functions; firstly, the initial reaction with an alcohol forms hydrogen chloride *in situ* under anhydrous conditions, and secondly it acts as a Lewis acid to activate the aldehyde towards acetal formation. This procedure proved moisture sensitive, and it was crucial to ensure the reaction remained strictly anhydrous. Once formed, acetal **135** was handled with care since exposure to

acid (such as DCl in deuterochloroform) promoted the unexpectedly facile hydrolysis of the acetal back to the aldehyde. The acetate **135** was then de-acetylated using the conditions developed in **Section 3.1.3**—cesium carbonate in THF/MeOH—which worked well on this system, delivering the requisite *ortho*-hydroxydiarylalkyne **136** in excellent yield (95%). With **136** in hand, the carbonylative annulation reaction could be examined once more. To our dismay, the acetal proved unstable and did not survive the conditions of the carbonylative annulation and a mixture of aldehyde **112** and acetal **137** (*ca.* 1:4, ~76% combined yield) were afforded and proved difficult to separate by column chromatography. It is likely that the Lewis acidic $CuCl_2$ is promoting acetal cleavage under these conditions. In light of this, a more stable protecting group system for the aldehyde was sought.

3.3.2 Aldehyde Protection as the Dioxane

It is known that the stability of cyclic acetals is dependant on ring size and the nature of the carbonyl being protected. For cyclic acetals derived from ketones, the 5-membered ring (dioxolane) is more stable than the 6-membered ring (dioxane). This situation is reversed, however, in the case of aldehydes, where the dioxane is the more stable cyclic acetal.[110] On this basis, the dioxane was chosen as a suitable system for the next aldehyde protection strategy.

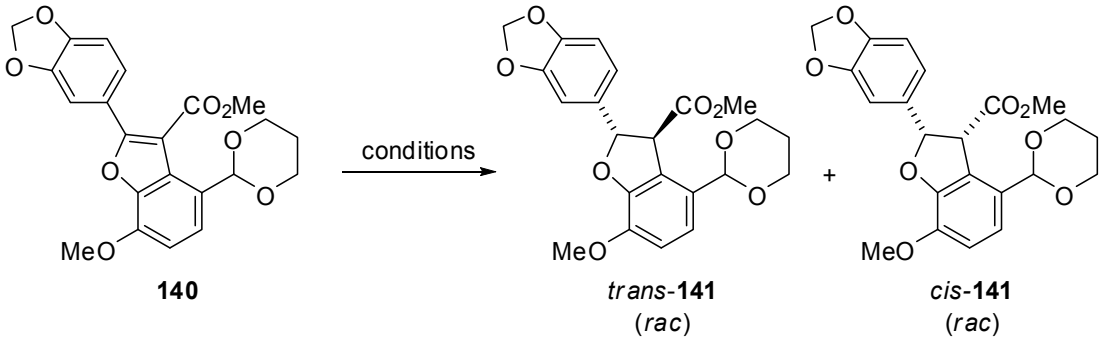


Scheme 47

Commencing once more with the Sonogashira coupling product **109**, the aldehyde was protected as the 6-membered cyclic acetal (dioxane) to give an excellent yield of **138** (97%). The quenching procedure

for this reaction had to be modified, since adding aqueous sodium hydrogen carbonate solution (to quench the reaction) tended to cleave the acetal and in some cases up to 30% of the aldehyde was isolated. It is speculated that in this biphasic situation, acid-promoted hydrolysis in the organic phase may compete in rate with the reaction of this acid with bicarbonate in the aqueous phase. An alternate quenching procedure involved the addition of anhydrous potassium carbonate, which neutralised the reaction without forming any aqueous acid. After rapid stirring for 10 min, the reaction mixture was sufficiently neutralised and could be subjected to the standard aqueous work-up. Subsequent to this, the acetate was cleaved, using the conditions developed previously, to give the desired *ortho*-hydroxydiarylalkyne **139** in excellent yield (94%). With **139** in hand, the carbonylative annulation could be investigated once more. To our delight, the reaction proved to be clean, reliable and importantly, high yielding, to give the desired tetrasubstituted benzofuran **140** in 75% yield. Having successfully developed a rapid route to the benzofuran ring system, it was now time to investigate the reduction, allowing access to the 2,3-dihydrobenzofuran segment present in the natural product.

3.4 Accessing the 2,3-dihydrobenzofuran



140 *trans*-**141** (*rac*) *cis*-**141** (*rac*)

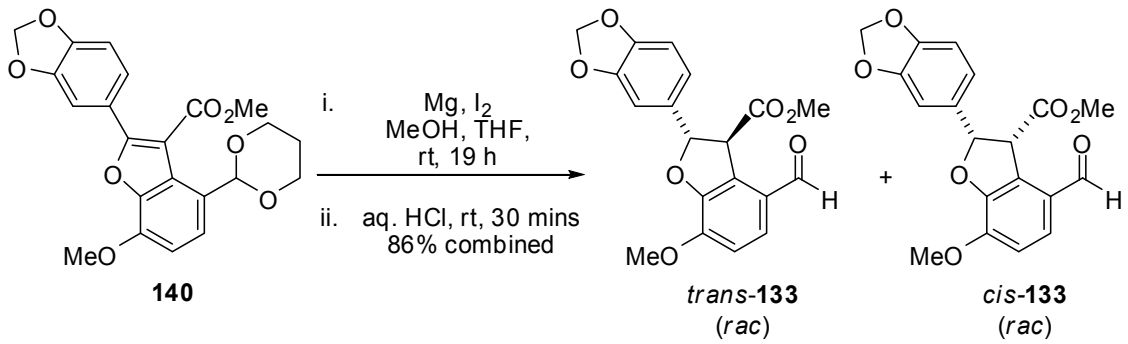
Scheme 48

A variety of conditions were explored to affect the reduction of benzofuran **140** to give the desired 2,3-dihydrobenzofurans (**Scheme 48**). The results from this investigation are summarised in **Table 6**.

Table 6

Entry	conditions	result
1	H_2, Pd/C, MeOH, rt, 46 h	no reaction, **140** recovered
2	H_2 (3 bar), Pd/C, EtOH, rt, 45 h	no reaction, **140** recovered
3	CF_3COOH, Et_3SiH, 0 °C, 30 min	complex mixture
4	(R)-*p*-tolBINAP, $CuCl_2$, *t*-BuONa, PMHS, *t*-AmOH, pentane, toluene, 0 °C → 45 °C, 48 h	no reaction, **140** recovered
5	Mg, MeOH, THF, rt, 28 h	*trans*-**141** (32%), **140** recovered (10%)

Hydrogenation conditions employed successfully by Juhász *et al.*[102] on a simple benzofuran system were unsuccessful on this more functionalised system. At both ambient pressure, using a balloon of hydrogen gas (**Entry 1**, **Table 6**), and at higher pressure in a Parr hydrogenator (**Entry 2**), the desired products *trans*- or *cis*-**141** were not observed. In both of these entries there was no reaction and the starting material **140** was simply recovered. With **140** proving impervious to these mild reducing conditions, the more forcing reagent combination of trifluoroacetic acid and triethylsilane was implemented (**Entry 3**). Unfortunately, this reagent combination consumed the starting material and returned a complex mixture of products with none of the indicative product peaks observed in the ^{1}H NMR spectrum. Interestingly, a small amount (*ca.* <3%) of compound **134** was observed in the ^{1}H NMR spectrum of a partially purified product. The failure of this reagent combination was presumably due to the acid lability of the acetal and subsequent reaction at this site. The use of the chiral copper hydride reagent developed by the Buchwald group[104, 105] was also investigated (**Entry 4**) but unfortunately this substrate proved unreceptive to these conditions. This is not entirely unexpected upon comparison of **140** with the substrates used by Buchwald and co-workers.[105] The Buchwald substrates were linear α,β-unsaturated esters which lacked substitution at the α-position. In another body of work by the Buchwald group,[104] lactones and lactams were investigated, however, these too lacked substitution at the α-position and the release of ring strain in the lactones and lactams would also drive this reduction. With these limitations considered, the substrate presented here represents a much more challenging system so it is perhaps not surprising that these conditions proved unsuitable. Eventually, the use of magnesium in methanol (**Entry 5**) proved to be the triumphant reagent combination for achieving this transformation, albeit in modest yield. Inspection of the ^{1}H NMR spectrum of the crude reaction mixture indicated a *ca.* 9:1 mixture of *trans*-**141** and *cis*-**141** respectively. The modest yield was, at least in part, a result of emulsion formation during work-up caused by the magnesium salts. The magnesium–methanol reduction conditions were subsequently investigated further (**Scheme 49**).



Scheme 49

Initially, this reaction was hampered by a number of factors. The starting material and product were almost identical in R_f, so it was critical that the reaction went to completion to circumvent problems associated with their separation. The insolubility of the substrate in MeOH led to reactions that would not go to completion. Higher dilution in MeOH did not solve these problems and the addition of THF as a co-solvent, whilst solving the solubility issues, prevented the reduction from taking place. Using a large excess of magnesium did not drive the reaction to completion and led to emulsions which made isolation problematic. Different types of magnesium were also investigated—powder, granules and turnings—all to no avail.

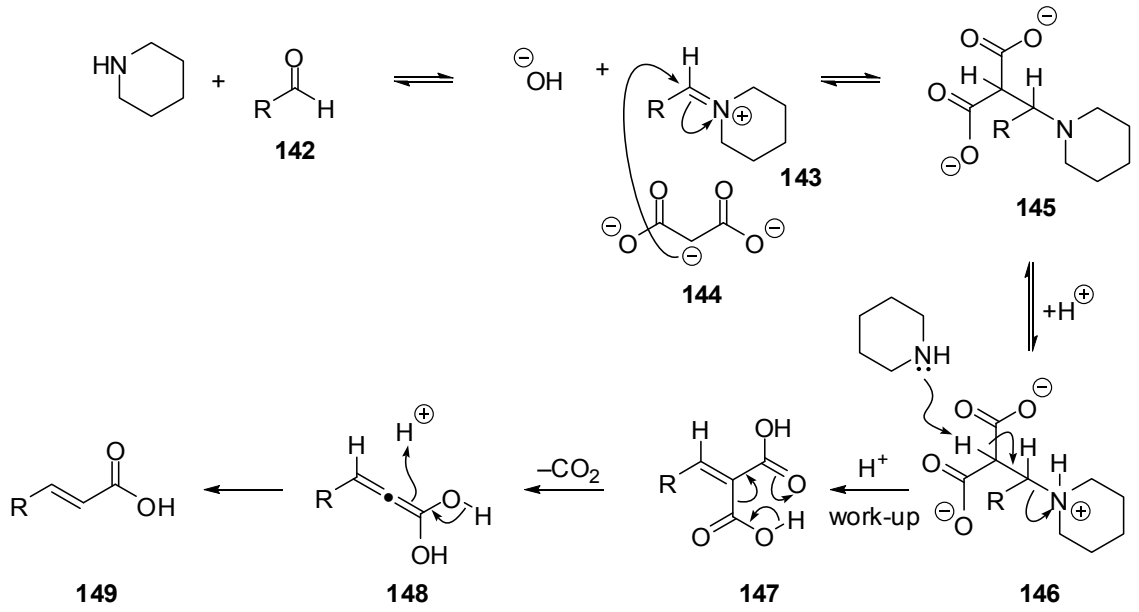
Ultimately, THF was used sparingly to overcome the solubility issues. On the assumption that THF was the cause of the problem, a crystal of iodine was added to successfully avert the problems previously encountered when using THF. It was also necessary to clean the surface of the magnesium turnings with dilute aqueous HCl prior to use. Quenching the reaction with aqueous HCl overcame the problems associated with emulsion formation by solubilisation of the magnesium salts. The use of aqueous acid also accomplished the next synthetic step by promoting hydrolysis of the acetal. When all of these procedural modifications were implemented, the desired 2,3-dihydrobenzofuran could be isolated in a pleasingly high 86% yield as a *ca*. 2.5:1 mixture of *trans*-**133** and *cis*-**133** respectively, as shown in **Scheme 49**.

Although *trans*-**133** and *cis*-**133** were separable by column chromatography, this was not strictly necessary as epimerisation occurred readily in the subsequent step. In practice, these were not separated, but carried on to the next step as a mixture.

This reduction is particularly noteworthy, as there exists only one method prior to this for the reduction of 2,3-disubstituted benzofurans, and this was accomplished on a much less functionalised example and only proceeded in 11% yield[102] and this approach represents a vast improvement on the known methods for the reduction of 2,3-disubstituted benzofurans. This synthetic sequence provides a novel route to access 2,3-disubstituted-2,3-dihydrobenzofuran ring systems in a rapid and efficient manner.

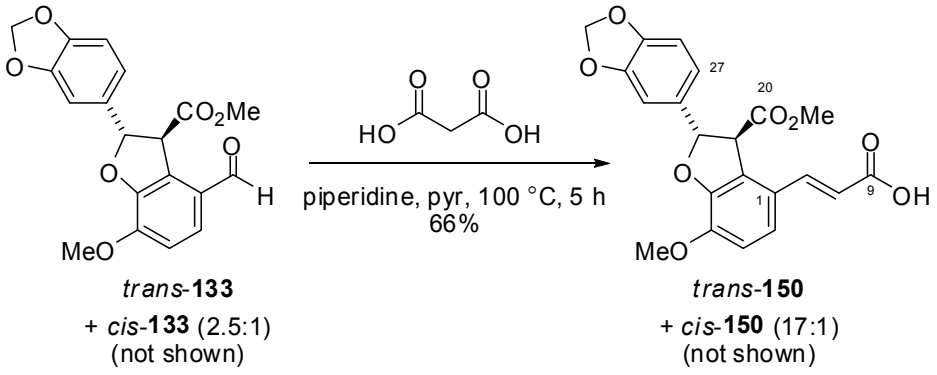
3.5 Completing the C_1–C_9/C_{19}–C_{27} Fragment

The final step to complete the synthesis of the C_1–C_9/C_{19}–C_{27} fragment of lithospermic acid was the conversion of *trans*-**133** to cinnamic acid *trans*-**150**. To achieve this transformation, the Knövenagel condensation reaction with malonic acid was investigated. The Knövenagel condensation is typically catalysed by an amine and involves a condensation reaction between a carbonyl and an activated methylene compound, leading to the formation of an α,β-unsaturated acid. The mechanism for this transformation is depicted in **Scheme 50**.



Scheme 50

The mechanism of the Knövenagel condensation begins with malonic acid deprotonation to give anion **144** whilst the amine and aldehyde **142** form iminium ion **143**. The iminium ion **143** is then attacked by **144** to form **145** which is then in turn protonated to give **146**. This then undergoes an E2 elimination event and after acidic work-up, gives diacid **147**. Diacid **147** undergoes spontaneous irreversible decarboxylation to form allene **148** which subsequently tautomerises to give the observed α,β-unsaturated acid **149**.



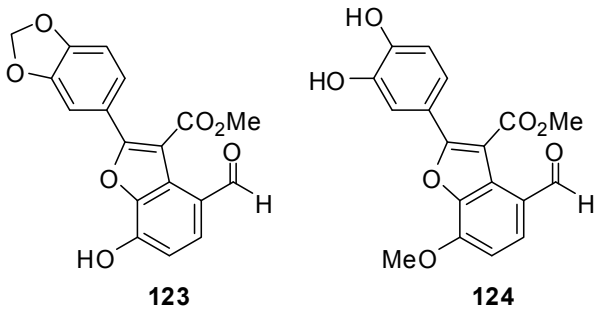
trans-**133**
+ *cis*-**133** (2.5:1)
(not shown)

trans-**150**
+ *cis*-**150** (17:1)
(not shown)

Scheme 51

The *ca*. 2.5:1 mixture of *trans*-**133** and *cis*-**133** were subjected to the conditions of the Knövenagel condensation, as performed by Ellman and co-workers,[49] and is shown in **Scheme 51**. The desired cinnamic acid was afforded in a modest yield of 66% as a *ca*. 17:1 mixture of the two diastereomers, *trans*-**150** to *cis*-**150** respectively. This experiment was only repeated twice, and not subjected to any optimisation studies, which accounts for the modest yield.

3.6 Biological Evaluation of Phenol 123 and Catechol 124



123 **124**

Figure 19

Although the chief aims of this research were to develop new methodology for the synthesis of lithospermic acid and to undertake that total synthesis, intermediates **123** and **124** were envisaged to be interesting compounds to screen against HIV-1 integrase. Prior to integrase screening, the cytotoxicity of these compounds was evaluated, since the assay is performed in live, HIV-infected cells. The results from this study concluded that **124** was too cytotoxic to be considered for screening against integrase, displaying cytotoxic effects as low as 0.05 μg mL^{-1}. In Contrast, **123** displayed minimal cell cytotoxicity up to 15 μg mL^{-1} and was therefore considered suitable for further screening.

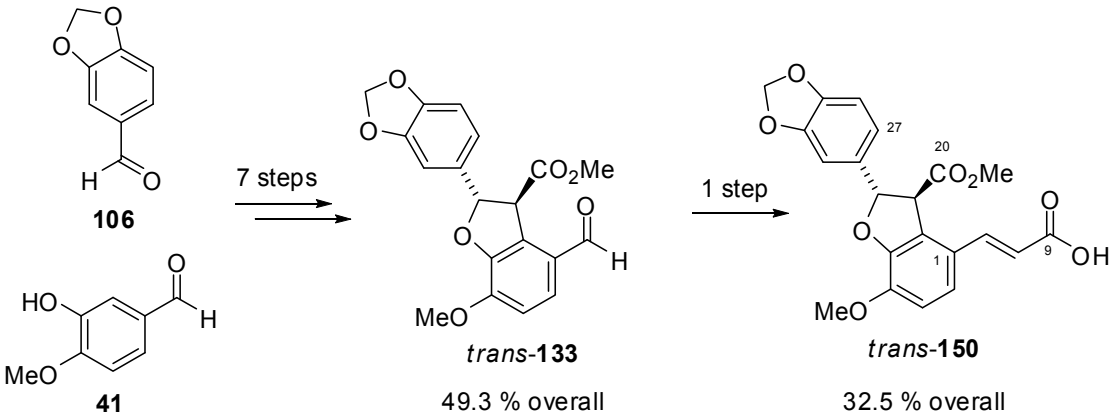
In the whole cell assay,[111,112,113] conducted in collaboration with Burrell, Li and co-workers, HUT-78 cells were preincubated with **123**. The quantities of unintegrated viral DNA (an indicator for reverse transcription) and integrated viral DNA (an indicator for integration) were measured at various time

points. These measurements indicated that **123** was having minimal effect on both of these pathways, even up to concentrations of 15 μg mL^{-1}.

From these initial, albeit limited, studies into a structure reactivity relationship, some patterns can already be observed and rationalised. Compound **124** which possesses a catechol moiety, is unsurprisingly cytotoxic. This can be rationalised by the fact that the catechol moiety is a potential ligand for a number of divalent metal centers which may be at the active site of a number of enzymes. Compared with lithospermic acid (**21**), it lacks any of the structural complexity that would confer selectivity to a specific enzyme such as HIV-1 integrase. Compound **123** contains no catechol moiety to give it the cytotoxic properties. It also lacks the functionality that would bind to the active site of integrase, as discussed in **Section 1.2**, thus it has no effect on the integrase enzyme. It was also noted that these compounds possessed an aldehyde functional group, and it is known that aldehydes are rarely suitable for medicinal applications.

3.7 Summary

In summary, fragment *trans*-**150** has been successfully constructed using the synthetic sequence developed throughout this body of work (**Scheme 52**). Fragment *trans*-**133** was afforded in 7 steps and 42.8% overall yield, in a longest linear sequence from isovanillin (**41**) (average yield: 88.6 % per step). This fragment is one step removed from the entire C_1–C_9/C_{19}–C_{27} fragment of lithospermic acid. Despite the unoptimised last step, the synthesis of this C_1–C_9/C_{19}–C_{27} fragment was completed in an overall 8 step synthetic sequence from isovanillin (**41**), 32.5 % overall yield (average yield: 87.8% per step).



Scheme 52

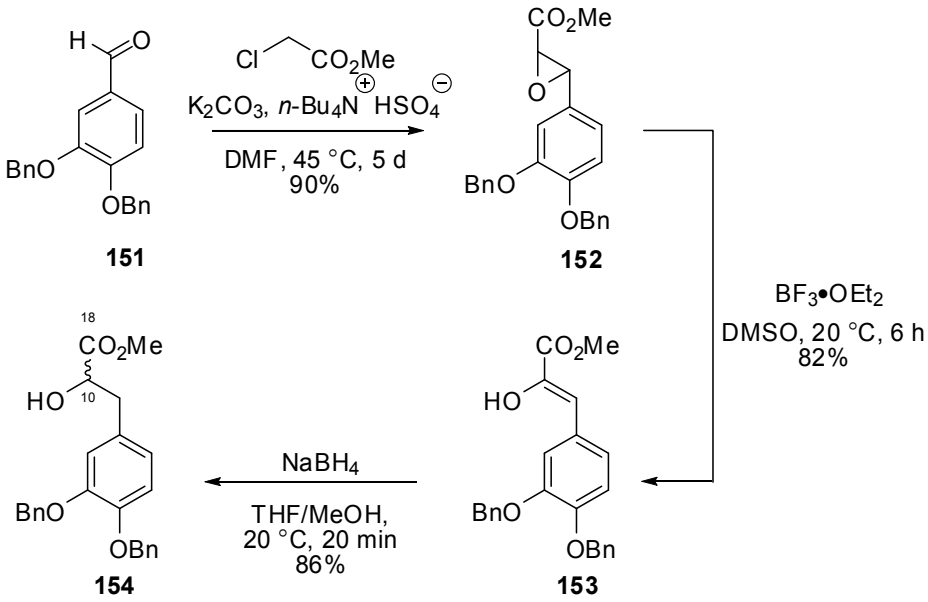
This demonstrates that this synthetic approach can be successfully used to access this type of dihydrobenzofuran framework. Importantly, this sequence does so in a very rapid and efficient manner whilst also displaying a high degree of modularity.

–Chapter 4–

Initial Approach to a Total Synthesis of Lithospermic Acid

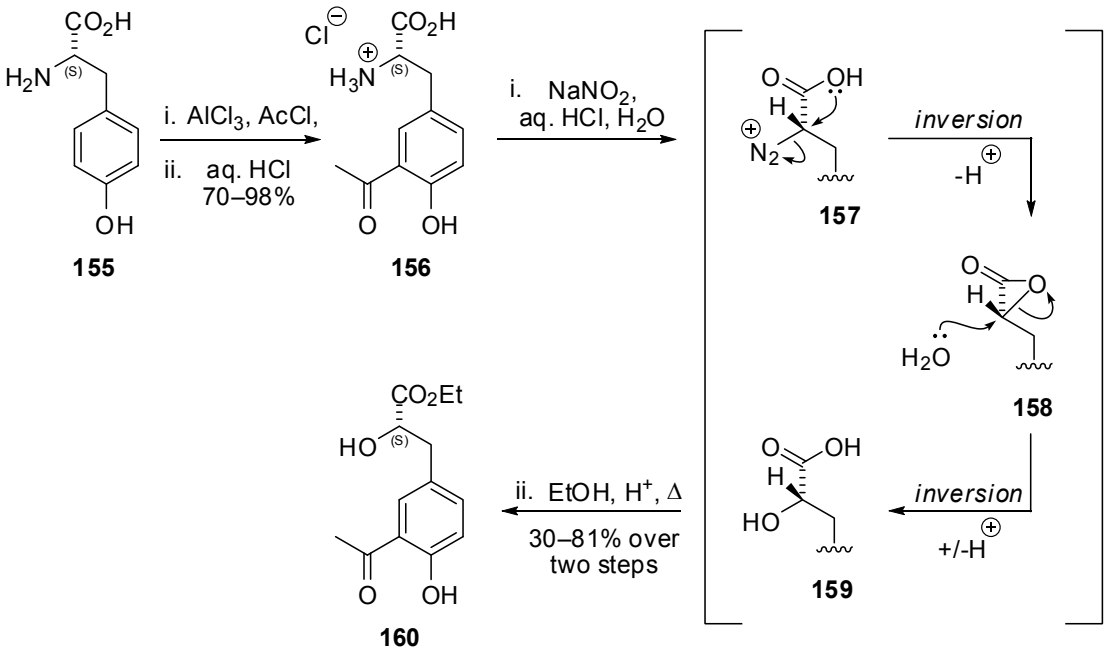
4.1 Construction of the C_{10}–C_{18} Fragment

Several synthetic routes to the C_{10}–C_{18} fragment of lithospermic acid have been reported.[57-60] Reimann *et al*.[58] accessed racemic **154** (**Scheme 53**) *via* conversion of benzaldehyde **151** to epoxide **152**, that was subsequently subjected to Lewis acid catalysed ring opening to provide alkene **153**. Alkene **153** was then reduced with sodium borohydride to give the desired alcohol **154**, as the racemate.



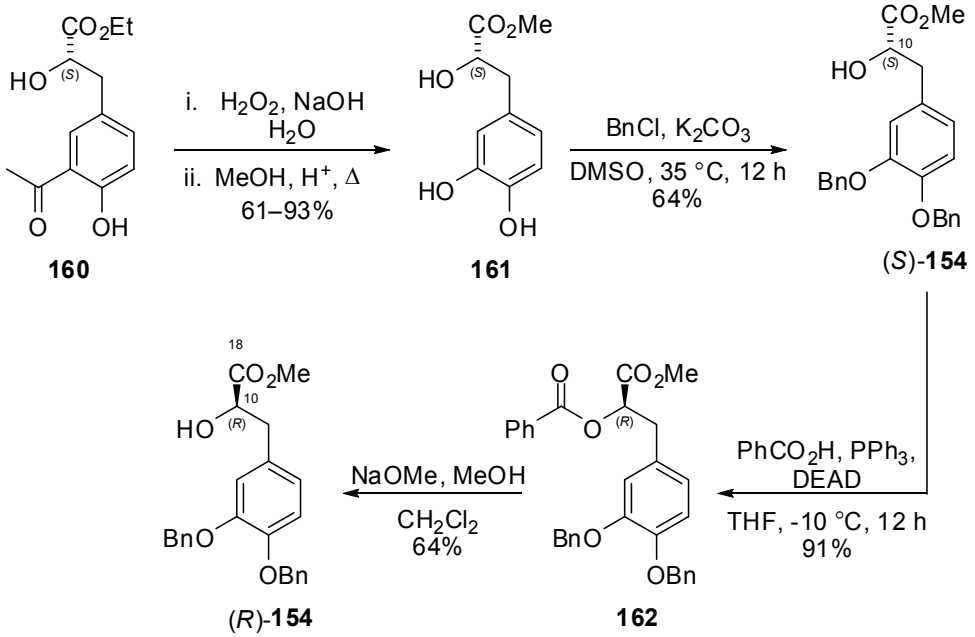
Scheme 53

An alternative approach that has been utilised by a number of groups to access the chiral alcohol involves the conversion of L-tyrosine (**155**) to the enantiopure *S*-alcohol (*S*)-**154**.[57,60] A representative strategy for these approaches is presented in **Scheme 54** and **Scheme 55**.



Scheme 54

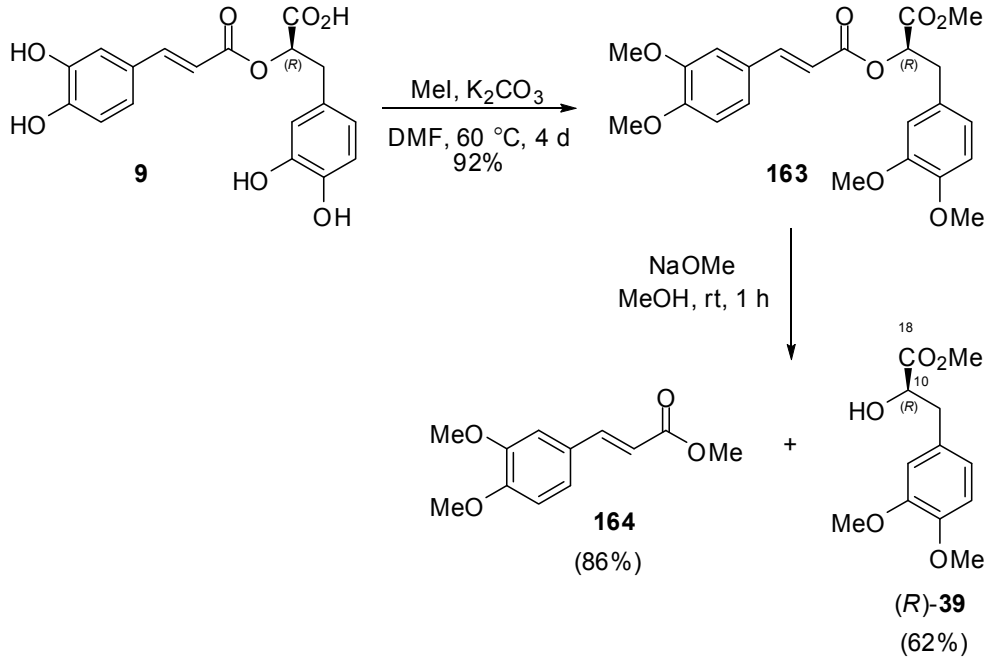
L-Tyrosine (**155**) was subjected to Friedel–Crafts acylation followed by acidic work-up to yield the aryl ketone **156** that was then subjected to diazotisation and the *in situ* hydrolysis that ensued yielded the α-hydroxyacid **159** with overall retention of configuration. The retention of configuration in this sequence is a result of two inversion steps. Known as "neighbouring group participation", the oxygen of **157** displaces the leaving group, N_2, in an intramolecular S_N2 sense, resulting in inversion of the stereocentre and formation of the transient α-lactone **158**. Lactone **158** is rapidly ring opened *via* nucleophilic attack of water, again with inversion of configuration in an S_N2 fashion, to give the observed α-hydroxyacid **159** with overall retention of configuration which was then esterified under standard conditions to give ester **160**.



Scheme 55

The aryl ketone **160** was then subjected to a Dakin oxidation and the resulting base-sensitive acetate was rapidly cleaved *in situ* to generate the free phenol. Subsequent transesterification of the ethyl ester delivered the methyl ester **161**. After accessing *S*-alcohol **161**, Riemann *et al.*[59] demonstrated that the desired *R*-alcohol could be obtained *via* a chiral inversion in 3 steps, although this could presumably be accessed directly from D-tyrosine. Benzylation of **161** afforded (*S*)-**154** which was subsequently subjected to a Mitsunobu reaction, which inverted the configuration about the C10 centre, giving **162**. Subjecting **162** to methanolysis afforded the required α-hydroxyester (*R*)-**154**, which constitutes the protected C_{10}–C_{18} fragment of lithospermic acid.

A more expeditious and synthetically efficient route to the C_{10}–C_{18} fragment was realised by Ellman and co-workers in a two step sequence, starting with the commercially available, and fully functionalised natural product, rosmarinic acid (**9**).[49] Our approach closely mirrors this synthesis and is illustrated in **Scheme 56**.

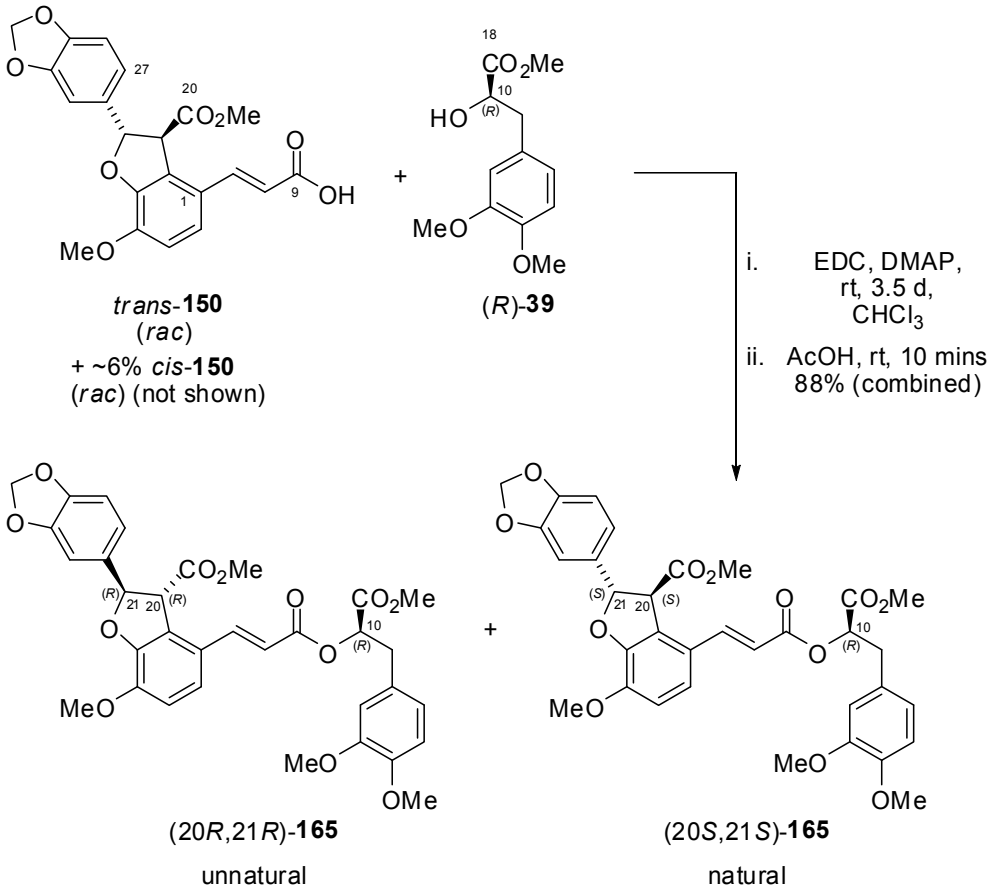


Scheme 56

The first step required methylation of rosmarinic acid (**9**) for which the Ellman group used dimethyl sulfate and potassium carbonate. Dimethyl sulfate is classed as a "notifiable carcinogenic substance" according to NSW occupational health and safety regulations[114] and as such, researchers are encouraged to explore alternatives. Ergo, methyl iodide, listed as a category 3 carcinogen (suspected of having carcinogenic potential) by Worksafe Australia, was investigated as an alternative. With little work in optimisation studies, the desired permethylated rosmarinic acid **163**, was afforded in 92% isolated yield. It was noted that when the reaction was carried out in acetone as the solvent, the desired product was not observed, presumably due to issues with solubility of **9** in this solvent. The desired alcohol (*R*)-**39** could then be accessed by subjecting **163** to methanolysis using sodium methoxide in MeOH. The modest yield of the alcohol (*R*)-**39** (62%) is attributed to the difficulties in purification. The polar alcohol (*R*)-**39** tended to streak during flash column chromatography, leading to a loss of material presumably due to some form of strong interaction with the silica gel. Adding an alcohol (e.g. MeOH) to the eluting solvent may improve the efficiency of this chromatographic purification leading to improved yields, however, this step remains unoptimised, having been performed only twice.

With the C_{10}–C_{18} fragment ((*R*)-**39**) of lithospermic acid in hand in an overall yield of 57%, the stage was set to investigate the final stages of the proposed synthetic route.

4.2 Uniting the C_1–C_9/C_{19}–C_{27} and C_{10}–C_{18} Fragments



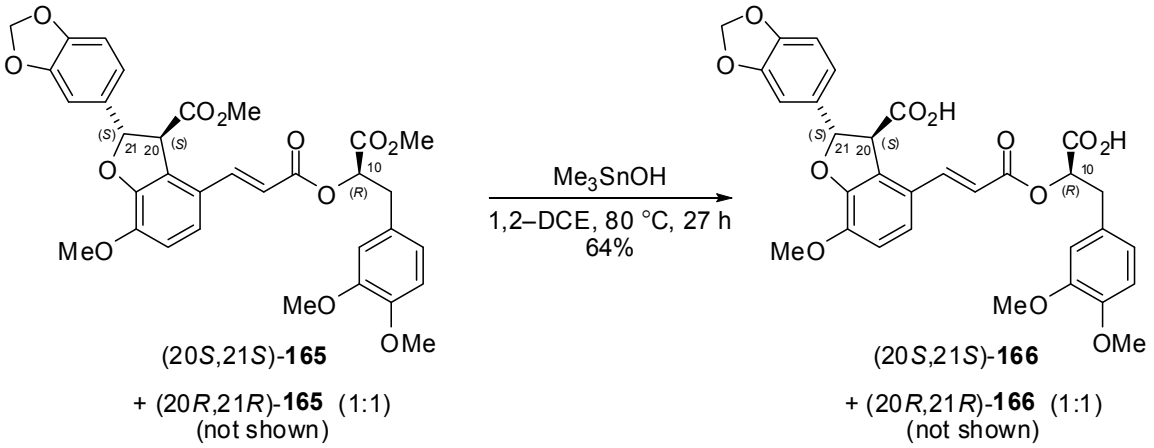
Scheme 57

Following the precedent set by the Ellman synthesis,[49] the two fragments *trans*-**150** and (*R*)-**39** were united using an esterification reaction promoted by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and 4-(dimethylamino)pyridine (DMAP) (**Scheme 57**). After coupling, acetic acid was used to convert excess alcohol (*R*)-**39** to the more easily separable acetate for ease of purification. Under these conditions, coupling of (*R*)-**39** with *trans*-**150** (containing ~6% *cis*-**150**), provided the desired ester products. Separation of the two *trans* dihydrobenzofurans (88% yield) from their 20,21-*cis* counterparts (not shown) was achieved by column chromatography, however, separation of the two diastereomeric *trans*-dihydrobenzofurans ((20*R*,21*R*)-**165** and (20*S*,21*S*)-**165**) was not possible using this technique. The difficulty in separating (20*R*,21*R*)-**165** and (20*S*,21*S*)-**165** is not surprising given the length and flexibility of the chain separating the C10 and C20/C21 stereocentres. The (20*R*,21*R*)-**165** and (20*S*,21*S*)-**165** mixture, assumed to be 1:1, appeared as a single spot by tlc and no further attempt was made to resolve these diastereomers. Thus, with a successful coupling of the C_1–C_9/C_{19}–C_{27} and C_{10}–C_{18} fragments, the entire carbon skeleton of lithospermic acid (**21**) was now in

place and all that remained to complete the total synthesis was removal of the protecting groups. Whilst it appears that global deprotection at this stage could deliver the natural product, there is a strong indication that this strategy would lead to decomposition, as discussed in **Section 1.3.3**. This decomposition occurs primarily through the ring opening of the dihydrobenzofuran through β-elimination of the C21 phenoxy group.[49] With this insight, a two-step deprotection procedure was undertaken.

4.3 Deprotection Stage 1: Ester Cleavage

The first step in the deprotection of (20*S*,21*S*)-**165** and (20*R*,21*R*)-**165** is the cleavage of the two methyl esters. On a similar system investigated by Ellman and co-workers,[49] the more traditional saponification conditions proved unsuitable and did not result in the selective hydrolysis of the methyl esters over the internal C9 ester linkage. An alternative approach for selective methyl ester cleavage relies on the S_N2 displacement of the methyl group by an appropriate nucleophile. One such reagent, trimethyltin hydroxide,[115-118] had been used successfully with sensitive substrates by Nicolaou *et al.*[119] and had also proven suitable in the Ellman synthesis. With this insight, esters (20*S*,21*S*)-**165** and (20*R*,21*R*)-**165** were subjected to the prescribed deprotective protocol as illustrated in **Scheme 58**.

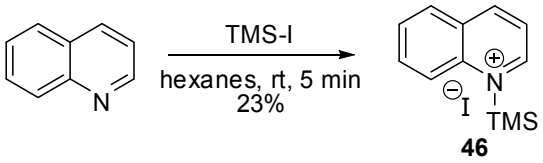


Scheme 58

Under these conditions, the desired diacids (20*S*,21*S*)-**166** and (20*R*,21*R*)-**166** were obtained as a presumably 1:1 mixture in an unoptimised 64% yield. Diacid (20*S*,21*S*)-**166** is now just a single step removed from the natural product lithospermic acid (**21**).

4.4 Deprotection Stage 2: The Final Deprotection

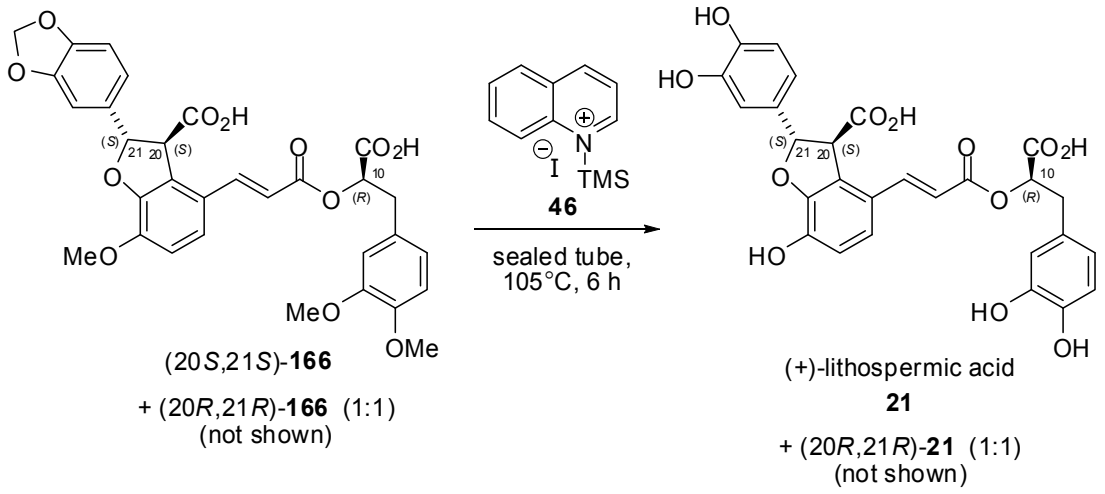
Following the precedent of Ellman and co-workers on their related system,[49] the final deprotection was attempted with the exotic reagent, 1-trimethylsilylquinolinium iodide (**46**). The synthesis of this highly moisture-sensitive reagent is depicted in **Scheme 59**.



Scheme 59

1-Trimethylsilylquinolinium iodide (**46**) was first documented by Brossi and co-workers[50] where it was postulated that this was the active species formed in the trimethylsilyl iodide/refluxing quinoline reagent combination and was involved in the demethylation of aromatic methyl ethers. The authors reported the ammonium iodide **46** to be an isolable, yet highly hygroscopic and relatively unstable, yellow crystalline material and noted that for practical purposes it seemed advantageous to prepare this *in situ* by adding trimethylsilyl iodide to quinoline. In contrast to this, Ellman stated specifically that "sublimed **46**" was used to carry out the demethylation, presumably this was in the interests of better yields and/or a cleaner reaction in comparison to the *in situ* conditions reported by Brossi.

Mindful of these considerations, the sensitive **46** was synthesised, isolated and purified *via* sublimation prior to use. This proved highly challenging as the required equipment (dry-box with vacuum and cooling facilities and sublimation apparatus capable of handling more than ~500 mg) were not readily available. Despite these obstacles, the requisite **46** was isolated as the reported yellow crystalline material in modest yield (23%). The low yield can be attributed to the fact that much was sacrificed in the interests of purity (during isolation) and also lost when trying to recover the material from the sublimation apparatus. It was found to be crucial to use freshly distilled quinoline for this reaction, as undistilled or old quinoline contained dark oily contaminants which hampered isolation and purification. Nonetheless, 2.67 g of pure **46** was obtained and with this in hand, the stage was set for the investigation into the final deprotection to give the natural product (**Scheme 60**).



Scheme 60

Due to constraints on the quantity of (20*S*,21*S*)-**166** and (20*R*,21*R*)-**166** at this very late stage in the synthetic sequence, only a limited number of attempts were viable for this final step and, in somewhat of an anticlimax, this reaction delivered a complicated mixture of products. Inspection of the ^{1}H NMR spectrum of this mixture indicated some peaks consistent with the natural product, though also present were many other related compounds possessing varying degrees of methylation. It was decided to pursue this further, so the crude residue was subjected to column chromatography on silica gel, and the most promising fractions from this column were carried through to reverse phase HPLC. Using UV and RI detection, HLPC confirmed the presence of many compounds, even after column chromatography. In spite of the difficulty in separation of this complicated mixture, a small sample, *ca*. 1.2 mg, <10% yield was isolated. The isolated sample appeared to contain approximately equal amounts of compounds tentatively assigned as lithospermic acid (**21**), the diastereomeric partner (20*R*,21*R*)-**21**, and an unidentified by-product. Based on ^{1}H NMR evidence, the unidentified by-product is speculated to be that of cinnamic acids **167** or **168** in **Figure 20**, based on an observed signal at ~δ 5.95 ppm corresponding to the intact methylenedioxy group, and a lack of peaks at ~δ 4.4 and 5.2 ppm, corresponding to C20-H and C21-H. Also lacking was the C10-H signal at ~δ 5.3 ppm.

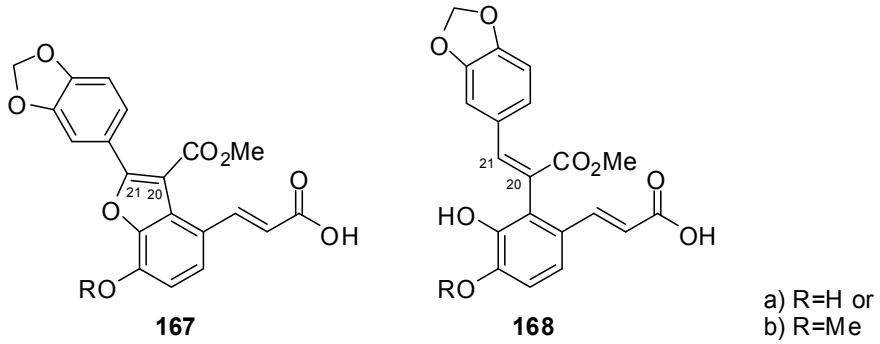


Figure 20

Although attempts to further purify the mixture were unsuccessful, several pieces of data provide evidence that lithospermic acid and its diastereomer are indeed present (*vide infra*).

The UV/Vis spectrum was obtained of the purported **21**, and its diastereomeric counterpart, as it eluted from the HPLC and was recorded with a diode array detector. Comparison of this spectrum (λ_{max}=255, 289, 310 nm) with that of the natural product (λ_{max}=255, 290, 311 nm),[42] shows a clear congruence.

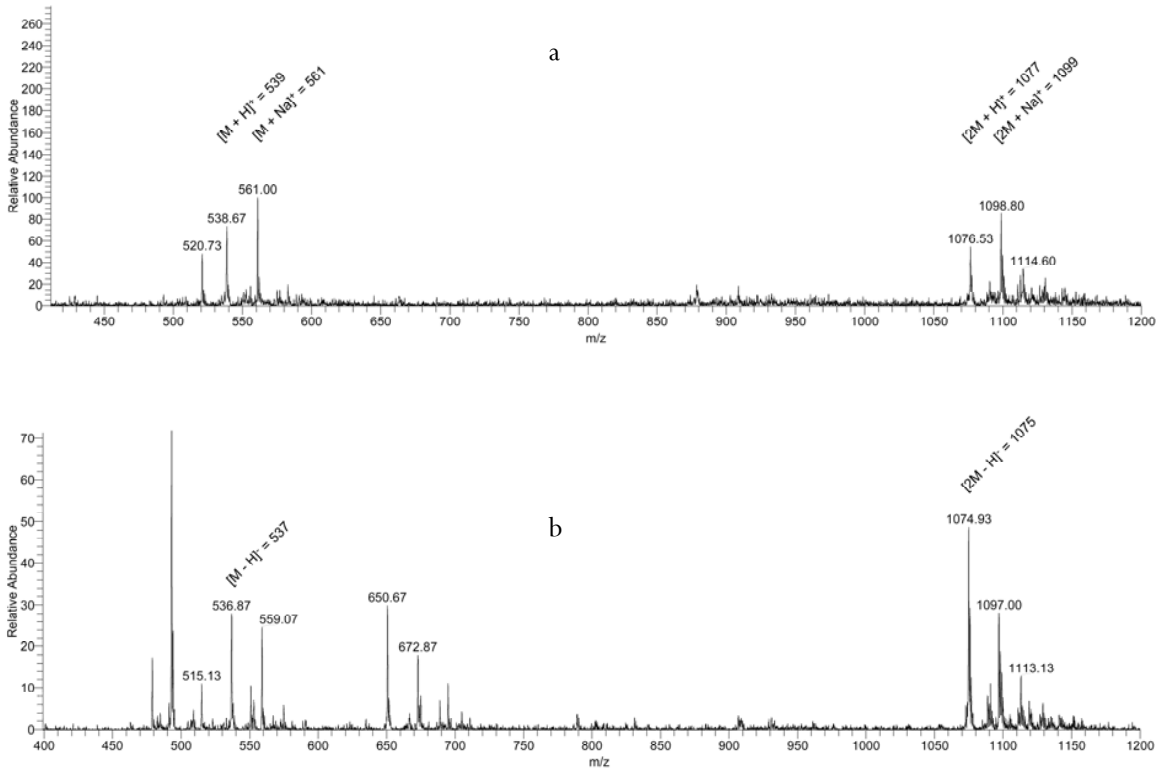


Figure 21

Positive ion electrospray mass spectrometric analysis (**Figure 21a**) shows species clearly corresponding to the protonated **21** (m/z 539), the sodiated **21** (m/z 561), the protonated dimer of **21** (m/z 1077) and the sodiated dimer of **21** (m/z 1099). This is further supported by the data displayed in **Figure 21b**, the negative ESI mass spectrum, where again the deprotonated **21** (m/z 537) and the deprotonated dimer of **21** (m/z 1075) are evident. These peaks can also be attributed to the diastereomeric counterpart, (20*R*,21*R*)-**21**.

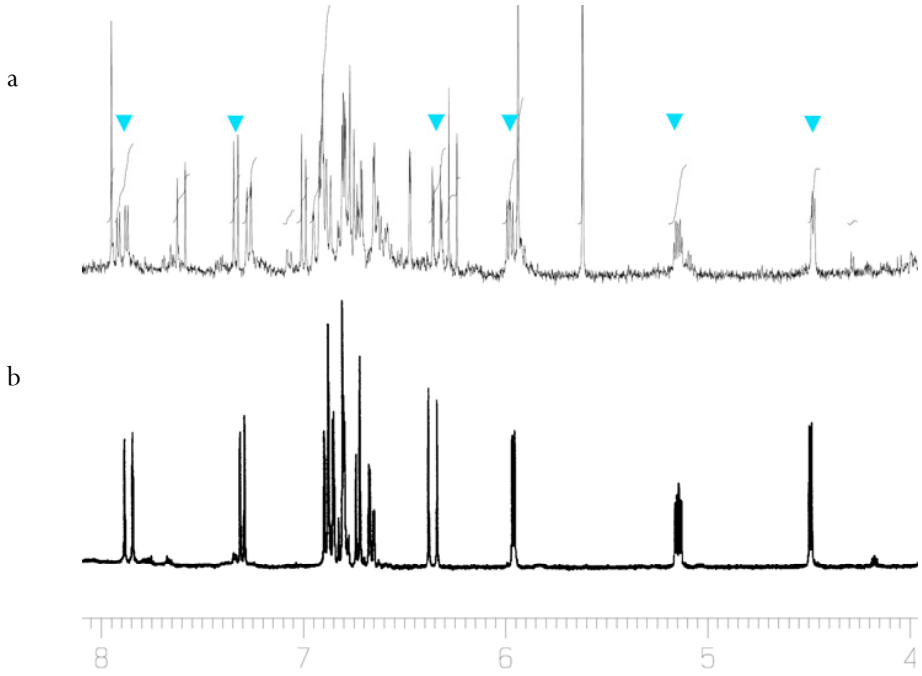
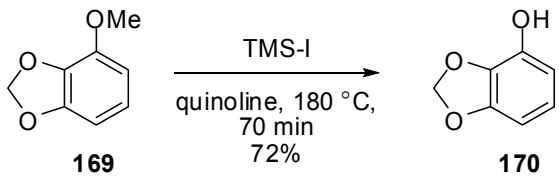


Figure 22

The ^{1}H NMR spectrum of the sample obtained from HPLC purification is shown in **Figure 22a** in comparison with an authentic spectrum of lithospermic acid (**21**) obtained by Ellman (**Figure 22b**).[49] It is apparent that our sample contains peaks that overlap with those reported for lithospermic acid, and these are marked with a blue triangle. Each of these peaks are accompanied by a very similar second peak (most visible in the peak at ~δ 7.9 ppm), corresponding to the diastereomer of lithospermic acid (20*R*,21*R*)-**21**. Unfortunately there were insufficient quantities of this material, preventing the acquisition of a suitable ^{13}C NMR spectrum, which would have further confirmed the presence of lithospermic acid (**21**) in this sample.

We are able to speculate as to why this reaction did not proceed with the same efficiency that Ellman had reported. There are two major differences between our approach and that of Ellman's. The first, and we believe crucial difference between the two systems, is the methylenedioxy protecting group. Upon further consultation of the literature, it was discovered that Brossi had reported earlier that the TMSI/quinoline reagent combination (forming **46** *in situ*) is effective at removing the methyl ether of **169** whilst leaving the methylenedioxy group intact, to give sesamol (**170**) in modest yield (**Scheme 61**),[50] thus indicating the stability of the methylene acetal to these conditions.



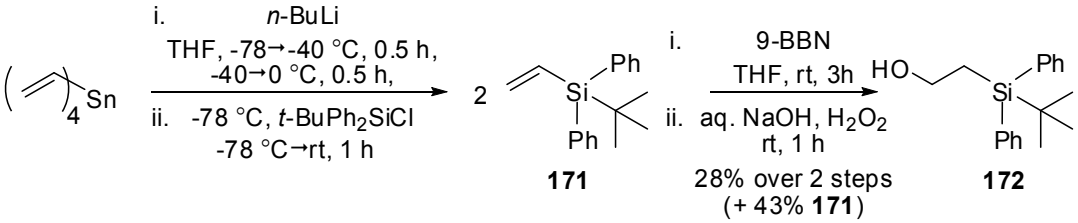
Scheme 61

The second difference is the scale on which this reaction could be conducted. Owing to the small stock of (20*S*,21*S*)-**166**, this reaction could only be performed on small scale (*ca*. 12.6 mg versus 185 mg in the Ellman synthesis). Given that molten **46** formed the solvent for the reaction, this could have a large impact on the experiment. Compounding this problem was the size of the glassware available for use, since the smallest sealed tube available still proved to be much larger than ideal. With limited time and stocks of advanced intermediates, further investigations into this final step were unable to be conducted.

During the course of our synthetic efforts utilising methylene acetal protection of the C24 and C25 hydroxyl groups, Ellman published his synthesis of lithospermic acid. Ellman's synthesis, having utilised a permethylation protecting group strategy, guided our attempts to complete a total synthesis of lithospermic acid as outlined so far in this chapter. However, having met significant problems in the final deprotection, and with literature precedent for the stability of the methylenedioxy group towards the TMSI/quinoline deprotection conditions, efforts were redirected accordingly.

4.5 Initial Investigations into a New Protecting Group Strategy

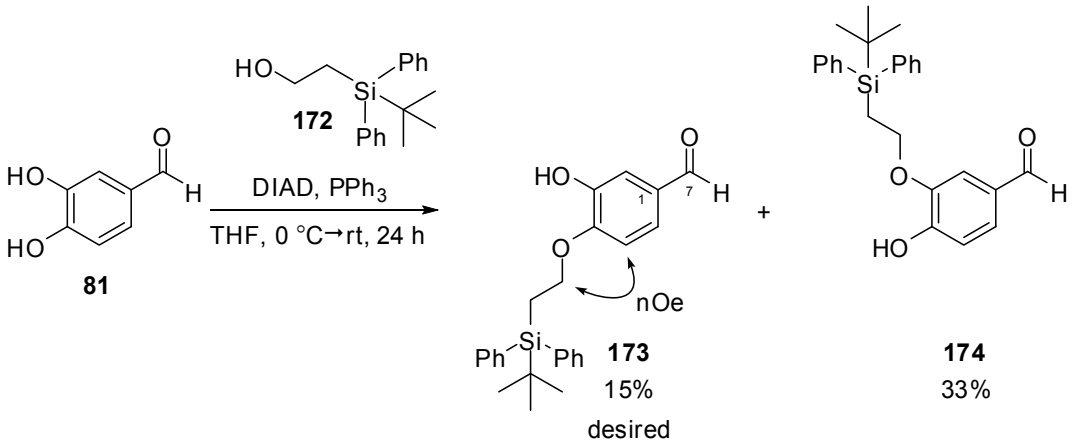
An alternative protecting group strategy that was briefly investigated was based on the *tert*-butyldiphenylsilylethyl (TBDPSE) ether, recently reported by Konopelski and co-workers.[120] It was anticipated that the stability of this group would be greater than that of a silyl ether, whilst still being labile under F^- conditions. This investigation required firstly, the synthesis of *tert*-butyldiphenysilylethyl alcohol **172**, which was achieved utilising Konopelski's conditions (**Scheme 62**).[120]



Scheme 62

Vinyllithium was generated *in situ* by treating tetravinyltin with *n*-butyllithium. This species was subsequently quenched with *tert*-butyldiphenylsilyl chloride to form alkene **171**. Regioselective hydroboration and hydrolysis of alkene **171** afforded the requisite alcohol **172** (28%), along with unreacted **171** (43%). Despite the modest, unoptimised yields, sufficient quantities of **172** were generated for use in the subsequent investigations.

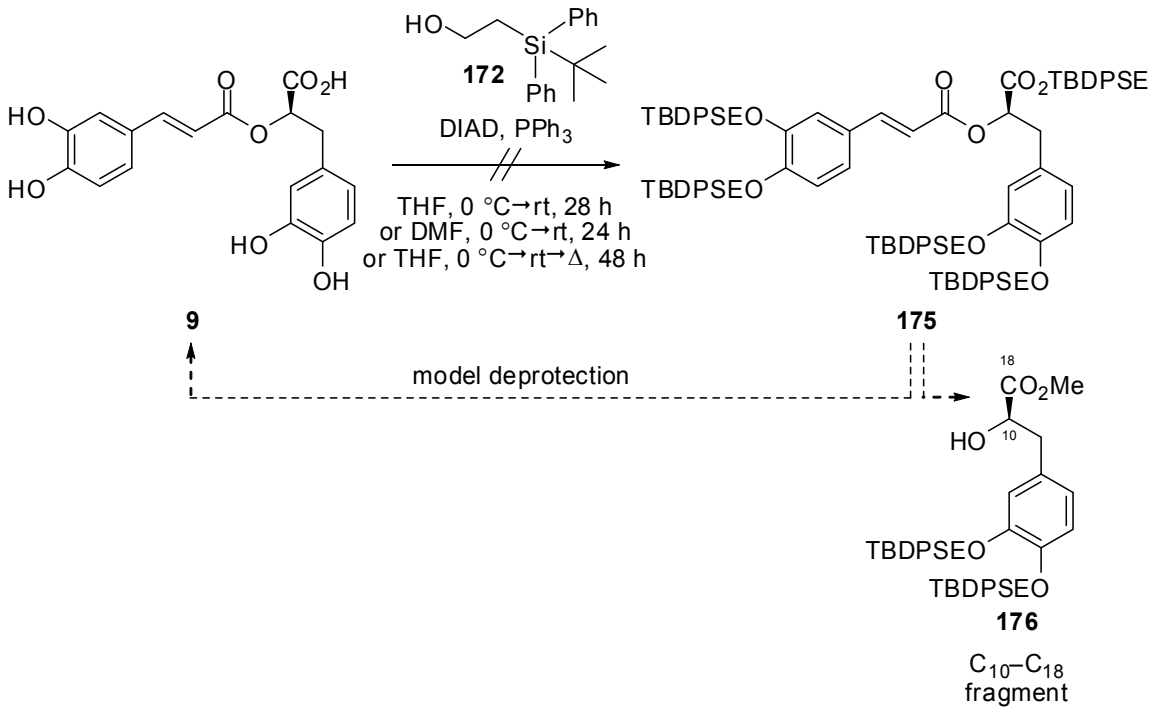
The first investigation conducted was the regioselective protection of 3,4-dihydroxybenzaldehyde (**81**) in an effort to form the C_1–C_7 fragment of lithospermic acid. The mono-protected **173** would form the starting material analogous to isovanillin (**41**) used in the previous cases.



Scheme 63

By treating 3,4-dihydroxybenzaldehyde (**81**) with 1.0 equivalent of **172** under Mitsunobu conditions, both **173** and **174** were isolated, and were distinguished by their nuclear Overhauser effect. It was anticipated that **173** would be the dominant product, owing to the increased acidity of the 4-hydroxy group (*para*- to the aldehyde). Unfortunately this was not the case and the undesired **174** was isolated as the dominant product. This could perhaps be controlled by performing the reaction under more basic conditions, however, time did not permit further exploration.

The second investigation of this protecting group entailed the protection of rosmarinic acid (**9**) to generate **175** (**Scheme 64**). It was envisaged that this protected compound **175** could serve as a model system for a final global deprotection of lithospermic acid. Further to this, the protected C_{10}–C_{18} fragment of lithospermic acid could also likely be synthesised.



Scheme 64

Despite evidence by ESI mass spectrometry (m/z $[M+H]^+$ = 1691) that the product **175** was present, purification proved problematic and **175** could not be isolated cleanly or in a substantial yield. Complete optimisation studies were not undertaken, and it is recognised that within this approach, there were still some problems still to be addressed, however, with the precedent of the Ellman synthesis in hand at this stage, we decided to target heptamethyl lithospermate (**37**).

4.6 Summary

In summary, the EDC/DMAP promoted coupling of *trans*-**150** with (*R*)-**39** was successful, providing the fully functionalised framework of lithospermic acid (**21**) and its (20*R*,21*R*)-diastereomer. The mixture of diastereomeric bis-methyl esters was converted to the corresponding diacids (20S*R*,21*S*)-**166** and (20*R*,21*R*)-**166** with trimethyltin hydroxide under mild conditions. Attempts to globally deprotect this mixture with 1-trimethylsilylquinolinium iodide (**46**) provided a complex mixture of products. Evidence has been provided that lithospermic acid (**21**) and its (20*R*,21*R*)-diastereomer were present in this complex mixture. Additionally, an initial investigation was undertaken to circumvent these global deprotection issues by implementing the TBDPSE protecting group, with limited success.

–Chapter 5–

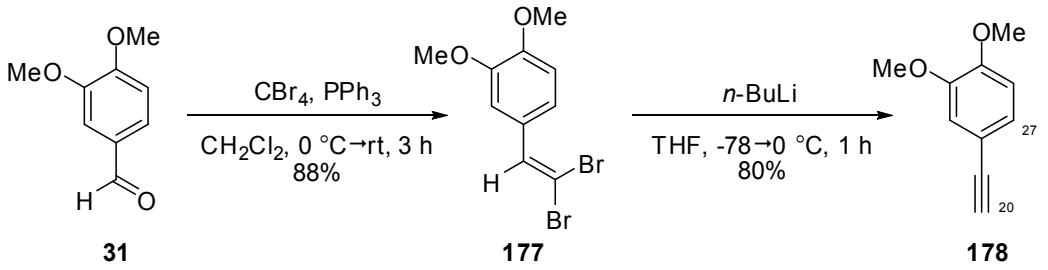
A Formal Total Synthesis of (+)-Lithospermic Acid

5.1 Introductory Remarks

A number of contributing factors led to the abandonment of the methylene acetal as a suitable protecting group for the C24 and C25 hydroxyl groups. Firstly, dwindling stocks of advanced intermediates in the methylene acetal series meant that more time would need to be invested to replenish them. Secondly, and most influentially, there was no guarantee that the methylene acetal could be removed using the exotic reagent **46**. As a result, it was considered prudent to pursue the same protecting group that had been used in the Ellman synthesis of lithospermic acid (**21**): the bis-methyl ether.[49] It was anticipated that the methodology developed thus far for the methylene acetal protected system should be transferable to the bis-methyl ether case due to comparable stability and electronics. Additionally, interception of an advanced intermediate of the Ellman synthesis would enable us to establish a formal total synthesis of lithospermic acid (**21**).

5.2 Synthesis of C_{20}–C_{27} ArylAlkyne

The first step of this approach required the construction of the suitably protected arylalkyne **178** (**Scheme 65**).



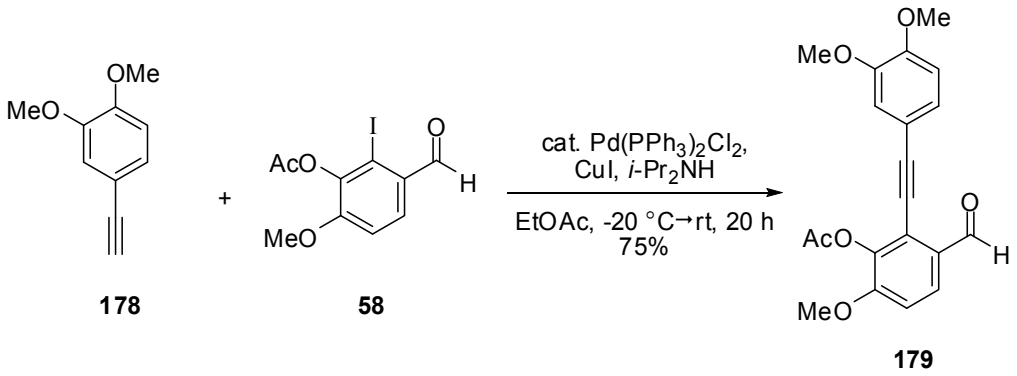
31 **177** **178**

Scheme 65

The starting material, methylvanillin (**31**), is cheap, readily available and incorporates the methyl protecting groups thus minimising the number of synthetic operations. Following literature procedures,[121, 122] aldehyde **31** was converted to the corresponding alkyne **178** in a two step process, using Corey–Fuchs chemistry.[83] The first step involved dibromoolefination of methylvanillin (**31**) to give **177** (88%). The next step involved a butyl lithium-mediated conversion of **177** to the corresponding alkyne **178**, as discussed in **Scheme 18**, which also proceeded in high yield (80%). This synthetic sequence was performed once to generate multi-gram quantities (*ca.* 3 g) of the requisite arylalkyne **178**.

5.3 Sonogashira Coupling

With the suitably functionalised arylalkyne **178** in hand, we were set to investigate the Sonogashira reaction with coupling partner **58**, analogous to the methylenedioxy series (**Section 3.1.2**). This reaction is depicted diagrammatically in **Scheme 66**.



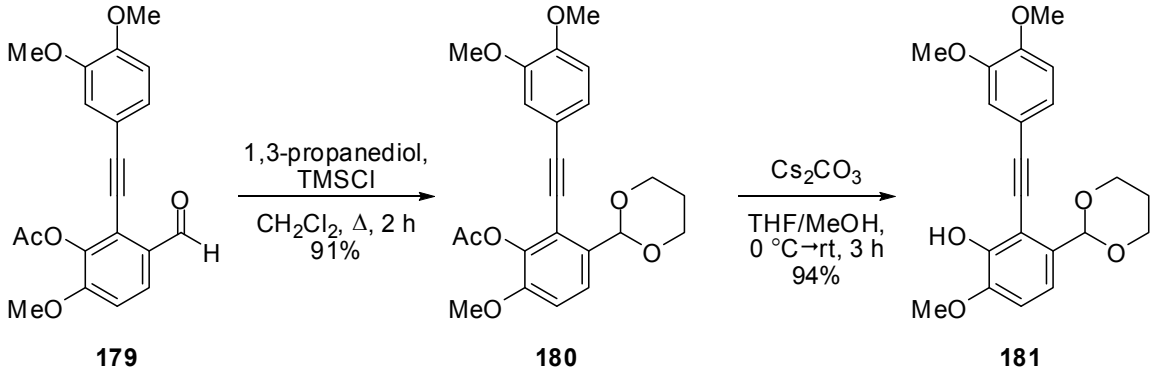
Scheme 66

Surprisingly, this reaction did not ensue as well as the previous methylenedioxy series. Although this step still proceeded in high yield, with 75% of the desired diarylalkyne **179** being isolated, a substantial quantity (*ca.* 56% of the mass of product[†]) of a by-product was also isolated. It is interesting to note that the analogous by-product was not observed for the methylenedioxy series, prompting further investigation into the nature of this side reaction. By lowering the catalyst loading, an increased amount of this by-product was formed in preference to the desired **179**. In an attempt to ascertain the structure of this by-product, extensive characterisation data was collected and it was subjected to an array of reagents in an attempt to affect decomposition, however, the structure could not be determined. The only conclusion that can be drawn is that the by-product must be closely related to **179**, having presented very similar spectral data. Despite the formation of this unidentified by-product, the desired product **179** was nonetheless obtained in good yield and therefore no further effort was expended to avoid the formation of this by-product.

5.4 Aldehyde Protection and Deacetylation

Previous experience had demonstrated that protection of the aldehyde group prior to further manipulations would be beneficial, and hence, protection of the aldehyde followed by deacetylation was undertaken as shown in **Scheme 67**.

[†] The quantity of by-product obtained indicates a molecular mass greater than that of the expected product.



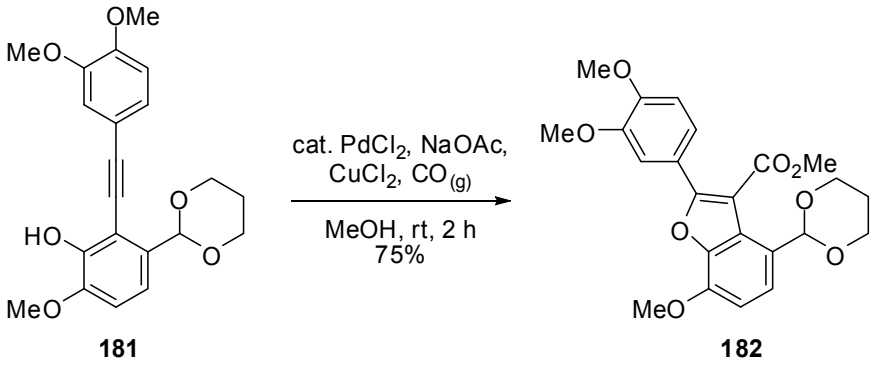
179 **180** **181**

Scheme 67

Subjecting **179** to the conditions used previously for acetal formation (**Section 3.3.2**), proved to be simple, efficient, and high yielding, with the desired six-membered cyclic acetal **180** being isolated in 91% yield without the need for optimisation. The deacetylation of **180** followed, delivering *ortho*-hydroxydiarylalkyne **181** in 94% yield. The mass balance contained small quantities (4%) of the protio-cyclised by-product (analogous to **72**), which could be removed by column chromatography.

5.5 The Carbonylative Annulation Reaction

With **181** in hand, we were ready to investigate the carbonylative annulation reaction once more, shown in **Scheme 68**.



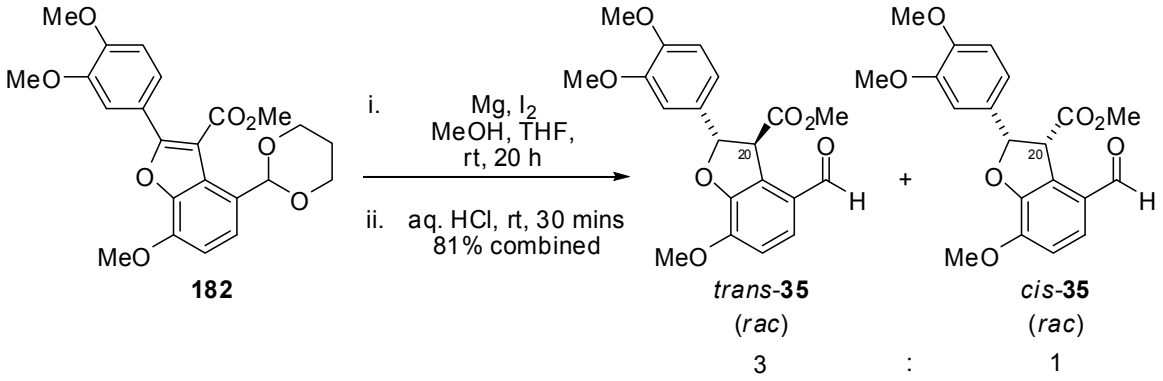
181 **182**

Scheme 68

Subjecting *ortho*-hydroxydiarylalkyne **181** to the conditions used previously, the desired benzofuran **182** was isolated in a respectable 75% yield. This was a gratifying result as it proved that the methodology developed thus far for forming benzofurans is completely transferable to this new protecting group strategy.

5.6 Reduction to give the 2,3-Dihydrobenzofuran

Drawing on previous experience (**Section 3.4**), benzofuran **182** was subjected to a one pot reduction and acetal hydrolysis protocol (**Scheme 69**).



Scheme 69

The magnesium–methanol reduction proved a little capricious, with the magnesium, on occasion, failing to initiate. The exact reason behind this anomaly could not be ascertained, although it did appear that the quality of the magnesium surface may have been responsible. Nonetheless, the desired 2,3-dihydrobenzofuran was delivered as a *ca*. 3:1 diastereomeric mixture of *trans*-**35** and *cis*-**35** respectively, which were separable by column chromatography. The ratio of *trans*-**35** to *cis*-**35** tended to fluctuate for this reaction, prompting a brief investigation into the epimerisation of *cis*-**35** to *trans*-**35**. **Figure 23** below shows a time course NMR study, in which a 1:1.75 mixture of *cis*-**35** and *trans*-**35**, respectively, in deuterochloroform was treated with DBU. The doublets at δ 4.91 and δ 4.71 correspond to the C20-H of *cis*-**35** and *trans*-**35**, respectively.

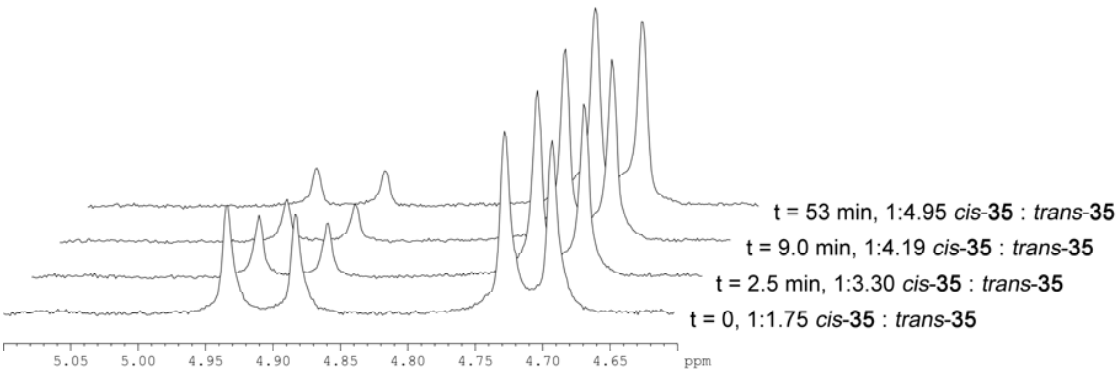
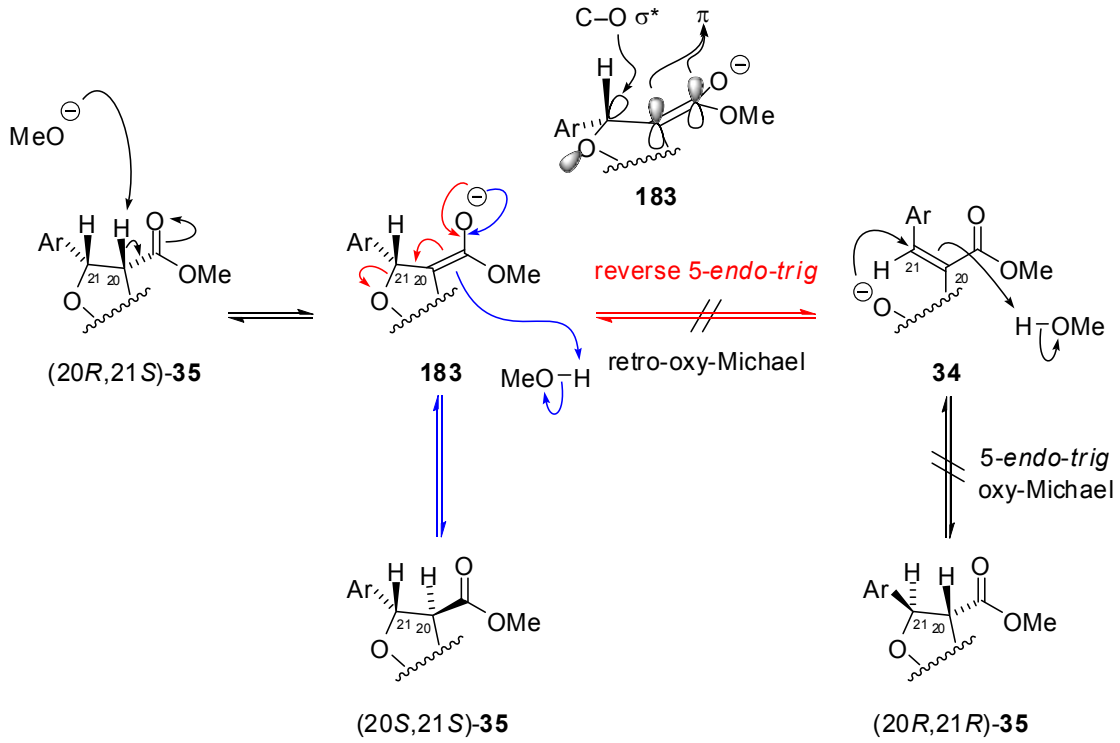


Figure 23

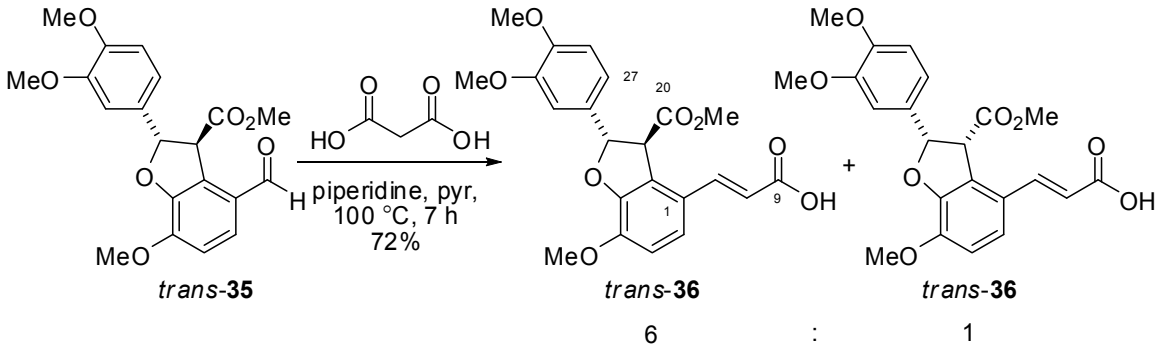
This clearly shows that simple base-promoted epimerisation is taking place to afford the more thermodynamically stable *trans*-dihydrobenzofuran (*trans*-**35**). It is believed that during the course of the magnesium–methanol reduction, both *cis*- and *trans*- diastereomers are formed, then magnesium hydroxide, generated *in situ*, is responsible for the base-promoted epimerisation to predominantly the *trans*-diatereomer. The variation in ratios observed for the reduction step is rationalised on the basis of differing concentrations of magnesium methoxide present. It is likely that this would vary according to the differing initiation periods of the magnesium and amount of iodine added. It is also worth noting at this point that the epimerisation is occurring at the C20 position *via* a deprotonation/reprotonation sequence (**Scheme 70**) at the position α- to the ester carbonyl. Upon first inspection, there is the potential for a retro-oxy-Michael/oxy-Michael racemisation pathway, however, the lack of racemisation in the Ellman synthesis (**Scheme 4**, **Section 1.3.3**), shows that this racemisation mechanism is not favourable. This is not surprising, given that the ring opening is the reverse of a disfavoured 5-*endo-trig* reaction, according to Baldwin's rules. This would suffer from unfavourable orbital overlap between the enolate π and the C–O σ* orbitals, which are positioned orthogonal to each other.



Scheme 70

The Knövenagel condensation of *trans*-**35** with malonic acid (**Scheme 71**) proceeded well to give a *ca.* 6:1 mixture of *trans*-**36** and *cis*-**36** diastereomers, in a combined yield of 72% (without optimisation). These diastereomers were separable by column chromatography, however, the concomitant base catalysed epimerisation that occurred during this step rendered the separation of the *trans*-**35** and *cis*-**35**

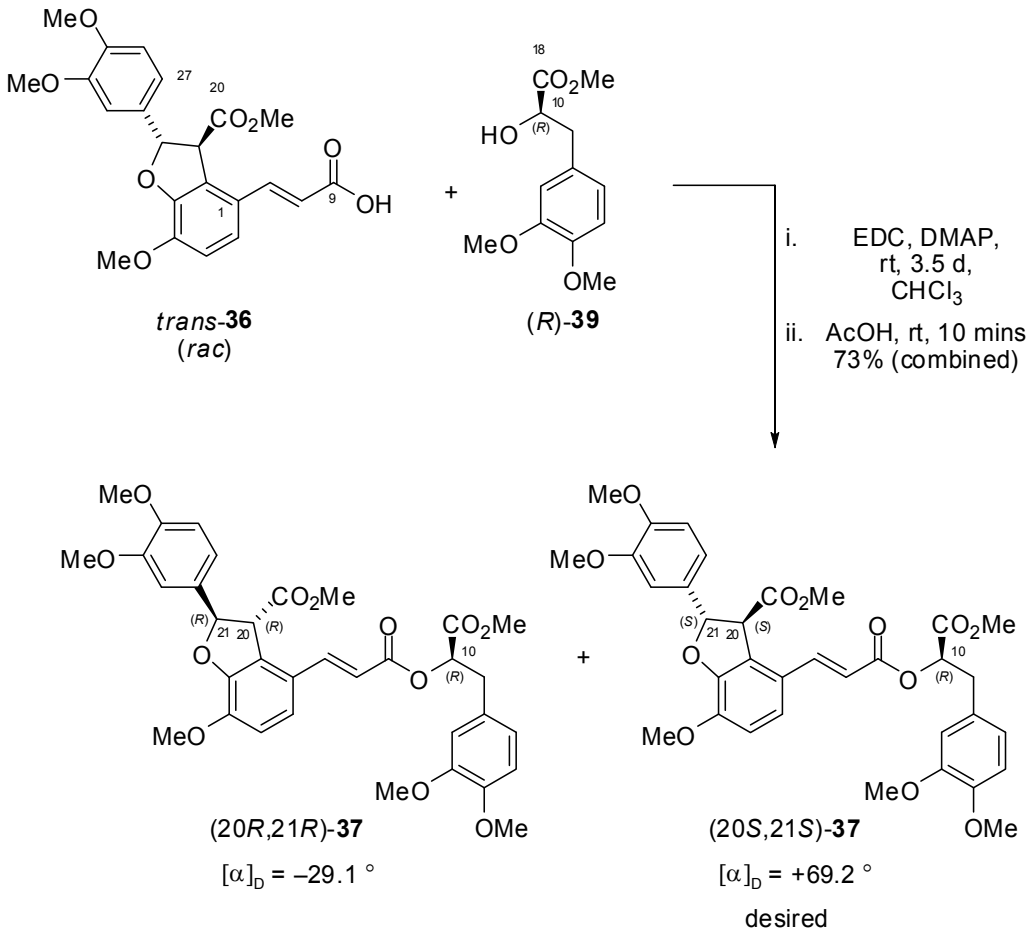
starting material redundant. Whilst there is scope to optimise the ratio of *trans*-**36** and *cis*-**36** *via* epimerisation, no such study was undertaken due to time constraints.



Scheme 71

5.7 Completion of a Formal Total Synthesis of (+)-Lithospermic Acid

With the C_1–C_9/C_{19}–C_{27} fragment of lithospermic acid *trans*-**36** in hand, albeit in racemic form, it was now possible to couple this with the chiral, enantiomerically pure, C_{10}–C_{18} fragment (*R*)-**39**. This would give rise to two diastereomers, (20*S*,21*S*)-**37** and (20*R*,21*R*)-**37,** that should, in principle, be separable by conventional chromatography. It was acknowledged from the outset that the large distance and flexible chain between the C20/C21 and C10 stereocentres could make the separation particularly challenging. With this in mind, we set about uniting these two fragments as shown in **Scheme 72**.



Scheme 72

Utilising the same protocol as in the methylendioxy series (**Section 4.2**) *trans*-**36** was coupled to (*R*)-**39** to afford a mixture of the two expected diastereomers (20*S*,21*S*)-**37** and (20*R*,21*R*)-**37** in a combined yield of 73% (unoptimised). These two diastereomers appeared as a single spot by tlc in multiple solvent systems, so it was deemed necessary to proceed to HPLC in an effort to separate them. Initial investigations into HPLC conditions, utilising an analytical Jones Zorbax silica HPLC column, determined that the maximum separation could be achieved using an *i*-PrOH/hexanes solvent system. Solubility issues rendered this ineffective on preparative scale and the addition of CH_2Cl_2 was necessary. Unfortunately, unexplained decomposition of the mixture resulted when conducted on preparative scale. This prompted the investigation into alternate columns. A reverse phase C18 column, eluting with a MeCN/H_2O solvent system proved ineffective, so a diol column was subsequently sought. The diol column proved effective for the resolution of the diastereomeric pair using a gradient elution of *i*-PrOH/hexanes as the solvent system. Importantly, a higher proportion of *i*-PrOH was used which meant that solubility, although still an issue, was better than the case with the silica column. Preparative scale separation was conducted with small quantities of material so as to avoid complications associated with insolubility. Ultimately, separation of the diastereomeric pair was achieved to give two distinct compounds, temporarily assigned as isolate 1 and isolate 2. Both diastereomers proved to have ^{13}C NMR

shifts almost identical to the synthetic heptamethyl lithospermate ((20*S*,21*S*)-**37**) reported by Ellman and co-workers.[49] Owing to this, further analysis was required to distinguish which of the two isolates corresponded to the desired (20*S*,21*S*)-**37** diastereomer. **Figure 24** shows the difference in recorded chemical shifts (Δδ), compared to the reported synthetic compound (20*S*,21*S*)-**37**. The fact that both isolates display some difference to that reported by Ellman is attributed to the sizeable difference in concentration that these spectra were recorded at, relative to Ellman's.

Comparison of the Difference in Recorded ^{13}C NMR Shifts

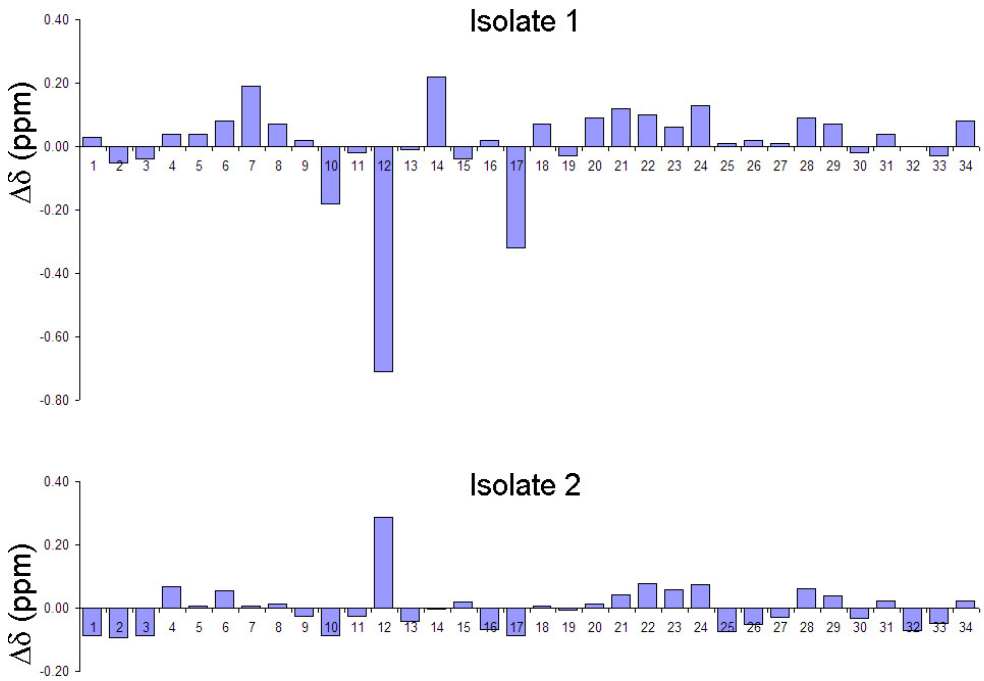


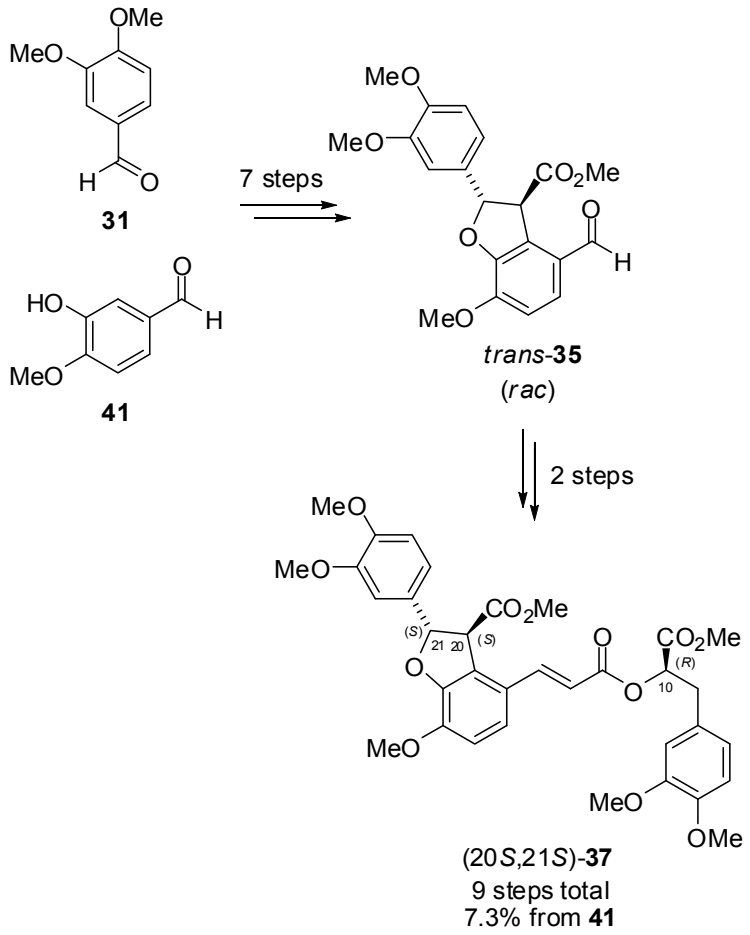
Figure 24

When comparing the two graphs, isolate 2 is clearly a better fit than isolate 1. This is confirmed when comparing the standard deviation of the two sets of data. The standard deviation in Δδ of isolate 1 (0.158) is significantly greater than that of isolate 2 (0.074) confirming this visual observation. This claim is further supported by the observed optical rotations of the two isolates. A value of $[\alpha]_D$ (*c* 0.10, CH_2Cl_2) –29.1 ° was obtained for isolate 1, whilst $[\alpha]_D$ (*c* 0.12, CH_2Cl_2) +69.2 ° was recorded for isolate 2. The positive value was reassuring, however, the magnitude is not as great as that reported by Ellman ($[\alpha]_D$ (*c* 0.49, CH_2Cl_2) +134.5 °). This disparity can be attributed to the small quantities obtained of isolate 2, (*ca.* <2 mg) that impeded an accurate measurement of optical rotation. Additionally, contamination with non-volatile impurities from the HPLC grade solvent (greases etc.) would also have a significant impact. High resolution electrospray mass spectrometric analysis revealed a peak at m/z 659.2099, corresponding to the sodiated compound $C_{34}H_{36}O_{12}Na$, for which the theoretical value is m/z 659.2119. All other spectroscopic data recorded were identical with that reported by

Ellman.[49] On this basis, isolate 2 was assigned as the desired (20*S*,21*S*)-**37** diastereomer, heptamethyl lithospermate, thereby constituting a successful formal total synthesis of lithospermic acid (**21**).

5.8 Summary

In conclusion, a formal total synthesis of lithospermic acid (**21**) has been achieved. Interception of the advanced intermediate (20*S*,21*S*)-**37** from the Ellman total synthesis was achieved in just 9 steps from commercially available isovanillin (**41**) as the longest linear sequence and in 7.3% overall yield. The overall yield suffered from a loss of 50% of the material as the unwanted diastereomeric partner (20*R*,21*R*)-**37**.



Scheme 73

Methylvanillin (**31**) was converted to the requisite arylalkyne (**178**) using Corey–Fuchs chemistry and this was then coupled to the aryliodide **58** derived from isovanillin (**41**) *via* a Sonogashira coupling. Protecting group manipulations followed by the carbonylative annulation reaction furnished the substituted benzofuran core, which was subsequently reduced to give racemic dihydrobenzofuran *trans*-**35**. Knövenagel condensation with malonic acid, followed by esterification with enantiomerically pure

(*R*)-**39** gave a pair of diastereomers. A challenging separation by HPLC afforded the desired (20*S*,21*S*)-**37**, a protected form of lithospermic acid (**21**). The spectroscopic data obtained for (20*S*,21*S*)-**37** was congruent with that previously reported, thus constituting a formal total synthesis of lithospermic acid (**21**). This confirms that the developed synthetic route can be successfully employed in the synthesis of lithospermic acid (**21**) in a flexible, convergent and modular fashion.

–Chapter 6–

Synthetic Studies Towards an Enantioenriched C_1–C_9 / C_{19}–C_{27} Fragment of Lithospermic Acid

6.1 Introductory remarks

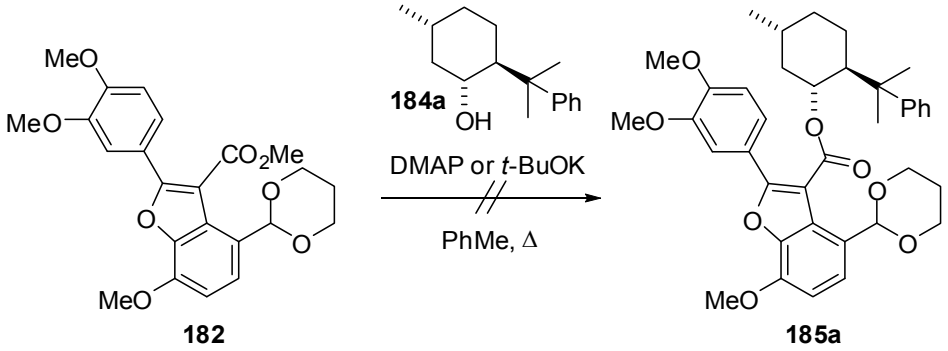
A conceivably attractive approach to the total synthesis of (+)-lithospermic acid (**21**) would be the construction of an enantiomerically pure, or enriched, C_1–C_9/C_{19}–C_{27} fragment. To this end, we have investigated three alternative strategies for achieving this enantiomeric enrichment: (i) chiral auxiliaries, (ii) resolution of the racemate, and (iii) catalytic enantioselective reduction. The exploration of these three strategies will form the basis for this chapter.

6.2 Chiral Auxiliary

Firstly, it was anticipated that the installation of a chiral auxiliary on benzofuran **182** may influence the reduction step, potentially allowing diastereoselective reduction of the benzofuran, and thus providing access to enantiomerically enriched 2,3-dihydrobenzofurans. If, however, there was no effect on the selectivity of the reduction and a 1:1 mixture were to result, it was anticipated that these diastereomers should be separable by chromatographic techniques.

6.2.1 Transesterification

It was decided that the best way to introduce a chiral auxiliary into the system at this point in the synthesis would be *via* transesterification of benzofuran methyl ester **182** with a suitable chiral alcohol. It was anticipated that introduction of a chiral ester at the C19 carbonyl group would have the maximum possible stereodirecting influence on the reduction step. (–)-8-Phenylmenthol (**184a**) was chosen as a suitable alcohol due to availability and literature precedence as a chiral auxiliary in several applications.[123-127] Our initial approach involved the more conventional and popular base catalysed transesterification conditions, however, transesterification did not take place under either DMAP or potassium *tert*-butoxide catalysed conditions (**Scheme 74**).

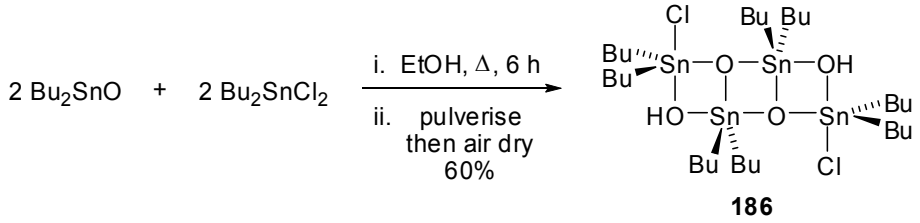


Scheme 74

Due to the inadequacy of these conditions, we investigated an alternate route for this transesterification. Owing to the positive results of Trost and co-workers[128] and an encouraging review,[129] Otera's catalyst was investigated as a mild alternative for accomplishing this transformation.

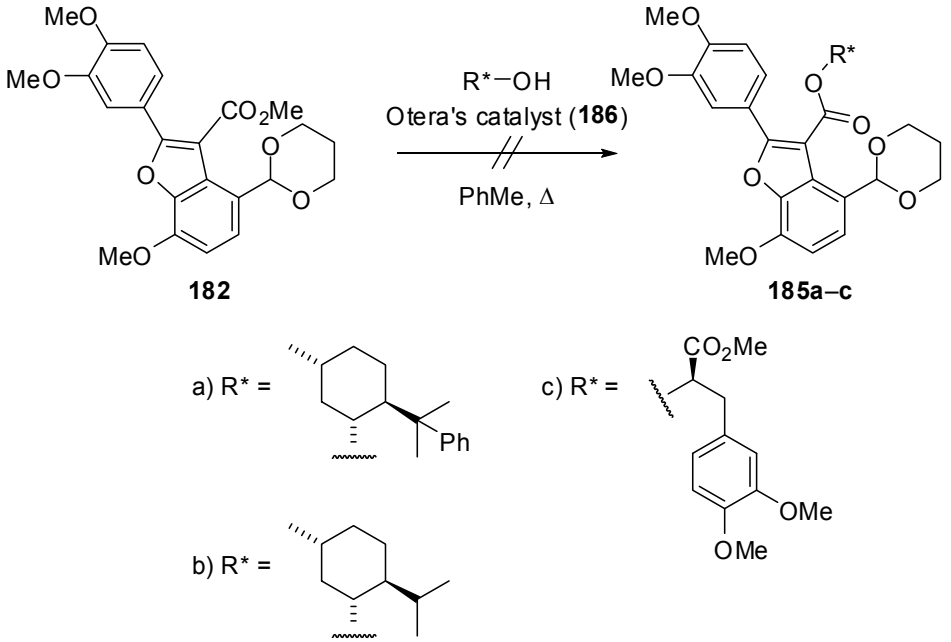
Originally reported by Okawara *et al.*,[130] distannoxane compounds such as **186** were further investigated by Otera *et al.*[131,132] This resulted in the birth of a series of compounds which have become known as Otera's catalysts, typified by **186**. A crucial aspect of these catalysts, are the two types of tin atoms in close proximity. These not only activate (*via* a Lewis acid interaction) the two reacting functional groups, but also bring them into close proximity.

Otera's catalyst is not commercially available but the air stable crystalline solid was readily accessed in a single step from commercially available dibutyltin oxide and dibutyltin dichloride as depicted in **Scheme 75**.[132]



Scheme 75

In the first part of this reaction, a mixture of the desired hydroxydistannoxane and ethoxydistannoxane were formed. Exposure to air, after pulverisation to maximise the surface area, converted the partially formed ethoxydistannoxane to the desired hydroxydistannoxane **186**. Otera's catalyst (**186**) was isolated in a modest yield of 60% on a *ca.* 6 g scale. The identity of this compound was verified by comparison of the observed melting point, 111–113 °C, with the literature values of 107–115 °C[132] and 109–121 °C.[130] With Otera's catalyst (**186**) in hand, the transesterification reaction depicted in **Scheme 76** could be investigated.



Scheme 76

Our initial investigation utilised the aforementioned (–)-8-phenylmenthol (**184a**), with Otera's catalyst (**186**) under the prescribed conditions in an attempt to access **185a** from benzofuran **182**. Unfortunately these conditions did not deliver the desired product, even after 48 hours at reflux compared to the prescribed 24 hours. Instead, the starting material **182** was recovered in ~75% yield. Suspecting that alcohol **184a** was too sterically encumbered, the slightly less sterically demanding (–)-menthol (**184b**) was trialed. This too resulted in none of the desired ester **185b** and only the starting material was recovered after 80 hours at reflux. An alternate strategy employed the alcohol (*R*)-**39**, the protected C_{10}–C_{18} fragment of lithospermic acid made in **Section 4.1**. This choice of chiral alcohol was a potentially interesting example, since the product **185c** embodies a protected form of lithospermic acid B (**24**). Unfortunately, only the starting material **182** was recovered from this reaction, with no sign of product formation.

A rationale for the failure of this approach is presented in **Figure 25**. Whilst Otera's catalyst is known to be tolerant of sterically demanding alcohols, sterically demanding esters are less well tolerated, and this is attributed to the order of events during the mechanism.

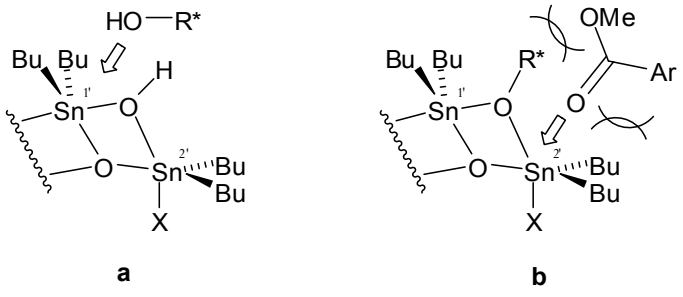
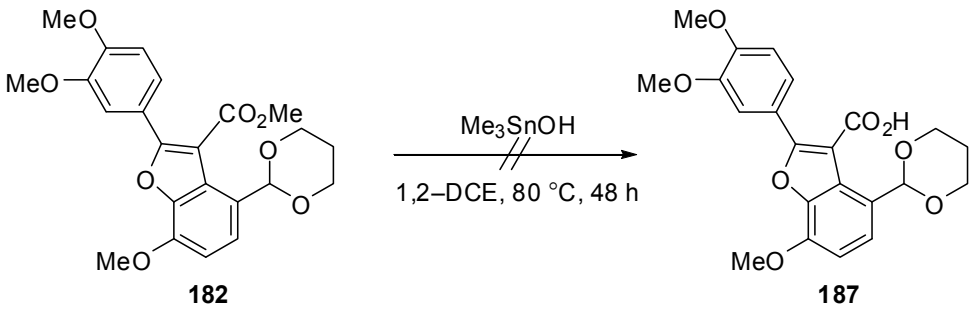


Figure 25

Early on in the mechanism, the alcohol approaches the distannoxane template (**Figure 25a**) and there is little steric resistance for this event. With the bulky alcohol in place at the catalytic site, approach of the ester to the second tin centre is impeded (**Figure 25b**) and Lewis acid activation is therefore not effective. This lack of reactivity is exacerbated by the fact that the ester carbonyl group is held remote from the alcohol, further preventing the reaction from occurring. The methyl ester **182** has thus far proven to be remarkably stable, surviving an array of conditions for transesterification, and hence a different approach was sought to carry out the desired transformation.

6.2.2 Two Step Conversion to the Chiral Ester

An alternate approach to install a chiral ester was to proceed *via* a two step protocol involving ester cleavage followed by esterification of the resultant acid with a chiral alcohol. The first step of this sequence, ester saponification, was initially investigated with trimethyltin hydroxide (**Scheme 77**), as it had previously proven successful on the related ester **165** (**Section 4.3**), differing most notably by the saturation of the furan ring.



Scheme 77

Despite the previous success of this reagent, when **182** was exposed to the same conditions, ester cleavage did not prevail. Addition of an extra 2 equivalents of trimethyltin hydroxide (4 equivalents total) and heating at reflux for 21 hours (48 hours total) did not facilitate the reaction and only starting material was recovered (91%). The lack of reactivity of this ester carbonyl is striking and the most likely rationale for this observation would be the extra stability conferred by conjugation with the aromatic ring system, and in particular, the benzofuran ring oxygen.

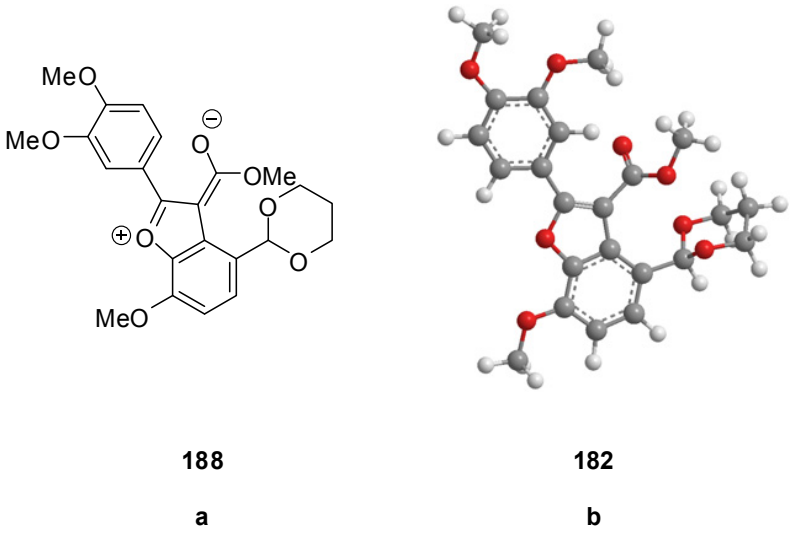
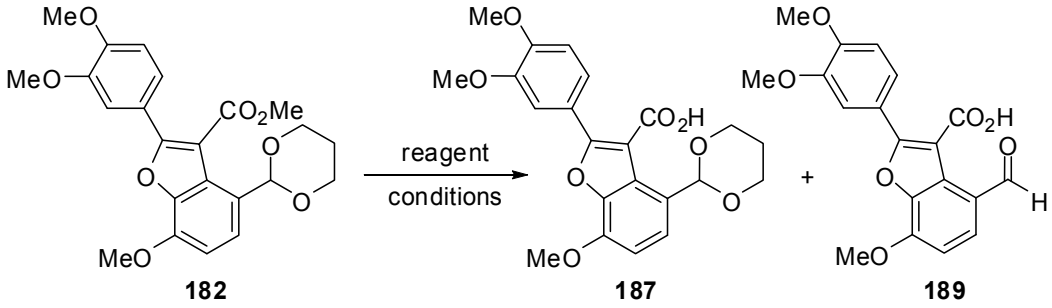


Figure 26

Structure **188** in **Figure 26a** indicates a potential resonance contributor that would account for the observed stability towards de-esterification. Due to the conjugation with the benzofuran ring, and in particular, the furan oxygen, the electrophilicity of the carbonyl carbon would be decreased, giving rise to the observed increased stability of the ester. Compounding this lack of reactivity would be the additional steric hindrance afforded by the presence of the acetal. **Figure 26b** shows the energy minimised structure of **182**, illustrating that the C19 carbonyl is sheltered quite effectively by the neighbouring acetal and aromatic ring.



Scheme 78

Owing to the stability of the methyl ester moiety of **182**, more forcing conditions were investigated for the saponification, as shown in **Scheme 78**, and the results of this investigation are summarised in **Table 7** below.

Table 7

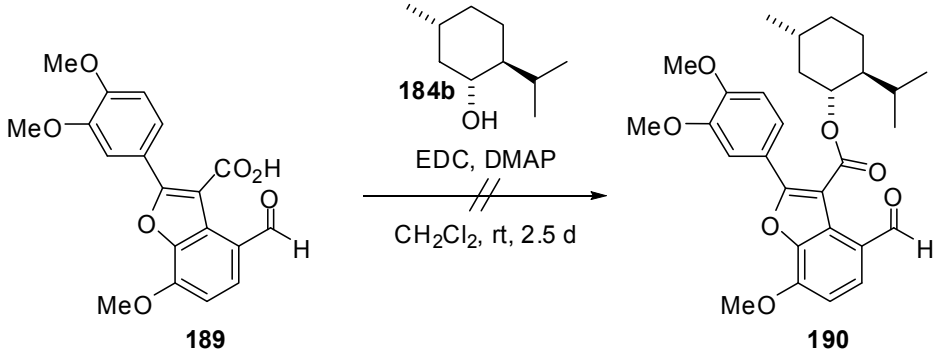
Entry	Reagent	Conditions	Product	
			187	**189**
1	LiOH (2.0 equiv.)	rt, 1 d.	–	–
2	LiOH (2.0 equiv.)	100 °C, 2 d.[†]	46%	–
3	NaOH (4→25 equiv.)	rt→100 °C, 2.5 d.	16%	–
4	LiOH (10.0 equiv.)	))), 80 °C, 2 d.[‡]	–	–
5	LiOH (10.0 equiv.)	110 °C, 13 h.[◊]	37%	–
6	LiOH (10.0 equiv.)	110 °C, 3 d.	~78%	~7%[§]
7	LiOH (10.0 equiv.)	110 °C, 2 d.[¤]	–	90%

[†] 42% starting material **182** recovered.
[‡] ~70% starting material **182** recovered.
[◊] 46% starting material **182** recovered.
[§] Mixture obtained, yields correspond to those estimated by integrals from the ^{1}H NMR spectra of the mixture.
[¤] Worked up with addition of aqueous HCl.

Exposure of **182** to a solution of lithium hydroxide in THF/H_2O at room temperature (**Entry 1**, **Table 7**) had no effect on the ester, and the starting material **182** was recovered. Upon heating to 100 °C (**Entry 2**), conversion to the desired acid **187** was observed (46%), however, starting material **182** still persisted (42%). Sodium hydroxide driven saponification (**Entry 3**) displayed minimal conversion after 20 hours at room temperature and more forcing conditions (heating to 100 °C and adding more sodium hydroxide) resulted in a poor yield of **187** (16%). The low yield was attributed to decomposition, as evidenced by the dominant species in the tlc being baseline material. The original approach was then revisited using greater quantities of lithium hydroxide (**Entry 4**). Solubility of the lithium hydroxide became an issue and as such, sonication and heating were briefly employed in an attempt to rectify the situation with only limited success. The reaction was aborted and starting material **187** was recovered (~70%). To attain higher temperatures, a sealed tube was employed (**Entries 5–7**) which abated the solubility issues and initial investigations (**Entry 5**) found the conversion to **187** to be rapid, as after 13 hours, a similar conversion to that observed in **Entry 2** was obtained. Extended reaction times (**Entry 6**) effected complete saponification, however, upon standing, conversion of **187** to **189** was noted. This is likely due to the fact that the molecule contains both the acid sensitive acetal and an acidic functional group. In light of this, the aldehyde **189** was targeted to circumvent purification problems. By implementing an aqueous acid work-up (**Entry 7**), the desired product **189** was isolated in a gratifying 90% yield.

With acid **189** in hand, the focus shifted towards the esterification of this acid with a chiral alcohol. The initial strategy centered on (–)-menthol (**184b**) as the chiral alcohol since it would be less sterically

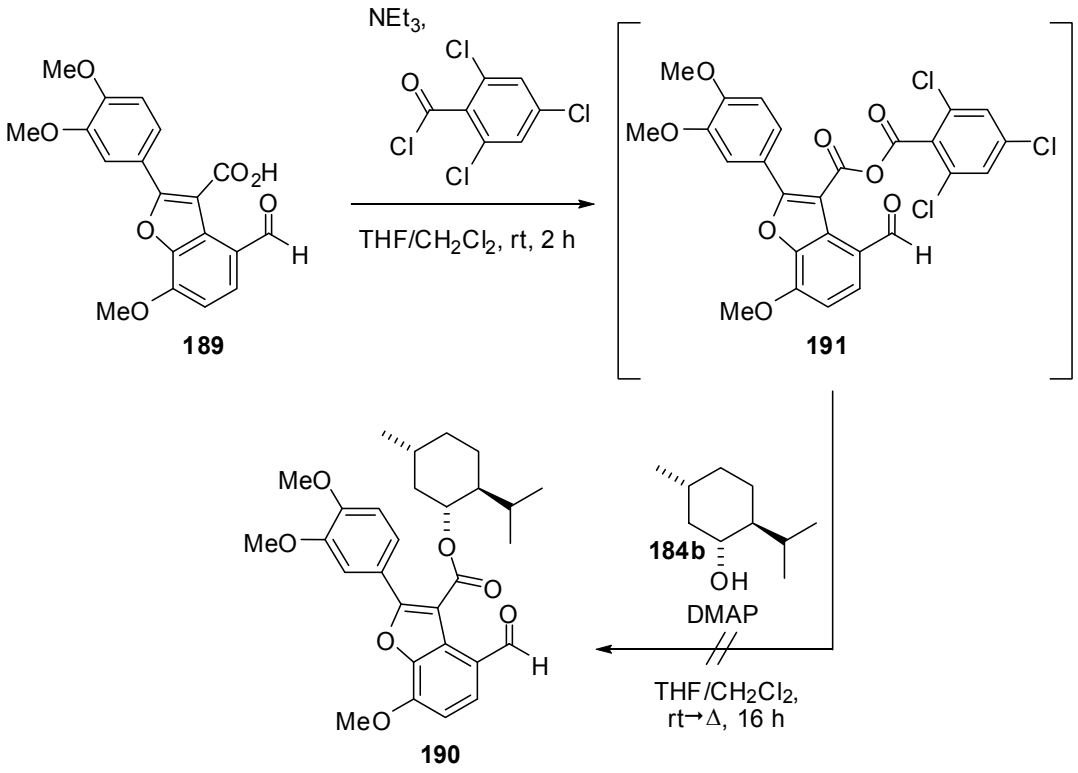
demanding than the corresponding (–)-8-phenylmenthol (**184a**) and would therefore be more likely to succeed in the coupling reaction depicted in **Scheme 79**.



Scheme 79

In an analogous reaction to that shown earlier (**Scheme 57**, **Section 4.2**), **189** was subjected to an EDC and DMAP promoted esterification. Unfortunately this did not result in the formation of the desired product **190**, but instead gave a very small quantity of a mixture of unidentifiable products. It is interesting to note that reaction at the C19 carbonyl still did not take place, despite the lack of steric hindrance previously attributed to the C7 acetal of compound **182**.

In an effort to address this lack of reactivity, an alternative esterification protocol was sought. It was anticipated that by utilising the Yamaguchi reaction,[133] the desired transformation could be achieved. The Yamaguchi reaction utilises 2,4,6-trichlorobenzoyl chloride which reacts, under basic conditions, with a carboxylic acid to form the more reactive mixed anhydride. The anhydride thus formed can then be treated with alcohols, amines and thiols to generate esters, amides and thioesters respectively. The case specifically employing alcohols to generate esters is known as Yamaguchi esterification. Once the mixed anhydride is formed, the chloro substituents on the aromatic ring serve two purposes. Firstly, they prevent nucleophilic attack (by either the alcohol or DMAP) of the carbonyl group adjacent to the aromatic ring on steric grounds, forcing the reaction to proceed at the desired carbonyl, and secondly, to stabilise the aromatic carboxylate anion as it becomes the leaving group.



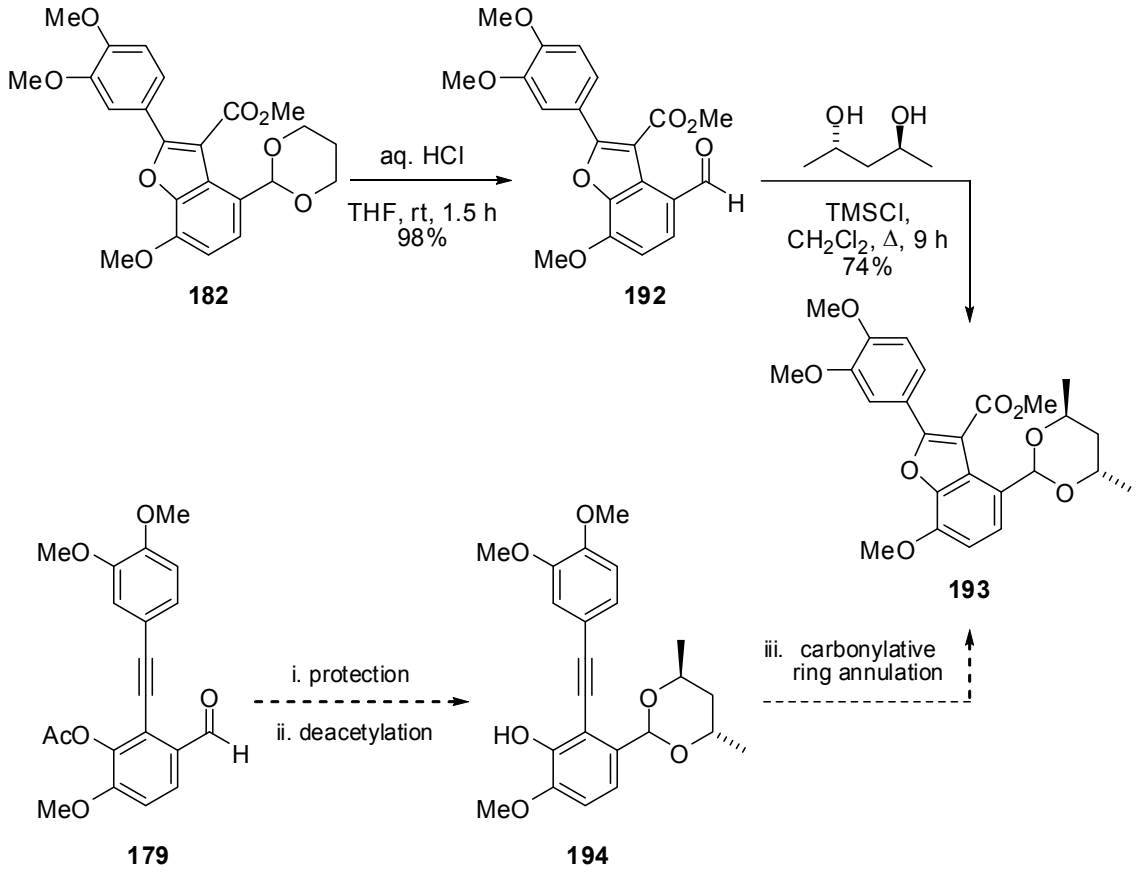
Scheme 80

The conditions employed for this attempted transformation were adapted from the work conducted by the Fürstner group[134] (**Scheme 80**). Unfortunately, these conditions did not afford the desired ester **190**, and acid **189** was recovered. Changing the solvent system to a THF/CH_2Cl_2 mixture had no effect on the reaction outcome and heating the reaction for extended periods of time, still did not yield the desired ester **190**. This observation suggests that the formation of the mixed anhydride **191** was not taking place and this may be attributed to the limited solubility of **189** in either of the solvent systems trialed. It may also be true that the carbonyl is simply too unreactive, owing to its conjugation with the aromatic ring system, as discussed previously, or that sterics may be impeding reaction at this C19 centre. On this basis, alternate approaches were sought that would not involve reaction at this surprisingly unreactive centre.

6.2.3 Chiral Acetal Approach

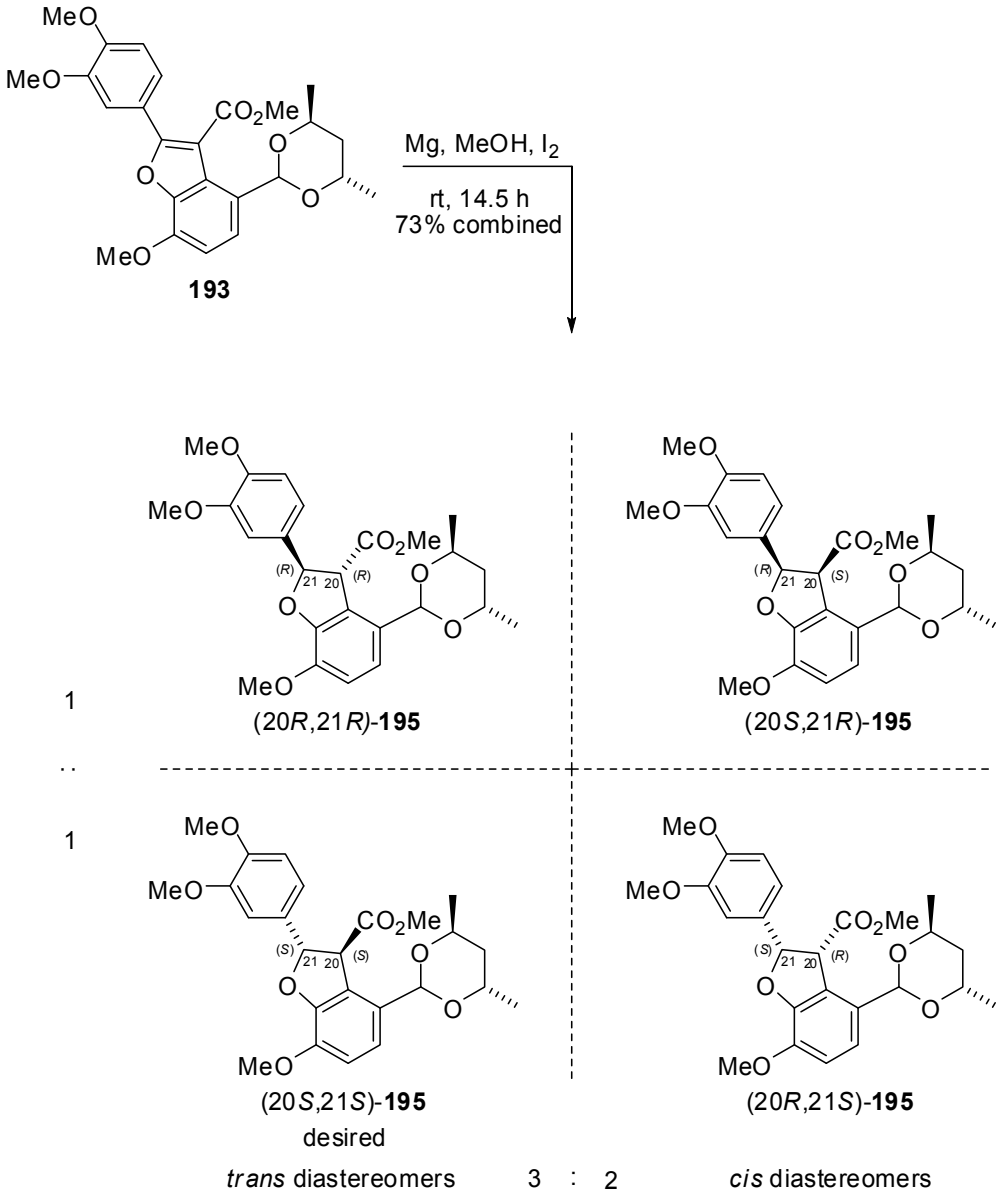
Since the installation of a chiral auxiliary at the C19 position had proven fruitless, an alternate strategy involving the manipulation of the C7 aldehyde became an increasingly favourable option. By protecting the aldehyde as a chiral acetal,[135] it was anticipated that this could conceivably invoke diastereoselectivity during the magnesium–methanol reduction, or at least allow separation of the diastereomeric reduction products. Another attractive feature of the chiral acetal approach was the ease of removal of the acetal once it had served its purpose.

The most rapid access to **193** from the compounds available was to start from **182** and following the route shown in the upper path of **Scheme 81**, obtain the chiral acetal **193** in two steps. This strategy would suffice for simply obtaining **193** and testing the applicability of this concept, however, if this were to prove successful, the chiral auxiliary could be installed earlier in the synthetic sequence where it would also serve as a protecting group for the aldehyde, thus minimising additional steps in the synthesis. This idea is shown in the lower path of **Scheme 81**.



Scheme 81

The acetal **182** was treated with aqueous HCl to affect acetal hydrolysis rapidly and cleanly, providing aldehyde **192** in excellent yield (98%). Using the previous protocol for acetal formation, aldehyde **192** was converted to the corresponding chiral acetal **193** in good yield (74%, unoptimised) using (2*S*,4*S*)-pentane-2,4-diol. With chiral acetal **193** in hand, investigations into the reduction could now be conducted (**Scheme 82**).



Scheme 82

The magnesium–methanol reduction conditions developed previously were applied to chiral acetal **193**, which gave a mixture of the four expected products shown in **Scheme 82**. ^{1}H NMR analysis of the crude product indicated a *ca*. 3:2 mixture of *trans* and *cis* diastereomers, respectively. This ratio was of little concern as it had been previously shown that the *cis* diastereomer could be readily epimerised to the more stable *trans* configuration. The *trans* and *cis* diastereomers were readily separable by column chromatography using a triethylamine doped eluting solvent to prevent acetal hydrolysis. The two *trans* diastereomers (20*R*,21*R*)-**195** and (20*S*,21*S*)-**195** were taken on to HPLC in an effort to separate them, however, despite exhaustive efforts, this was not achievable. The best result by analytical HPLC showed two overlapping peaks that were not resolved, but upon inspection appeared to have a *ca*. 1:1 ratio. This

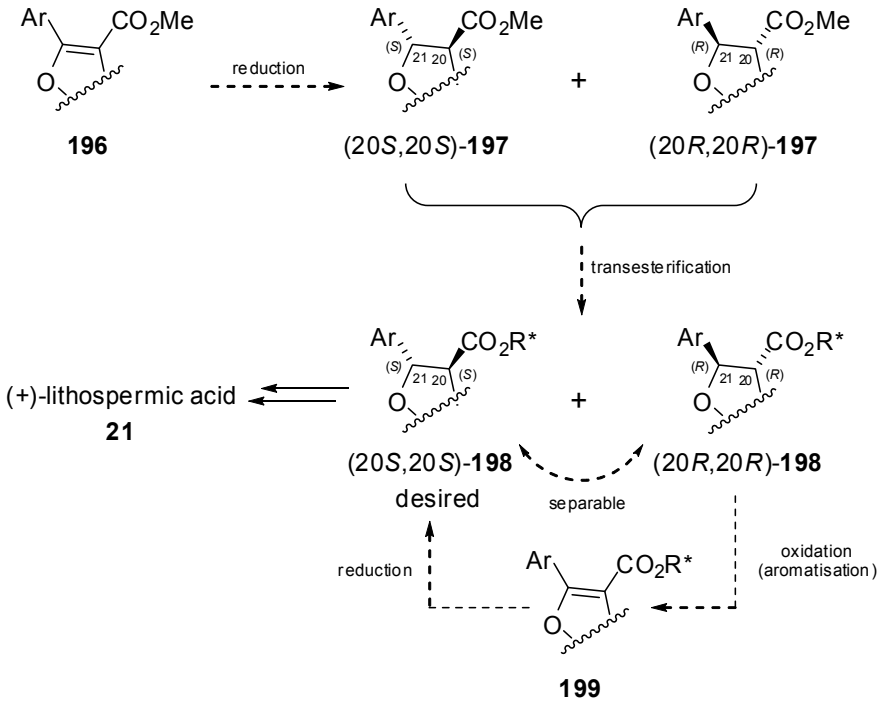
result showed that there had been no diastereoselectivity in the reduction step, and separation of the diastereomers by chromatographic techniques was not feasible.

We conceded that this line of investigation was proving unrewarding, and thus our focus shifted towards an alternate strategy to enable the separation of the (20*R*,21*R*) and (20*S*,21*S*) enantiomers.

6.3 Resolution of the Racemate

6.3.1 Reduction to Racemic 2,3-Dihydrobenzofuran then Separation

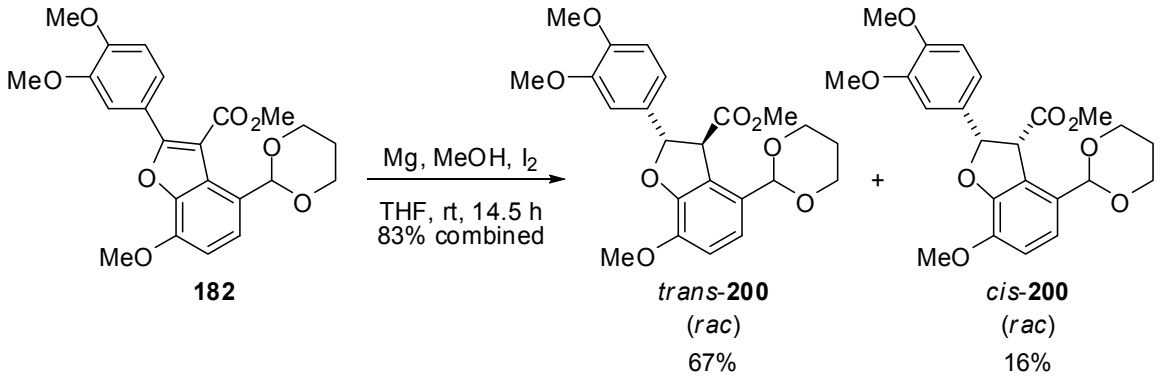
In light of the fact that a chiral auxiliary could not be installed prior to the reduction step, and the attempted asymmetric reductions had proven unfeasible, it made sense to perform a non-selective reduction, followed by resolution of the resulting enantiomeric pair by formation of a diastereomeric mixture. This idea is presented diagramatically in **Scheme 83**.



Scheme 83

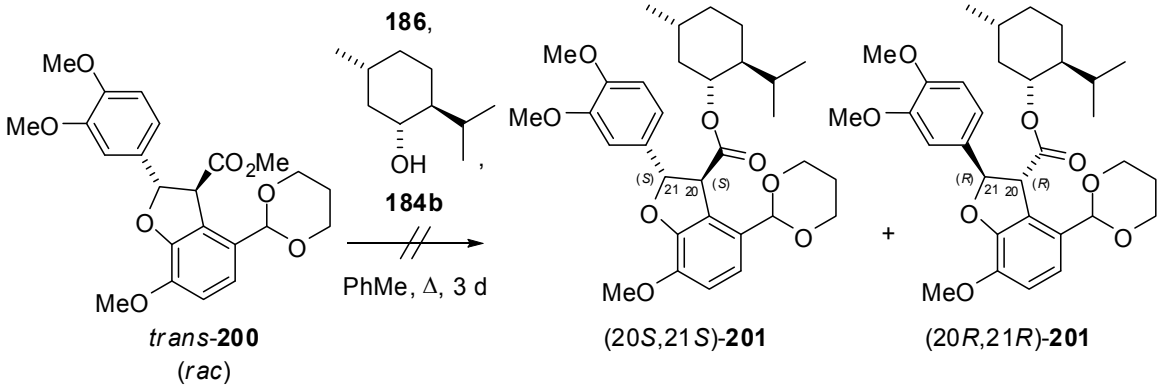
In this approach, a magnesium–methanol reduction of **196** should afford the two *trans* enantiomers ((20*S*,21*S*)-**197** and (20*R*,21*R*)-**197**) after epimerisation. Subsequent transesterification with a chiral alcohol would afford a mixture of hopefully separable diastereomers (20*S*,21*S*)-**198** and (20*R*,21*R*)-**198**. It was envisaged that the ester moiety present in dihydrobenzofuran **197** would be more reactive than the corresponding ester of benzofuran **196**, since the carbonyl is no longer in conjugation with an aromatic ring system. The difference in electronics should make the ester more reactive by decreasing

the stability of the ester carbonyl. After separation, the undesired diastereomer, (20*R*,21*R*)-**198**, could potentially be recycled *via* a two step process involving oxidation to **199** then chiral auxiliary directed asymmetric reduction to give enriched (20*S*,21*S*)-**198**. The chiral auxiliary could be chosen and optimised to give the desired (20*S*,21*S*)-diastereomer if need be. Although not as attractive as the chiral induction methods, this would still provide access to an asymmetric synthesis of 2,3-disubstituted-2,3-dihydrobenzofurans. To begin this investigation, the benzofuran **182** was reduced according to **Scheme 84**.



Scheme 84

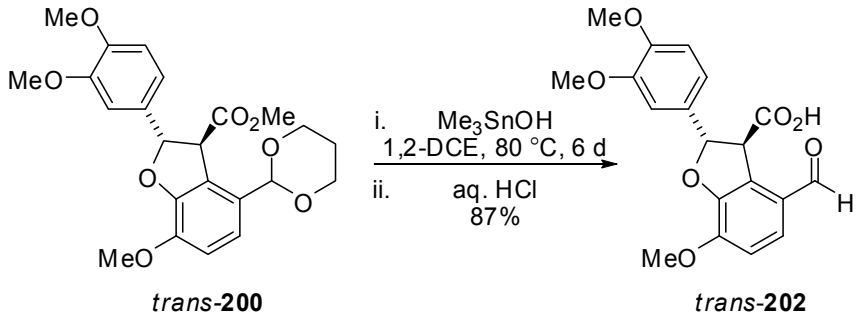
Using the previously developed conditions for the magnesium–methanol reduction, **182** was reduced smoothly, in an overall isolated yield of 83%, to a *ca*. 4:1 mixture of *trans*-**200** and *cis*-**200**, respectively. An aqueous NH_4Cl work-up was employed to avoid acetal hydrolysis. The *trans* diastereomer, was separated from the *cis* diastereomer by column chromatography and was carried forward to the next synthetic step.



Scheme 85

Unfortunately, transesterification using Otera's catalyst with (–)-menthol (**184b**) did not deliver the expected (–)-menthyl esters (20*S*,21*S*)-**201** and (20*R*,21*R*)-**201**. Starting material persisted after 3 days of refluxing in toluene, and was isolated in 22% recovery. The mass balance consisted of unidentifiable baseline by-products. A comparison between this system and the system in **Scheme 76** reveals a

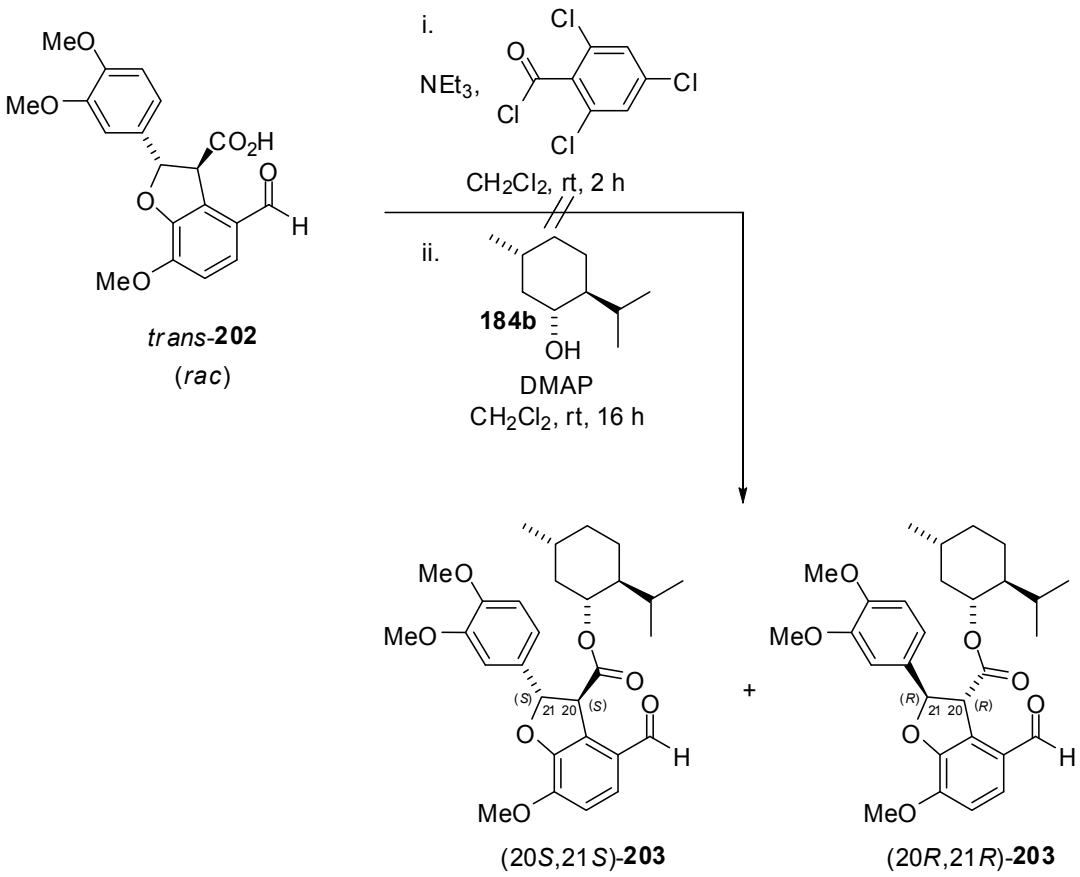
significant difference in the electronics of the ester carbonyl group whereas the sterics are fairly similar. This data provides further evidence to support the prior claims that Otera's catalyst appears to encounter limitations when bulky esters are used in conjunction with bulky alcohols. Employing similar logic to **Section 6.6.2**, a two step protocol involving ester rupture to give acid *trans*-**202**, followed by esterification, was utilised and the first step is shown in **Scheme 86**.



trans-**200** *trans*-**202**

Scheme 86

Trimethyltin hydroxide promoted ester cleavage proceeded smoothly and in high yield, although extended reaction times were needed to affect complete conversion. As was observed in **Section 6.2.2**, the presence of an acidic functional group promoted the hydrolysis of the acetal upon standing and hence it proved prudent to use an aqueous acid work-up and isolate solely the aldehyde *trans*-**202**. Shorter reaction times (*ca*. 30 h) were realised by using larger excesses of the tin reagent (20 equiv.), however, the yield suffered as a consequence (74%). Ultimately, using 10 equivalents of trimethyltin hydroxide in refluxing 1,2-dichloroethane for 6 days provided the highest yield of acid *trans*-**202** (87%), without the need for column chromatography. With *trans*-**202** in hand, the esterification reaction could then be explored.



Scheme 87

Unfortunately when the Yamaguchi esterification conditions were applied to this system, the desired methyl esters (20*S*,21*S*)-**203** and (20*R*,21*R*)-**203** were not observed. The only species isolated from this reaction mixture was the starting material *trans*-**202** and once again, it was unclear as to which of the two steps, anhydride formation or DMAP promoted alcohol addition, were causing the problems in this reaction.

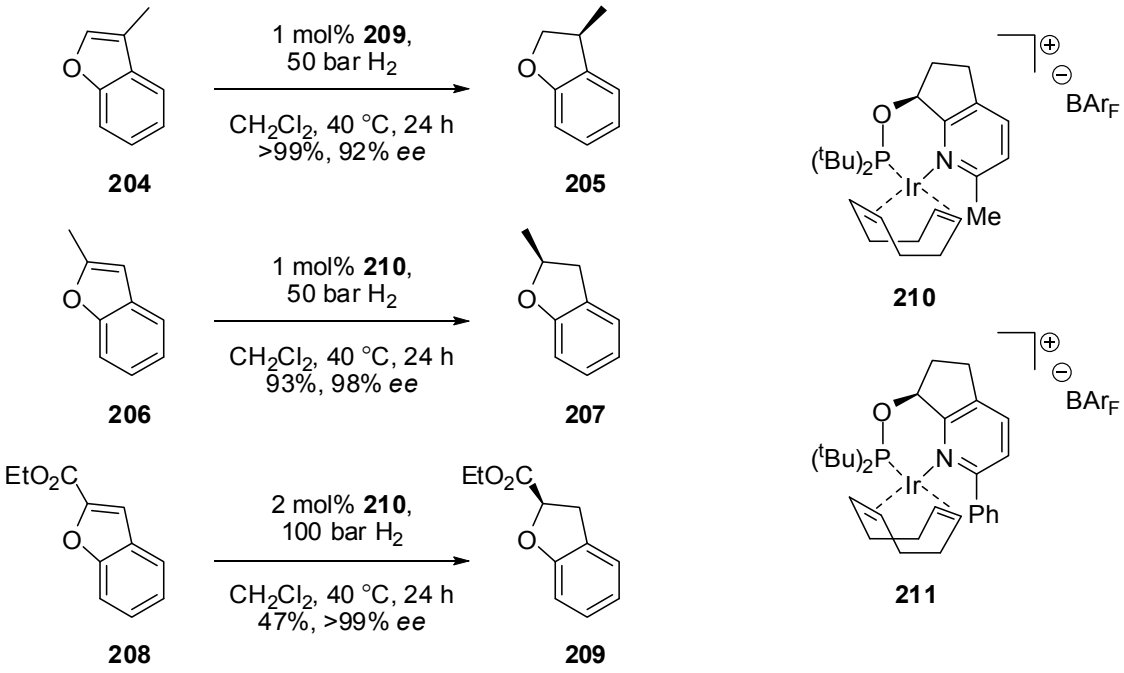
At this stage of the project, time and manageable quantities of advanced intermediates were in short supply. This approach was therefore abandoned due to these time constraints and in favour of other investigations being conducted simultaneously.

6.4 Catalytic Enantioselective Reduction

Previously, we had observed that the Buchwald conjugate reduction conditions[104-108] were not applicable to our system (**Section 3.2.7**, **Table 6**, **Entry 4**), and so our focus for a catalytic enantioselective reduction was aimed towards an alternative reduction protocol recently reported by the Pfaltz group.[136]

6.4.1 Attempted Reduction with Pfaltz's Catalyst

In 2006, the Pfaltz group reported chiral iridium catalysts that successfully reduce 2- and 3- substituted benzofuran ring systems to the corresponding 2- and 3- substituted 2,3-dihydrobenzofurans, with excellent enantioselectivity, as shown in **Scheme 88**.[136]

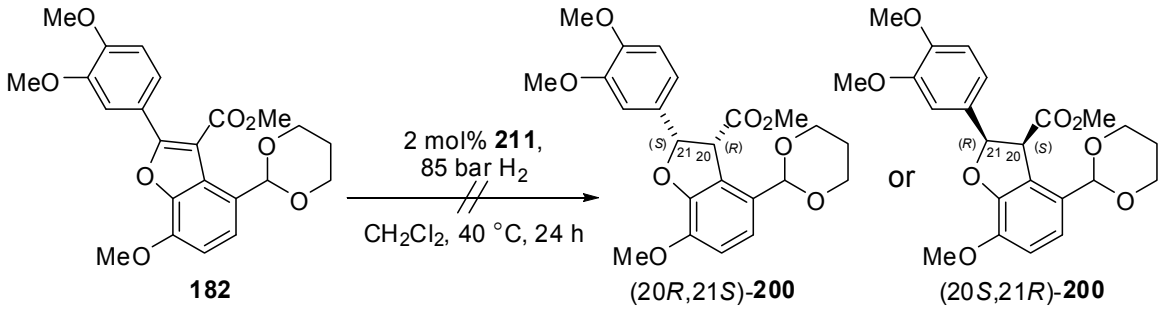


Scheme 88[†]

Upon inspection of **Scheme 88**, it can be seen that excellent yields and *ee*'s are obtained for the methyl substituted examples **204** and **206**. In the case possessing an ester substituent (**208**), the reaction is reportedly more sluggish, requiring higher pressure and increased catalyst loading, however, an excellent *ee* is maintained (>99% *ee*). Although no 2,3-disubstituted benzofuran examples were investigated by Pfaltz and co-workers, we were eager to examine this strategy as a route to an asymmetric synthesis of 2,3-disubstituted-2,3-dihydrobenzofurans. We were extremely fortunate to

[†] Absolute configuration of product dihydrobenzofurans was not determined by the authors and the configuration displayed is indicative only, *not* absolute.

obtain a sample of catalyst **211**‡ in order to explore the reduction of our system, as depicted in **Scheme 89**.



Scheme 89

Owing to the fact that it is a hydrogenation reaction, it is assumed that the *cis* isomer would be the most likely product, but it would be difficult to predict whether it would be the (20*R*,21*S*)-**200** or the (20*S*,21*R*)-**200** enantiomer. In this preliminary investigation we were simply assessing the ability of this reagent system to perform the reduction and a significant enrichment of either of these enantiomers would represent a monumental success. If this were the case, either enantiomer could be obtained, as both enantiomers of the catalyst are available. The *cis* diastereomer thus obtained could be subsequently epimerised to the *trans* diastereomer in the subsequent step.

The reaction was conducted at 40 °C and 85 bar (H_2) for two days and at 30 °C and 130 bar (H_2) for three days. Disappointingly, these conditions led to a continuum of products as observed by tlc. ^{1}H NMR analysis of the crude product indicated that the desired products (20*R*,21*S*)-**200** or (20*S*,21*R*)-**200** had not been formed, and the only identifiable species present was the starting material **182**. Column chromatography proved futile, and a lack of time and substrate **182** prevented further investigation into this approach. It was felt that enough insight had been gained to declare this route as a non-viable option to access chiral 2,3-disubstituted-2,3-dihydrobenzofuran systems. The failure of this catalyst system is probably due to steric hindrance of the C20/C21 double bond as it is flanked by sterically demanding groups. It is also possible that the Lewis acidic catalyst caused side-reactions to occur at the sensitive acetal protecting group. The cases reported by Pfaltz indicated that only 2- or 3- substituted benzofurans were amenable to these conditions, but no 2,3-disubstituted examples were reported. This is most likely due to their observed lack in reactivity as a result of the size of the catalyst coupled with steric crowding of the double bond.

‡ Catalyst kindly donated by Pfaltz and co-workers.

6.5 Summary

In summary, the three major routes for an enantioselective approach to (+)-lithospermic acid (**21**) have all been investigated, entailing (i) chiral auxiliaries, (ii) resolution of enantiomers and (iii) catalytic enantioselective reductions.

The chiral auxiliary approach initially centered upon the functionalisation of the C19 ester, however, this carbonyl group proved exceedingly unreactive and functionalisation at this position proved an insurmountable task. Conversion to the corresponding acid **189** was achieved, however, this carbonyl was similarly unreactive. A chiral acetal approach was investigated that both protected the aldehyde, and served as a chiral auxiliary. The synthesis of chiral acetal **193** was successful, however, the introduced chiral group was too far removed from the reduction site and hence, had little effect on the selectivity of the reduction. Further to this, separation of the corresponding diastereomers could not be achieved, presumably also due to the distance between the stereocentres, and the flexible nature of the groups that linked them.

The resolution of diastereomers was also investigated by first reducing the benzofuran to the corresponding 2,3-dihydrobenzofuran. Transesterification of *trans*-**200** with a chiral alcohol did not transpire under the conditions examined. Although the methyl ester was saponified under milder conditions than the corresponding benzofuran **182**, functionalisation of the C19 acid proved elusive, and as such, diastereomeric pairs were not generated and their separation was not investigated.

Finally, a state of the art catalytic enantioselective reduction was attempted. Unfortunately, our substrate **182** proved unsuitable for this type of transformation that had thus far only been demonstrated on much less functionalised benzofuran systems.

–Chapter 7–

Synthetic Studies Towards the Tetramic Acid Subunit of Integramycin

7.1 Retrosynthetic Analysis of Integramycin

Integramycin (**47**) exhibits a unique structural framework and as such, synthetic approaches to the various fragments have been reported.[55,56] Integramycin can be viewed as three disparate and chemically quite distinct domains (**A–C**, **Figure 27**).

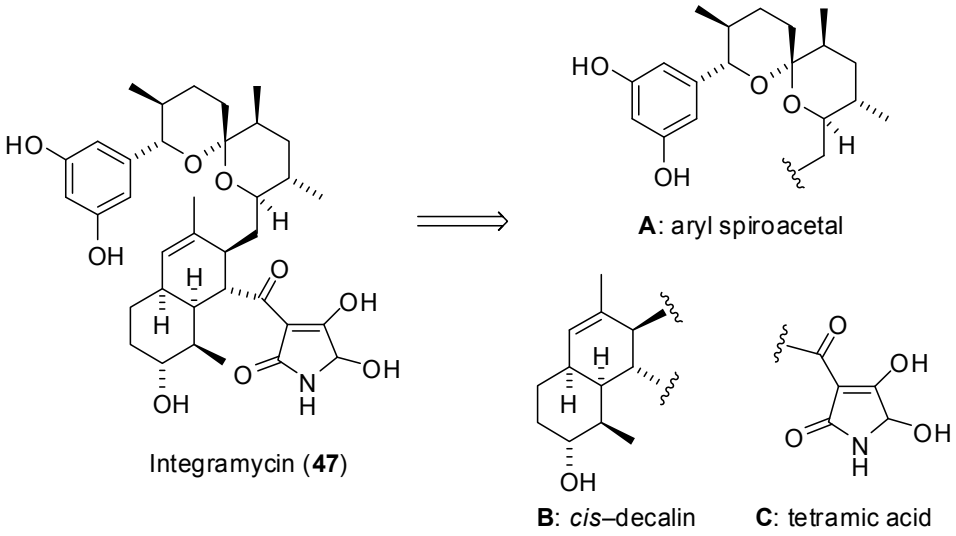
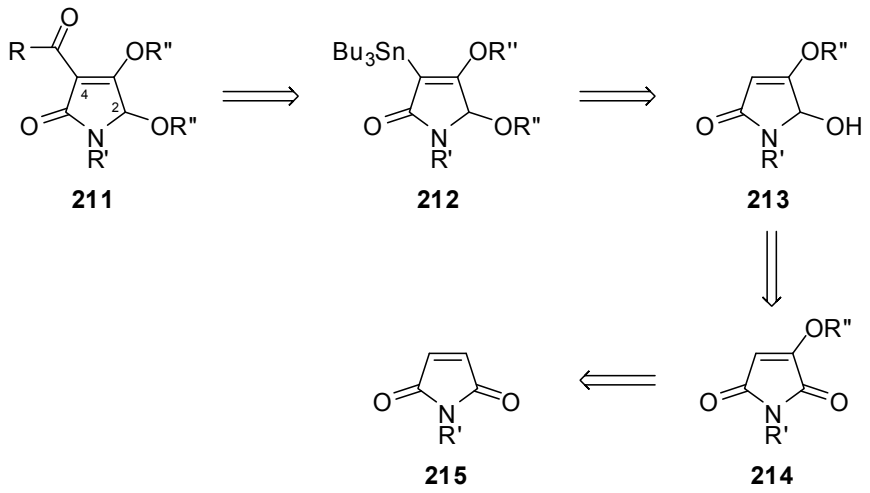


Figure 27

The presence of these three distinct domains allows for a highly modular synthetic approach towards integramycin whereby the subunits can be synthesised independently and then united in a late stage of the synthesis. This property of the synthetic approach allows for the production of analogues that may be used to gain structure-activity relationship data of a potentially new class of integrase inhibitors.

Whilst other members of our research group are devoted to the synthesis of the aryl spiroacetal and *cis*-decalin subunits(**A** and **B**), this chapter will focus only on synthetic efforts towards the tetramic acid subunit (**C**) of integramycin (**47**).

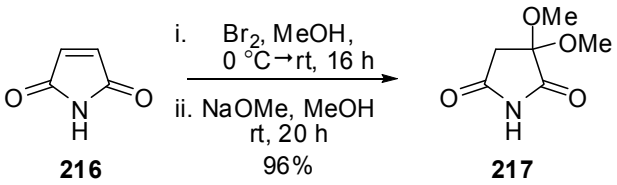


Scheme 90

To the best of our knowledge, there are no previous reports for the synthesis of 4-acyl-2-hydroxytetramic acids, such as **211**, within the literature. It is anticipated that this could be made from substituted maleimide **215** according to the retrosynthetic analysis in **Scheme 90**. It proposed that the desired 4-acyl-2-hydroxytetramic acid **211** would be generated *via* the palladium catalysed acylation of **212** using the protocol established by Ley and co-workers, who had performed this on the related system, *O*-methyl 4-(tri-*n*-butylstannyl) tetronate.[137] The tributylstannane **212** would be made from **213** *via* bromination at the C4 position, followed by halogen-metal exchange. We anticipated **213** could be generated from the regioselective reduction of **214** which, in turn, would be derived from maleimide, using the protocol of Booker–Milburn *et al*.[138]

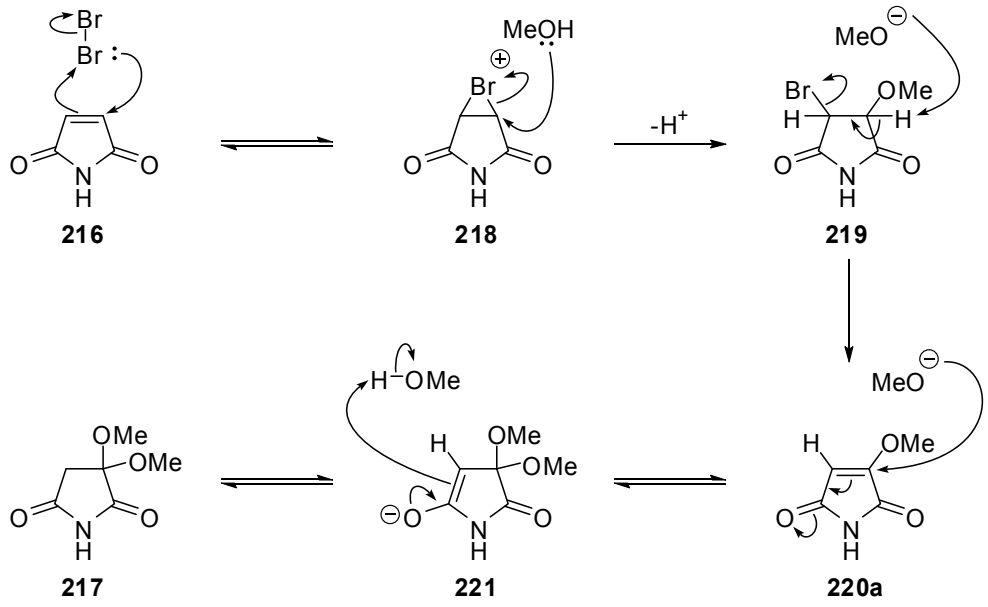
7.2 Preparation of 3-Methoxymaleimide

3-Methoxymaleimide (**220a**) was prepared in two steps from commercially available maleimide (**216**) according to the procedure reported by Booker–Milburn *et al*.[138] (**Scheme 91**). The first step in this sequence involved bromination of **216** with Br_2, followed by treatment with sodium methoxide to generate the bis-methyl acetal **217**.



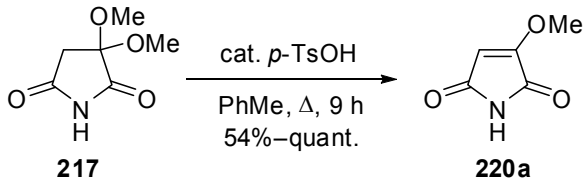
Scheme 91

This reaction proceeds *via* the mechanism in **Scheme 92** whereby formation of the bromonium ion (**218**) is followed with ring opening by the methanol solvent to give **219**. Sodium methoxide then eliminates a proton and a bromide to give **220a**, and subsequent rapid attack by methoxide gives **221** which then abstracts a proton to afford the observed species **217**.



Scheme 92

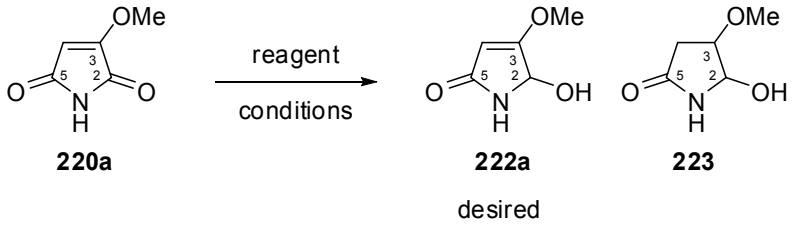
The product **217** was then converted to methoxymaleimide **220a** by acid catalysed elimination of methanol (**Scheme 93**).



Scheme 93

The eliminated methanol was removed from the reaction mixture by azeotropic distillation with toluene from the reaction to drive the equilibrium towards **220a**. This necessitated the addition of fresh toluene so as to maintain a roughly constant reaction volume. This afforded the desired methoxymaleimide **220a** in 54% after column chromatography. When performed on large scale (*ca*. 7 g), quantitative yields of **220a** were obtained, however, purification by column chromatography was hampered by solubility issues of the product **220a** in the mobile phase and recrystallisation proved inadequate. Owing to these issues, **220a** was carried forward to the next step of the synthesis without further purification, despite containing traces of *p*-TsOH.

7.3 The Regioselective Reduction of 3-Methoxymaleimide



Scheme 94

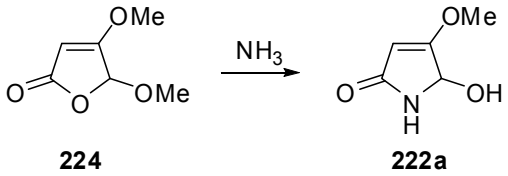
With **220a** in hand, we were set to investigate the crucial regioselective reduction of the C2 carbonyl in the presence of the C5 carbonyl and the C3–C4 double bond. The results of this investigation are summarised in **Table 8**.

Table 8

Entry	Reagent	Conditions	**222a**	**223**
1	DIBAL–H	THF, -78 °C, 20 min	–	–
2	$NaBH_4$	THF/H_2O, 0 °C, 20 min, aq. NH_4Cl work-up	–	–
3	$NaBH_4$	THF/H_2O, 0 °C, 20 min, no aqueous work-up	~50%	~25%
4	$NaBH_4$	THF/H_2O, 0 °C, 20 min, acetone quench	81%	–
5	$NaBH_4$	THF/H_2O, 0 °C, 30 min, acetone quench	87%	–

DIBAL–H was initially employed in the reduction (**Entry 1**), however, the aluminium salts formed during the reaction caused emulsions, which, coupled with the hydrophilicity of the product **222a**, hampered extraction and thus no product was isolated from the reaction mixture. $NaBH_4$ was then employed as the reducing agent (**Entry 2**), however, isolation was again hampered by the hydrophilicity of **222a**, despite using 3:1 $CHCl_3$/*i*-PrOH for extraction. In an effort to avoid an aqueous work-up, an alternate strategy was employed (**Entry 3**). When the reaction was deemed complete by tlc, the solvent was removed *in vacuo*, without quenching, and the resulting residue was subjected to column chromatography. This afforded an inseparable mixture of **222a** and **223** in moderate yield (75% combined, *ca*. 2:1). This indicated that quenching excess sodium borohydride was indeed necessary, as the over-reduced product **223** was not observed by tlc during the reaction. Ultimately, the optimal isolation conditions (**Entries 4** and **5**) proved to be quenching the excess sodium borohydride with acetone. The advantages of this protocol were that both acetone and the reduced partner, *i*-PrOH, are volatile and can be removed *in vacuo* prior to purification *via* column chromatography. Elution with a

polar solvent (10 % MeOH in CH_2Cl_2, v/v) gave the desired product **222a** in good yield (87%), with no evidence for the formation of the regioisomeric product resulting from borohydride attack at C5 carbonyl. The identity of **222a** was confirmed by comparison with the physical and spectroscopic data reported previously for this compound, synthesised by a different synthetic route (**Scheme 95**).[139] This congruence of physical and spectroscopic data unambiguously confirmed the regioselectivity of the reduction step.



224 **222a**

Scheme 95

The impressive regioselectivity of this reaction can be rationalised by two separate arguments. Firstly, the sterics involved dictate that the C2 carbonyl is more prone to attack than the C5 carbonyl. When considering hydride approach along the Bürgi–Dunitz trajectory (107 °),[140] shown in **Figure 28**, the more favourable approach is that of model **a**, as model **b** has unfavourable steric interactions between the hydride and the methoxy substituent. Thus, as observed, the product of model **a** should be the dominant product.

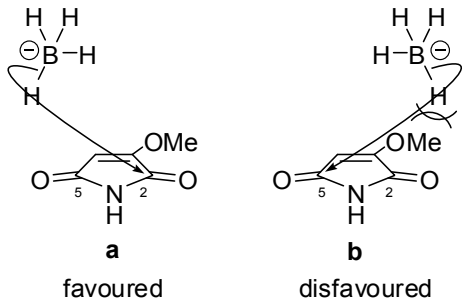
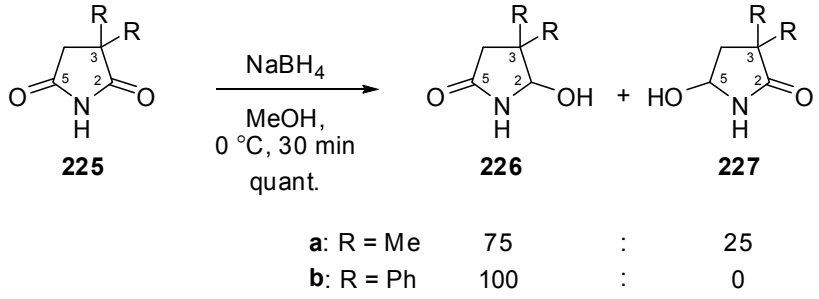


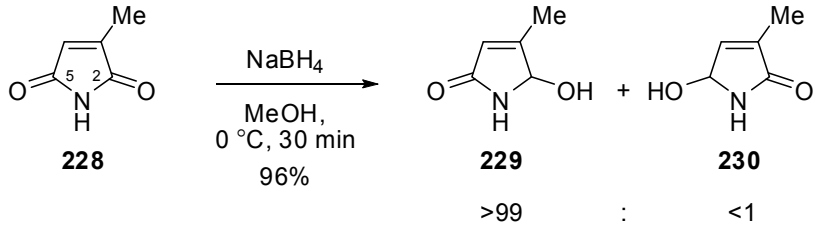
Figure 28

This remarkable preference for attack at the more hindered C2 carbonyl has also been observed in a related system—the *gem*-disubstituted succinamides—by Speckamp and co-workers (**Scheme 96**).[141,142] The authors also employed similar logic to account for the predominance of the C2 adduct.



Scheme 96

Similar regioselectivity was also observed in the reduction of citraconimide (**228**) by Takabe and co-workers[143] (**Scheme 97**) who employ the same rationale to justify their observations. Interestingly, there was a reversal in regioselectivity when DIBAL–H was used, or when $NaBH_4$ was used in conjunction with the Lewis acid cerium (III) chloride heptahydrate ($CeCl_3 \bullet 7H_2O$). This was attributed to the cerium or aluminium activating the less hindered C5 carbonyl, *via* coordination, in preference to the C2 carbonyl.



Scheme 97

The second rationale for the observed regioselectivity is based on the electronics of this system which are unique to our example and therefore were not examined in the aforementioned examples of regioselective reductions. The lone pair of electrons on the C3-methoxy group can be delocalised into the rest of the π-system, giving rise to the resonance contributor **231** in **Figure 29**. This delocalisation renders the C5 carbonyl less electrophilic compared to the C2 carbonyl. Importantly, there exists no resonance contributor that can place an analogous negative charge on the C2 carbonyl oxygen. This is the critical electronic difference between these two carbonyl groups and helps to rationalise the observed regioselectivity.

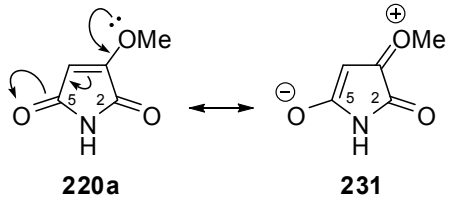


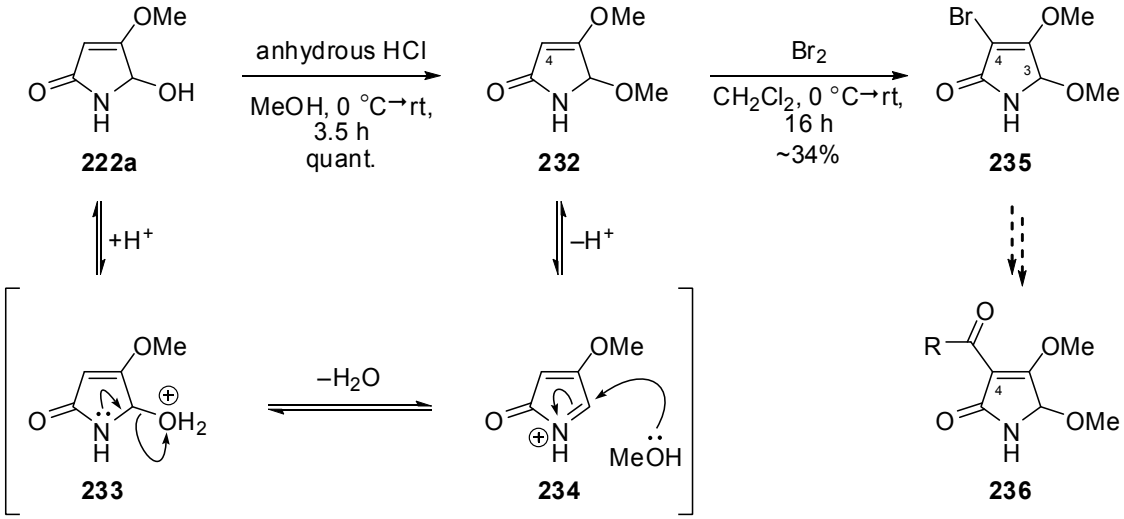
Figure 29

Whilst discussing electronics, it is worth noting that once the reduction of the first carbonyl takes place, the reduction of the second carbonyl is extremely unlikely due to the fact that this carbonyl is now part of and amide system, rather than the original imide system. For example, once the C2 carbonyl is reduced, the C5 carbonyl is part of an amide system, which renders it inactive towards reduction by borohydride, hence the reduction halts after a single reductive step and will not proceed to the diol. This effect, when combined with the resonance structure and the sterically less demanding Bürgi–Dunitz trajectory argument, provides a solid rationale for the observed regioselectivity and the preponderance of the C2 reduced adduct, **222a**, over the C5 reduced adduct, which was not observed.

7.4 Attempted Functionalisation of the C4 Position

The next step in the synthesis would require the installation of a C4-acyl group. Initially, small acyl groups could be trialed as a model for the eventual introduction of the integramycin subunits. The added advantage of this approach would be that by introduction of a variety of acyl groups, a range of compounds could be generated that would form valuable probes into the gathering of SAR data for this novel integrase inhibitor.

The newly generated hydroxyl group was first converted to the methyl *N*-acyl aminal **232** by treatment with anhydrous methanolic HCl in quantitative yield (**Scheme 98**). This mechanism presumably involves formation of the highly reactive *N*-acyl iminium ion **234**, followed by trapping with methanol to give the observed **232**.



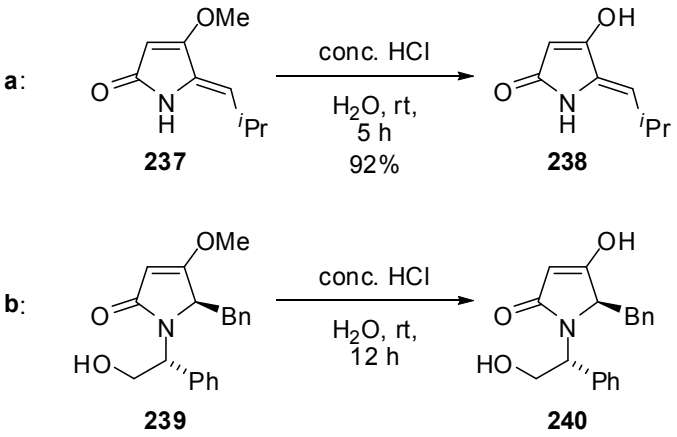
Scheme 98

The next step was the bromination at the C4 position, which was carried out using Br_2. The product **235** was generated, as confirmed by ^{1}H NMR and mass spectrometry, however, isolation of the product proved difficult and **235** was isolated as a *ca.* 3:1 mixture with an unidentified by-product. No further

attempts were made to optimise this sequence and unfortunately this avenue of investigation was abandoned since experiments being conducted simultaneously indicated that the methyl ether at the C3 position may prove difficult to deprotect. This is elaborated further in the following section.

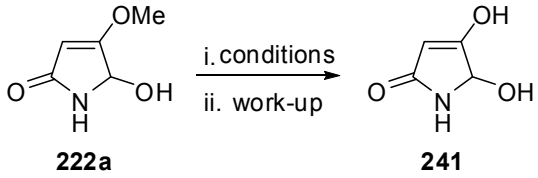
7.5 Attempted Demethylation

The demethylation of **222a** relies on the hydrolysis of a vinylogous ester. In related systems, Bänziger *et al.*[144] and Huang *et al.*[145] accomplished analogous transformations using aqueous HCl (**Scheme 99**, **a** and **b**, respectively).



Scheme 99

Employing similar logic, these conditions were applied to **222a** (**Scheme 100**), and tlc analysis indicated the formation of a more polar compound, as expected. In the Bänziger system,[144] when the reaction was complete, neutralisation with aqueous sodium hydroxide caused the product **238** to precipitate, and this was collected *via* filtration and washed with water. This protocol proved unsuitable for our system (**Entry 1**, **Table 9**), as no precipitate was observed, most likely due to the hydrophilicity of **241**. It was believed that by removal of the solvent, only **241** and salt would remain and to this end, the solvent was removed and the residue was subjected to column chromatography. The product isolated proved to be an impure sample that, upon electrospray mass spectrometric analysis, displayed peaks indicative of the desired **241** (m/z $[M+H]^+$ = 116). The ^{1}H NMR spectrum was complicated by impurities, and further attempts to purify this sample proved unsatisfactory. Efforts were made to reproduce this experiment using identical procedures, however, **241** was not observed in these subsequent attempts. This prompted a more thorough investigation into the formation and isolation of **241** and these results are summarised in **Table 9**.



222a **241**

Scheme 100

Table 9

Entry	Conditions	Work-up	Result
1	conc. HCl, rt †	NaOH added, solvent removed *in vacuo*	**241** observed
2	conc. HCl, rt †	aqueous NaOH to pH 13, then freeze dry	decomposition
3	conc. HCl, rt †	aqueous NaOH to pH 5.5, then freeze dry	decomposition
4	conc. HCl, rt †	aqueous NaOH to pH 1, then freeze dry	decomposition
5	conc. HCl, rt †	freeze dry without neutralisation	decomposition
6	conc. HCl, rt †	neutralise with basic resin (Bio-Rad AG 3-X4)	No material isolated
7	Amberlyst-15, 80 °C	filtration	no reaction

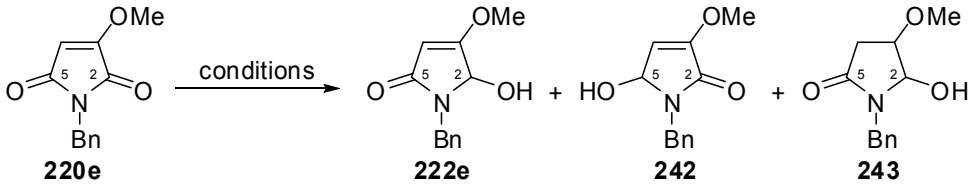
† By tlc, **222a** appeared to be consumed and form a new spot of lower R_f, consistent with that expected for this transformation, prior to work-up.

Upon inspection of **Table 9**, **Entries 2–5**, it can be seen that decomposition, as indicated by the complicated ^{1}H NMR spectrum of the crude residue, resulted regardless of the pH that the reaction mixture was adjusted to. It is suspected that the decomposition is simply a result of concentration of **241**. An alternative work-up strategy was employed, **Entry 6**, using a polymer bound base (Bio-Rad AG 3-X4). In this case no material was isolated, presumably due to the large quantity of beads that were needed for neutralisation. The beads could potentially have bound **241** through some form of irreversible binding or could have deprotonated **241** to form the ion pair. In either scenario, **241** would have been removed from the solution giving rise to the fact that nothing was isolated from the reaction. A polymer bound acid was also used in place of aqueous HCl (**Entry 7**). It was anticipated that the product could be isolated by simply filtering off the polymer beads. Unfortunately **222a** proved inert to these conditions and starting material was recovered.

At this stage we questioned whether **241** could indeed be isolated in pure form given the instabilities and problems encountered thus far. We felt the main issue of contention was the large number of heteroatoms in a small molecule which would render the molecule exceedingly polar and lead to the observed difficulties in handling. It was anticipated that this could be circumvented by introducing more lipophilicity to the molecule; the most judicious choice was in the form of a nitrogen protecting group. Our synthetic efforts were redirected accordingly and possessed the added benefit of the ability to explore the scope of the regioselective sodium borohydride reduction from **Section 7.3**.

7.6 Further Exploration into Reagents for the Regioselective Reduction[†]

It was anticipated that the physical properties of the *N*-substituted analogues would be different to the parent compounds **220a** and **222a**. Fortuitously, from studies being conducted simultaneously, the *N*-benzyl analogues **220e** and **222e** proved to be much easier to handle than **220a** and **222a** and for this reason, the *N*-benzyl analogue was chosen for further study. The synthesis of **220e** is discussed in **Section 7.7.1**.



Scheme 101

Table 10

Entry	Reagent	Ratio of Products	
		222e	**242**
1	DIBAL–H, CH_2Cl_2	50	50
2	DIBAL–H, THF	50	50
3	$LiAlH_4$	88	12[‡]
4	$NaBH_4/CeCl_3$	97	3
5	$NaBH_4$	100	–

[‡] over-reduced product **243** also isolated.

A survey of common reducing agents showed that DIBAL–H, (**Entries 1–2**, **Table 10**) was surprisingly non-selective in the reduction of **220e**. Reduction with $LiAlH_4$ gave an 88:12 mixture of **222e** and **242**, as well as appreciable amounts of the over-reduced compound **243** (**Entry 3**). In contrast to the observation by Takabe and co-workers,[143] $NaBH_4$ in conjunction with $CeCl_3$ (**Entry 4**) gave a 97:3 mixture of **222e** and **242** respectively. This observation indicates that the Lewis acid is not effectively activating the C5-carbonyl of **220e** as it had done in the system of Takabe and co-workers. Chelation of the Lewis acid with both the C3-methoxy oxygen and the C2-carbonyl oxygen is presumably a more favourable process than *monodentate* coordination of the C5-carbonyl. Comparison of the $CeCl_3$ containing system with the non-$CeCl_3$ containing system (**Entry 5**), indicates that there must be some activation of the C5 carbonyl by $CeCl_3$, however, this effect is minimal when compared to the selectivity of $NaBH_4$ individually.

[†] The remainder of the work in this chapter was conducted in conjunction with Dr Fatiah Issa.

The structure of **222e** was confirmed by single-crystal X-ray diffraction, the ORTEP depiction of which is shown in **Figure 30**. In this diagram, it is very clear that it is the carbonyl adjacent to the methoxy group that has been reduced.

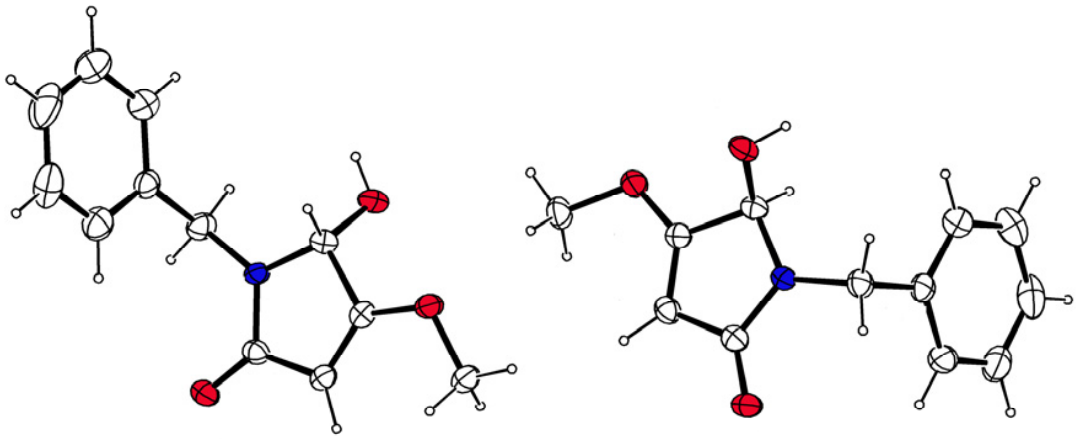


Figure 30

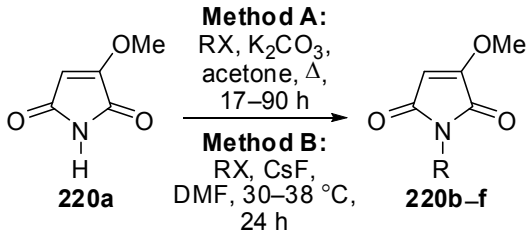
Throughout this study, it was determined that the methine C4 carbon of the reduced products **222e** and **242**, had a very characteristic shift in the ^{13}C NMR spectrum. For **222e**, the C4 methine carbon had a characteristic shift at ~δ 93 ppm. In the regioisomeric product **242**, this carbon was found to have a characteristic shift of ~δ 107 ppm. These characteristic shifts of this C4 methine carbon could be used to distinguish between the two regioisomeric products in further studies.

7.7 Further Investigations into the Scope of the Regioselective Reduction

An investigation into the regioselectivity of the reduction of various *N*-substituted 3-methoxymaleimides was conducted. As anticipated, out of this investigation also transpired the *N*-benzyl analogues **220e** and **222e** that proved to have desirable properties in terms of handling, and formed the basis for the studies in **Section 7.6**.

7.7.1 Synthesis of Reduction Precursors

A number of *N*-substituted 3-methoxymaleimides were prepared *via* two alternate alkylation protocols of **220a** according to **Scheme 102** and these results are summarised in **Table 11**.



Scheme 102

Table 11

Entry	RX	Product	Yield (%)	
			Method A	Method B
1	MeI	**220b**	87	90
2	EtI	**220c**	92	61
3	allyl chloride	**220d**	10	84
4	BnCl	**220e**	99[†]	94
5	PMBCl	**220f**	91	68

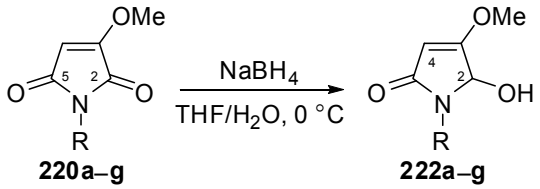
[†] MeCN as solvent, 50 °C (55% yield with acetone).

The potassium carbonate-promoted reaction of **220a** in acetone with an assortment of alkylating reagents (Method A) provided the desired *N*-alkyl-3-methoxymaleimides **220b**, **220c**, and **220f** in good yields (87–92%) when MeI, EtI, or PMBCl were employed (**Entries 1, 2,** and **5** respectively). Alkylation with BnCl did not proceed in high yield under these conditions (55%), however, this situation was rectified by employing MeCN as solvent, bringing the yield to a near quantitative 99% (**Entry 4**). This modification did not prove satisfactory for the allylation of **220a**, where **220d** was isolated in 10% yield with acetone and 2% with MeCN (**Entry 3**). An alternative procedure, employing

cesium fluoride in DMF (Method B), inspired by the facile CsF-promoted *N*-alkylation of phthalimide with alkyl chlorides reported by Clark and Miller,[146] proved to be transferable for most of these alkylations. In particular, reaction of **220a** with allyl chloride under these conditions gave **220d** in 84% yield. One more substrate for trial in the regioselective reduction, **220g**, was prepared[‡] in three steps from *N*-phenylmaleimide by the method of Argade and co-workers.[147]

7.7.2 Scope of the Regioselective Reduction

With a range of *N*-substituted 3-methoxymaleimides (**220a–g**) in hand, the stage was set to explore the scope of the regioselective reduction as shown in **Scheme 103**. The results of this investigation are summarised in **Table 12**.



Scheme 103

Table 12

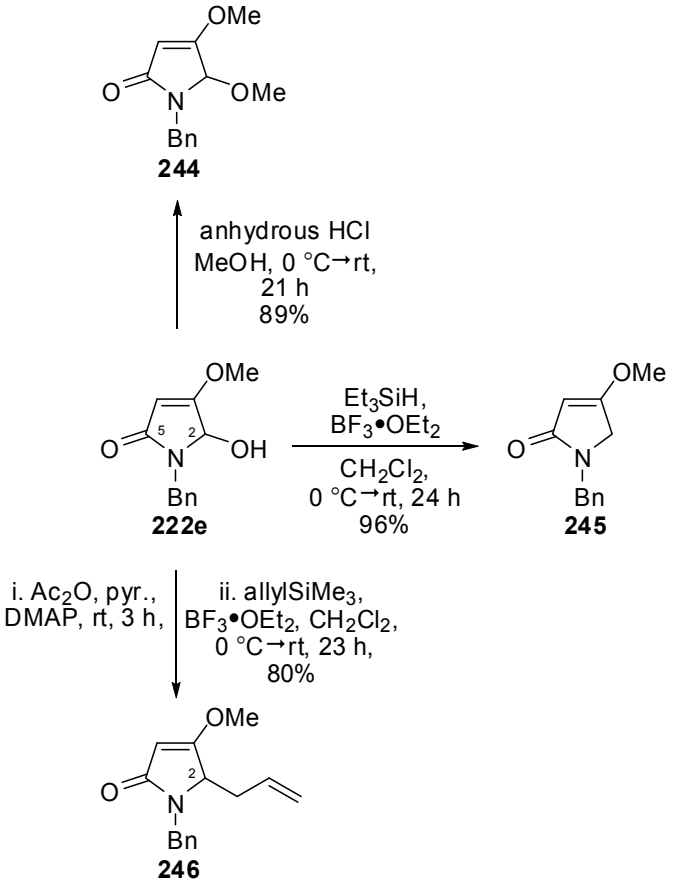
Entry	Substrate	R	Time	Product	Yield (%)
1	**220a**	H	30 min	**222a**	87
2	**220b**	Me	45 min	**222b**	87
3	**220c**	Et	90 min	**222c**	84
4	**220d**	allyl	30 min	**222d**	85
5	**220e**	Bn	100 min	**222e**	83
6	**220f**	PMB	180 min	**222f**	76
7	**220g**	Ph	60 min	**222g**	70

In all cases (**Table 12**, **Entries 1–7**), the conditions developed in **Section 7.3** proved completely transferable and the desired *N*-alkyl methyl 2-hydroxytetramates **222a–g** were isolated in high yield (70–87%). The physical and spectroscopic data of **222b** matched that previously reported,[148] whilst the remainder of the methyl 5-hydroxytetramates, **222c–d**, **222f–g** could be assigned on the basis of comparison of their ^{13}C NMR data.

[‡] Prepared by Dr Fatiah Issa.

Importantly, this study proved that *N*-alkyl methyl 2-hydroxytetramates **222a–g** can be accessed with remarkable regioselectivity using the methodology developed herein. In all cases studied, there was no evidence for the formation of the other regioisomeric product, resulting from hydride attack at the C5 carbonyl of **220a–g**, confirming this outstanding regioselectivity. Further to this, the consistently high yields obtained emphasise the power of this protocol.

To highlight the fact that compounds such as **222a–g** exemplify useful building blocks for tetramate synthesis through exploitation of *N*-acyl iminium ion chemistry, methyl *N*-benzyl-2-hydroxytetramate **222e** was further functionalised according to **Scheme 104**.



Scheme 104

Treatment of **222e** with anhydrous HCl in MeOH afforded methyl 3-methoxytetramate **244** in 89% yield. Alternatively, **222e** could be reduced using triethylsilane and boron trifluoride etherate in CH_2Cl_2 to give **245** (96% yield) thus demonstrating that access to methyl *N*-alkyltetramates can be realised *via* this methodology. 2-Allyltetramates can also be accessed by first forming the acetate of **222e**, then treatment with allyltrimethylsilane in the presence of boron trifluoride etherate, thus generating **246** in good yield (80% over two steps). This series of transformations demonstrates the versatility of **222e** as a building block for more complex systems.

7.8 Biological Evaluation of Tetramic Acid Fragments

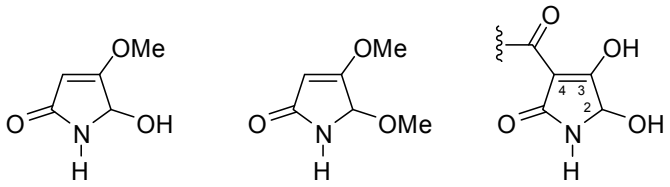


Figure 31

During this body of work, compounds **222a** and **232** were evaluated for activity against HIV-1 integrase. Neither of these compounds displayed any anti-integrase activity in the whole cell assay of Burrel, Li and co-workers.[111-113] These results indicate that there is a fundamental feature for anti-integrase activity that is missing from these structures. This is in fact, not surprising when considering the structures of the compounds tested. Both **222a** and **232** possess a protected 3-hydroxy group, and neither contains the 4-acyl group. These are the major differences between these structures and the native tetramic acid subunit of integramycin (**47**). These differences correlate to the fact that **222a** and **232** do not display the 1,3-dicarbonyl moiety, a crucial feature of the DKA motif. This observation is consistent with the hypothesis that the tetramic acid of integramycin interacts with integrase *via* chelation to a metal ion through the 1,3-dicarbonyl motif, as discussed in **Section 1.4**.

7.9 Summary and Future Work

In summary, an investigation into the synthesis of the tetramic acid subunit of integramycin has been conducted. With this ultimate goal in mind, a protocol for the remarkably selective reduction of 3-methoxymaleimide was developed, and a rationale behind this selectivity has been presented. This reduction protocol proved to proceed with high efficiency and the same remarkable selectivity on a range of *N*-substituted analogues.

Demethylation of **222a** was thwarted by difficulties associated with handling. A brief investigation into the functionalisation of the 4-position concluded that, whilst it was possible to form suitably functionalised systems (**235**), purification proved difficult. Future studies in this area should be conducted on the *N*-benzyl analogue for ease of handling.

A host of derivatives were prepared from **220a** and **220e** to show that the systems generated from this reduction protocol can be utilised as useful building blocks in tetramate synthesis.

–Chapter 8–

Experimental

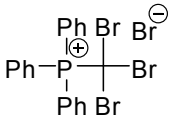
8.1 General Methods

Unless otherwise stated, reactions were conducted under a nitrogen atmosphere and glassware was flame dried under vacuum prior to use. Temperatures quoted as 0 °C and -78 °C were obtained by cooling the reaction vessel in baths of ice/water and dry ice/acetone respectively. Tetrahydrofuran and diethyl ether were dried over sodium wire and distilled from sodium benzophenone ketyl. Toluene was dried over, and distilled from, sodium. Dichloromethane and methanol were distilled from calcium hydride. Where specified as anhydrous methanol, the solvent was distilled from calcium hydride and stored over beaded 3 Å molecular sieves for at least 24 h in accordance with Burfield *et al.*[149] Unless noted otherwise, commercially available reagents were used as purchased without further purification. Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} (0.2 mm) precoated aluminium sheets. Analytical HPLC was performed on a Jones Zorbax SIL (5 μm, 250 mm × 4.6 mm) column and a YMC-Pack DIOL 5 μm 120 Å column (150 × 4.6mm I.D.). Semi-preparative HPLC was performed on a Whatman Partisil 10 (10 μm, 500 mm × 9.4 mm) column and a YMC-Pack DIOL 5 μm 120 Å column (150 × 10mm I.D.). Preparative HPLC was performed on a RTI Zorbax SIL (7 μm, 250 mm × 21.2 mm) column. Solvents for chromatography were distilled prior to use and are quoted as volume/volume mixtures where applicable. Melting points were determined using a Reichert heating stage with microscope and are uncorrected. Optical rotations of enantiopure compounds were recorded on a POLAAR 2001 polarimeter and a JASCO P-1020 polarimeter at 589 nm (sodium D line) with a cell path length of 1 dm and concentrations are reported in g per 100 mL. Infrared absorption spectra were recorded on BioRad FTS-40, BioRad FTS-7, Perkin-Elmer 1600 FTIR or Shimadzu FTIR-8400s spectrophotometers. Absorption maxima are expressed in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200, AVANCE DPX300, DPX400, DRX400 or Varian Unity INOVA 500 MHz spectrometers at 300±1 K. Temperatures quoted for acquisition are approximate and were obtained from the uncalibrated variable temperature unit. ^{1}H NMR chemical shifts are reported in parts per million relative to the residual isotopomer with one less deuterium than the perdeuterated solvent. Splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; m, multiplet. Coupling constants (*J*) are reported in Hz and are reciprocal except where second order effects are manifest. ^{1}H NMR assignments are made where unambiguous. ^{13}C NMR chemical shifts are reported in ppm relative to the internal perdeuterated solvent resonance and are specified as quaternary (C), tertiary (CH), secondary (CH_2) or primary (CH_3) where appropriate, using additional information obtained from DEPT experiments. Two dimensional NMR spectra were recorded on a Bruker DPX400 equipped

with a gradient inverse BB probe. Low resolution and high resolution mass spectra were recorded on Kratos MS25RFA or VG Quattro II triple quadrupole mass spectrometers. Additional low resolution mass spectra were recorded using an Applied Biosystems Mariner ESI-TOF Biospectrometry workstation, and additional high resolution mass spectra were recorded on a Bruker Daltonics Apex III 4.7e Fourier-transform mass spectrometer, fitted with an Apollo API source. The molecular ion, designated as M^+, and major fragment peaks are quoted as percentages relative to the base peak intensity.

8.2 Synthesis of Reagents

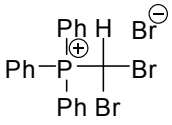
Tribromomethyltriphenylphosphonium bromide (91)



91

The title compound **91** was prepared according to the procedures of Michel and Rassat *et al.*[85] To a suspension of PPh_3 (5.24 g, 20.0 mmol) in bench grade MeCN (25 mL) at rt was added CBr_4 (6.63 g, 20 mmol, 1.0 equiv.) portion-wise. After stirring for 10 min, the precipitate was collected at the pump and washed with Et_2O (20 mL) to afford the title compound **91** (11.13 g, 94%) as a pale yellow powder. This was used immediately in the next step.

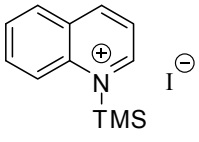
Dibromomethyltriphenylphosphonium bromide (88)



88

The title compound **88** was prepared according to the procedures of Michel and Rassat *et al.*[85] To a suspension of **91** (11.13 g, 18.7 mmol) in bench grade MeCN (50 mL) at rt was added PPh_3 (4.92 g, 18.7 mmol, 1.0 equiv.). The resulting suspension was heated at reflux for 30 min before cooling to rt and allowing to stand for 16 h to affect complete precipitation of the product. The precipitate was collected at the pump and washed with Et_2O (20 mL) to afford the title compound **88** (8.00 g, 83%) as a light yellow powder: **m.p.** 213–215 °C, lit.[86] 144–147 °C. The purity of this compound was assessed by utilising it in a test reaction.

1-Trimethylsilylquinolinium iodide (46)

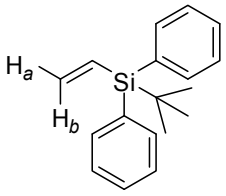


46

The title compound **46** was prepared according to a modified procedure of Ellman *et al.*[49] and Minamikawa *et al.*[50] A solution of iodotrimethylsilane (4.3 mL, 0.032 mmol, 1.0 equiv.) in hexanes (20 mL) was slowly added to a solution of quinoline (7.5 mL, 0.063 mmol, 8.2 g, 2.0 equiv., freshly distilled) in hexanes (50 mL) with vigorous stirring. A yellow precipitate formed immediately and was

collected at the pump under an N_2 atmosphere. The resulting yellow powder was transferred to a sublimation apparatus and sublimed at 104 °C under vacuum (*ca*. 0.2 mm Hg). The whole apparatus was transferred to a dry box and the title compound **46** was recovered from the apparatus and isolated as yellow crystals (2.67 g, 23%) that were used without any further purification in the subsequent step.

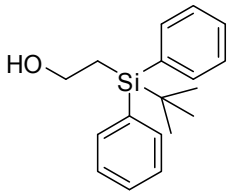
tert-Butyldiphenylvinylsilane (171)



171

Prepared according to the methods of Konopelski and co-workers.[120] A solution of tetravinyltin (3.0 mL, 97%, 3.63 g, 16.0 mmol, 1.0 equiv.) in THF (16 mL) was cooled to -78 °C. *n*-Butyllithium (2.25M in hexanes, 15.6 mL, 35.2 mmol, 2.2 equiv.) was slowly added dropwise and the resulting mixture stirred at -40 °C for 30 min then at 0 °C for a further 30 min. The resulting vinyllithium solution was cooled to -78 °C then *tert*-butyldiphenylchlorosilane (8.35 mL, 98%, 8.79 g, 32.0 mmol, 2.0 equiv.) was slowly added dropwise and the resulting solution allowed to slowly warm to rt and stirring continued for 1 h. The reaction was then quenched by the dropwise addition of H_2O (30 mL), extracted with *n*-pentane (4 × 30 mL) then combined, dried over $MgSO_4$ and the solvent removed *in vacuo* to give a colourless oil. Partial purification by running through a plug of silica (100% hexanes) afforded the title compound **171** (10 g) as a colourless oil that was used without further purification in the subsequent step: $\mathbf{R_f}$ 0.67 (20:80, EtOAc/hexanes); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.66–7.55 (4H, m, 4 × Ar<u>H</u>), 7.41–7.31 (6H, m, 6 × Ar<u>H</u>), 6.57 (1H, dd, *J* = 20.0, 14.8 Hz, SiC<u>H</u>=CH_2), 6.26 (1H, dd, *J* = 14.9, 4.0 Hz, C<u>H</u>$_a$H$_b$=CHSi), 5.71 (1H, dd, *J* = 20.1, 4.0 Hz, CH$_a$<u>H</u>$_b$=CHSi), 1.08 (9H, s, C(C<u>H</u>$_3$)$_3$) ppm. Spectral data were consistent to those previously reported.[120]

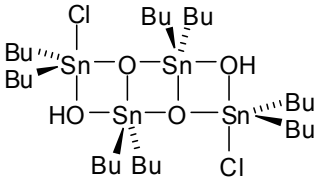
2-(*tert*-Butyldiphenylsilyl)ethanol (172)



172

The title compound **172** was prepared according to the methods of Konopelski and co-workers.[120] To a solution of alkene **171** (8.49 g, 32.0 mmol, 1.0 equiv.) in THF (20 mL) was added 9-BBN dimer (0.5 M in THF, 63.95 mL, 32.0 mmol, 1.0 equiv.) slowly *via* syringe and the resulting solution allowed to stir at rt for 3 h. H_2O (30 mL) and saturated aqueous NaOH (30 mL) were then added followed by the slow addition of aqueous H_2O_2 (30%, 31 mL). After 1 h of stirring at rt, the organic phase was isolated and the aqueous phase extracted with EtOAc (3 × 20 mL), combined and dried over $MgSO_4$.This was concentrated *in vacuo* to give a colourless wax-like solid (14.3 g) that was subjected to column chromatography (20:80 EtOAc/hexanes) which afforded unreacted **171**, (3.63 g, 43%) as a colourless oil whose spectral data were identical to the previously characterised sample, and the title compound **172** (2.58 g, 28% over 2 steps) as a white solid: **m.p.** 65–70 °C (lit.[120] 66–68 °C); $\mathbf{R_f}$ 0.20 (20:80 EtOAc/hexanes); ^{1}**H NMR** (200 MHz, $CDCl_3$) δ 7.70–7.53 (4H, m, 4 × ArH), 7.51–7.30 (6H, m, 6 × ArH), 3.77–3.62 (2H, m, $SiCH_2CH_2OH$), 1.70–1.53 (2H, m, $SiCH_2CH_2OH$), 1.30 (1H, br s, OH), 1.05 (9H, s, $C(CH_3)_3$) ppm. Physical and spectroscopic data were consistent with those previously reported.[120]

Otera's Catalyst (186)

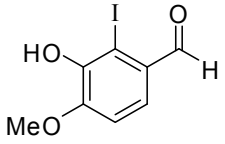


186

Otera's catalyst (**186**) was prepared according to the procedures of Otera *et al.*[132] A suspension of dibutyltin chloride (3.04 g, 10.0 mmol, 1.0 equiv.) and dibutyltin oxide (7.47 g, 30.0 mmol, 3.0 equiv.) in EtOH (100 mL, 95% aqueous) was heated at reflux under ambient atmosphere for 6 h during which time it formed a colourless solution. The solution was cooled to rt and the solvent removed *in vacuo* to give a white powder that was pulverized and left exposed to the atmosphere for 16 h to convert the partially formed ethoxydistannoxane to the corresponding hydroxydistannoxane. Recrystallisation of the crude product from cold hexane afforded Otera's Catalyst **186** (6.43 g, 60%) as a white solid: **m.p.** 111–113 °C (lit.[132,130] 107–115 °C, 109–121 °C).

8.3 Synthesis of Compounds from Chapter 2

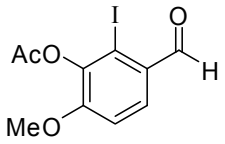
2-Iodoisovanillin (57)



57

Isovanillin (7.77g, 50.0 mmol) was dissolved in pyridine (30 mL) and cooled to 0 °C. A solution of iodine monochloride (2.57 mL, 8.17 g, 50.0 mmol, 1.0 equiv.) in 1,4-dioxane (50 mL) was transferred *via* cannula and the resulting solution protected from light and allowed to warm to rt. Stirring was continued for 6 d, whereupon the solvents were removed *in vacuo*. H_2O (150 mL) was added, and the resulting solution acidified to pH 1 with aqueous HCl (6M, ~7 mL). This was extracted with EtOAc (3 × 150 mL), and the extracts combined and washed sequentially with saturated aqueous sodium bisulfite (2 × 100 mL), H_2O (2 × 150 mL), saturated aqueous NaCl solution (150 mL). The solution was dried over $MgSO_4$ and solvent removed *in vacuo* to yield the title compound **57** (13.10 g, 94%) as a light yellow solid that was used in the subsequent step without further purification: $\mathbf{R_f}$ 0.30 (30:70, hexanes/CH_2Cl_2); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 10.03 (1H, d, J = 0.7 Hz, C<u>H</u>O), 7.55 (1H, d, J = 8.5 Hz, Ar<u>H</u>), 6.92 (1H, d, J = 8.5 Hz, Ar<u>H</u>), 6.32 (1H, s, Ar<u>H</u>), 4.00 (3H, s, OC<u>H</u>$_3$) ppm. Spectroscopic data were in accordance with literature values.[61]

3-Acetoxy-2-iodo-4-methoxybenzaldehyde (58)

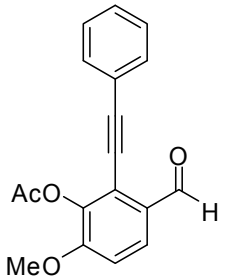


58

To a stirred solution of 2-iodoisovanillin **57** (2.00 g, 7.19 mmol) in pyridine (7.2 mL) was added acetic anhydride (1.02 mL, 1.10 g, 10.8 mmol, 1.5 equiv.) dropwise at rt. The resulting solution was protected from light and allowed to stir at rt for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (100 mL) and stirred for 45 min. This was extracted with EtOAc (3 × 40 mL) and washed with aqueous HCl (1M, 2 × 30 mL), saturated aqueous NaCl solution (30 mL), then dried over $MgSO_4$ before being concentrated *in vacuo* to yield the crude product as a brown solid (2.32 g). This was purified by column chromatography (70:30 CH_2Cl_2/hexanes) to afford the title compound **58** (2.09 g, 91%) as a white solid: **m.p.** 103–105 °C; $\mathbf{R_f}$ 0.25 (30:70, EtOAc/hexanes); **IR** (KBr disc) 3097, 2845, 1770, 1755, 1678, 1485, 1369 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.97 (1H, s, C<u>H</u>O), 7.82 (1H, d, J = 8.7 Hz, Ar<u>H</u>), 7.02 (1H, d, J = 8.7 Hz, Ar<u>H</u>), 3.90 (3H, s, OC<u>H</u>$_3$), 2.40 (3H, s,

OCOC<u>H</u>$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.2 (CH), 167.8 (C), 156.6 (C), 141.0 (C), 129.6 (CH), 128.9 (C), 111.9 (CH), 99.5 (C), 56.6 (CH_3), 20.9 (CH_3) ppm; **HRMS** (EI) Calcd. for $C_{10}H_9IO_4$ $[M]^{\bullet+}$: 319.9546, found 319.9550; **MS** (EI) *m/z* 320 ($[M]^{\bullet+}$, 73%), 278 (100), 150 (14), 122 (15).

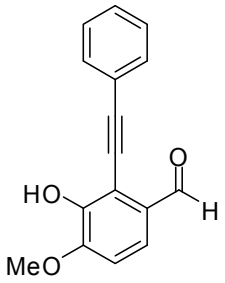
3-Acetoxy-4-methoxy-2-(phenylethynyl)benzaldehyde (70)



70

To a stirred solution of the aryl iodide **58** (581.0 mg, 1.815 mmol) and Et_3N (1.45 mL, 1.05 g, 10.4 mmol, 5.7 equiv.) in MeCN (3.6 mL) was added, in one portion, $Pd(PPh_3)_2Cl_2$ (64 mg, 0.091 mmol, 5 mol%) and CuI (35 mg, 0.18 mmol, 10 mol%). After stirring at rt for 10 min, phenylacetylene (250 μL, 223 mg, 2.18 mmol, 1.2 equiv.) was added dropwise *via* syringe. The resulting solution was allowed to stir for 24 h before being quenched with saturated aqueous $NaHCO_3$ solution (10 mL). This was then diluted with H_2O (100 mL), and extracted with EtOAc (3 × 40 mL) before being washed with saturated aqueous NaCl solution (40 mL) and dried over $MgSO_4$. Concentration *in vacuo* afforded a dark brown oil (757 mg) which was purified by column chromatography (20:80→35:65 EtOAc/hexanes) to yield the title compound **70** (469 mg, 88%) as a white solid: **m.p.** 151–152 °C; **R_f** 0.33 (40:60 EtOAc/hexanes); **IR** (KBr disc) 2937, 2839, 2754, 2214, 1767, 1687, 1309, 1251, 1205, 1192, 1175, 1074 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.44 (1H, d, *J* = 0.5 Hz, C<u>H</u>O), 7.86 (1H, d, *J* = 8.7 Hz, Ar<u>H</u>), 7.54–7.51 (2H, m, 2 × Ar<u>H</u>), 7.40–7.37 (3H, m, 3 × Ar<u>H</u>), 7.04 (1H, d, *J* = 8.7 Hz, Ar<u>H</u>), 3.91 (3H, s, OC<u>H</u>$_3$), 2.41 (3H, s, OCOC<u>H</u>$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.9 (CH), 168.2 (C), 156.3 (C), 141.0 (C), 131.8 (CH), 129.44 (CH), 129.43 (C), 128.7 (CH), 126.9 (CH), 122.24 (C), 122.18 (C), 112.1 (CH), 100.9 (C), 79.8 (C), 56.4 (CH_3), 20.5 (CH_3) ppm; **HRMS** (EI) Calcd. for $C_{18}H_{14}O_4$ $[M]^{\bullet+}$: 294.0892, found : 294.0898; **MS** (EI) *m/z* 294 ($[M]^{\bullet+}$, 14%), 252 (100), 223 (52), 195 (17), 165 (30), 152 (52); Anal. calcd. for $C_{18}H_{14}O_4$: C, 73.46, H, 4.79. Found: C, 73.48, H, 4.94.

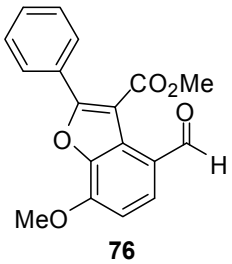
3-Hydroxy-4-methoxy-2-(phenylethynyl)benzaldehyde (71)



71

The acetate **70** (500 mg, 1.70 mmol) was dissolved in 1:1 THF (10 mL) and MeOH (10 mL) and cooled to -10 °C. Aqueous NH_4OH (30% w/v, *ca.* 9M, 2.26 mL, 20 mmol, 12.0 equiv.) was added dropwise and the resulting solution was allowed to stir at -10 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL), then diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with H_2O (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product (436 mg) as a dark brown oil. The oil was purified by column chromatography (40:60 EtOAc/hexanes) to afford the title compound **71** (348 mg, 81%) as a white solid: **m.p.** 127–128 °C; $\mathbf{R_f}$ 0.26 (40:60 EtOAc/hexanes); **IR** (KBr disc) 3212, 1666, 1582, 1485, 1273 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.45 (1H, s, C<u>H</u>O), 7.61–7.57 (2H, m, 2 × Ar<u>H</u>), 7.57 (1H, d, J = 8.6 Hz, Ar<u>H</u>), 7.40–7.37 (3H, m, 3 × Ar<u>H</u>), 6.95 (1H, d, J = 8.6 Hz, Ar<u>H</u>), 6.17 (1H, s, ArO<u>H</u>), 3.99 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.6 (CH), 151.4 (C), 147.1 (C), 131.9 (CH), 129.5 (C), 129.2 (CH), 128.6 (CH), 122.5 (C), 121.3 (CH), 112.8 (C), 110.7 (CH), 101.2 (C), 80.1 (C), 56.5 (CH_3) ppm; **HRMS** (EI) Calc. for $C_{16}H_{12}O_3$ $[M]^{\bullet+}$: 252.0786, found: 252.0785; **MS** (EI) *m/z* 252 ($[M]^{\bullet+}$, 45%), 237 (12), 223 (100), 205 (10), 175 (12), 152 (64); Anal. calcd. for $C_{16}H_{12}O_3$: C, 76.18, H, 4.79, found C, 75.80, H, 4.54.

Methyl 4-formyl-7-methoxy-2-phenyl-1-benzofuran-3-carboxylate(76)



76

Procedure 1[†]

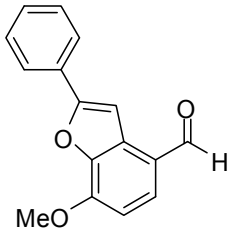
Phenol **71** (21.2 mg, 0.084 mmol), $Pd(PPh_3)_2Cl_2$ (6.0 mg, 0.0085 mmol, 10 mol%), Cs_2CO_3 (137 mg, 0.419 mmol, 5.0 equiv.) and CBr_4 (139 mg, 0.420 mmol, 5.0 equiv.) were dissolved in MeOH (1.0 mL) and purged with $CO_{(g)}$ (× 4). The resulting solution was heated to 50 °C for 3 h before cooling to rt

[†] Reaction conducted by Dr M. J. Coster.

and diluting with Et_2O (2 mL). This was then filtered through a plug of silica, eluting with Et_2O and concentrated *in vacuo* to yield a brown oil which was purified by column chromatography (20:80→40:60 EtOAc/hexanes) to afford the title compound **76** (4.9 mg, 19%) as an off-white solid: **m.p.** 138–140 °C; $\mathbf{R_f}$ 0.25 (40:60 EtOAc/hexanes); **IR** (KBr disc) 2951, 2841, 1728, 1678, 1618, 1566, 1300, 1238, 1058 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.08 (1H, s, C<u>H</u>O), 7.93–7.91 (2H, m, 2 × Ar<u>H</u>), 7.77 (1H, d, J = 8.4 Hz, Ar<u>H</u>), 7.49–7.26 (3H, m, 3 × Ar<u>H</u>), 6.96 (1H, d, J = 8.5 Hz, Ar<u>H</u>), 4.12 (3H, s, COOC<u>H</u>$_3$), 4.00 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.9 (CH), 166.2 (C), 157.2 (C), 150.1 (C), 143.5 (C), 131.9 (CH), 130.3 (CH), 129.0 (C), 128.9 (CH), 127.7 (CH), 126.9 (C), 123.4 (C), 111.5 (C), 106.7 (CH), 56.6 (CH_3), 52.8 (CH_3) ppm; **HRMS** (EI) Calcd. for $C_{18}H_{14}O_5$ $[M]^{\bullet+}$: 310.0841, found: 310.0836; **MS** (EI) *m/z* 310 ($[M]^{\bullet+}$, 82%), 295 (82), 279 (41), 251 (100), 221 (45), 165 (31), 152 (28).

Procedure 2

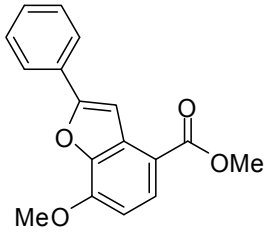
Diarylalkyne **70** (147.0 mg, 0.500 mmol), PdI_2 (9.0 mg, 0.025 mmol, 5 mol%), thiourea (2 mg, 0.025 mmol, 5 mol%), Cs_2CO_3 (815 mg, 2.50 mmol, 5.0 equiv.) and CBr_4 (830 mg, 2.05 mmol, 5.0 equiv.) were dissolved in MeOH (4.0 mL) and purged with $CO_{(g)}$ (× 4). The resulting solution was heated to 45 °C for 2 h before cooling to rt and diluting with Et_2O (30 mL). This was then filtered through a plug of silica, eluting with Et_2O and concentrated *in vacuo* to yield a brown oil which was purified by column chromatography (40:60 EtOAc/hexanes) to afford the title compound **76** (42.0 mg, 27%) as an off-white solid, spectroscopically identical to that isolated from procedure 1, and the protio-cyclised by-product **72** (31.1 mg, 25%).



72

7-Methoxy-2-phenyl-1-benzofuran-4-carbaldehyde (72): off-white solid: **m.p.** 138–140 °C; $\mathbf{R_f}$ 0.37 (40:60 EtOAc/hexanes); **IR** (KBr disc) 2817, 2727, 1681, 1672, 1622, 1581, 1415, 1178, 1101 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.04 (1H, s, C<u>H</u>O), 7.95–7.92 (2H, m, 2 × Ar<u>H</u>), 7.78 (1H, s, Ar<u>H</u>), 7.64 (1H, d, J = 8.4 Hz, Ar<u>H</u>), 7.49–7.38 (3H, m, 3 × Ar<u>H</u>), 6.87 (1H, d, J = 8.3 Hz, Ar<u>H</u>), 4.11 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.8 (CH), 159.1 (C), 149.9 (C), 144.2 (C), 132.1 (CH), 130.1 (C), 129.8 (C), 129.4 (CH), 129.0 (CH), 125.5 (CH), 123.1 (C), 106.2 (CH), 102.1 (CH), 56.6 (CH_3) ppm; **HRMS** (EI) calcd. for $C_{16}H_{12}O_3$ $[M]^{\bullet+}$: 252.0786, found 252.0789; **MS** (EI) *m/z* 252 ($[M]^{\bullet+}$, 100%), 223 (14), 165 (14), 152 (17).

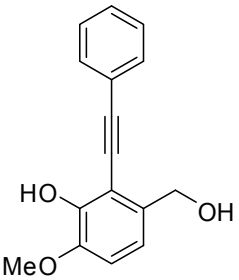
Methyl 7-methoxy-2-phenyl-1-benzofuran-4-carboxylate (73)



73

Protio-cyclised benzofuran **72** (100.0 mg, 0.396 mmol), PdI_2 (7 mg, 0.02 mmol, 5 mol%), thiourea (1.5 mg, 0.02 mmol, 5 mol%), Cs_2CO_3 (652 mg, 1.98 mmol, 5.0 equiv.) and CBr_4 (657 mg, 1.98 mmol, 5.0 equiv.) were dissolved in MeOH (3.2 mL) and purged with $CO_{(g)}$ (× 4). The resulting solution was heated to 45 °C for 3 h before cooling to rt and diluting with Et_2O (8 mL). This was then filtered through a plug of silica eluting with Et_2O and concentrated *in vacuo* to yield a brown oil which was purified by column chromatography (40:60 EtOAc/hexanes) to afford the title compound **73** (11.2 mg, 10%) as a brown solid: $\mathbf{R_f}$ 0.50 (40:60 EtOAc/hexanes); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.63–7.50 (3H, m, 3 × Ar<u>H</u>), 7.16–6.94 (4H, m, 4 × Ar<u>H</u>), 6.45 (1H, d, J = 8.5 Hz, Ar<u>H</u>), 3.73 (3H, s, OC<u>H</u>$_3$), 3.61 (3H, s, OC<u>H</u>$_3$) ppm; **MS** (EI) m/z 282 ($[M]^{\bullet+}$, 100%), 251 (72), 165 (12).

3-(Hydroxymethyl)-6-methoxy-2-(phenylethynyl)phenol (79)

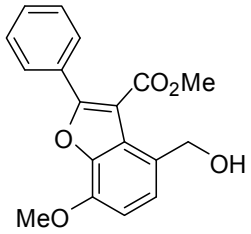


79

Aldehyde **71** (50.0 mg, 0.198 mmol) was dissolved in MeOH (1.5 mL) and THF (0.25 mL) and cooled to 0 °C before the addition of $NaBH_4$ (7.7 mg, 0.20 mmol, 1.0 equiv.) in one portion. This was allowed to stir at 0 °C for 40 min before being quenched with acetone (2 mL), diluted with H_2O (20 mL) and extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield a colourless wax-like solid (48.3 mg) that was subjected to column chromatography (50:50 EtOAc/hexanes) to afford the title compound **79** (40.5 mg, 80%) as an off-white solid: **m.p.** 112–114 °C; $\mathbf{R_f}$ 0.23 (50:50 EtOAc/hexanes); **IR** (KBr disc) 3500, 3404, 2204, 1610, 1485, 1441, 1274, 1236, 1074 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59–7.56 (2H, m, 2 × Ar<u>H</u>), 7.37–7.35 (3H, m, 3 × Ar<u>H</u>), 6.95 (1H, d, J = 8.4 Hz, Ar<u>H</u>), 6.85 (1H, d, J = 8.3 Hz, Ar<u>H</u>), 6.02 (1H, s, ArO<u>H</u>), 4.81 (2H, d, J = 5.9 Hz, C<u>H</u>$_2$OH), 3.91 (3H, s, OC<u>H</u>$_3$), 2.05 (1H, t, J = 6.2 Hz, CH$_2$O<u>H</u>) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.2 (C), 146.3 (C), 135.6 (C), 131.8 (CH),

128.8 (CH), 128.5 (CH), 123.0 (C), 119.1 (CH), 111.2 (CH), 108.4 (C), 99.1 (C), 82.0 (C), 64.2 (CH_2), 56.3 (CH_3) ppm; **HRMS** (EI) Calcd. for $C_{16}H_{14}O_3$ $[M]^{\bullet+}$: 254.0943, found: 254.0939; **MS** (EI) *m/z* 254 ($[M]^{\bullet+}$, 83%), 237 (47), 223 (22), 194 (90), 165 (100), 152 (45), 105 (20), 77 (20).

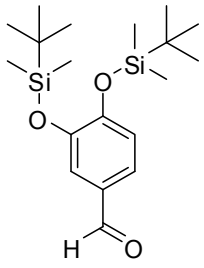
Methyl 4-(hydroxymethyl)-7-methoxy-2-phenyl-1-benzofuran-3-carboxylate (80)



80

The *ortho*-hydroxydiarylalkyne **79** (20.0 mg, 0.079 mmol), PdI_2 (4.3 mg, 0.012 mmol, 15 mol%), thiourea (0.9 mg, 0.0118 mmol, 15 mol%), Cs_2CO_3 (129 mg, 0.393 mmol, 5.0 equiv.), and CBr_4 (130 mg, 0.393 mmol, 5.0 equiv.) were dissolved in MeOH (0.63 mL) and THF (0.20 mL) and flushed with $CO_{(g)}$ 4 times. The resulting solution was heated at 45 °C for 6 h before being cooled and diluted with Et_2O (2 mL). This was then filtered through a plug of silica eluting with Et_2O and concentrated *in vacuo* to yield a brown oil (51 mg) which was purified by column chromatography (50:50 EtOAc/hexanes) to afford the title compound **80** (19.6 mg, 80%) as a pale yellow film: $\mathbf{R_f}$ 0.29 (50:50 EtOAc/hexanes); **IR** (thin film) 3412, 3003, 2949, 2839, 1724, 1514, 1283, 1236, 1041 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75–7.73 (2H, m, 2 × ArH), 7.48–7.45 (3H, m, 3 × ArH), 7.19 (1H, d, J = 8.0 Hz, ArH), 6.81 (1H, d, J = 8.2 Hz, ArH), 4.79 (2H, d, J = 3.0 Hz, $ArCH_2OH$), 4.01 (3H, s, $COOCH_3$), 3.84 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9 (C), 159.3 (C), 145.4 (C), 144.2 (C), 130.1 (CH), 129.9 (C), 128.9 (CH), 128.4 (CH), 127.1 (C), 126.3 (C), 126.1 (CH), 110.0 (C), 107.0 (CH), 63.7 (CH_2), 56.3 (CH_3), 52.4 (CH_3) ppm; **HRMS** Calcd. for $C_{18}H_{16}O_5$ $[M]^{\bullet+}$: 312.0998, found 312.0995; **MS** (EI) *m/z* 312 ($[M]^{\bullet+}$, 63%), 279 (100), 251 (97), 236 (16), 165 (27), 152 (25).

3,4-Bis(*tert*-butyldimethylsilyloxy)benzaldehyde (82)

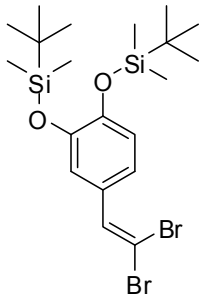


82

To a solution of 3,4-dihydroxybenzaldehyde (2.00 g, 14.48 mmol) in DMF (6.0 mL) at rt was added, *via* cannula, a solution of *tert*-butyldimethylsilyl chloride (4.73 g, 30.4 mmol, 2.1 equiv.) and imidazole (3.98 g, 57.9 mmol, 4 equiv.) in DMF (7.5 mL). The resulting solution was left to stir at rt for 20 h

before being diluted with H_2O (200 mL). This was extracted with Et_2O (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil (6.03 g) that was subjected to column chromatography (15:85 EtOAc/hexanes) to afford the title compound **82** (4.55 g, 86%) as a colourless oil: **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.80 (1H, s, C<u>H</u>O), 7.45–7.29 (2H, m, 2 × Ar<u>H</u>), 6.94 (1H, d, *J* = 8.7 Hz, Ar<u>H</u>), 0.99 (18H, s, 2 × C(C<u>H</u>$_3$)$_3$), 0.25 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.23 (6H, s, Si(C<u>H</u>$_3$)$_2$) ppm. ^{1}H NMR data in accordance with literature values.[150]

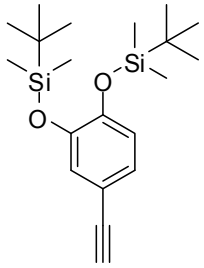
4-(2',2'-Dibromoethenyl)-1,2-bis(*tert*-butyldimethylsilyloxy)benzene (89)



89

To a suspension of the phosphonium salt **88** (10.30 g, 20.00 mmol, 2.0 equiv.) in THF (100 mL) at rt was added *t*-BuOK (1M solution in THF, 19.0 mL, 19.0 mmol, 1.9 equiv.). The resulting suspension was allowed to stir for 5 min before a solution of aldehyde **82** (3.67 g, 10.0 mmol) in THF (20.0 mL) was added *via* syringe. The resulting suspension was allowed to stir at rt for 40 min before being quenched by the addition of saturated aqueous NaCl solution (150 mL) then extracted with EtOAc (3 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product as a dark brown solid (10.21 g). This was purified by column chromatography (100% hexanes) to afford the title compound **89** (5.097 g, 97%) as a colourless oil that was used as soon as possible in the next step: **R_f** 0.24 (100% hexanes); **IR** (thin film) 2955, 2930, 2856, 1597, 1559, 1510, 1502, 1296, 1254 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (1H, s, Ar<u>H</u>), 7.22 (1H, d, *J* = 2.2 Hz, Ar<u>H</u>), 6.96 (1H, ddd, *J* = 8.4 Hz, *J* = 2.2 Hz, *J* = 0.5 Hz, Ar<u>H</u>), 6.80 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 1.00 (18H, s, 2 × OSiC(C<u>H</u>$_3$)$_3$), 0.23 (6H, s, OSi(C<u>H</u>$_3$)$_2$), 0.22 (6H, s, OSi(C<u>H</u>$_3$)$_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.7 (C), 146.8 (C), 136.5 (CH), 128.6 (C), 122.7 (CH), 120.9 (CH), 120.7 (CH), 87.0 (C), 26.08 (CH_3), 26.07 (CH_3), 18.6 (C), -3.9 (CH_3) ppm; **HRMS** (EI) Calcd. for $C_{20}H_{34}Br_2O_2Si_2$ $[M]^{\bullet+}$: 520.0464, found 520.0464; **MS** (+ESI) *m/z* 523 ($[M^{81}Br^{79}Br+H]^+$, 25%), 465 (50%), 271 (44%), 269 (47%), 73 (100%).

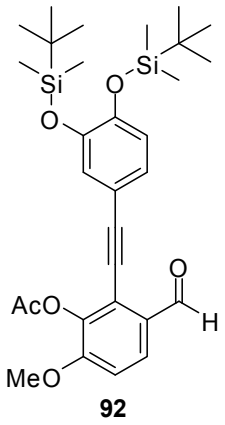
4-Ethynyl-1,2-bis(*tert*butyldimethylsilyloxy)benzene (90)



90

To a solution of dibromoalkene **89** (5.07 g, 9.71 mmol) in THF (130 mL) at -78 °C was added *n*-butyllithium (16.75 ml, 1.45 M solution in hexanes, 24.27 mmol, 2.5 equiv.) and left to stir at -78 °C for 1 h. The reaction was quenched with saturated aqueous NaCl solution (100 mL) at -78 °C and stirred for 10 min whilst warming to rt, then extracted with EtOAc (2 × 100 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield a yellow oil (3.71 g) which was subjected to column chromatography (5:95 CH_2Cl_2/hexanes) to afford the title compound **90** (2.99 g, 85%) as a colourless oil: $\mathbf{R_f}$ 0.28 (5:95 CH_2Cl_2/hexanes); **IR** (thin film) 3313, 2957, 2930, 2858, 2106, 1595, 1506, 1300, 1256, 980, 904, 839 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.98 (1H, dd, J = 8.7 Hz, J = 2.0 Hz, ArH), 6.97 (1H, s, ArH), 6.76 (1H, d, J = 8.0 Hz, ArH), 2.96 (1H, s, C≡CH), 0.99 (9H, s, $SiC(CH_3)_3$), 0.98 (9H, s, $SiC(CH_3)_3$), 0.21 (12H, s, 2 × $Si(CH_3)_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.4 (C), 146.8 (C), 126.1 (CH), 124.9 (CH), 121.1 (CH), 115.0 (C), 83.9 (CH), 75.6 (C), 26.1 (CH_3), 18.63 (C), 18.57 (C), -3.9 (CH_3), -4.0 (CH_3) ppm; **HRMS** (EI) Calcd. for $C_{20}H_{34}O_2Si_2$ $[M]^{\bullet+}$: 362.2097, found 362.2093; **MS** (EI) *m/z* 362 ($[M]^{\bullet+}$, 73%), 347 (20), 305 (87), 249 (23), 115 (43), 73 (100).

2-{[3',4'-Bis(*tert*butyldimethylsilyloxy)phenyl]ethynyl}-3-acetoxy-4-methoxybenzaldehyde (92)

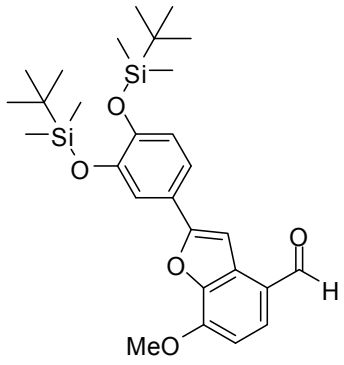


92

Procedure 1

To a solution of arylacetylene **90** (217.6 mg, 0.600 mmol, 1.2 equiv.) in MeCN (500 μL), was added NEt_3 (400 μL), followed by CuI (9.5 mg, 0.05 mmol, 10 mol%) then $Pd(PPh_3)_2Cl_2$ (17.5 mg, 0.025 mmol, 5 mol%) and the resulting solution allowed to stir at rt for 10 min. A solution of aryliodide **58** (160.0 mg, 0.500 mmol, 1.0 equiv.) in MeCN (250 μL) was then added, and rinsed in with a further portion of MeCN (250 μL). The reaction was excluded from light by aluminium foil, and allowed to stir at rt for 19 h before addition of a further portion of arylacetylene **90** (54.4 mg, 0.150 mmol, 0.3 equiv.) in MeCN (250 μL). After an additional 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (3 mL) and diluted with H_2O (20 mL) before extraction with EtOAc (3 × 20 mL). The combined organic extracts were washed sequentially with H_2O (2 × 20 mL), saturated aqueous NaCl solution (20 mL) then dried over $MgSO_4$ and concentrated *in vacuo* to give a brown foam (352 mg). This crude material was purified by column chromatography (15:85 EtOAc/hexanes) to afford the proti-cyclised benzofuran **93** (34.6 mg, 14%) and the title compound **92** (45.3 mg, 16%).

Diarylalkyne 92: off-white solid; **m.p.** 111–112 °C; $\mathbf{R_f}$ 0.18 (20:80 EtOAc/hexanes); **IR** (KBr disc) 2955, 2930, 2208, 1769, 1688, 1512, 1321, 1193, 835 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.43 (1H, d, J = 0.5 Hz, C<u>H</u>O), 7.86 (1H, d, J = 8.7 Hz, Ar<u>H</u>), 7.02 (1H, dd, J = 8.2 Hz, J = 1.7 Hz, Ar<u>H</u>), 7.02 (1H, d, J = 8.2 Hz, Ar<u>H</u>), 6.99 (1H, d, J = 2.0 Hz, Ar<u>H</u>), 6.82 (1H, d, J = 8.2 Hz, Ar<u>H</u>), 3.92 (3H, s, OC<u>H</u>$_3$), 2.40 (3H, s, OCOC<u>H</u>$_3$), 1.00 (18H, s, 2 × SiC(C<u>H</u>$_3$)$_3$), 0.23 (12H, s, 2 × Si(C<u>H</u>$_3$)$_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.1 (CH), 168.2 (C), 156.3 (C), 149.1 (C), 147.1 (C), 140.9 (C), 129.4 (C), 126.9 (CH), 125.8 (CH), 124.4 (CH), 122.8 (C), 121.4 (CH), 114.9 (C), 111.8 (CH), 101.5 (C), 78.5 (C), 56.5 (CH_3), 26.0 (CH_3), 20.6 (CH_3), 18.7 (C), 18.6 (C), -3.9 (CH_3), -4.0 (CH_3) ppm; **HRMS** (+ESI) Calcd. for $C_{30}H_{43}O_6Si_2$ $[M+H]^+$: 555.2595, found: 555.2611; **MS** (+ESI) *m/z* 578 ($[M+Na]^+$, 49%), 555 ($[M+H]^+$, 100), 513 (30).

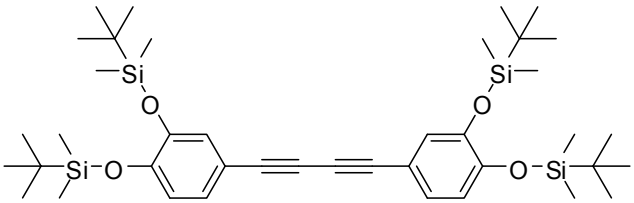


93

7-Methoxy-2-[3',4'-Bis(*tert*butyldimethylsilyloxy)phenyl]-1-benzofuran-4-carbaldehyde (93): off-white solid; **m.p.** 104–106 °C; $\mathbf{R_f}$ 0.31 (20:80 EtOAc/hexanes); **IR** (thin film) 2955, 2930, 2858, 2721, 1682, 1620, 1580, 1495, 1396, 1286, 1207 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.05 (1H, s, C<u>H</u>O), 7.64 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 7.60 (1H, s, Ar<u>H</u>), 7.44 (1H, dd, *J* = 8.4 Hz, *J* = 2.1 Hz, Ar<u>H</u>), 7.37 (1H, d, *J* = 2.1 Hz, Ar<u>H</u>), 6.91 (1H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.86 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 4.14 (3H, s, ArOC<u>H</u>$_3$), 1.03 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 1.00 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.26 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.24 (6H, s, Si(C<u>H</u>$_3$)$_2$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.6 (CH), 159.4 (C), 149.8 (C), 148.7 (C), 147.4 (C), 144.0 (C), 132.0 (CH), 130.6 (C), 123.5 (C), 122.9 (C), 121.5 (CH), 119.4 (CH), 118.5 (CH), 106.2 (CH), 100.7 (CH), 56.7 (CH_3), 26.11 (CH_3), 26.08 (CH_3), 18.68 (C), 18.60 (C), -3.88 (CH_3), -3.89 (CH_3) ppm; **HRMS** (EI) Calcd. For $C_{28}H_{40}O_5Si_2$ $[M]^{\bullet+}$: 512.2414, found 512.2416; **MS** (EI) *m/z* 512 ($[M]^{\bullet+}$, 15%), 455 (100), 341 (320), 339 (33).

Procedure 2

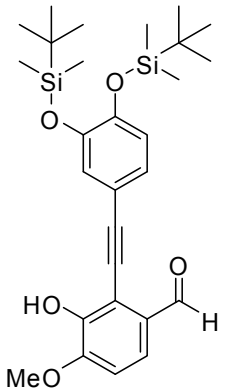
To the arylacetylene **90** (79.7 mg, 0.220 mmol, 1.1 equiv.) and aryliodide **58** (64.0 mg, 0.200 mmol, 1.0 equiv.) in a flask at -20 °C was added degassed, anhydrous EtOAc (10.0 mL) then *i*-Pr_2NH (34 μL, 22 mg, 0.24 mmol, 1.2 equiv.). This was promptly followed by the addition of CuI (4 mg, 0.02 mmol, 10 mol%) then $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol, 5 mol%). The reaction vessel was excluded from light by foil and allowed to warm to rt over 1 h and stirring was continued for 17 h. The reaction was quenched with H_2O (10 mL) and saturated aqueous NaCl solution (40 mL). The resulting mixture was extracted with EtOAc (3 × 40 mL) and the combined organic extracts were washed with saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil (141 mg). 110 mg of this crude material was purified by column chromatography (20:80 EtOAc/hexanes) to afford the title compound **92** (70.4 mg, 63% isolated, 81% extrapolated yield) as an off-white solid that was spectroscopically identical to that isolated in *procedure 1*. This was accompanied by the formation of the homocoupled by-product **94** (17.7 mg, 12% isolated, 16% extrapolated yield).



94

1,1'-Buta-1,3-diyne-1,4-diylbis[3,4-Bis(*tert*butyldimethylsilyloxy)benzene] (94): yellow solid; **m.p.** 145–146 °C; $\mathbf{R_f}$ 0.83 (20:80 EtOAc/hexanes); **IR** (thin film) 2956, 2931, 2859, 2147, 1506, 1300, 900, 839 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.01 (2H, dd, *J* = 8.2 Hz, *J* = 2.0 Hz, ArH), 6.98 (2H, d, *J* = 2.0 Hz, ArH), 6.76 (2H, d, *J* = 8.2 Hz, ArH) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.9 (C), 146.9 (C), 126.6 (CH), 125.0 (CH), 121.2 (CH), 114.7 (C), 81.5 (C), 72.8 (C), 26.0 (CH_3), 18.64 (C), 18.58 (C), -3.92 (CH_3), -3.98 (CH_3) ppm; **HRMS** (EI) Calc. for $C_{40}H_{66}O_4Si_4$ $[M]^{\bullet+}$: 722.4038, found: 722.4042; **MS** (EI) *m/z* 722 ($[M]^{\bullet+}$, 50%), 665 (23), 609 (12), 535 (10), 479 (45), 73 (100).

2-{[3',4'-Bis(*tert*butyldimethylsilyloxy)phenyl]ethynyl}-3-hydroxy-4-methoxybenzaldehyde (95)

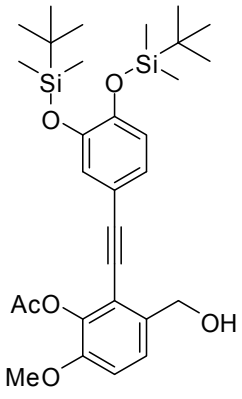


95

The acetate **92** (62.4 mg, 0.112 mmol) was dissolved in 1:1 THF (0.66 mL) and MeOH (0.66 mL) and cooled to -15 °C. Aqueous NH_4OH (30% w/v, *ca.* 9M, 150 μL, 1.344 mmol, 12 equiv.) was added dropwise and the resulting solution was placed in the freezer (-15 °C) for 18 h before being allowed to warm to rt. The solution was again cooled to -15 °C to quench with saturated aqueous NH_4Cl solution (3 mL). This was then diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield a yellow film (53 mg) which was purified by column chromatography (40:60 EtOAc/hexanes) to afford the title compound **95** as a wax-like pale yellow solid (50.4 mg, 87%); $\mathbf{R_f}$ 0.54 (40:60 EtOAc/hexanes); **IR** (thin film) 2955, 2930, 2858, 2206, 1688, 1591, 1510, 1273, 1256 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (1H, s, CHO), 7.56 (1H, d, *J* = 8.6 Hz, ArH), 7.09 (1H, dd, *J* = 8.3 Hz, *J* = 2.1 Hz, ArH), 7.05 (1H, d, *J* = 2.0 Hz, ArH), 6.94 (1H, d, *J* = 8.5 Hz, ArH), 6.82 (1H, d, *J* = 8.3 Hz, ArH), 6.08

(1H, s, ArO<u>H</u>), 3.99 (3H, s, OC<u>H</u>$_3$), 0.999 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.988 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.22 (12H, s, 2 × Si(C<u>H</u>$_3$)$_2$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.8 (CH), 151.4 (C), 148.9 (C), 147.1 (C), 146.9 (C), 129.4 (C), 125.9 (CH), 124.5 (CH), 121.4 (CH), 121.2 (CH), 115.1 (C), 113.4 (C), 110.5 (CH), 101.7 (C), 78.5 (C), 56.5 (CH_3), 26.2 (CH_3) ppm, 18.67 (C), 18.58 (C), -3.89 (CH_3), -3.95 (CH_3); **HRMS** (EI) Calcd. for $C_{28}H_{40}O_5Si_2$ $[M]^{\bullet+}$: 512.2414, found 512.2406; **MS** (EI) *m/z* 512 ($[M]^{\bullet+}$, 61%), 497 (12), 483 (32), 455 (100), 383 (32), 341 (46), 325 (40), 232 (26).

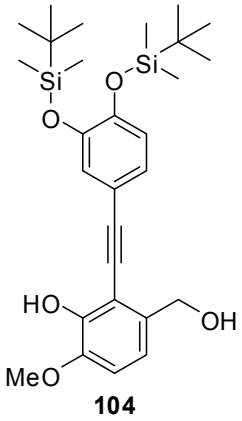
2-{[3',4'-Bis(*tert*butyldimethylsilyloxy)phenyl]ethynyl}-3-(hydroxymethyl)-6-methoxyphenyl acetate (103)



103

To a stirred solution of **92** (200 mg, 0.360 mmol) in THF (8 mL) and H_2O (4 mL) at 0 °C was added $NaBH_4$ (68 mg, 1.8 mmol, 5.0 equiv.) in one portion. After stirring for 1 h at 0 °C, the reaction was quenched by the addition of acetone (~3 mL, bench grade) and then allowed to warm to rt. To the resulting solution was added saturated aqueous NH_4Cl solution (40 mL) and then extracted with Et_2O (4 × 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to yield an off-white foam (206 mg) which was purified by column chromatography (50:50 EtOAc/hexanes) to afford the title compound **103** (172 mg, 86%) as a wax-like white solid: $\mathbf{R_f}$ 0.32 (40:60 EtOAc/hexanes); **IR** (thin film) 2955, 2930, 2858, 1771, 1595, 1512, 1406, 1317, 1269, 1202, 1074, 989, 901, 835, 783 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.27 (1H, m, Ar<u>H</u>), 6.99–6.93 (3H, m, 3 × Ar<u>H</u>), 6.79 (1H, d, J = 8.2 Hz, Ar<u>H</u>), 4.81 (2H, s, ArC<u>H</u>$_2$OH), 3.84 (3H, s, ArOC<u>H</u>$_3$), 2.37 (3H, s, ArO(CO)C<u>H</u>$_3$), 2.02 (1H, br s, ArCH$_2$O<u>H</u>), 1.00 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.99 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.22 (12H, s, 2 × Si(CH$_3$)$_2$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6 (C), 151.0 (C), 148.6 (C), 147.0 (C), 140.9 (C), 135.4 (C), 125.69 (CH), 125.59 (CH), 124.3 (CH), 121.3 (CH), 117.5 (C), 115.5 (C), 112.2 (CH), 99.1 (C), 80.3 (C), 63.8 (CH_2), 56.3 (CH_3), 29.8 (C), 26.0 (CH_3), 20.7 (CH_3), 18.65 (C), 18.58 (C), -3.92 (CH_3), -3.97 (CH_3) ppm; **HRMS** Calcd. for $C_{30}H_{44}O_6Si_2$ $[M]^{\bullet+}$: 556.2676, found 556.2670; **MS** (EI) *m/z* 556 ($[M]^{\bullet+}$, 4%), 499 (2), 367 (100), 325 (49), 179 (19), 73 (47).

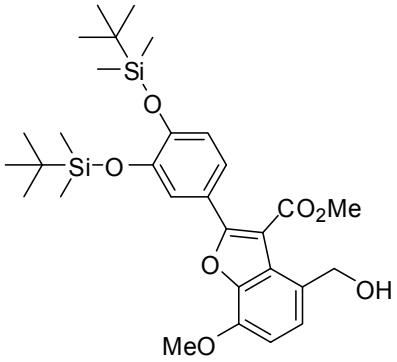
2-{[3',4'-Bis(*tert*butyldimethylsilyloxy)phenyl]ethynyl}-3-(hydroxymethyl)-6-methoxyphenol (104)



104

To a solution of **95** (25.0 mg, 0.0486 mmol) in 2:1 THF (2.0 mL) and H_2O (1.0 mL) at 0 °C was added $NaBH_4$ (1.8 mg, 0.048 mmol, 1.0 equiv.) in one portion. After stirring at 0 °C for 3 h, the reaction was quenched with acetone (~2 mL, bench grade) and allowed to warm to rt before being partitioned between saturated aqueous NH_4Cl solution (20 mL) and Et_2O (30 mL). The organic phase was isolated and the aqueous phase extracted with Et_2O (2 × 30 mL). The combined organic phases were dried over $MgSO_4$ then concentrated *in vacuo* to give a yellow oil (24 mg) that was subjected to column chromatography (50:50 EtOAc/hexanes) to afford the title compound **104** (22.9 mg, 92%) as a colourless oil: $\mathbf{R_f}$ 0.50 (50:50 EtOAc/hexanes); **IR** (thin film) 2955, 2930, 2858, 1593, 1558, 1510, 1485, 1471, 1283, 1256, 1074, 987, 897, 833, 783 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (1H, dd, J = 8.2 Hz, J = 2.0 Hz, ArH), 7.02 (1H, d, J = 2.0 Hz, ArH), 6.93 (1H, d, J = 8.2 Hz, ArH), 6.83 (1H, d, J = 8.3 Hz, ArH), 6.80 (1H, d, J = 8.3 Hz, ArH), 5.99 (1H, s, ArOH), 4.78 (2H, d, J = 6.1 Hz $ArCH_2OH$), 3.91 (3H, s, $ArOCH_3$), 2.07 (1H, br t, J = 6.5 Hz, $ArCH_2OH$), 1.00 (9H, s, $SiC(CH_3)_3$), 0.99 (9H, s, $SiC(CH_3)_3$), 0.22 (12H, s, 2 × $Si(CH_3)_2$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.5 (C), 147.0 (C), 146.3 (C), 135.5 (C), 125.7 (CH), 124.4 (CH), 121.3 (CH), 119.2 (CH), 115.6 (C), 111.0 (CH), 108.8 (C), 99.5 (C), 80.3 (C), 64.2 (CH_2), 56.4 (CH_3), 26.1 (CH_3), 18.68 (C), 18.58 (C), -3.90 (CH_3), -3.95 (CH_3) ppm; **HRMS** (–ESI) Calc. for $C_{28}H_{41}O_5Si_2$ $[M–H]^-$: 513.2501, found: 513.2520; **MS** (–ESI) *m/z* 513 ($[M–H]^-$, 5%), 400 (100).

Methyl 2-[3',4'-Bis(*tert*butyldimethylsilyloxy)phenyl]-4-(hydroxymethyl)-7-methoxy-1-benzofuran-3-carboxylate (105)

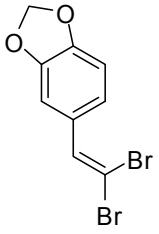


105

To a flask containing *ortho*-hydroxydiarylalkyne **104** (30.0 mg, 0.058 mmol), anhydrous $CuCl_2$ (23.5 mg, 0.175 mmol, 3.0 equiv.), anhydrous NaOAc (19.1 mg, 0.233 mmol, 4.0 equiv.) and $PdCl_2$ (1 mg, 0.005 mmol, 10 mol%), was added anhydrous MeOH (0.6 mL) and the system quickly purged with $CO_{(g)}$ (× 4). The resulting suspension was allowed to stir at rt under an atmosphere of $CO_{(g)}$ for 2.5 h before being quenched by the addition of H_2O (1 mL). The resulting mixture was then partitioned between saturated aqueous NaCl solution (30 mL) and CH_2Cl_2 (25 mL) and the organic phase isolated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (33 mg) that was subjected to column chromatography (35:65 EtOAc/hexanes) to afford the title compound **105** (9.1 mg, 27%) as a colourless film: $\mathbf{R_f}$ 0.22 (35:65 EtOAc/hexanes); **IR** (thin film) 2953, 2930, 2856, 1728, 1558, 1506, 1281, 901, 839 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.25–7.20 (2H, m, 2 × ArH), 7.17 (1H, d, J = 8.1 Hz, ArH), 6.90 (1H, d, J = 8.9 Hz, ArH), 6.79 (1H, d, J = 8.1 Hz, ArH), 4.77 (2H, s, $ArCH_2OH$), 4.01 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 0.98 (18H, s, 2 × $SiC(CH_3)_3$), 0.25 (6H, s, $Si(CH_3)_2$), 0.23 (6H, s, $Si(CH_3)_2$) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ 167.0 (C), 159.2 (C), 149.1 (C), 146.9 (C), 145.3 (C), 126.9 (C), 126.0 (CH), 123.2 (C), 122.5 (CH), 121.7 (CH), 121.0 (CH), 109.1 (C), 107.0 (CH), 63.8 (CH_2), 56.4 (CH_3), 52.5 (CH_3), 26.1 (6 × CH_3), 18.7 (C), 18.6 (C), -3.8 (2 × CH_3), -3.9 (2 × CH_3) ppm; **MS** (+ESI) *m/z* 596 ($[M+Na]^+$, 60%), 539 (100).

8.4 Synthesis of Compounds from Chapter 3

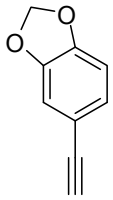
5-(2',2'-Dibromoethenyl)-1,3-benzodioxole (107)



107

To a suspension of the phosphonium salt **88** (6.86 g, 13.3 mmol, 2.0 equiv.) in THF (66 mL) was added *t*-BuOK (1M solution in THF, 12.7 mL, 12.7 mmol, 1.9 equiv.) and the resulting suspension allowed to stir at rt for 5 min. To this suspension was added, *via* cannula, a solution of piperonal (1.00 g, 6.66 mmol, 1.0 equiv.) in THF (13 mL) followed by subsequent rinsing with aliquots of THF (2 × 5 mL). The reaction mixture was allowed to stir for 2.5 h prior to further treatment with a solution of **88** (686 mg, 1.33 mmol, 0.2 equiv.) with *t*-BuOK (1M solution in THF, 1.27 mL, 1.27 mmol, 0.19 equiv.) in THF (6.6 mL) that had been stirring at rt for 10 min. After stirring for a further 1.5 h, the reaction was quenched by the addition of saturated aqueous NaCl solution (100 mL) and the organic phase isolated. The aqueous phase was extracted with EtOAc (3 × 70 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to yield a dark brown oil (5.39 g) which was purified by column chromatography (100% hexanes) to afford the title compound **107** (1.73g, 85%) as a colourless oil: $\mathbf{R_f}$ 0.22 (100% hexanes); **IR** (thin film) 3070, 3011, 2893, 2777, 2046, 1958, 1853, 1607, 1504, 1485, 1447, 1435, 1258, 1040, 932, 874, 839, 754, 696 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$), δ 7.37 (1H, s, ArC<u>H</u>CBr_2), 7.18 (1H, d, J = 1.7 Hz, Ar<u>H</u>), 6.95 (1H, ddd, J = 8.1 Hz, J = 1.7 Hz, J = 0.7 Hz, Ar<u>H</u>), 6.80 (1H, d, J = 8.1 Hz, Ar<u>H</u>), 5.99 (1H, s, OC<u>H_2</u>O) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.9 (C), 147.8 (C), 136.4 (CH), 129.3 (C), 123.5 (CH), 108.4 (CH), 108.3 (CH) , 101.5 (CH_2), 88.0 (C) ppm; **HRMS** (EI) Calcd. for $C_9H_6{}^{79}Br_2O_2$ $[M]^{\bullet+}$: 303.8735, found 303.8739; **MS** (EI) *m/z* 308 ($[^{81}Br^{81}BrM]^{\bullet+}$, 34%), 306 ($[^{81}Br^{79}BrM]^{\bullet+}$, 67%), 304 ($[^{79}Br^{79}BrM]^{\bullet+}$, 35%), 303 (10), 227 (11), 225 (13), 146 (100), 145 (68), 116 (17). Physical properties and spectroscopic data were in accordance with the literature values.[122]

5-Ethynyl-1,3-benzodioxole (108)



108

Procedure 1

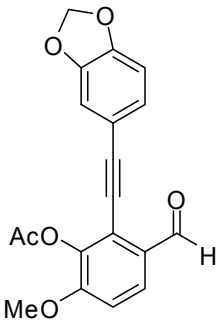
To a solution of the dibromoalkene **107** (1.50 g, 4.90 mmol) in THF (5 mL) at -78 °C, was added *n*-butyllithium (7.63 mL, 1.61 M solution in hexanes, 12.3 mmol, 2.5 equiv.) and the resulting solution left to stir at -78 °C for 1 h before being allowed to warm to rt over 1 h. The reaction was then quenched by the addition of saturated aqueous NaCl solution (2 mL) and stirred vigorously for 10 min. A further portion of saturated aqueous NaCl solution (50 mL) was added and the product was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to yield a brown oil (499.7 mg) which was purified by column chromatography (100% hexanes) to afford the title compound **108** (126.5 mg, 18%) as a colourless oil which solidified to a wax-like white solid upon storage at -15 °C: **b.p.** 84 °C at 3 mmHg; $\mathbf{R_f}$ 0.24 (6:94 CH_2Cl_2/hexanes); **IR** (thin film) 3290, 2899, 2781, 2102, 1855, 1605, 1504, 1479, 1335, 1246, 1190, 1040, 939, 921, 864, 814 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (1H, dd, J = 8.0 Hz, J = 1.5 Hz, ArH), 6.93 (1H, d, J = 1.5 Hz, ArH), 6.75 (1H, d, J = 8.0 Hz, ArH), 5.97 (2H, s, OCH_2O), 2.97 (1H, s, C≡CH) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.4 (C), 147.5 (C), 127.0 (CH), 115.4 (C), 112.1 (CH), 108.5 (CH), 101.5 (CH_2), 83.7 (CH), 75.7 (CH) ppm; **HRMS** Calcd. for $C_9H_6O_2$ $[M]^{\bullet+}$: 146.0368, found 146.0367; **MS** (EI) *m/z* 146 ($[M]^{\bullet+}$, 98%), 145 (79), 121 (7), 89 (39), 62 (100). Physical and spectroscopic data were in accordance with literature values.[122,151]

Procedure 2

To a solution of carbon tetrabromide (44.1 g, 133 mmol, 2.0 equiv.) in CH_2Cl_2 (80 mL) at 0 °C was added a solution of triphenylphosphine (69.9 g, 266 mmol, 4.0 equiv.) in CH_2Cl_2 (80 mL) over 5 min. After stirring for a further 5 min at 0 °C, a solution of piperonal (10.0 g, 66.6 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) was added dropwise over 40 min and the resulting solution allowed to stir at 0 °C for a further 30 min. Hexane (400 mL) was then added dropwise to induce the precipitation of triphenylphosphine oxide. The solid triphenylphosphine oxide was removed at the pump and rinsed with hexane (2 × 200 mL). The filtrates were combined and concentrated *in vacuo* to give a paste that was triturated with hexanes (400 mL). The solid was removed at the pump and washed with a further portion of hexane (300 mL). The combined hexane portions were concentrated *in vacuo* to give **107** as a wax-like solid that was subsequently dissolved in THF (200 mL) and cooled to -78 °C. *n*-Butyllithium (1.25 M solution in THF, 105 mL, 133 mmol, 2.2 equiv.) was then added and the reaction allowed to

stir at -78 °C for 1 h, before being warmed to 0 °C for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and was stirred vigorously for 10 min at 0 °C. The resulting solution was then warmed to rt and extracted with Et_2O (3 × 300 mL). The combined organic phases were washed sequentially with H_2O (300 mL), saturated aqueous NaCl solution (300 mL) then dried over $MgSO_4$ and concentrated *in vacuo* to give a dark brown oil (14.04 g). This was then purified by distillation to give the title compound **108** (2.28 g, 23%) as a colourless oil. More product could be obtained by subjecting the residue to column chromatography (100% low boiling petroleum ether, 30–40 °C) to give more of the title compound **108** (2.20 g, 23%) as a colourless oil which solidified to a wax-like white solid upon storage at -15 °C (total yield 4.48g, 46%). Spectroscopic data were identical to that obtained for the product of procedure 1.

2-(1',3'-Benzodioxol-5'-ylethynyl)-3-acetoxy-4-methoxybenzaldehyde (109)

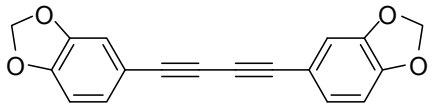


109

A solution of aryl iodide **58** (5.00 g, 15.6 mmol) and arylalkyne **108** (2.97 g, 20.3 mmol, 1.3 equiv.) in degassed, anhydrous EtOAc (750 mL) was cooled to -20 °C. $Pd(PPh_3)_2Cl_2$ (550 mg, 0.781 mmol, 5 mol%) and CuI (300 mg, 1.56 mmol, 10 mol%) were then added followed immediately by the addition of *i*-Pr_2NH (2.41 mL, 1.73 g, 17.2 mmol, 1.1 equiv.). The reaction was allowed to warm to rt and stir for 21 h before being quenched by the addition of H_2O (200 mL), diluted with saturated aqueous NaCl solution (200 mL) then extracted with EtOAc (3 × 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a dark brown solid (6.91 g) that was subjected to column chromatography (30:70→50:50 EtOAc/hexanes) to afford the title compound **109** (5.18 g, 98%) and the homocoupled by-product **110** (680 mg, 15%).

Diarylalkyne 109: pale yellow solid; **m.p.** 182–184 °C; $\mathbf{R_f}$ 0.31 (30:70 EtOAc/hexanes); **IR** (KBr disc) 2966, 2914, 2840, 2206, 1772, 1690, 1597, 1491, 1304, 1232, 1209, 1059, 1032, 932, 864 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.41 (1H, s, ArC<u>H</u>O), 7.85 (1H, d, *J* = 8.8 Hz, Ar<u>H</u>), 7.06 (1H, dd, *J* = 8.1 Hz, *J* = 1.5 Hz, Ar<u>H</u>), 7.01 (1H, d, *J* = 8.7 Hz, Ar<u>H</u>), 6.95 (1H, d, *J* = 1.5 Hz, Ar<u>H</u>), 6.81 (1H, d, *J* = 8.1 Hz, Ar<u>H</u>), 6.01 (2H, s, OC<u>H</u>$_2$O), 3.92 (3H, s, ArOC<u>H</u>$_3$), 2.40 (3H, s, ArOCOC<u>H</u>$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.0 (CH), 163.3 (C), 156.3 (C), 149.0 (C), 147.8 (C), 140.9 (C), 129.4 (C), 127.0 (CH), 126.9 (CH), 122.5 (C), 115.4 (C), 111.9 (CH), 111.6 (CH), 108.8 (CH),

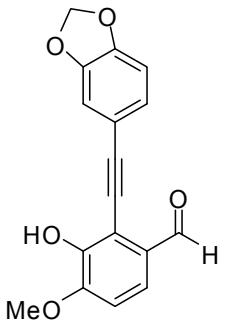
101.7 (CH_2), 101.1 (C), 78.5 (C), 56.5 (CH_3), 20.6 (CH_3) ppm; **HRMS** (EI) Calc. for $C_{19}H_{14}O_6$ $[M]^{\bullet+}$: 338.0790, found: 338.0787; **MS** (EI) *m/z* 338 ($[M]^{\bullet+}$, 4%), 296 (100), 281 (21), 267 (18), 253 (27), 237 (8), 195 (16), 139 (42).



110

5,5'-Buta-1,3-diyne-1,4-diylbis(1,3-benzodioxole) (110): white solid; **m.p.** 193–195 °C; $\mathbf{R_f}$ 0.57 (30:70 EtOAc/hexanes); **IR** (KBr Disc) 3007, 2914, 2795, 2139, 1848, 1599, 1489, 1439, 1337, 1248, 1190, 1038, 932, 918, 856, 812 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (2H, dd, *J* = 8.1 Hz, *J* = 1.6 Hz, ArH), 6.94 (2H, d, *J* = 1.6 Hz, ArH), 6.76 (2H, d, *J* = 8.1 Hz, ArH), 5.99 (4H, s, OCH_2O) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.9 (C), 147.6 (C), 127.8 (CH), 115.2 (C), 112.2 (CH), 108.8 (CH), 101.6 (CH_2), 81.4 (C), 72.7 (C) ppm; **HRMS** (EI) Calc. for $C_{18}H_{10}O_4$ $[M]^{\bullet+}$: 290.0579, found: 290.0583; **MS** (EI) *m/z* 290 ($[M]^{\bullet+}$, 100%), 144 (9).

2-(1',3'-Benzodioxol-5'-ylethynyl)-3-hydroxy-4-methoxybenzaldehyde (111)



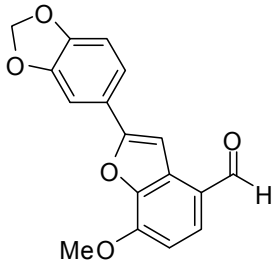
111

Procedure 1

To a solution of acetate **109** (100 mg, 0.296 mmol) in THF (10.0 mL) and MeOH (7.0 mL) at -10 °C was added aqueous NH_4OH (30% w/v, *ca.* 9M, 1.91 mL, 17.2 mmol, 60 equiv.) and the reaction allowed to stir at -10 °C. After 20 h, the reaction was quenched with saturated aqueous NH_4Cl solution (18 mL) and partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid (90 mg) that was purified by column chromatography (10:40:50 EtOAc/hexanes/CH_2Cl_2) to afford the title compound **111** (54 mg, 61%) and the protio-cyclised by-product **115** (21.8 mg, 25%).

***ortho*-Hydroxydiarylalkyne 111**: pale yellow solid; **m.p.** 159–162 °C; $\mathbf{R_f}$ 0.21 (10:40:50 EtOAc/hexanes/CH_2Cl_2); **IR** (KBr disc) 3161, 2203, 1666, 1583, 1487, 1277, 1231, 1182, 1124, 1061, 1032, 928, 851, 800 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.40 (1H, s, ArCHO), 7.54 (1H, d, *J* = 8.5 Hz, ArH), 7.13 (1H, dd, *J* = 8.1 Hz, *J* = 1.6 Hz, ArH), 7.03 (1H, d, *J* = 1.5 Hz, ArH), 6.93

(1H, d, J = 8.5 Hz, ArH), 6.81 (1H, d, J = 8.1 Hz, ArH), 6.15 (1H, br s, ArOH), 6.00 (2H, s, OCH_2O), 3.98 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.7 (CH), 151.3 (C), 148.7 (C), 147.7 (C), 147.0 (C), 129.4 (C), 126.8 (CH), 121.3 (CH), 115.7 (C), 113.0 (C), 111.7 (CH), 110.5 (CH), 108.8 (CH), 101.6 (CH_2), 101.3 (C), 78.7 (C), 56.5 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{17}H_{12}O_5Na$ $[M+Na]^+$: 319.0577, found: 319.0583; **MS** (+ESI) *m/z* 319 ($[M+Na]^+$, 100%), 297 ($[M+H]^+$, 49).



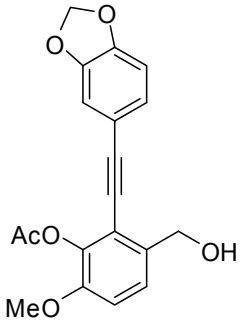
115

2-(1',3'-Benzodioxol-5'-yl)-7-methoxy-1-benzofuran-4-carbaldehyde (115): pale yellow solid; **m.p.** 164–166 °C; $\mathbf{R_f}$ 0.45 (50:50 EtOAc/hexanes); **IR** (KBr Disc) 2914, 2710, 1676, 1574, 1495, 1398, 1277, 1238, 1103, 1034, 926, 793 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.03 (1H, s, CHO), 7.63 (1H, d, J = 4.7 Hz, ArH), 7.62 (1H, d, J = 3.6 Hz, ArH), 7.46 (1H, dd, J = 8.1 Hz, J = 1.7 Hz, ArH), 7.37 (1H, d, J = 1.7 Hz, ArH), 6.88 (1H, d, J = 8.1 Hz, ArH), 6.85 (1H, d, J = 8.3 Hz, ArH), 6.02 (2H, s, OCH_2O), 4.11 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.8 (CH), 159.0 (C), 149.7 (C), 148.8 (C), 148.3 (C), 143.9 (C), 132.0 (CH), 130.3 (C), 124.1 (C), 122.9 (C), 120.0 (CH), 108.9 (CH), 106.0 (CH), 105.9 (CH), 101.6 (CH_2), 101.0 (CH), 56.5 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{17}H_{13}O_5$ $[M+H]^+$: 297.0758, found: 297.0755; **MS** (+ESI) *m/z* 297 ($[M+H]^+$, 100%).

Procedure 2

To a solution of acetate **109** (17.6 mg, 0.052 mmol) in THF (1.0 mL) and MeOH (1.0 mL) at rt was added Cs_2CO_3 (84.7 mg, 0.260 mmol, 5.0 equiv.) and the resulting solution allowed to stir at rt for 20 min. After this period, the reaction was quenched with saturated aqueous NH_4Cl solution (2 mL) and partitioned between H_2O (15 mL) and CH_2Cl_2 (15 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **111** (13.0 mg, 78%) as a yellow film that was spectroscopically identical to the product obtained from procedure 1.

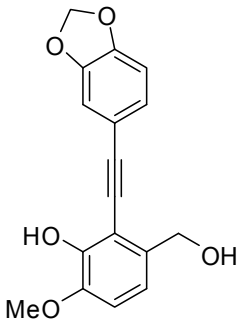
2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(hydroxymethyl)-6-methoxyphenyl acetate (116)



116

To a suspension of aldehyde **109** (400 mg, 1.182 mmol) in 2:1 THF (20 mL) and MeOH (10 mL) at 0 °C was added $NaBH_4$ (224 mg, 5.91 mmol, 5.0 equiv.). The reaction was allowed to stir at 0 °C for 1 h before being quenched by the addition of acetone (10 mL, AR grade). Saturated aqueous NH_4Cl solution (100 mL) was added and the resulting mixture extracted with Et_2O (4 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a tan solid (414 mg) that was purified by column chromatography (100% CH_2Cl_2→10:90 EtOAc/CH_2Cl_2) to afford 343 mg (85%) of the title compound **116** as a white solid: **m.p.** 120–122 °C; $\mathbf{R_f}$ 0.39 (10:90 EtOAc/CH_2Cl_2); **IR** (KBr disc) 3531, 3304, 2889, 2843, 2789, 2206, 1762, 1610, 1570, 1504, 1454, 1232, 1209, 1178, 1128, 1040, 933, 810 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (1H, d, *J* = 8.5 Hz, ArH), 6.99 (1H, dd, *J* = 8.0 Hz, *J* = 1.5 Hz, ArH), 6.89 (1H, d, *J* = 8.5 Hz, ArH), 6.76 (1H, d, *J* = 8.0 Hz, ArH), 5.95 (2H, s, OCH_2O), 4.75 (2H, s, $ArCH_2OH$), 3.79 (3H, s, $ArOCH_3$), 2.61 (1H, br s, $ArCH_2OH$), 2.37 (3H, s, $ArOCOCH_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6 (C), 150.6 (C), 148.4 (C), 147.5 (C), 140.6 (C), 135.3 (C), 126.4 (CH), 125.4(CH), 116.8 (C), 115.9 (C), 112.2 (CH), 111.4 (CH), 108.6 (CH), 101.5 (CH_2), 98.6 (C), 80.2 (C), 63.2 (CH_2), 56.1 (CH_3), 20.6 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{19}H_{16}O_6Na$ $[M+Na]^+$: 363.0839, found: 363.0831; **MS** (+ESI) *m/z* 363 ($[M+Na]^+$, 68%), 341 ($[M+H]^+$, 3%), 323 (100%), 281 (57%).

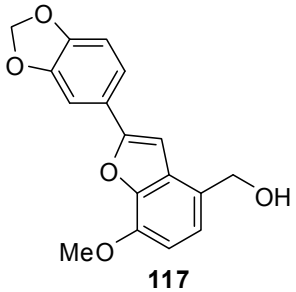
2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(hydroxymethyl)-6-methoxyphenol (113)



113

To a solution of **116** (1.25 g, 3.67 mmol) in 1:1 THF (75 mL) and MeOH (75 mL) at 10 °C was added Cs_2CO_3 (2.47 g, 18.4 mmol, 2.06 equiv.) in two portions before being allowed to warm to rt. After stirring for 40 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and H_2O (50 mL) followed by extraction with CH_2Cl_2 (3 × 200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid (1.10 g), which was subjected to column chromatography (100% CH_2Cl_2→10:90 EtOAc/CH_2Cl_2) to afford the title compound **113** (1.05 g, 96%) as a white solid. An analytical sample was obtained by recrystallisation from CH_2Cl_2 at -20 °C to give small white needles: **m.p.** 145–146 °C; $\mathbf{R_f}$ 0.26 (10:90 EtOAc/CH_2Cl_2); **IR** (KBr disc) 3458, 3080, 2968, 2929, 2839, 2206, 1607, 1574, 1485, 1427, 1335, 1236, 1198, 1121, 1063, 1030, 982, 930, 878, 808 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10 (1H, d, *J* = 8.0 Hz, ArH), 7.01 (1H, s, ArH), 6.93 (1H, d, *J* = 8.1 Hz, ArH), 6.83 (1H, d, *J* = 8.2 Hz, ArH), 6.80 (1H, d, *J* = 8.1 Hz, ArH), 6.01 (1H, br s, ArOH), 6.00 (2H, s, OCH_2O), 4.78 (2H, d, *J* = 5.2 Hz, $ArCH_2OH$), 3.91 (3H, s, $ArOCH_3$), 2.06 (1H, t, 5.2 Hz, $ArCH_2OH$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.4 (C), 147.7 (C), 147.0 (C), 146.3 (C), 135.5 (C), 126.6 (CH), 119.2 (CH), 116.1 (C), 111.7 (CH), 111.0 (CH), 108.7 (CH), 101.5 (CH_2), 99.1 (C), 80.4 (C), 64.2 (CH_2), 56.3 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{17}H_{14}O_5Na$ $[M+Na]^+$: 321.0734, found: 321.0730; **MS** (+ESI) *m/z* 321 ($[M+Na]^+$, 66%), 299 ($[M+Na]^+$, 23), 281 (100).

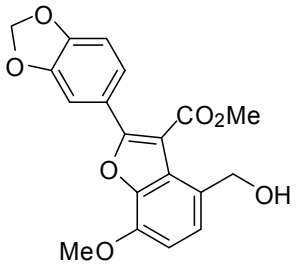
[2-(1',3'-Benzodioxol-5'-yl)-7-methoxy-1-benzofuran-4-yl]methanol (117)



117

During the attempted formation of **113** by subjecting **109** to a DIBAL–H reduction (**Table 3**, **Entry 5**), the by-product **117** was afforded (51%) as an off-white wax-like solid: **m.p.** 101–103 °C; $\mathbf{R_f}$ 0.18 (40:60 EtOAc/hexanes); **IR** (thin film) 3407, 2904, 1484, 1251 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1H, dd, *J* = 8.1 Hz, *J* = 1.7 Hz, ArH), 7.59 (1H, d, *J* = 1.6 Hz, ArH), 7.34 (1H, d, *J* = 8.1 Hz, ArH), 7.13 (1H, d, *J* = 8.1 Hz, ArH), 6.98 (1H, d, *J* = 8.1 Hz, ArH), 6.26 (2H, s, OCH_2O), 5.10 (2H, s, $ArCH_2OH$), 4.28 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.2 (C), 148.2 (C), 148.2 (C), 145.1 (C), 144.0 (C), 129.9 (C), 125.6 (C), 124.6 (C), 122.6 (CH), 119.5 (CH), 108.7 (CH), 106.3 (CH), 105.7 (CH), 101.4 (CH_2), 99.2 (CH), 63.6 (CH_2), 56.3 (CH_3) ppm.

Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(hydroxymethyl)-7-methoxy-1-benzofuran-3-carboxylate (114)

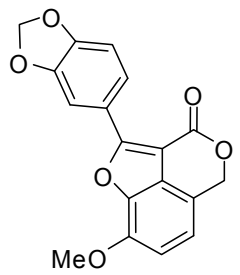


114

To *ortho*-hydroxydiarylalkyne **113** (100.0 mg, 0.335 mmol), anhydrous NaOAc (110 mg, 1.34 mmol, 4.0 equiv.) and anhydrous $CuCl_2$ (135 mg, 1.01 mmol, 3.0 equiv.) at 0 °C was added MeOH (3.34 mL) and immediately after, $PdCl_2$ (6 mg, 0.03 mmol, 10 mol%) was added. This was immediately purged with $CO_{(g)}$ (× 4) and allowed to warm to rt whilst $CO_{(g)}$ was being bubbled through the solution. After 5 min, the bubbling was ceased and the reaction allowed to stir vigorously under a $CO_{(g)}$ atmosphere for 3.5 h. The reaction mixture was then concentrated *in vacuo* and partitioned between H_2O (50 mL) and $CHCl_3$ (50 mL). The organic phase was isolated and the aqueous phase was extracted with $CHCl_3$ (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (118 mg) that was subjected to column chromatography (90:9:1 CH_2Cl_2/EtOAc/MeOH) to afford the title compound **114** (95.0 mg, 80%) and the lactone by-product **118** (16.3 mg, 14%).

Benzofuran 114: off-white solid; **m.p.** 121–122 °C; $\mathbf{R_f}$ 0.37 (90:9:1 CH_2Cl_2/EtOAc/MeOH); **IR** (KBr disc) 3547, 2959, 2899, 1712, 1628, 1593, 1508, 1491, 1442, 1248, 1236, 1082, 1036, 814 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (1H, dd, *J* = 8.1 Hz, *J* = 1.7 Hz, ArH), 7.22 (1H, d, *J* = 1.7 Hz, ArH), 6.89 (1H, d, *J* = 8.1 Hz, ArH), 6.79 (1H, d, *J* = 8.1 Hz, ArH), 6.04 (2H, s, OCH_2O), 7.77 (2H, d, *J* = 6.8 Hz, CH_2OH), 4.00 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.63 (1H, br t, *J* = 6.9 Hz, CH_2OH) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9 (C), 158.8 (C), 149.3 (C), 147.8 (C), 145.3 (C), 143.8 (C), 127.0 (C), 126.4 (C), 126.0 (CH), 123.64 (CH), 123.61 (C), 109.3 (C), 109.1 (CH), 108.4 (CH), 106.9 (CH), 101.7 (CH_2), 63.7 (CH_2), 56.2 (CH_3), 52.5 (CH_3) ppm; **HRMS** (EI) Calc.

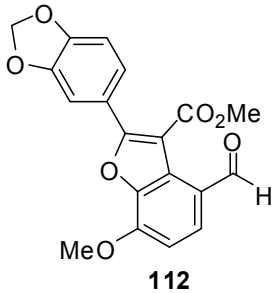
for $C_{19}H_{16}O_7$ $[M]^{\bullet+}$: 356.0896, found: 356.0890; **MS** (EI) *m/z* 356 ($[M]^{\bullet+}$, 22%), 339 (5), 324 (100), 295 (61), 265 (19), 251 (35), 237 (72).



118

2-(1',3'-Benzodioxol-5'-yl)-8-methoxy-3*H*,5*H*-furo[4,3,2-*de*]isochromen-3-one (118): off-white solid; **m.p.** 210–212 °C; $\mathbf{R_f}$ 0.80 (5:95 EtOAc/CH_2Cl_2); **IR** (thin film) 2934, 1713, 1651, 1558, 1501, 1485, 1269, 1151, 1107, 1038 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (1H, dd, *J* = 8.3 Hz, *J* = 1.8 Hz, ArH), 8.12 (1H, d, *J* = 1.7 Hz, ArH), 6.97 (1H, d, *J* = 7.8 Hz, ArH), 6.95 (1H, d, *J* = 8.2 Hz, ArH), 6.84 (1H, d, *J* = 7.9 Hz, ArH), 6.06 (2H, s, OCH_2O), 5.79 (2H, s, $ArCH_2O$), 4.08 (3H, s, $ArOCH_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.3 (C), 159.6 (C), 150.3 (C), 148.2 (C), 144.1 (C), 139.4 (C), 129.1 (C), 124.2 (CH), 122.6 (C), 118.2 (CH), 116.1 (C), 110.1 (CH), 108.8 (CH), 108.5 (CH), 101.8 (CH_2), 101.0 (C), 72.9 (CH_2), 57.0 (CH_3) ppm; **HRMS** Calcd. for $C_{18}H_{13}O_6$ $[M+H]^+$: 325.07121, found 325.071372; **MS** (+ESI) *m/z* 671 ($[2M+Na]^+$, 84%), 325 ($[M+H]^+$, 100).

Methyl 2-(1',3'-benzodioxol-5'-yl)-4-formyl-7-methoxy-1-benzofuran-3-carboxylate (112)

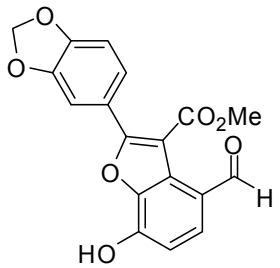


112

To a solution of **114** (190 mg, 0.535 mmol) in CH_2Cl_2 (54 mL) was added MnO_2 (<5 μm, activated, ~85%, 697 mg, 12.8 equiv.) in one portion. After stirring at rt for 4 h, the reaction mixture was filtered through a plug of celite and concentrated *in vacuo* to afford the title compound **112** (155 mg, 82%) as a white solid: **m.p.** 160–162 °C; $\mathbf{R_f}$ 0.53 (10:90 EtOAc/CH_2Cl_2); **IR** (KBr disc) 2953, 2912, 2723, 1728, 1678, 1618, 1572, 1501, 1489, 1408, 1296, 1265, 1236, 1209, 1070, 1041, 1024, 929, 800 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.04 (1H, s, CHO), 7.73 (1H, d, *J* = 8.4 Hz, ArH), 7.47 (1H, dd, *J* = 8.2 Hz, *J* = 1.7 Hz, ArH), 7.39 (1H, d, *J* = 1.7 Hz, ArH), 6.92 (1H, d, *J* = 8.4 Hz, ArH), 6.89 (1H, d, *J* = 8.2 Hz, ArH), 6.03 (2H, s, OCH_2O), 4.09 (3H, s, OCH_3), 3.99 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.9 (CH), 166.3 (C), 157.0 (C), 149.9 (C), 149.5 (C), 148.2 (C),

143.1 (C), 131.8 (CH), 127.0 (C), 123.2 (C), 122.8 (C), 122.7 (CH), 110.5 (C), 108.8 (CH), 107.9 (CH), 106.5 (CH), 101.7 (CH_2), 56.6 (CH_3), 52.8 (CH_3) ppm; **HRMS** (EI) Calc. for $C_{19}H_{14}O_7$ $[M]^{\bullet+}$: 354.0740, found: 354.0745; **MS** (EI) *m/z* 354 ($[M]^{\bullet+}$, 100%), 339 (47), 326 (31), 322 (27), 294 (90), 265 (47), 237 (49), 223 (18).

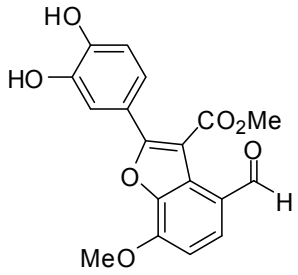
Methyl 2-(1',3'-benzodioxol-5'-yl)-4-formyl-7-hydroxy-1-benzofuran-3-carboxylate (123)



123

A stock solution of NaSEt (0.2 M in DMF) was prepared by dissolving EtSH (802 µL, 652 mg, 10.5 mmol) in DMF (50 mL) and treating with NaH (400 mg of 60%w/w dispersion, 240 mg NaH, 10.0 mmol). To **112** (50.0 mg, 0.142 mmol) was added an aliquot of the NaSEt solution (780 µL, 1.1 equiv.) and the resulting solution was allowed to stir at rt for 17 h before a second aliquot of NaSEt solution (780 µL, 1.1 equiv.) was added. Stirring was continued for a further 1 h before the solvent was removed *in vacuo* and the residue partitioned between $CHCl_3$ (30 mL) and saturated aqueous NH_4Cl solution (30 mL). This was then acidified to ~pH 1 with aqueous HCl (1 M) before the organic phase was isolated and the aqueous phase extracted with $CHCl_3$ (2 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid (39.5 mg) that was subjected to column chromatography (dry loaded) (10:90 EtOAc/CH_2Cl_2) to afford the title compound **123** (5.2 mg, 11%) as a pale brown solid: **m.p.** 115–118 °C; $\mathbf{R_f}$ 0.29 (10:90 EtOAc/CH_2Cl_2); **IR** (KBr disc) 3125, 2919, 2850, 2765, 1723, 1573, 1557, 1262, 1233, 1078 cm^{-1}; **^{1}H NMR** (400 MHz, CD_3OD) δ 9.88 (1H, s, C<u>H</u>O), 7.72 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 7.47 (1H, dd, *J* = 8.2, 1.8 Hz, Ar<u>H</u>), 7.38 (1H, d, *J* = 1.7 Hz, Ar<u>H</u>), 6.96 (1H, d, *J* = 8.2 Hz, Ar<u>H</u>), 6.92 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 6.05 (2H, s, OC<u>H</u>$_2$O), 3.95 (3H, s, $CO_2C\underline{H}_3$) ppm; **^{13}C NMR** (100 MHz, CD_3OD) δ 191.5 (CH), 168.3 (C), 157.5 (C), 151.0 (C), 150.8 (C), 149.7 (C), 144.2 (C), 134.3 (CH), 128.1 (C), 124.1 (C), 123.3 (CH), 122.7 (C), 112.5 (CH), 111.8 (C), 109.7 (CH), 108.3 (CH), 103.2 (CH_2), 53.1 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{18}H_{12}O_7Na$ $[M+Na]^+$: 363.0475, found: 363.0459; **MS** (+ESI) *m/z* 703 ($[2M+Na]^+$, 93), 363 ($[M+Na]^+$, 71), 341 ($[M+H]^+$, 100).

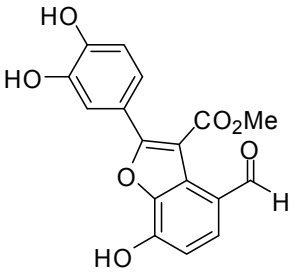
Methyl 2-(3',4'-dihydroxyphenyl)-4-formyl-7-methoxy-1-benzofuran-3-carboxylate (124)



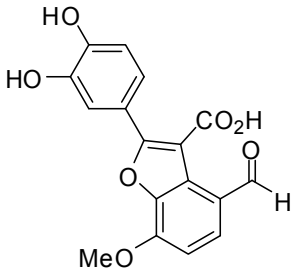
124

To a stirred solution of **112** (50.0 mg, 0.142 mmol) in CH_2Cl_2 (2.8 mL) at -20 °C was added BBr_3 (1M solution in CH_2Cl_2, 1.42 mL, 1.42 mmol, 10.0 equiv.). The reaction was allowed to stir at -20 °C for 2.75 h before being quenched by the addition of 3:1 CH_2Cl_2/*i*-PrOH (5 mL). Stirring was continued at -15 °C for 5 min prior to the addition of pH 7 buffer solution and isolation of the organic phase. The aqueous phase was then extracted with 3:1 CH_2Cl_2/*i*-PrOH (2 × 20 mL) and the combined organic phases were dried over $MgSO_4$ then concentrated *in vacuo* to give a yellow oil that was subjected to column chromatography (5:95 MeOH/CH_2Cl_2) to afford the title compound **124** (28.8 mg, 59%) and 6.6 mg (*ca*. 14%) of a by-product tentatively assigned as either **125** or **126**.

Catechol 124: off-white solid; **m.p.** 197–199 °C; $\mathbf{R_f}$ 0.42 (5:95 MeOH/CH_2Cl_2); **IR** (KBr disc) 3384, 2923, 2849, 2619, 1702, 1656, 1615, 1300 cm^{-1}; **^{1}H NMR** (400 MHz, CD_3OD) δ 9.93 (1H, s, C<u>H</u>O), 7.79 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 7.32 (1H, d, *J* = 2.1 Hz, Ar<u>H</u>), 7.25 (1H, dd, *J* = 8.4 Hz, *J* = 2.2 Hz, Ar<u>H</u>), 7.07 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 6.87 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 4.10 (3H, s, OC<u>H</u>$_3$), 3.97 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (100 MHz, CD_3OD) δ 191.8 (CH), 168.4 (C), 158.5 (C), 151.5 (C), 149.2 (C), 146.8 (C), 144.1 (C), 133.9 (CH), 127.8 (C), 124.0 (C), 121.6 (C), 120.8 (CH), 116.6 (CH), 115.2 (CH), 110.6 (C), 107.7 (CH), 57.1 (CH_3), 53.0 (CH_3) ppm; **HRMS** (EI) Calc. for $C_{18}H_{14}O_7$ $[M]^{\bullet+}$: 342.0740, found: 342.0737; **MS** (EI) *m/z* 342 ($[M]^{\bullet+}$, 72%), 327 (32), 310 (27), 282 (100), 254 (40), 237 (17).



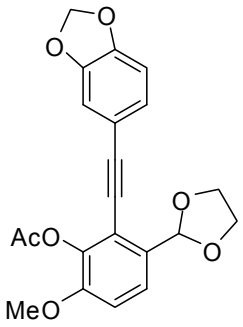
125



126

By-product 125 or **126**: (partial data) $\mathbf{R_f}$ 0.02 (5:95 MeOH/CH_2Cl_2); **^{1}H NMR** (200 MHz, CD_3OD) δ 9.87 (1H, s, C<u>H</u>O), 7.70 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 7.39–7.24 (2H, m, 2 × Ar<u>H</u>), 6.89 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 6.88 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 3.97 (3H, s, OC<u>H</u>$_3$).

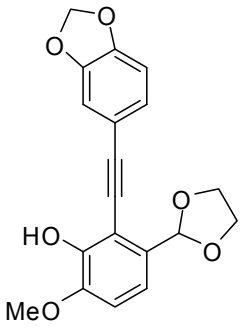
2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(1'',3''-dioxolan-2''-yl)-6-methoxyphenyl acetate (135)



135

To a solution of aldehyde **109** (110.8 mg, 0.3275 mmol) in CH_2Cl_2 (14.5 mL) was added ethylene glycol (146 μL, 163 mg, 2.62 mmol, 8.0 equiv.) followed by TMSCl (251 μL, 214 mg, 1.97 mmol, 6.0 equiv.). The resulting solution was stirred at rt for 20 h before heating to reflux for 2 h. The solution was cooled to rt and quenched by the addition of saturated aqueous $NaHCO_3$ solution (30 mL). After 10 min of vigorous stirring, the biphasic mixture was diluted with CH_2Cl_2 (35 mL) and the organic phase isolated. The aqueous phase was further extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a wax-like white solid (127.2 mg). This was purified by column chromatography (40:60 EtOAc/hexanes) to afford the title compound **135** (95.5 mg, 76%) as a white solid: **m.p.** 120–122 °C; $\mathbf{R_f}$ 0.22 (40:60 EtOAc/hexanes); **IR** (thin film) 2891, 2208, 1769, 1493, 1202, 1036 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (1H, d, J = 8.7 Hz, 1H, ArH), 7.03 (1H, dd, J = 8.0 Hz, 1.6 Hz, ArH), 6.95 (1H, d, J = 8.7 Hz, ArH), 6.93 (1H, d, J = 1.6 Hz, ArH), 6.79 (1H, d, J = 8.0 Hz, ArH), 6.15 (1H, s, ArCH), 5.99 (2H, s, OCH_2O), 4.28–4.10 (2H, m, 2 × $OCH_aH_bCH_2$), 4.10–3.97 (2H, m, 2 × $OCH_aH_bCH_2$), 3.85 (3H, s, OCH_3), 2.36 (3H, s, $OCOCH_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ168.4 (C), 152.1 (C), 148.4 (C), 147.6 (C), 140.9 (C), 131.8 (C), 126.5 (CH), 124.6 (CH), 118.3 (C), 116.3 (C), 112.0 (CH), 111.6 (CH), 108.7 (CH), 102.0 (CH), 101.5 (CH_2), 98.7 (C), 80.1 (C), 65.6 (2 × CH_2), 56.3 (CH_3), 20.7 (CH_3) ppm; **HRMS** (EI) Calc. for $C_{21}H_{19}O_7$ $[M+H]^{\bullet+}$:383.1125, found: 383.1132; **MS** (+ESI) *m/z* 787 ($[2M+Na]^+$, 15%), 383 ($[M+H]^+$, 100), 353 (14), 339 (5).

2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(1'',3''-dioxolan-2''-yl)-6-methoxyphenol (136)



136

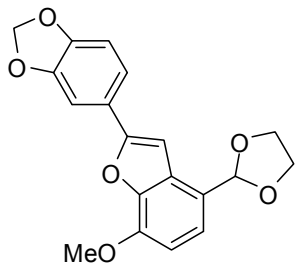
Procedure 1

Acetate **135** (85 mg, 0.22 mmol) was dissolved in 1:1 in THF (4.5 mL) and MeOH (4.5 mL) and cooled to 8 °C whereupon Cs_2CO_3 (149 mg, 0.457 mmol, 2.06 equiv.) was added in a single portion. The resulting suspension was allowed to slowly warm to rt and after 45 min was cooled to 0 °C and quenched by the addition of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a light brown film (77.3 mg). This was then purified by column chromatography (50:50 EtOAc/hexanes) to afford the title compound **136** (71.9 mg, 95%) as an off-white solid: **m.p.** 127–129 °C; $\mathbf{R_f}$ 0.20 (40:60 EtOAc/hexanes); **IR** (thin film) 3445, 2893, 2204, 1489, 1231, 1036 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.100 (1H, dd, *J* = 8.1,1.6 Hz, ArH), 7.098 (1H, d, *J* = 8.2 Hz, ArH), 7.01 (1H, d, *J* = 1.5 Hz, ArH), 6.86 (1H, d, *J* = 8.5 Hz, ArH), 6.80 (1H, d, *J* = 8.0 Hz, ArH), 6.13 (1H, s, ArCH), 5.99 (2H, s, OCH_2O), 4.20–4.12 (2H, m, 2 × $OCH_aH_bCH_2$), 4.09–4.02 (2H, m, 2 × $OCH_aH_bCH_2$), 3.91 (3H, s, OCH_3) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.3(C), 147.6 (C), 147.4 (C), 147.0 (C), 131.7 (C), 126.6 (CH), 118.2 (CH), 116.4 (C), 111.8 (C), 110.9 (CH), 109.4 (C), 108.6 (C), 102.4 (CH), 101.5 (CH_2), 99.3 (C), 80.0 (C), 65.6 (2 × CH_2), 56.3 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{19}H_{16}O_6Na$ $[M+Na]^+$: 363.0839, found: 363.0824; **MS** (+ESI) *m/z* 703 ($[2M+Na]^+$, 4), 341 ($[M+H]^+$, 100), 297 (5).

Procedure 2

To a solution of **111** (450 mg, 1.519 mmol) in CH_2Cl_2 (100 mL) was added ethylene glycol (2.70 mL, 3.00 g, 48.3 mmol, 31.8 equiv.) and TMSCl (0.90 mL, 770.4 mg, 7.09 mmol, 4.67 equiv.) and the resulting solution heated at reflux for 2 h before cooling to rt and quenching by the addition of anhydrous K_2CO_3. After 10 min of stirring, the mixture was partitioned between saturated aqueous $NaHCO_3$ solution (200 mL) and CH_2Cl_2 (200 mL). The organic phase was isolated, and the aqueous phase extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil that was purified by column chromatography (50:50:0.5 EtOAc/hexanes/NEt_3) to afford the title compound **136** (229.5 mg, 44%) as an off-white solid,

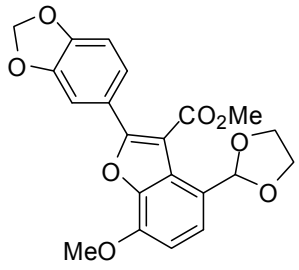
spectroscopically identical to the material isolated from procedure 1, and the protio-cyclised by-product **248** (90.4 mg, 17%).



248

5-[4'-(1'',3''-Dioxolan-2''-yl)-7'-methoxy-1'-benzofuran-2'-yl]-1,3-benzodioxole (248): off-white solid; **m.p.** 150–152 °C; $\mathbf{R_f}$ 0.42 (40:60:0.5 EtOAc/hexanes/NEt_3); **IR** (thin film) 2891, 1483, 1273, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (1H, dd, *J* = 8.1, 1.7 Hz, ArH), 7.36 (1H, d, *J* = 1.58 Hz, ArH), 7.26 (1H, d, *J* = 8.0 Hz, ArH), 7.04 (1H, s, ArH), 6.87 (1H, d, *J* = 8.14 Hz, ArH), 6.76 (1H, d, *J* = 8.18 Hz, ArH), 6.03 (1H, s, ArCH), 6.01 (2H, s, OCH_2O), 4.23–4.16 (2H, m, 2 × $OCH_aH_bCH_2$), 4.15–4.07 (2H, m, 2 × $OCH_aH_bCH_2$), 4.04 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.4 (C), 148.3 (C), 148.2 (C), 146.0 (C), 144.2 (C), 129.1 (C), 124.7 (C), 122.3 (CH), 122.2 (C), 119.6 (CH), 108.8 (CH), 105.94 (CH), 105.87 (CH), 103.5 (CH), 101.5 (CH_2), 99.9 (CH), 65.4 (2 × CH_2), 56.3 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{19}H_{17}O_6$ $[M+H]^+$: 341.1020, found: 341.1009; **MS** (+ESI) *m/z* 703 ($[2M+Na]^+$, 4%), 341 ($[M+H]^+$, 100), 297 (28).

Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(1'',3''-dioxolan-2''-yl)-7-methoxy-1-benzofuran-3-carboxylate (137)

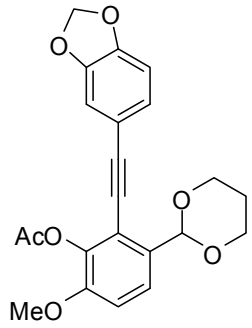


137

To a flask containing **136** (60.0 mg, 0.176 mmol) was added anhydrous $CuCl_2$ (71 mg, 0.53 mmol, 3.0 equiv.) and anhydrous NaOAc (58 mg, 0.71 mmol, 4.0 equiv.). The flask was then cooled to 0 °C before $PdCl_2$ (3 mg, 0.02 mmol, 0.1 equiv.) was added followed as soon as possible by the addition of anhydrous MeOH (1.75 mL). The system was quickly purged with $CO_{(g)}$ (× 4) and the resulting suspension left to stir at rt under an atmosphere of $CO_{(g)}$. After 70 min, the solvent was removed *in vacuo* and the residue partitioned between H_2O (40 mL) and CH_2Cl_2 (40 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow film (64.2 mg) that was subjected to

column chromatography (50:50 EtOAc/hexanes) to afford a *ca*. 4:1 mixture of the title compound **137** and **112** (~76%), respectively. For analytical purposes, this mixture was resubjected to column chromatography (2:98:0.5 $Et_2O/CH_2Cl_2/NEt_3$) to afford the title compound **137** as a white solid: **m.p.** 159–161 °C; $\mathbf{R_f}$ 0.56 (50:50 EtOAc/hexanes); **IR** (thin film) 2893, 1724, 1489, 1250, 1231, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (1H, dd, *J* = 8.3, *J* = 0.7 Hz, ArH), 7.43 (1H, dd, *J* = 8.2, *J* = 1.8 Hz, ArH), 7.36 (1H, d, *J* = 1.7 Hz, ArH), 6.88 (1H, d, *J* = 8.2 Hz, ArH), 6.81 (1H, d, *J* = 8.3 Hz, ArH), 6.36 (1H, s, ArCH), 6.03 (2H, s, OCH_2O), 4.02 (3H, s, OCH_3), 4.03–3.99 (2H, m, 2 × $OCH_aH_bCH_2$), 3.98–3.95 (2H, m, 2 × $OCH_aH_bCH_2$), 3.90 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.2 (C), 156.5 (C), 149.2 (C), 147.9 (C), 145.6 (C), 143.3 (C), 126.1 (C), 123.8 (C), 123.4 (C), 123.(CH), 121.7 (CH), 110.1 (C), 108.6 (2 × CH), 106.4 (CH), 101.6 (CH_2), 101.4 (CH), 64.8 (2 × CH_2), 56.3 (CH_3), 52.4 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{21}H_{18}O_8Na$ $[M+Na]^+$: 421.0893, found: 421.0880; **MS** (+ESI) *m/z* 819 ($[2M+Na]^+$, 21%), 399 ($[M+H]^+$, 95), 383 (100), 369 (37), 341 (64).

2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenyl acetate (138)



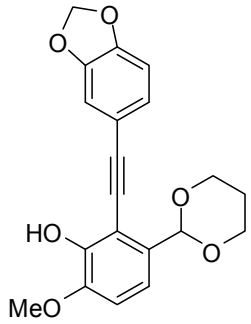
138

To a solution of **109** (500.0 mg, 1.478 mmol) in CH_2Cl_2 (65 mL) was added 1,3-propanediol (872 µL, 963 mg, 11.8 mmol, 8.0 equiv.) followed by TMSCl (1.13 mL, 963 mg, 8.87 mmol, 6.0 equiv.). The resulting solution was heated at reflux for 2 h[†] before cooling to rt then quenched by the addition of solid anhydrous K_2CO_3 (~0.5 g). After 10 min of vigorous stirring, saturated aqueous $NaHCO_3$ solution (80 mL) was added and stirring continued for a further 10 min. The organic phase was isolated and the aqueous phase was extracted with CH_2Cl_2 (2 × 80 mL), combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a brown foam (643.9 mg) that was subjected to column chromatography (40:60:0.5 EtOAc/hexanes/NEt_3) to afford the title compound **138** (570.7 mg, 97%) as a white solid: **m.p.** 118–120 °C; $\mathbf{R_f}$ 0.28 (40:60:0.5 EtOAc/hexanes/NEt_3); **IR** (thin film) 2962, 2845, 2210, 1771, 1609, 1504, 1202, 1107, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 8.7 Hz, ArH), 7.04

[†] reaction was monitored by ^{1}H NMR as the acetal hydrolyses on the tlc plate.

(1H, dd, J = 8.0, 1.6 Hz, ArH), 6.96 (1H, d, J = 8.7 Hz, ArH), 6.94 (1H, d, J = 1.4 Hz, ArH), 6.80 (1, d, J = 8.0 Hz, ArH), 6.00 (2H, s, OCH_2O), 5.82 (1H, s, ArCH), 4.30–4.25 (2H, m, $2 \times OCH_aH_bCH_2$), 4.05–3.97 (2H, m, $2 \times OCH_aH_bCH_2$), 3.83 (3H, s, OCH_3), 2.36 (3H, s, $OCOCH_3$), 2.31–2.16 (1H, m, $OCH_2CH_aH_bCH_2O$), 1.47–1.41 (1H, m, $OCH_2CH_aH_bCH_2O$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.4 (C), 151.7 (C), 148.4 (C), 147.6 (C), 140.5 (C), 132.9 (C), 126.4 (CH), 124.3 (CH), 117.5 (C), 116.4 (C), 112.2 (CH), 111.5 (CH), 108.7 (CH), 101.6 (CH_2), 100.1 (CH), 98.3 (C), 80.2 (C), 67.8 ($2 \times CH_2$), 56.2 (CH_3), 25.9 (CH_2), 20.7 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{22}H_{20}O_7Na$ $[M+Na]^+$: 419.1101, found: 419.1085; **MS** (+ESI) *m/z* 815 ($[2M+Na]^+$, 100%), 419 ($[M+Na]^+$, 46), 397 ($[M+H]^+$, 81), 353 (4).

2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenol (139)

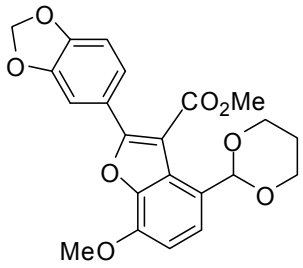


139

Acetate **138** (500 mg, 1.21 mmol) was dissolved in 1:1 THF (25 mL) and MeOH (25 mL) and cooled to 0 °C. Cs_2CO_3 (810 mg, 2.49 mmol, 2.06 equiv.) was added and the resulting suspension allowed to slowly warm to rt. After 3 h the reaction was cooled back to 0 °C and quenched by the addition of saturated aqueous NH_4Cl solution (50 mL) and the resulting biphasic mixture allowed to warm to rt before being diluted with H_2O (20 mL) and CH_2Cl_2 (150 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil (550 mg) that was subjected to column chromatography (60:40:0.5 EtOAc/hexanes/NEt_3) to afford the title compound **139** (421 mg, 94%) as an off-white solid: **m.p.** 137–139 °C; **R_f** 0.32 (60:40:0.5 EtOAc/hexanes/NEt_3); **IR** (thin film) 3491, 2966, 2916, 2847, 2206, 1504, 1234, 1107, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (1H, d, J = 8.5 Hz, ArH), 7.11 (1H, dd, J = 8.0, 1.6 Hz, ArH), 7.02 (1H, d, J = 1.5 Hz, ArH), 6.86 (1H, d, J = 8.5 Hz, ArH), 6.81 (1H, d, J = 8.0 Hz, ArH), 6.00 (2H, s, OCH_2O), 5.95 (1H, br s, OH), 5.82 (1H, s, ArCH), 4.31–4.25 (2H, m, $2 \times OCH_aH_bCH_2$), 4.06–3.98 (2H, m, $2 \times OCH_aH_bCH_2$), 3.89 (3H, s, OCH_3), 2.31–2.15 (1H, m, $OCH_2CH_aH_bCH_2O$), 1.47–1.40 (1H, m, $OCH_2CH_aH_bCH_2O$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.2 (C), 147.6 (C), 147.0 (C), 146.6 (C), 132.9 (C), 126.5 (CH), 117.7 (CH), 116.6 (C), 111.7 (CH), 111.1 (CH), 108.8 (C), 108.7 (CH), 101.5 (CH_2), 100.4 (CH), 98.8

(C), 80.2 (C), 67.9 (2 × CH_2), 56.4 (CH_3), 25.9 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{20}H_{18}O_6Na$ $[M+Na]^+$: 377.0996, found: 377.0994; **MS** (+ESI) *m/z* 731 ($[2M+Na]^+$, 31%), 355 ($[M+H]^+$, 100).

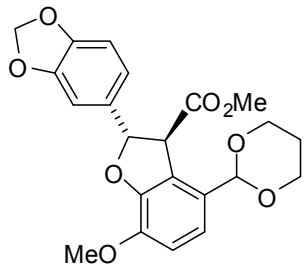
Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(1'',3''-dioxan-2''-yl)-7-methoxybenzofuran-3-carboxylate (140)



140

To a flask containing *ortho*-hydroxydiarylalkyne **139** (60.0 mg, 0.169 mmol), anhydrous $CuCl_2$ (68 mg, 0.507 mmol, 3.0 equiv.), anhydrous NaOAc (56.0 mg, 0.677 mmol, 4.0 equiv.) and $PdCl_2$ (3 mg, 0.017 mmol, 10 mol%), was added anhydrous MeOH (1.7 mL) and the system quickly purged with $CO_{(g)}$ (× 4) and the resulting suspension allowed to stir at rt under an atmosphere of $CO_{(g)}$ for 1.5 h. The reaction was then quenched by the addition of H_2O (2 mL) and the resulting mixture partitioned between H_2O (30 mL) and $CHCl_3$ (30 mL). The organic phase was isolated and the aqueous phase extracted with $CHCl_3$ (2 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (81 mg) that was subjected to column chromatography (25:75:0.1 EtOAc/hexanes/NEt_3) to afford the title compound **140** (52.5 mg, 75%) as a white solid: **m.p.** 194–195 °C; $\mathbf{R_f}$ 0.12 (25:75:0.1 EtOAc/hexanes/NEt_3); **IR** (thin film) 2959, 2854, 1724, 1627, 1489, 1230, 1111, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (1H, dd, *J* = 8.4, 0.8 Hz, Ar<u>H</u>), 7.30 (1H, dd, *J* = 8.2, 1.8 Hz, Ar<u>H</u>), 7.25 (1H, d, *J* = 1.7 Hz, Ar<u>H</u>), 6.88 (1H, d, *J* = 8.1 Hz, Ar<u>H</u>), 6.82 (1H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.02 (2H, s, OC<u>H</u>$_2$O), 5.91 (1H, s, ArC<u>H</u>), 4.22–4.15 (2H, m, 2 × OC<u>H</u>$_a$H$_b$CH$_2$), 4.07–3.99 (2H, m, 2 × OCH$_a$<u>H</u>$_b$CH$_2$), 4.00 (3H, s,OC<u>H</u>$_3$), 3.89 (3H, s, OC<u>H</u>$_3$), 2.27–2.12 (1H, m, OCH$_2$C<u>H</u>$_a$H$_b$CH$_2$O), 1.47–1.40 (1H, m, OCH$_2$CH$_a$<u>H</u>$_b$CH$_2$O) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3 (C), 156.2 (C), 149.0 (C), 147.9 (C), 145.5 (C), 143.3 (C), 125.6 (C), 124.1 (C), 123.6 (C), 122.9 (CH), 121.2 (CH), 110.1 (C), 108.5 (CH), 108.4 (CH), 106.6 (CH), 101.6 (CH_2), 98.5 (CH), 66.8 (2 × CH_2), 56.3 (CH_3), 52.3 (CH_3), 25.9 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{22}H_{20}O_8Na$ $[M+Na]^+$: 435.1050, found: 435.1056; **MS** (+ESI) *m/z* 847 ($[2M+Na]^+$, 27%), 435 ($[M+Na]^+$, 11), 413 ($[M+H]^+$, 100), 369 (21).

Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(1'',3''-dioxan-2''-yl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-141)



trans-**141**

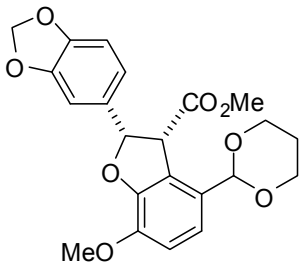
Procedure 1

To a flask containing benzofuran **140** (41.2 mg, 0.100 mmol) and Mg turnings (49 mg, 2.0 mmol, 20 equiv.), was added MeOH (2.5 mL) and the resulting mixture stirred for 2.5 h before THF (2.0 mL) was added to aid the solubility of substrate **140**. After a further 25 h, the reaction mixture was partitioned between H_2O (40 mL) and CH_2Cl_2 (40 mL) which formed an emulsion. A pH 7 buffer was added (40 mL) and the organic phase was isolated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with H_2O (50 mL), dried over $MgSO_4$, then concentrated *in vacuo* to give a colourless/cloudy film (36 mg). The crude residue was purified by column chromatography (100% CH_2Cl_2→3:97 EtOAc/CH_2Cl_2) to afford the title compound *trans*-**141** as a white foam (13.1 mg, 32%): **m.p.** 54–57 °C; $\mathbf{R_f}$ 0.27 (3:97 EtOAc/CH_2Cl_2); **IR** (thin film) 2955, 2851, 1740, 1628, 1439, 1281, 1250, 1107 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.01 (1H, d, J = 8.4 Hz, ArH), 6.86–6.80 (1H, m, ArH), 6.75 (1H, d, J = 8.4 Hz, ArH), 5.93 (2H, s, OCH_2O), 5.75 (1H, d, J = 6.5 Hz, ArOCHAr), 5.43 (1H, s, ArCH), 4.50 (1H, d, J = 6.5 Hz, $ArCHCO_2CH_3$), 4.23–4.07 (2H, m, 2 × $OCH_aH_bCH_2$), 3.94–3.78 (2H, m, 2 × $OCH_aH_bCH_2$), 3.88 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.24–2.06 (1H, m, $OCH_2CH_aH_bCH_2O$), 1.41–1.33 (1H, m, $OCH_2CH_aH_bCH_2O$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.6 (C), 148.8 (C), 148.1 (C), 147.8 (C), 145.0 (C), 134.5 (C), 128.1 (C), 123.1 (C), 119.7 (CH), 119.5 (CH), 112.2 (CH), 108.3 (CH), 106.4 (CH), 101.3 (CH_2), 100.4 (CH), 87.9 (CH), 67.18 (CH_2), 67.15 (CH_2), 57.2, 56.2, 52.5 (1 × CH, 2 × CH_3), 25.6 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{22}H_{22}O_8Na$ $[M+Na]^+$: 437.1207, found: 437.1194; **MS** (+ESI) *m/z* 851 ($[2M+Na]^+$, 74%), 437 ($[M+Na]^+$, 15), 415 ($[M+H]^+$, 100), 383 (17), 371 (13).

Procedure 2

To a flask containing benzofuran **140** (58.4 mg, 0.142 mmol) and Mg turnings was added MeOH (35 mL) followed by a single crystal of iodine (*ca*. 8 mg) and the resulting mixture stirred at rt for 18 h before an additional portion of Mg turnings (170 mg, 7.09 mmol, 50 equiv.) and THF (15 mL), was added. After a further 16 h, the reaction mixture was diluted with saturated aqueous NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, then concentrated *in vacuo* to give a colourless film (60 mg) that was purified by column chromatography

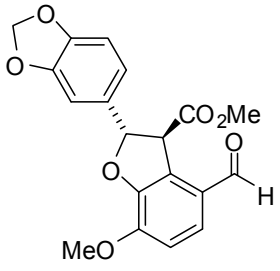
(1.8:88.2:10:0.5 Et_2O/CH_2Cl_2/hexanes/NEt_3) to afford the title compound *trans*-**141** (34.0 mg, 58%), spectroscopically identical to the material isolated from procedure 1, and the diastereomeric partner *cis*-**141** (6.1 mg, 10%).



cis-**141**

Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(1'',3''-dioxan-2''-yl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*cis*-141): white solid; **m.p.** 119–122 °C; $\mathbf{R_f}$ 0.24 (2:98:0.5 $Et_2O/CH_2Cl_2/NEt_3$); **IR** (thin film) 2952, 2924, 2853, 1732, 1441, 1282, 1109, 1091, 1037 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 6.96–6.92 (2H, m, 2 × ArH), 6.92–6.88 (1H, m, ArH), 6.83 (1H, d, J = 8.4 Hz, ArH), 6.77 (1H, d, J = 8.0 Hz), 5.95 (2H, s, OCH_2O), 5.90 (1H, d, J = 9.5 Hz, ArOCHAr), 5.39 (1H, s, ArCH), 4.72 (1H, d, J = 9.5 Hz, $ArCHCO_2CH_3$), 4.22–4.06 (2H, m, 2 × $OCH_aH_bCH_2$), 3.91 (3H, s, OCH_3), 3.93–3.78 (2H, m, 2 × $OCH_aH_bCH_2$), 3.31 (3H, s, OCH_3), 2.23–2.10 (1H, m, $OCH_2CH_aH_bCH_2O$), 1.40–1.34 (1H, m, $OCH_2CH_aH_bCH_2O$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4 (C), 149.5 (C), 147.6 (2 × C), 145.3 (C), 130.3 (C), 128.0 (C), 124.6 (C), 120.3 (CH), 119.9 (CH), 112.1 (CH), 108.0 (CH), 107.4 (CH), 101.2 (CH_2), 101.1 (CH), 87.3 (CH), 67.3 (CH_2), 67.2 (CH_2), 56.2, 54.7, 51.7 (1 × CH, 2 × CH_3), 25.7 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{22}H_{23}O_8$ $[M+H]^+$: 415.1387, found: 415.1406; **MS** (+ESI) *m/z* 851 ($[2M+Na]^+$, 56%), 415 ($[M+H]^+$, 100), 383 (5), 371 (12), 355 (4).

Methyl 2-(1',3'-benzodioxol-5'-yl)-4-formyl-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-133)

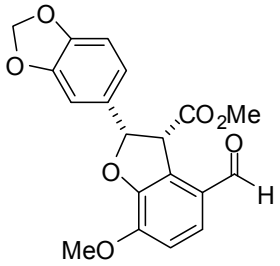


trans-**133**

To benzofuran **140** (41.2 mg, 0.100 mmol) was added Mg turnings (100 mg, 4.00 mmol, 40.0 equiv.) followed by MeOH (2.0 mL) and THF (3.5 mL). A single crystal of iodine (*ca*. 9 mg) was added and the resulting mixture allowed to stir at rt. After 17 h, the reaction was quenched by the addition of aqueous HCl (1 M, 10mL) which formed a gel that dissipated after ~30 min. The resulting solution was diluted

with CH_2Cl_2 (40 mL), saturated aqueous $Na_2S_2O_3$ solution (20 mL) and H_2O (20 mL). The organic phase was isolated, the aqueous phase extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless film (34 mg) that was purified by column chromatography (44:55 EtOAc/hexanes) to afford a *ca*. 2.5:1 mixture of *trans*-**133** and *cis*-**133** respectively (30.7 mg, 86%). For analytical purposes, the two diastereomers could be separated by column chromatography (2:98:0.5 $Et_2O/CH_2Cl_2/NEt_3$).

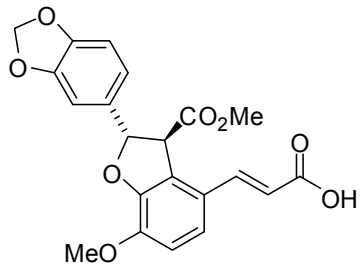
Dihydrobenzofuran *trans*-**133**: white solid; **m.p.** 105–106 °C; $\mathbf{R_f}$ 0.29 (2:98:0.5 $Et_2O/CH_2Cl_2/NEt_3$); **IR** (thin film) 2951, 2916, 1740, 1685, 1612, 1582, 1288, 1238, 1095 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.85 (1H, s, C<u>H</u>O), 7.42 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 6.99 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 6.91–6.83 (2H, m, 2 × Ar<u>H</u>), 6.78 (1H, d, *J* = 7.7 Hz, Ar<u>H</u>), 5.95 (2H, s, OC<u>H</u>$_2$O), 5.84 (1H, d, *J* = 6.5 Hz, ArOC<u>H</u>Ar), 4.66 (1H, d, *J* = 6.5 Hz, ArC<u>H</u>CO_2CH_3), 3.99 (3H, s, OC<u>H</u>$_3$), 3.78 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.6 (CH), 171.8 (C), 149.8 (C), 149.7 (C), 148.2 (C), 148.0 (C), 134.0 (C), 128.6 (CH), 126.8 (C), 124.5 (C), 119.5 (CH), 111.9 (CH), 108.5 (CH), 106.1 (CH), 101.4 (CH_2), 88.7 (CH), 56.9, 56.4, 52.8 (1 × CH, 2 × CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{19}H_{16}O_7Na$ $[M+Na]^+$: 379.0788, found: 379.0770; **MS** (+ESI) *m/z* 735 ($[2M+Na]^+$, 44%), 357 ($[M+Na]^+$, 8), ($[M+H]^+$, 100), 325 (32).



cis-**133**

Dihydrobenzofuran *cis*-**133**: colourless film; $\mathbf{R_f}$ 0.42 (5:95 Et_2O/CH_2Cl_2); **IR** (thin film) 2951, 2923, 2852, 1738, 1681, 1617, 1450, 1285, 1241, 1094, 934 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (1H, s, C<u>H</u>O), 7.41 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 7.00 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 6.90–6.85 (2H, m, 2 × Ar<u>H</u>), 6.78 (1H, d, *J* = 8.6 Hz, Ar<u>H</u>), 5.99 (1H, d, *J* = 10.2 Hz, ArOC<u>H</u>Ar), 5.95 (2H, s, OC<u>H</u>$_2$O), 4.91 (1H, d, *J* = 10.2 Hz, ArC<u>H</u>CO_2CH_3), 4.01 (3H, s, OC<u>H</u>$_3$), 3.30 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.7 (CH), 169.6 (C), 150.3 (C), 149.7 (C), 147.9 (C), 147.7 (C), 130.1 (C), 128.8 (CH), 126.9 (C), 125.6 (C), 120.6 (CH), 112.0 (CH), 108.1 (CH), 107.4 (CH), 101.3 (CH_2), 87.9 (CH), 56.4, 54.5, 51.9 (1 × CH, 2 × CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{19}H_{16}O_7Na$ $[M+Na]^+$: 379.0788, found: 379.0783; **MS** (+ESI) *m/z*735 ($[2M+Na]^+$, 100%), 379 ($[M+Na]^+$, 50), 357 ($[M+H]^+$, 15).

(2*E*)-3-[2'-(1'',3''-benzodioxol-5''-yl)-7'-methoxy-3'-(methoxycarbonyl)-2',3'-dihydro-1'-benzofuran-4'-yl]prop-2-enoic acid (*trans*-150)

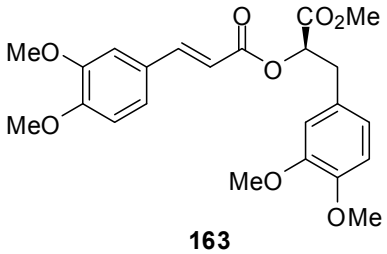


trans-**150**

To a flask equipped with an air condenser, was added a *ca*. 2.5:1 mixture of aldehydes *trans*-**133** and *cis*-**133** (100 mg, 0.281 mmol) and malonic acid (88.0 mg, 0.842 mmol, 3.0 equiv.) followed by pyridine (9.3 mL) and piperidine (285 μL, 2.86 mmol, 10.2 equiv.). The resulting solution was then heated to 100 °C for 5 h before cooling to rt and diluting with EtOAc (100 mL) and aqueous HCl (1 M, 100 mL). The organic phase was isolated and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil that was purified by column chromatography (1:3:96 MeOH/Et_2O/CH_2Cl_2) to afford the title compound *trans*-**150** (74.3 mg, 66%, containing *ca*. 5.6% of *cis*-**150**). This mixture was used in the subsequent step without further purification. For analytical purposes, *trans*-**150** could be obtained, by subjecting the mixture to column chromatography (1:3:96 MeOH/Et_2O/CH_2Cl_2), as a white solid: **m.p.** 199–201 °C; $\mathbf{R_f}$ 0.64 (10:30:60 MeOH/Et_2O/CH_2Cl_2); **IR** (thin film) 2916, 2588, 1740, 1682, 1612, 1510, 1285, 1204, 1038, 910 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CHCO$_2$H), 7.23 (1H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.89 (1H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.85–6.73 (3H, m, 3 × Ar<u>H</u>), 6.28 (1H, d, *J* = 15.8 Hz, ArCH=C<u>H</u>CO$_2$H), 6.02 (1H, d, *J* = 5.2 Hz, ArOC<u>H</u>Ar), 5.94 (2H, s, OC<u>H$_2$</u>O), 4.43 (1H, d, *J* = 5.3 Hz, ArC<u>H</u>CO$_2$Me), 3.94 (3H, s, OC<u>H$_3$</u>), 3.79 (3H, s, OC<u>H$_3$</u>) ppm; ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 171.9 (C), 171.7 (C), 148.6 (C), 148.3 (C), 148.0 (C), 146.7 (C), 143.3 (CH), 134.1 (C), 125.1 (C), 124.4 (C), 121.0 (CH), 119.4 (CH), 116.8 (CH), 113.2 (CH), 108.5 (CH), 106.0 (CH), 101.4 (CH_2), 87.4 (CH), 56.3, 56.2, 53.1 (1 × CH, 2 × CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{21}H_{18}O_8Na$ $[M+Na]^+$: 421.0894, found: 421.0885; **MS** (+ESI) *m/z* 819 ($[2M+Na]^+$, 95%), 421 ($[M+Na]^+$, 49), 416 ($[M+NH_4]^+$, 100), 399 (5).

8.5 Synthesis of Compounds from Chapter 4

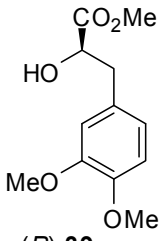
Pentamethyl rosmarinic acid (163)



163

To a flask containing rosmarinic acid (900.8 mg, 2.50 mmol) and anhydrous K_2CO_3 (2.59 g, 18.75 mmol, 7.5 equiv.), was added DMF (30 mL) followed by methyl iodide (1.18 mL, 18.8 mmol, 7.5 equiv.) and the resulting solution heated to 60 °C for 2 d before a further aliquot of methyl iodide (1.18 mL, 18.8 mmol, 7.5 equiv.) was added. Heating was continued for a further 2 d before cooling to rt and quenching by the addition of H_2O (150 mL). The resulting mixture was extracted with Et_2O (1 × 200 ml, 2 × 150 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil that was subjected to column chromatography (40:60 EtOAc/hexanes) to afford the title compound **163** (995.2 mg, 92%) as a pale yellow foam: $\mathbf{R_f}$ 0.20 (40:60 EtOAc/hexanes); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CHCO$_2$CH), 7.01 (1H, d, *J* = 8.2 Hz, Ar<u>H</u>), 6.97 (1H, s, Ar<u>H</u>), 6.79 (1H, d, *J* = 8.2 Hz, Ar<u>H</u>), 6.75–6.69 (3H, m, 3 × Ar<u>H</u>), 6.25 (1H, d, *J* = 15.9 Hz, ArCH=C<u>H</u>CO$_2$CH), 5.30 (1H, dd, *J* = 7.5, 5.4 Hz, C<u>H</u>CO$_2$CH$_3$), 3.84 (6H, s, 2 × OC<u>H</u>$_3$), 3.79 (3H, s, OC<u>H</u>$_3$), 3.78 (3H, s, OC<u>H</u>$_3$), 3.67 (3H, s, OC<u>H</u>$_3$), 3.12–3.05 (2H, m, ArC<u>H</u>$_2$CHCO$_2$CH$_3$) ppm; $[\alpha]_D$ +40.9 ° (*c* 7.70, CH_2Cl_2), (lit. +40.7 ° (*c* 0.50, CH_2Cl_2)). Spectral data were consistent with literature values.[49]

Methyl (2*R*)-3-(3',4'-dimethoxyphenyl)-2-hydroxypropanoate ((*R*)-39)

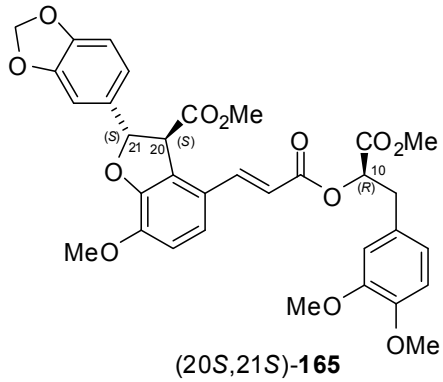


(*R*)-**39**

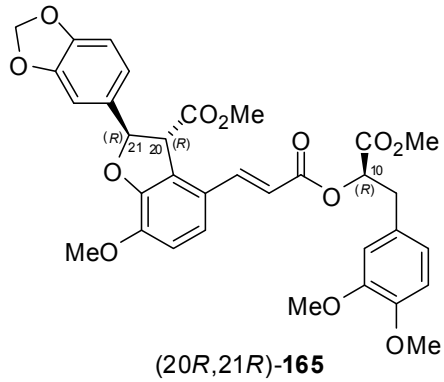
The title compound (*R*)-**39** was prepared according to Ellman *et al*.[49] A 1.0 M stock solution of NaOMe in MeOH was generated by the addition of Na metal (549.5 mg, 23.91 mmol) to MeOH (24.0 mL) with cooling in an ice bath to maintain a reasonable temperature (<50 °C). To a solution of ester **163** (854.5 mg, 1.986 mmol) in MeOH (7.1 mL) was added stock NaOMe solution (2.20 mL, 1.0 M, 2.20

mmol, 1.1 equiv.) and the resulting solution allowed to stir at rt for 1 h before being quenched by the addition of saturated aqueous NH_4Cl solution (~5 mL). This was then diluted with saturated aqueous NH_4Cl solution (180 mL), H_2O (20 mL) and EtOAc (200 mL). The organic phase was isolated and the aqueous phase extracted with EtOAc (2 × 200 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil (822 mg). The crude oil was then purified by column chromatography (3:97→10:90 Et_2O/CH_2Cl_2) to afford 295.7 mg (62%) of the title compound (*R*)-**39** as a white solid: **m.p.** 63–65 °C (lit.[49] 53–54 °C); $\mathbf{R_f}$ 0.25 (10:90 Et_2O/CH_2Cl_2); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 6.83–6.65 (3H, m, 3 × Ar<u>H</u>), 4.45–4.34 (1H, m, C<u>H</u>OH), 3.82 (3H, s, OC<u>H</u>$_3$), 3.81 (3H, s, OC<u>H</u>$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 3.09–2.96 (1H, m, O<u>H</u>), 2.88 (1H, d, J = 14.8 Hz, ArC<u>H</u>$_a$H$_b$CH(OH)CO_2Me), 2.85 (1H, d, J = 13.4 Hz, ArCH$_a$<u>H</u>$_b$CH(OH)CO_2Me) ppm; $[\alpha]_D$ +10.1 ° (*c* 1.50, CH_2Cl_2), (lit. +10.6 ° (*c* 0.67, CH_2Cl_2)). Spectral data were consistent with literature values.[49]

(2*S*,3*S*)-Methyl 2-(1',3'-benzodioxol-5'-yl)-4-{(E)-3'-[(*R*)-3'-(3',4'-dimethoxyphenyl)-1'-methoxy-1'-oxopropan-2'-yloxy]-3'-oxoprop-1'-enyl}-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate ((20*S*,21*S*)-165) and the diastereomeric partner ((20*R*,21*R*)-165)



(20*S*,21*S*)-**165**

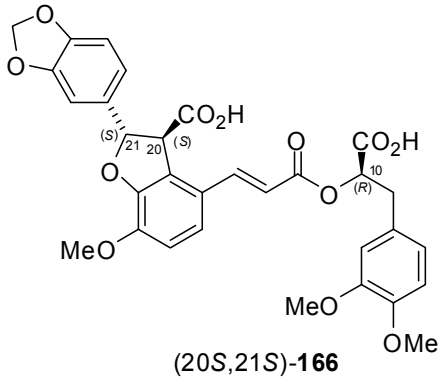


(20*R*,21*R*)-**165**

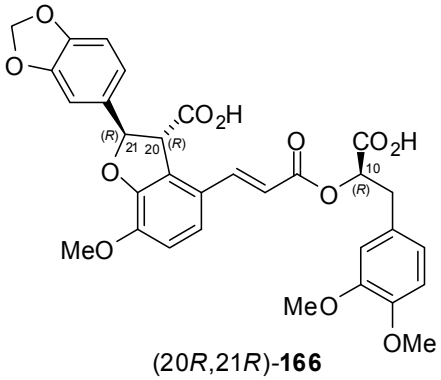
To a flask containing *ca*. 17:1 *trans*-**150** and *cis*-**150** (69.2 mg, 0.174 mmol), alcohol (*R*)-**39** (67.0 mg, 0.278 mmol, 1.6 equiv.), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC.HCl) (180 mg, 0.938 mmol, 5.4 equiv.) and 4-(dimethylamino)pyridine (DMAP) (115 mg, 0.938 mmol, 5.4 equiv.), was added $CHCl_3$ (1.2 mL). The resulting solution was flushed with $Ar_{(g)}$, sealed and allowed to stir at rt for 3.5 d before the addition of AcOH (~6 drops) to convert excess alcohol (*R*)-**39** to a more easily separable acetate. After 10 min the reaction was partitioned between saturated aqueous NH_4Cl solution (50 mL) and Et_2O (50 mL). The organic phase was isolated and the aqueous phase extracted with Et_2O (3 × 50 mL) and the combined organic phases were dried over $MgSO_4$ then concentrated *in vacuo* to yield a yellow oil. This was subjected to column chromatography (40:60 EtOAc/hexanes) to afford a presumably 1:1 mixture of the title compounds (20*S*,21*S*)-**165** and (20*R*,21*R*)-**165** (94.7 mg, 88%) as a white foam: **m.p.** 62–64 °C; $\mathbf{R_f}$ 0.22 (40:60 EtOAc/hexanes); **IR** (thin film) 2955, 1736, 1713, 1639, 1613, 1506, 1439, 1203, 1158, 807 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) (some signals

appeared doubled due to the presence of two diastereomers) δ 7.73 (1 × 1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CHCO$_2$), 7.72 (1 × 1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CHCO$_2$), 7.20 (1 × 1H, d, *J* = 8.5 Hz, Ar<u>H</u>), 7.18 (1 × 1H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.96–6.70 (2 × 7H, m, 7 × Ar<u>H</u>), 6.29 (1 × 1H, d, *J* = 15.9 Hz, ArCH=C<u>H</u>CO$_2$), 6.29 (1 × 1H, d, *J* = 15.9 Hz, ArCH=C<u>H</u>CO$_2$), 6.00 (1 × 1H, d, *J* = 5.4 Hz, ArOC<u>H</u>Ar), 5.99 (1 × 1H, d, *J* = 5.0 Hz, ArOC<u>H</u>Ar), 5.94 (2 × 2H, s, 2 × OC<u>H$_2$</u>O), 5.33 (2 × 1H, dd, *J* = 8.1, 4.9 Hz, 2 × ArCH$_2$C<u>H</u>CO$_2$CH$_3$), 4.39 (1 × 1H, d, *J* = 5.2 Hz, ArC<u>H</u>CO$_2$CH$_3$), 4.39 (1 × 1H, d, *J* = 5.3 Hz, ArC<u>H</u>CO$_2$CH$_3$), 3.94 (2 × 3H, s, 2 × OC<u>H$_3$</u>), 3.84 (1 × 3H, s, 1 × OC<u>H$_3$</u>), 3.83 (1 × 3H, s, 1 × OC<u>H$_3$</u>), 3.83 (2 × 3H, s, 2 × OC<u>H$_3$</u>), 3.74 (1 × 3H, s, 1 × OC<u>H$_3$</u>), 3.73 (3 × 3H, s, 3 × OC<u>H$_3$</u>) 3.21–3.06 (2 × 2H, m, 2 × ArC<u>H$_2$</u>CHCO$_2$CH$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) (some signals appeared doubled due to the presence of two diastereomers) δ 171.70+171.62 (C), 170.38 (2 × C), 166.17 (2 × C), 149.07 (2 × C), 148.68+148.64 (C), 148.33+148.30 (C), 148.05 (2 × C), 146.56 (2 × C), 142.60+142.46 (CH), 134.19+134.17 (C), 128.59 (2 × C), 125.10+124.92 (C), 124.66+124.57 (C), 121.70+121.66 (CH), 121.08+120.81 (CH), 119.44+119.39 (CH), 116.71+116.66 (CH), 113.31+113.28 (CH), 112.83+112.78 (CH), 111.48 (2 × CH), 108.54 (2 × CH), 106.03+106.01 (CH), 101.39 (2 × CH$_2$), 87.46+87.40 (CH), 73.27+73.23 (CH), 56.37 (2 × CH$_3$), 56.25 (2 × CH$_3$), 56.03 (2 × CH$_3$), 52.95+52.92 (CH$_3$), 52.51+52.42 (CH$_3$), 37.37+37.33 (2 × CH$_2$) ppm; **HRMS** (+ESI) Calc. for $C_{33}H_{32}O_{12}Na$ $[M+Na]^+$: 643.1786, found: 643.1769; **MS** (+ESI) *m/z* 643 ($[M+Na]^+$, 97%), 638 ($[M+NH_4]^+$, 100).

(2*S*,3*S*)-2-(1',3'-Benzodioxol-5'-yl)-4-((E)-3'-((*R*)-1'-carboxy-2'-(3',4'-dimethoxyphenyl)ethoxy)-3'-oxoprop-1'-enyl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylic acid ((20*S*,21*S*)-166) and the diastereomeric partner ((20*R*,21*R*)-166)



(20*S*,21*S*)-**166**

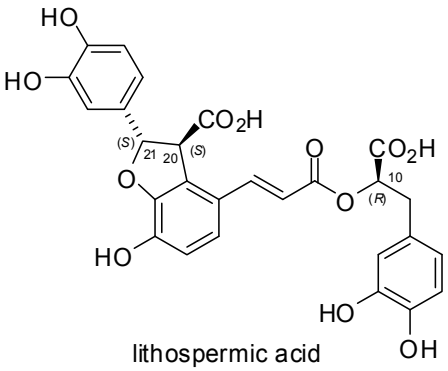


(20*R*,21*R*)-**166**

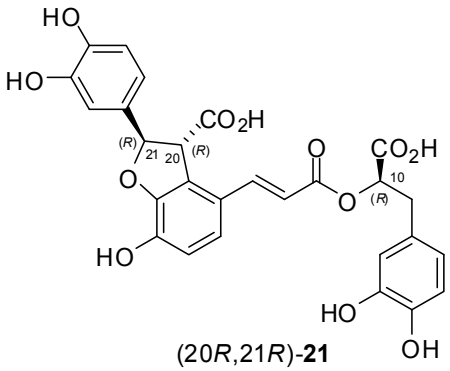
To a solution of the diester (20*S*,21*S*)-**165** (94.7 mg, 0.153 mmol, including the diastereomeric partner (20*R*,21*R*)-**165**, 1:1) in 1,2-dichloroethane (7.6 mL) was added Me_3SnOH (140.8 mg, 98%, 0.763 mmol, 5.0 equiv.) and the resulting solution heated to 80 °C for 27 h before cooling to rt and adding aqueous HCl (1 M, 50 mL) and EtOAc (50 mL). The organic phase was isolated and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and

concentrated *in vacuo* to give a colourless film (125 mg) that was subjected to column chromatography (15:85:1→40:60:1 acetone/CH_2Cl_2/AcOH) to afford a presumably 1:1 mixture of title compound (20*S*,21*S*)-**166** and the diastereomeric partner (20*R*,21*R*)-**166** (57.6 mg, 64%) as a white solid: **m.p.** 103–105 °C; $\mathbf{R_f}$ 0.47 (5:30:65 MeOH/Et_2O/CH_2Cl_2); **IR** (thin film) 3180, 2926, 2569, 1713, 1608, 1504, 1263, 1159, 1086, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) (some signals appeared doubled due to the presence of two diastereomers) δ 7.66 (1 × 1H, d, *J* = 15.6 Hz, ArC<u>H</u>=CHCO$_2$), 7.64 (1 × 1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CHCO$_2$), 7.14 (1 × 1H, d, *J* = 8.2 Hz, Ar<u>H</u>), 7.01 (1 × 1H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.89–6.59 (2 × 7H, m, 7 × Ar<u>H</u>), 6.26 (1 × 1H, d, *J* = 15.8 Hz, ArCH=C<u>H</u>CO$_2$), 6.01 (1 × 1H, d, *J* = 15.8 Hz, ArCH=C<u>H</u>CO$_2$), 5.97 (1 × 1H, d, *J* = 5.6 Hz, ArOC<u>H</u>Ar), 5.93 (1 × 1H, d, *J* = 7.2 Hz, ArOC<u>H</u>Ar), 5.90 (2 × 2H, s, 2 × OC<u>H</u>$_2$O), 5.25–5.17 (1 × 1H, m, 1 × ArCH$_2$C<u>H</u>CO$_2$CH$_3$), 5.06–5.00 (1 × 1H, m, 1 × ArCH$_2$C<u>H</u>CO$_2$CH$_3$), 4.35 (1 × 1H, d, *J* = 5.3 Hz, ArC<u>H</u>CO$_2$CH$_3$), 4.29 (1 × 1H, d, *J* = 5.2 Hz, ArC<u>H</u>CO$_2$CH$_3$), 3.91 (2 × 3H, s, 2 × OC<u>H</u>$_3$), 3.84 (1 × 3H, s, 1 × OC<u>H</u>$_3$), 3.83 (1 × 3H, s, 1 × OC<u>H</u>$_3$), 3.74 (1 × 3H, s, 1 × OC<u>H</u>$_3$), 3.68 (1 × 3H, s, 1 × OC<u>H</u>$_3$), 3.19–2.88 (2 × 2H, m, 2 × ArC<u>H</u>$_2$CHCO$_2$CH$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) (some signals appeared doubled due to the presence of two diastereomers) δ 170.11 (2 × C), 168.00+167.97 (C), 166.37 (2 × C), 148.96+148.90 (C), 148.76+148.52 (C), 148.29+148.25 (C), 148.21+148.19 (C), 147.96+147.91 (C), 146.56 (2 × C), 143.4 (2 × CH), 134.53+134.41 (C), 129.11+128.86 (C), 124.44+124.39 (C), 124.03+123.93 (C), 121.65+121.62 (CH), 120.29 (2 × CH), 119.50+119.44 (CH), 116.54 (2 × CH), 113.26+113.15 (CH), 113.15+113.02 (CH), 111.53+111.40 (CH), 108.49+108.46 (CH), 106.11+105.99 (CH), 101.38+101.34 (2 × CH_2), 87.49+87.28 (CH), 73.68+73.45 (CH), 56.36, 56.21, 56.05, 55.94, 2 × (3 × CH_3+1 × CH), 37.10+36.94 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{31}H_{28}O_{12}Na$ $[M+Na]^+$: 615.1473, found: 615.1490; **MS** (+ESI) *m/z* 615 ($[M+Na]^+$, 100%), 610 ($[M+NH_4]^+$, 59).

Attempted formation of lithospermic acid (21) and the diastereomeric partner (20*R*,21*R*)-21



lithospermic acid (**21**)

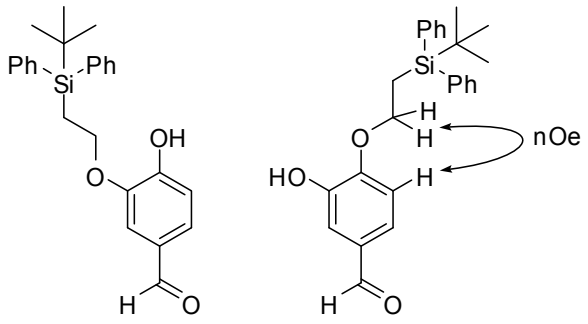


(20*R*,21*R*)-**21**

The substrate (20*S*,21*S*)-**166** (12.6 mg, 0.021 mmol, including the diastereomeric partner (20*R*,21*R*)-**166**, 1:1) was placed into a 20 mL sealed tube equipped with a stirrer bar and the whole assembly transferred to a dry box. 1-Trimethylsilylquinolinium iodide (**46**) (310 mg, 0.850 mmol, 40 equiv.) was added to the tube which was then sealed and removed from the dry box. The sealed tube was then placed in a tall oil bath and stirred at 105 °C for 5 h before cooling to rt and adding aqueous HCl (1 M, 50 mL). The mixture was rinsed into a separating funnel with aqueous HCl (30 mL) and EtOAc (30 mL) before the organic phase was isolated. The aqueous phase was extracted with EtOAc (4 × 30 mL) and the combined organic phases were dried over $MgSO_4$ before being concentrated *in vacuo* to give a dark brown oil (32 mg). This crude residue was subjected to column chromatography (1:5:94→1:20:79 AcOH/MeOH/CH_2Cl_2) to afford 8.9 mg of a brown solid. Further purification by HPLC (gradient elution, 90:10:0.05 H_2O/MeCN/TFA→40.5:59.5:0.05 H_2O/MeCN/TFA over 45 min at 2 mL/min on an Alltech C18 semi-preparative reverse phase column) afforded 1.2 mg of a brown solid that appeared to contain a *ca*. 1:1:1 mixture of **21**, (20*R*,21*R*)-**21**, and an unknown by-product.

R_f 0.48 (40:60 MeOH/CH_2Cl_2); **HPLC T_r** 29.0 min; **UV** λ_{max} 255, 289, 310 nm; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.88 (1H, d, *J* = 8.5 Hz, ArC<u>H</u>=CHCO$_2$), 7.34 (1H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.96–6.54 (7H, m, 7 × Ar<u>H</u>), 6.34 (1H, d, *J* = 15.9 Hz, ArCH=C<u>H</u>CO$_2$), 5.99 (1H, d, *J* = 5.5 Hz, ArOC<u>H</u>Ar), 5.15 (1H, dd, *J* = 8.6 Hz, *J* = 3.9 Hz, ArCH$_2$C<u>H</u>CO$_2$H), 4.48 (1H, d, *J* = 4.7 Hz, ArC<u>H</u>CO$_2$H), 3.14–2.96 (2H, m, ArC<u>H$_2$</u>CHCO$_2$H) ppm; **MS** (+ESI) *m/z* 1099 ([2M+Na]$^+$, 90%), 1077 ([2M+H]$^+$, 53), 561 ([M+Na]$^+$, 100), 539 ([M+H]$^+$, 80); **MS** (–ESI) *m/z* 1075 ([2M–H]$^-$, 100%), 537 ([M–H]$^-$, 56).

3-(2'-(*tert*-Butyldiphenylsilyl)ethoxy)-4-hydroxybenzaldehyde (173) and 4-(2'-(*tert*-butyldiphenylsilyl)ethoxy)-3-hydroxybenzaldehyde (174)



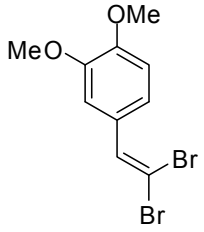
To a solution of triphenylphosphine (95.0 mg, 0.362 mmol, 1.0 equiv.) in THF (3 mL) at 0 °C were added diisopropyl azodicarboxylate (DIAD) (75 µL, 73 mg, 0.36 mmol, 1.0 equiv.), 3,4-dihydroxybenzaldehyde (50.0 mg, 0.362 mmol, 1.0 equiv.) and 2-(*tert*-butyldiphenylsilyl)ethanol **172** (103 mg, 0.362 mmol, 1.0 equiv.) and the resulting solution allowed to slowly warm to rt. After 24 h of stirring at rt, the solvent was removed *in vacuo* and the crude residue subjected to column chromatography (50:50 CH_2Cl_2/hexanes→100% CH_2Cl_2→20:80 Et_2O/CH_2Cl_2) to afford regioisomer 1 (**173**) (48.5 mg, 33%) and regioisomer 2 (**174**) (21.2 mg, 15%).

Regioisomer 1 (173): white solid: **m.p.** 129–130 °C; $\mathbf{R_f}$ 0.26 (70:30 CH_2Cl_2/hexanes); **IR** (thin film) 3475, 3367, 2930, 2856, 2727, 1678, 1589, 1286, 1269, 1107, 702 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.73 (1H, s, C<u>H</u>O), 7.71–7.63 (4H, m, 4 × Ar<u>H</u>), 7.49–7.37 (6H, m, 6 × Ar<u>H</u>), 7.33 (1H, dd, *J* = 8.1, 1.7 Hz, Ar<u>H</u>), 7.15 (1H, d, *J* = 1.7 Hz, Ar<u>H</u>), 6.93 (1H, d, *J* = 8.1 Hz, Ar<u>H</u>), 5.71 (1H, s, OH), 4.16 (2H, t, *J* = 7.7 Hz, OC<u>H</u>$_2$CH$_2$Si), 1.83 (2H, t, *J* = 7.7 Hz, SiC<u>H</u>$_2$CH$_2$O), 1.09 (9H, s, C(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.9 (CH), 151.8 (C), 146.3 (C), 135.8 (CH), 133.8 (C), 129.8 (C), 129.7 (CH), 128.1 (CH), 127.2 (CH), 114.4 (CH), 109.6 (CH), 66.8 (CH_2), 27.8 (CH_3), 18.2 (C), 11.7 (CH_2) ppm; **MS** (+ESI) *m/z* 405 ($[M+H]^+$, 100%); **NOESY**: No noteworthy nOe correlation was observed.

Regioisomer 2 (174): wax-like off-white solid: **m.p.** 102–105 °C; $\mathbf{R_f}$ 0.12 (70:30 CH_2Cl_2/hexanes); **IR** (thin film) 3494, 3352, 2930, 2856, 2727, 1688, 1607, 1585, 1504, 1273, 1194, 1109, 702 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (1H, s, C<u>H</u>O), 7.68–7.62 (4H, m, 4 × Ar<u>H</u>), 7.47–7.35 (6H, m, 6 × Ar<u>H</u>), 7.33 (1H, d, *J* = 1.9 Hz, Ar<u>H</u>), 7.28 (1H, dd, *J* = 8.3, 1.9 Hz, Ar<u>H</u>), 6.65 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 5.30 (1H, s, O<u>H</u>), 4.14 (2H, t, *J* = 7.9 Hz, OC<u>H</u>$_2$CH$_2$Si), 1.83 (2H, t, *J* = 7.9 Hz, SiC<u>H</u>$_2$CH$_2$O), 1.08 (9H, s, C(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.1 (CH), 151.1 (C), 146.2 (C), 135.8 (CH), 133.7 (C), 130.5 (C), 129.8 (CH), 128.2 (CH), 124.4 (CH), 114.2 (CH), 110.8 (CH), 67.0 (CH_2), 27.8 (CH3), 18.2 (C), 11.7 (CH_2) ppm; **MS** (+ESI) *m/z* 405 ($[M+H]^+$, 100%); **NOESY**: A significant nOe correlation was observed between the protons indicated above.

8.6 Synthesis of Compounds from Chapter 5

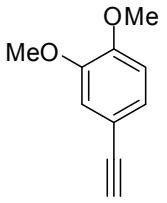
4-(2',2'-Dibromoethenyl)-1,2-dimethoxybenzene (177)



177

Carbon tetrabromide (10.08 g, 30.09 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C before adding triphenylphosphine (15.78 g, 60.17 mmol, 2.0 equiv.) and stirring at 0 °C for 30 min. Methylvanillin (**31**) (5.10 g, 30.09 mmol, 1.0 equiv.) was added and after stirring at 0 °C for 2.5 h was warmed to rt and stirred for a further 2 h. With rapid stirring, *n*-pentane (180 mL) was added dropwise to induce precipitation of triphenylphosphine oxide and the precipitate was removed at the pump and rinsed with *n*-pentane (200 mL). The filtrate was concentrated *in vacuo* and the residue triturated with *n*-pentane (200 mL). The precipitate was removed at the pump and the filtrate concentrated once more *in vacuo* to give a light yellow oil (9.56 g) that was purified by column chromatography (20:80 EtOAc/hexanes) to give the title compound **177** (8.53 g, 88%) as a colourless oil: $\mathbf{R_f}$ 0.34 (20:80 EtOAc/hexanes); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.17 (1H, d, J = 1.9 Hz, Ar<u>H</u>), 7.08 (1H, dd, J = 8.4, 1.9 Hz, Ar<u>H</u>), 6.83 (1H, d, J = 8.4 Hz, Ar<u>H</u>), 3.87 (6H, s, 2 × O<u>CH</u>$_3$) ppm. Spectral data were in accordance with the literature values.[122]

4-Ethynyl-1,2-dimethoxybenzene (178)

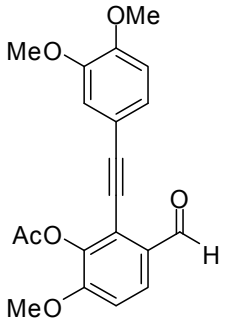


178

Dibromoalkene **177** (7.32 g, 22.7 mmol) was dissolved in THF (70 mL) and cooled to -78 °C before adding *n*-butyllithium (24.4 mL, 2.25 M in hexanes, 54.9 mmol, 2.4 equiv.). The resulting solution was allowed to slowly warm to 0 °C and stir for 1 h before being quenched by the addition of saturated aqueous NH_4Cl solution (50 mL). Stirring was continued at 0 °C for 30 min before warming to rt and extracting with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a dark brown solid (5.3 g) that was purified by column chromatography (20:80 Et_2O/*n*-pentane) to afford the title alkyne **178** (2.97 g, 80%) as a white solid: **m.p.** 70–71 °C

(lit.[122] 76 °C); $\mathbf{R_f}$ 0.35 (20:80 Et_2O/*n*-pentane); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.11 (1H, dd, *J* = 8.3, 1.8 Hz, ArH), 6.99 (1H, d, *J* = 1.8 Hz, ArH), 6.80 (1H, d, *J* = 8.3 Hz, ArH), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.00 (1H, s, C≡CH) ppm. Physical properties and spectral data were in accordance with literature values.[122]

2-((3',4'-Dimethoxyphenyl)ethynyl)-3-acetoxy-4-methoxybenzaldehyde (179)



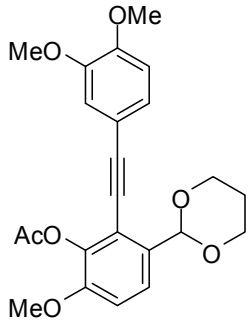
179

To a solution of aryl iodide **58** (3.29 g, 10.3 mmol) and arylalkyne **178** (2.00 g, 12.3 mmol, 1.2 equiv.) in degassed, anhydrous EtOAc (500 mL) at -20 °C, was added CuI (192 mg, 1.03 mmol, 10 mol%) and $Pd(PPh_3)_2Cl_2$ (361 mg, 0.514 mmol, 5 mol%) followed by *i*-Pr_2NH (1.60 mL, 1.14 g, 11.3 mmol, 1.1 equiv.). The resulting solution was protected from light by aluminium foil and allowed to slowly warm to rt over 5 h and left to continue stirring at rt for 21 h. The reaction mixture was then quenched by the addition of H_2O (100 mL) and saturated aqueous NaCl solution (100 mL). The organic phase was isolated and the aqueous phase was extracted with EtOAc (2 × 150 mL). The combined organic phases were washed with saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ then concentrated *in vacuo* to give a dark brown solid (4.9 g) that was purified by column chromatography (30:70→50:50 EtOAc/hexanes) to afford the title compound **179** (2.72 g, 75%) and an unknown yet related by-product (1.53 g, *ca*. 42%).

Diarylalkyne 179: white solid; **m.p.** 140–145 °C; $\mathbf{R_f}$ 0.33 (50:50 EtOAc/hexanes); **IR** (thin film) 2939, 2841, 2210, 1771, 1681, 1593, 1514, 1250, 1070, 1022 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.45 (1H, d, *J* = 0.7 Hz, CHO), 7.87 (1H, d, *J* = 8.7 Hz, ArH), 7.14 (1H, dd, *J* = 8.3, 1.9 Hz, ArH), 7.03 (1H, d, *J* = 8.3 Hz, ArH), 7.00 (1H, d, *J* = 1.9 Hz, ArH), 6.86 (1H, d, *J* = 8.3 Hz, ArH), 3.93 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.41 (3H, s, $OCOCH_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.1(CH), 168.3 (C), 156.4 (C), 150.6 (C), 149.0 (C), 140.9 (C), 129.4 (C), 127.0 (CH), 125.5 (CH), 122.7 (C), 114.36 (C), 114.33 (CH), 111.9 (CH), 111.3 (CH), 101.4 (C), 78.6 (C), 56.5 (CH_3), 56.15 (CH_3), 56.11 (CH_3), 20.6 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{20}H_{18}O_6Na$ $[M+Na]^+$: 377.0996, found: 377.1005; **MS** (+ESI) *m/z* 355 ($[M+H]^+$, 100%), 731 ($[2M+Na]^+$, 20).

Related by-product: off-white solid; $\mathbf{R_f}$ 0.44 (50:50 EtOAc/hexanes); **IR** (thin film) 3438, 2937, 2839, 2141, 1774, 1686, 1582, 1263, 1136, 1022 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.98 (1H, d, *J* = 0.7 Hz, C<u>H</u>O), 7.83 (1H, d, *J* = 8.7 Hz, Ar<u>H</u>), 7.14 (1H, dd, *J* = 8.3, 1.9 Hz, Ar<u>H</u>), 7.05–6.96 (2H, m, 2 × Ar<u>H</u>), 6.81 (1H, d, *J* = 8.4 Hz, Ar<u>H</u>), 3.91 (3H, s, OC<u>H</u>$_3$), 3.89 (3H, s, OC<u>H</u>$_3$), 3.88 (3H, s, OC<u>H</u>$_3$), 2.41 (3H, s, OCOC<u>H</u>$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.2 (CH), 167.7 (C), 156.5 (C), 150.4 (C), 148.8 (C), 141.0 (C), 129.6 (CH), 128.9 (C), 126.2 (CH), 114.9 (CH), 114.0 (C), 111.8 (CH), 111.2 (CH), 99.5 (C), 81.6 (C), 72.9 (C), 56.6 (CH_3), 56.0 (2 × CH_3), 20.8 (CH_3) ppm; **MS** (+ESI) *m/z* 763 (14%), 371 (100), 335 (86), 321 (49).

2-((3',4'-Dimethoxyphenyl)ethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenyl acetate (180)

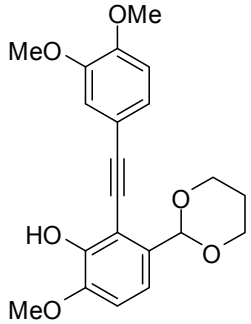


180

To a solution of aldehyde **179** (1.745 g, 4.942 mmol) in CH_2Cl_2 (220 mL) was added 1,3-propanediol (2.90 mL, 3.00 g, 39.4 mmol, 8.0 equiv.) followed by TMSCl (3.75 mL, 3.21 g, 29.5 mmol, 6.0 equiv.) and the resulting solution heated to reflux. After 2 h the reaction was cooled to rt and anhydrous K_2CO_3 (~10 g) was added and stirred vigorously for 10 min before the addition of saturated aqueous $NaHCO_3$ solution (200 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown solid (2.07 g) that was subjected to column chromatography (60:40:0.5 EtOAc/hexanes/NEt_3) to afford the title compound **180** (1.84 g, 91%) as an off-white solid: **m.p.** 163–164 °C; $\mathbf{R_f}$ 0.36 (60:40:0.5 EtOAc/hexanes/NEt_3); **IR** (thin film) 2962, 2934, 2847, 2210, 1772, 1514, 1202, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 8.7 Hz, Ar<u>H</u>), 7.12 (1H, d, *J* = 8.2 Hz, Ar<u>H</u>), 7.00 (1H, s, Ar<u>H</u>), 6.96 (1H, d, *J* = 8.7 Hz, Ar<u>H</u>), 6.85 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 5.84 (1H, s, ArC<u>H</u>), 4.31–4.24 (2H, m, 2 × OC<u>H</u>$_a$H$_b$CH$_2$), 4.05–3.96 (2H, m, 2 × OCH$_a$<u>H</u>$_b$CH$_2$), 3.91 (3H, s, OC<u>H</u>$_3$), 3.90 (3H, s, OC<u>H</u>$_3$), 3.84 (3H, s, OC<u>H</u>$_3$), 2.35 (3H, s, OCOC<u>H</u>$_3$), 2.32–2.15 (1H, m, OCH$_2$C<u>H</u>$_a$H$_b$CH$_2$O), 1.46–1.40 (1H, m, OCH$_2$CH$_a$<u>H</u>$_b$CH$_2$O) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.4 (C), 151.8 (C), 150.0 (C), 148.9 (C), 140.6 (C), 132.9 (C), 125.1 (CH), 124.3 (CH), 117.6 (C), 115.4 (C), 114.4 (CH), 112.2 (CH), 111.3 (CH), 100.1 (CH), 98.4 (C), 80.3 (C), 67.8 (2 × CH_2), 56.3 (CH_3), 56.1(2 × CH_3), 25.9 (CH_2), 20.7 (CH_3) ppm; **HRMS** (+ESI) Calc. for

$C_{23}H_{24}O_7Na$ $[M+Na]^+$: 435.1414, found: 435.1414; **MS** (+ESI) *m/z* 842 ($[2M+NH_4]^+$, 68%), 435 ($[M+Na]^+$, 11), 413 ($[M+H]^+$, 100), 369 (4).

2-((3',4'-Dimethoxyphenyl)ethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenol (181)



181

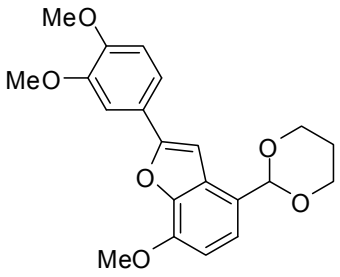
Procedure 1

To a solution of the acetate **180** (500 mg, 1.21 mmol) in 1:1 THF (25 mL) and MeOH (25 mL) at 0 °C was added Cs_2CO_3 (810 mg, 2.49 mmol, 2.06 equiv.) in one portion. The resulting solution was allowed to slowly warm to rt and stir for 3 h before being cooled to 0 °C and quenching by the addition of saturated aqueous NH_4Cl solution (50 mL). This was diluted with H_2O (20 mL) and CH_2Cl_2 (150 mL), the organic phase isolated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil (550 mg) that was purified by column chromatography (60:40:0.5 EtOAc/hexanes/NEt_3) to afford the title compound **181** (421 mg, 94%) as an off-white solid: **m.p.** 145–147 °C; $\mathbf{R_f}$ 0.30 (60:40:0.5 EtOAc/hexanes/NEt_3); **IR** (thin film) 3506, 3420, 2961, 2841, 2204, 1514, 1250, 1234, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (1H, d, *J* = 8.5 Hz, Ar<u>H</u>), 7.17 (1H, dd, *J* = 8.3, 1.9 Hz, Ar<u>H</u>), 7.07 (1H, d, *J* = 1.8 Hz, Ar<u>H</u>), 6.85 (1H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.84 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 6.01 (1H, br s, O<u>H</u>), 5.83 (1H, s, ArC<u>H</u>), 4.31–4.23 (2H, m, 2 × OC<u>H$_a$</u>H$_b$CH2), 4.05–3.96 (2H, m, 2 × OCH$_a$<u>H$_b$</u>CH$_2$), 3.89 (6H, s, 2 × OC<u>H$_3$</u>), 3.87 (3H, s, OC<u>H$_3$</u>), 2.30–2.16 (1H, m, OCH$_2$C<u>H$_a$</u>H$_b$CH$_2$O), 1.45–1.38 (1H, m, OCH$_2$CH$_a$<u>H$_b$</u>CH$_2$O) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.8 (C), 148.7 (C), 146.9 (C), 146.4 (C), 132.8 (C), 125.1 (CH), 117.6 (CH), 115.4 (C), 114.4 (CH), 111.1 (CH), 111.0 (CH), 108.8 (C), 100.3 (CH), 98.9 (C), 80.3 (C), 67.8 (2 × CH_2), 56.3 (CH_3), 56.04 (CH_3), 56.0 (CH_3), 25.8 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{21}H_{23}O_6$ $[M+H]^+$: 371.1489, found: 371.1474; **MS** (+ESI) *m/z* 763 ($[2M+Na]^+$, 34%), 371 ($[M+H]^+$, 100), 327 (6).

Procedure 2

To a solution of the acetate **180** (1.09 g, 2.65 mmol) in 1:1 THF (50 mL) and MeOH (50 mL) at 0 °C was added Cs_2CO_3 (1.77 g, 5.43 mmol, 2.06 equiv.) in one portion. The resulting solution was allowed to slowly warm to rt and stir for 2 h before being cooled once more to 0 °C and quenching by the addition of saturated aqueous NH_4Cl solution (70 mL). This was diluted with H_2O (30 mL) then

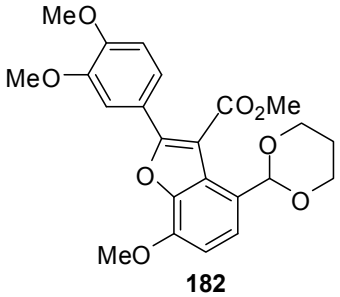
extracted with CH_2Cl_2 (4 × 70 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a white foam (1.05 g) that was purified by column chromatography (5:95:0.5 $Et_2O/CH_2Cl_2/NEt_3$) to afford the title compound **181** (804.7 mg, 93%), spectroscopically identical to the compound isolated from procedure 1, and the protio-cyclised by-product **249** (43.3 mg, 4%).



249

2-(3',4'-Dimethoxyphenyl)-4-(1'',3''-dioxan-2''-yl)-7-methoxy-1-benzofuran (249): yellow oil: $\mathbf{R_f}$ 0.60 (5:95:0.5 $Et_2O/CH_2Cl_2/NEt_3$); **IR** (thin film) 2961, 2839, 2723, 1504, 1275, 1095 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (1H, dd, *J* = 8.4, 2.0 Hz, ArH), 7.40 (1H, d, *J* = 2.0 Hz, ArH), 7.24 (1H, d, *J* = 8.2 Hz, ArH), 7.14 (1H, s, ArH), 6.92 (1H, d, *J* = 8.4 Hz, ArH), 6.74 (1H, d, *J* = 8.2 Hz, ArH), 5.72 (1H, s, ArCH), 4.35–4.29 (2H, m, 2 × $OCH_aH_bCH_2$), 4.12–4.00 (2H, m, 2 × $OCH_aH_bCH_2$), 4.02 (3H, s), 3.99 (3H, s), 3.92 (3H, s), 2.38–2.24 (1H, m, $OCH_2CH_aH_bCH_2O$), 1.53–1.46 (1H, m, $OCH_2CH_aH_bCH_2O$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.3 (C), 149.7 (C), 149.2 (C), 145.6 (C), 144.1 (C), 128.8 (C), 123.54 (C), 123.53 (C), 121.6 (CH), 118.4 (CH), 111.3 (CH), 108.5 (CH), 105.7 (CH), 101.8 (CH), 100.1 (CH), 67.6 (2 × CH_2), 56.2 (2 × CH_3), 56.1 (CH_3), 26.1 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{21}H_{23}O_6$ $[M+H]^+$: 371.1489, found: 371.1493; **MS** (+ESI) *m/z* 763 ($[2M+Na]^+$, 32%), 371 ($[M+H]^+$, 100), 327 (20).

Methyl 2-(3',4'-dimethoxyphenyl)-4-(1'',3''-dioxan-2''-yl)-7-methoxybenzofuran-3-carboxylate (182)

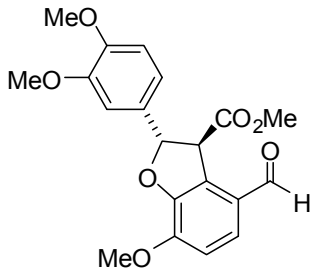


182

To a flask containing the alcohol **181** (250.0 mg, 0.675 mmol), anhydrous $CuCl_2$ (272 mg, 2.02 mmol, 3.0 equiv.), anhydrous NaOAc (221 mg, 2.70 mmol, 4.0 equiv.) and $PdCl_2$ (12 mg, 0.067 mmol, 10 mol%) was added anhydrous MeOH (6.7 mL) and the system quickly purged with $CO_{(g)}$ (× 4). The resulting suspension was allowed to stir at rt under an atmosphere of $CO_{(g)}$ for 2 h before being

quenched by the addition of H_2O (20 mL) and the resulting mixture partitioned between H_2O (30 mL) and CH_2Cl_2 (50 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL) and EtOAc (1 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (304 mg) that was subjected to column chromatography (5:95:0.5 $Et_2O/CH_2Cl_2/NEt_3$) to afford the title compound **182** (216.9 mg, 75%) as a white foam: **m.p.** 62–64 °C; $\mathbf{R_f}$ 0.36 (5:95:0.5 $Et_2O/CH_2Cl_2/NEt_3$); **IR** (thin film) 2959, 2843, 1724, 1512, 1261, 1110, 1045 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (1H, dd, *J* = 8.4, 0.8 Hz, ArH), 7.39–7.34 (2H, m, 2 × ArH), 6.93 (1H, d, *J* = 8.3 Hz, ArH), 6.82 (1H, d, *J* = 8.4 Hz, ArH), 5.91 (1H, s, ArCH), 4.23–4.16 (2H, m, 2 × $OCH_aH_bCH_2$), 4.06–3.99 (2H, m, 2 × $OCH_aH_bCH_2$), 4.01 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 2.27–2.13 (1H, m, $OCH_2CH_aH_bCH_2O$), 1.47–1.41 (1H, m, $OCH_2CH_aH_bCH_2O$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5 (C), 156.5 (C), 150.5 (C), 148.9 (C), 145.4 (C), 143.3 (C), 125.6 (C), 124.1 (C), 122.4 (C), 121.5 (CH), 121.2 (CH), 111.2 (CH), 111.0 (CH), 110.0 (C), 106.5 (CH), 98.6 (CH), 66.8 (2 × CH_2), 56.3 (CH_3), 56.15 (CH_3), 56.07 (CH_3), 52.2 (CH_3), 25.9 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{23}H_{24}O_8Na$ $[M+Na]^+$: 451.1363, found: 451.1348; **MS** (+ESI) *m/z* 879 ($[2M+Na]^+$, 45%), 451 ($[M+Na]^+$, 11), 429 ($[M+H]^+$, 100), 385 (38), 371 (4).

Methyl 2-(3',4'-dimethoxyphenyl)-4-formyl-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-35)



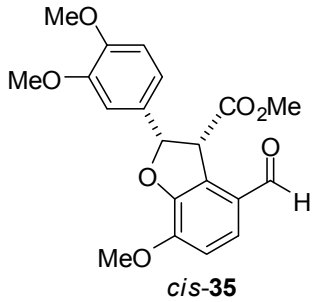
trans-**35**

Procedure 1

To a flask containing benzofuran **182** (50.0 mg, 0.117 mmol) and Mg turnings (113 mg, 4.67 mmol, 40.0 equiv.) was added MeOH (2.3 mL) and THF (4.1 mL). A single crystal of iodine was then added (*ca*. 10 mg) and the mixture shielded from light by aluminium foil. The reaction was allowed to stir at rt for 20 h before being quenched by the addition of aqueous HCl (2M, ~4 mL). The resulting gel was allowed to stir for 15 min during which time it dissolved and the resulting biphasic mixture was partitioned between aqueous $Na_2S_2O_3$ solution (10% w/v, 30 mL) and CH_2Cl_2 (50 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil (40 mg) that was purified by column chromatography (70:30 EtOAc/hexanes) to afford a *ca*. 3:1 mixture of *trans*-**35** and

cis-**35** respectively (35.3 mg, 81%). For analytical purposes, the two diastereomers could be separated by column chromatography (2:98:0.5 $Et_2O/CH_2Cl_2/NEt_3$).

Dihydrobenzofuran *trans*-**35**: wax-like white solid; **m.p.** 47–49 °C; $\mathbf{R_f}$ 0.30 (50:50 EtOAc/hexanes); **IR** (thin film) 2951, 2839, 2739, 1739, 1686, 1612, 1516, 1288, 1026 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.84 (1H, s, CHO), 7.41 (1H, d, *J* = 8.3 Hz, ArH), 7.01–6.90 (3H, m, 3 × ArH), 6.83 (1H, d, *J* = 8.2 Hz, ArH), 5.86 (1H, d, *J* = 7.0 Hz, ArOCHAr), 4.70 (1H, d, *J* = 7.0 Hz, $ArCHCO_2CH_3$), 3.98 (3H, s, OCH_3), 3.86 (6H, s, 2 × OCH_3), 3.77 (3H, s, OCH_3) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.6 (CH), 171.9 (C), 149.74 (C), 149.64 (C), 149.45 (C), 149.36 (C), 132.3 (C), 128.6 (CH), 126.7 (C), 124.7 (C), 118.3 (CH), 111.8 (CH), 111.2 (CH), 109.0 (CH), 88.9 (CH), 56.7, 56.3, 56.00, 56.00, 52.7 (1 × CH, 4 × CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{20}H_{20}O_7Na$ $[M+Na]^+$: 395.1101, found: 395.1101; **MS** (+ESI) *m/z* 737 ($[2M+Na]^+$, 92%), 373 ($[M+H]^+$, 100), 341 (23), 313 (6).



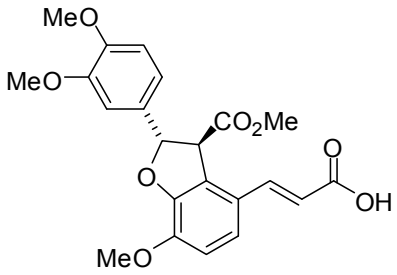
cis-**35**

Dihydrobenzofuran *cis*-**35**: light yellow solid; **m.p.** 57–63 °C; $\mathbf{R_f}$ 0.30 (5:95 Et_2O/CH_2Cl_2); **IR** (thin film) 2951, 2840, 1739, 1685, 1518, 1452, 1286, 1095, 734 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (1H, s, CHO), 7.41 (1H, d, *J* = 8.3 Hz, ArH), 7.01 (1H, d, *J* = 8.3 Hz, ArH), 6.98–6.90 (2H, m, 2 × ArH), 6.83 (1H, d, *J* = 8.2 Hz, ArH), 6.01 (1H, d, *J* = 10.1 Hz, ArOCHAr), 4.91 (1H, d, *J* = 10.2 Hz, $ArCHCO_2CH_3$), 4.01 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.25 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.7 (CH), 169.9 (C), 150.3 (C), 149.7 (C), 149.3 (C), 148.9 (C), 128.8 (CH), 128.5 (C), 126.7 (C), 125.7 (C), 119.6 (CH), 111.9 (CH), 110.7 (CH), 109.9 (CH), 88.0 (CH), 56.3, 56.1, 56.0, 54.3, 51.9 (1 × CH, 4 × CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{20}H_{20}O_7Na$ $[M+Na]^+$: 395.1101, found: 395.1112 **MS** (+ESI) *m/z* 395 ($[M+Na]^+$, 100), 373 ($[M+H]^+$, 14).

Procedure 2

To a solution of dihydrobenzofuran *trans*-**200** (80.2 mg, 0.187 mmol) in THF (10 mL) was added aqueous HCl (2M, 1 mL) and the resulting solution allowed to stir at rt for 10 min before diluting with H_2O and extracting with CH_2Cl_2 (4 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound *trans*-**35** (62.7 mg, 90%), which was spectroscopically identical to the material isolated in procedure 1.

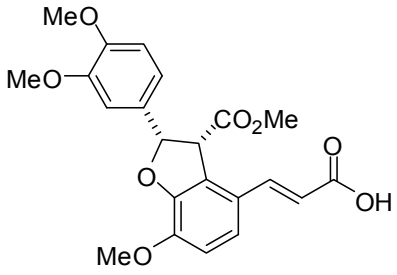
(2*E*)-3-[2'-(3'',4''-Dimethoxyphenyl)-7'-methoxy-3'-(methoxycarbonyl)-2',3'-dihydro-1'-benzofuran-4'-yl]prop-2-enoic acid (*trans*-36)



trans-**36**

To a solution of aldehyde *trans*-**35** (57.7 mg, 0.155 mmol) and malonic acid (49.0 mg, 0.465 mmol, 3.0 equiv.) in pyridine (5.1 mL) was added piperidine (156 μL, 1.58 mmol, 10.2 equiv.). The resulting solution was then heated to 100 °C for 7 h before cooling to rt and diluting with EtOAc (50 mL) and aqueous HCl (1M, 50 mL). The organic phase was isolated and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil that was purified by column chromatography (1:5:94→5:30:65 MeOH/Et_2O/CH_2Cl_2) to afford the title compound *trans*-**36** (38.2 mg, 60%) and the diastereomeric partner *cis*-**36** (7.6 mg, 12%, impure).

Cinnamic acid *trans*-36: off-white solid; **m.p.** 63–67 °C; $\mathbf{R_f}$ 0.46 (100% EtOAc); **IR** (CH_2Cl_2 solution) 3503, 2958, 2841, 1739, 1689, 1611, 1517, 1202, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CHCO$_2$), 7.24 (1H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.94–6.80 (5H, m, 5 × Ar<u>H</u>), 6.28 (1H, d, *J* = 15.9 Hz, ArCH=C<u>H</u>CO$_2$), 6.05 (1H, d, *J* = 5.7 Hz, ArOC<u>H</u>Ar), 4.49 (1H, d, *J* = 5.7 Hz, ArC<u>H</u>CO$_2$CH$_3$), 3.95 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.80 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.88 (C), 171.85 (C), 149.48 (C), 149.42 (C), 148.6 (C), 146.7 (C), 143.5 (CH), 132.4 (C), 125.3 (C), 124.2 (C), 121.0 (CH), 118.1 (CH), 116.6 (CH), 113.1 (CH), 111.3 (CH), 108.9 (CH), 87.6 (CH), 56.3 (CH_3), 56.1 (2 × CH_3), 53.0 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{22}H_{22}O_8Na$ $[M+Na]^+$: 437.1207, found: 437.1226; **MS** (+ESI) *m/z* 851 ($[2M+Na]^+$, 100%), 437 ($[M+Na]^+$, 36), 432 ($[M+NH_4]^+$, 57), 371 (37).

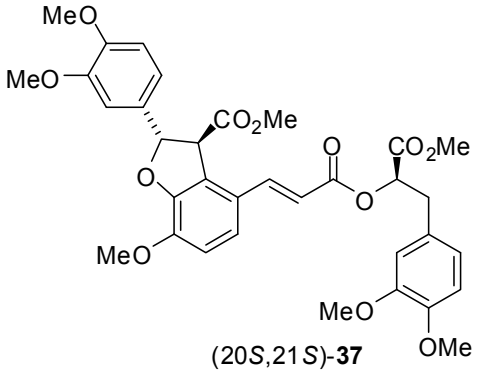


cis-**36**

Cinnamic acid *cis*-36: (partial data) white solid; $\mathbf{R_f}$ 0.39 (5:30:70 MeOH/Et_2O/CH_2Cl_2); **^{1}H NMR** (200 MHz, $CDCl_3$) 7.62 (1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CHCO$_2$), 7.32 (1H, d, *J* = 8.6 Hz, Ar<u>H</u>), 7.04–6.63 (4H, m, 4 × Ar<u>H</u>), 6.21 (1H, d, *J* = 15.9 Hz, ArCH=C<u>H</u>CO$_2$), 5.99 (1H, d, *J* = 9.4 Hz,

ArOC<u>H</u>Ar), 4.64 (1H, d, J = 9.5 Hz, ArC<u>H</u>CO_2CH_3), 3.95 (3H, s, OC<u>H</u>$_3$), 3.82 (3H, s, OC<u>H</u>$_3$), 3.77 (3H, s, OC<u>H</u>$_3$), 3.45 (3H, s, OC<u>H</u>$_3$) ppm.

Heptamethyl lithospermate (20*S*,21*S*)-37

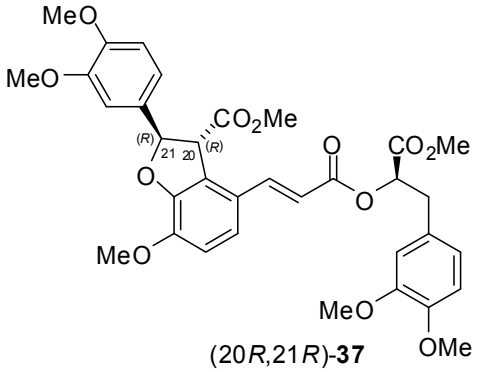


(20*S*,21*S*)-**37**

To a 1 mL sample vial containing *trans*-**36** (27.7 mg, 0.0668 mmol), alcohol (*R*)-**39** (26.0 mg, 0.107 mmol, 1.6 equiv.), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC.HCl) (70 mg, 0.36 mmol, 5.4 equiv.) and 4-(dimethylamino)pyridine (DMAP) (45 mg, 0.36 mmol, 5.4 equiv.) was added $CHCl_3$ (400 µL). The resulting solution was flushed with $Ar_{(g)}$, sealed and allowed to stir at rt for 62 h before the addition of AcOH (~4 drops) to convert excess alcohol (*R*)-**39** to a more easily separable acetate. After 30 min the reaction was partitioned between saturated aqueous NH_4Cl solution (20 mL) and Et_2O (25 mL). The organic phase was isolated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ then concentrated *in vacuo* to give a yellow film (49 mg) that was subjected to column chromatography (50:50 EtOAc/hexanes) to afford a presumably 1:1 mixture of the title compound (20*S*,21*S*)-**37** and the corresponding diastereomeric counterpart (20*R*,21*R*)-**37**, (31.1 mg combined, 73%). Approximately 10 mg of the diastereomeric mixture was then subjected to HPLC (gradient elution, 5:95→15:85 *i*-PrOH/hexanes over 40 min at 5 mL/min on a semi-preparative YMC-Pack DIOL column) to afford both the title heptamethyl lithospermate (20*S*,21*S*)-**37**, (1.05 mg, 7.7% extrapolated yield) and the diastereomeric counterpart (20*R*,21*R*)-**37**, (1.30 mg, 9.5% extrapolated yield) as white solids. Fractions containing a mixture of the two were also isolated (6.4 mg, 46.7% extrapolated yield).

Heptamethyl lithospermate (20*S*,21*S*)-**37**: **m.p.** 59–64 °C; $\mathbf{R_f}$ 0.25 (50:50 EtOAc/hexanes); **HPLC** $\mathbf{T_r}$ 26.1 min; **IR** (thin film) 2956, 2921, 2852, 1736, 1717, 1609, 1517, 1463, 1438, 1261, 1157, 1085, 1025, 801 cm^{-1}; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.74 (1H, d, J = 15.9 Hz, ArC<u>H</u>=CHCO$_2$), 7.20 (1H, d, J = 8.6 Hz, Ar<u>H</u>), 6.90–6.86 (3H, m, 3 × Ar<u>H</u>), 6.83 (1H, d, J = 8.1 Hz, Ar<u>H</u>), 6.80–6.75 (3H, m, 3 × Ar<u>H</u>), 6.31 (1H, d, J = 15.7 Hz, ArCH=C<u>H</u>CO$_2$), 6.03 (1H, d, J = 5.8 Hz, ArOC<u>H</u>Ar), 5.32 (1H, dd, J = 7.8, 5.0 Hz, ArCH$_2$C<u>H</u>CO_2CH_3), 4.45 (1H, d, J = 5.5 Hz, ArC<u>H</u>CO_2CH_3), 3.94 (3H, s, OC<u>H</u>$_3$), 3.87 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.83 (6H, s, 2 × OC<u>H</u>$_3$), 3.75 (3H, s, OC<u>H</u>$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 3.19–3.08 (2H, m, ArC<u>H</u>$_2$CHCO$_2$CH$_3$) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.66, 170.25, 166.06, 149.41, 149.35, 148.90, 148.55, 148.16, 146.42, 142.46, 132.42, 129.43, 128.40, 125.04, 124.46, 121.48, 120.86, 118.05, 116.54, 113.06, 112.59, 111.32, 111.30, 108.92, 87.47, 73.09, 56.22, 56.01, 55.98, 55.91, 55.87, 52.77, 52.30, 37.17 ppm; **$[\alpha]_D$** +69.2 ° (*c* 0.12, CH_2Cl_2), lit.[49] $[\alpha]_D$ +134.5 ° (*c* 0.49, CH_2Cl_2); **HRMS** (+ESI) Calc. for $C_{34}H_{36}O_{12}Na$ $[M+Na]^+$: 659.2099, found: 659.2119; **MS** (+ESI) m/z 659 ($[M+Na]^+$, 19%), 654 ($[M+NH_4]^+$, 100), 637 ($[M+H]^+$, 20). All data were in accordance with literature values.[49]

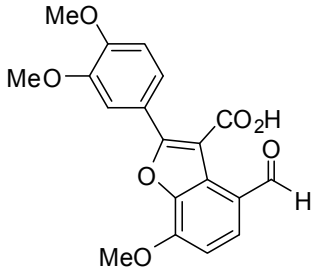


(20*R*,21*R*)-**37**

Unnatural diastereomeric partner (20*R*,21*R*)-**37**: **m.p.** 64–70 °C; **R_f** 0.25 (50:50 EtOAc/hexanes); **HPLC T_r** 24.6 min; **IR** (thin film) 2957, 2918, 2850, 1739, 1715, 1614, 1517, 1463, 1262, 1157, 1086, 1026, 802 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 16.0 Hz, ArC<u>H</u>=CHCO$_2$), 7.19 (1H, d, *J* = 8.5 Hz, Ar<u>H</u>), 6.92–6.85 (3H, m, 3 × Ar<u>H</u>), 6.83 (1H, d, *J* = 8.1 Hz, Ar<u>H</u>), 6.81–6.73 (3H, m, 3 × Ar<u>H</u>), 6.30 (1H, d, *J* = 15.9 Hz, ArCH=C<u>H</u>CO$_2$), 6.03 (1H, d, *J* = 5.6 Hz, ArOC<u>H</u>Ar), 5.34 (1H, dd, *J* = 8.1, 4.8 Hz, ArCH$_2$C<u>H</u>CO$_2$CH$_3$), 4.46 (1 H, d, *J* = 5.5 Hz, ArC<u>H</u>CO$_2$CH$_3$), 3.94 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.84 (3H, s, OC<u>H</u>$_3$), 3.83 (3H, s, OC<u>H</u>$_3$), 3.73 (6H, s, 2 × OC<u>H</u>$_3$), 3.20–3.07 (2H, m, ArC<u>H</u>$_2$CHCO$_2$CH$_3$) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.74, 170.26, 166.07, 149.35, 149.35, 148.89, 148.70, 148.18, 146.43, 142.33, 132.39, 128.40, 128.40, 125.23, 124.37, 121.53, 120.59, 118.08, 116.48, 113.10, 112.63, 111.31, 111.27, 108.94, 87.52, 73.13, 56.22, 56.00, 55.98, 55.89, 55.85, 52.81, 52.28, 37.19 ppm; **$[\alpha]_D$** –29.1 ° (*c* 0.10, CH_2Cl_2).

8.7 Synthesis of Compounds from Chapter 6

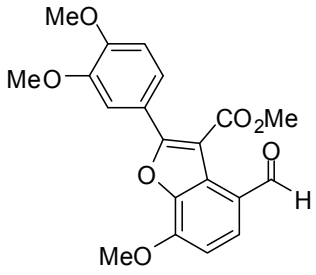
2-(3',4'-Dimethoxyphenyl)-4-formyl-7-methoxy-1-benzofuran-3-carboxylic acid (189)



189

To a 20 mL sealed tube containing ester **182** (21.0 mg, 0.049 mmol) was added LiOH (12.0 mg, 0.490 mmol, 10.0 equiv.) and the vessel was purged with nitrogen. THF (0.4 mL) and H_2O (0.3 mL) were added and the tube was sealed and heated to 110 °C for 48 h before cooling to rt and diluting with H_2O (~5 mL) and THF (~5 mL). The mixture was then acidified with aqueous HCl (2M, ~2mL) then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown solid (23.6 mg) that was purified by column chromatography (30:70:1 Et_2O/CH_2Cl_2/AcOH) to afford the title compound **189** (15.8 mg, 90%) as a pale yellow solid: **m.p.** 215–216 °C; $\mathbf{R_f}$ 0.20 (30:70:1 Et_2O/CH_2Cl_2/AcOH); **IR** (KBr disc) 3455, 2918, 2849, 1710, 1692, 1674, 1618, 1297, 1274, 1025, 800 cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 10.27 (1H, s, CHO), 7.90 (1H, d, J = 8.4 Hz, ArH), 7.65–7.58 (2H, m, 2 × ArH), 7.19 (1H, d, J = 8.4 Hz, ArH), 7.13 (1H, d, J = 8.4 Hz, ArH), 4.15 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, acetone-d_6) δ 190.1 (CH), 166.7 (C), 158.1 (C), 152.3 (C), 150.6 (C), 150.2 (C), 143.8 (C), 130.9 (CH), 128.0 (C), 124.2 (C), 122.5 (C), 122.1 (CH), 112.6 (CH), 112.3 (CH), 111.5 (C), 107.9 (CH), 57.0 (CH_3), 56.24 (CH_3), 56.18 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{19}H_{16}O_7Na$ $[M+Na]^+$: 379.0788, found: 379.0800; **MS** (+ESI) *m/z* 735 ($[2M+Na]^+$, 100%), 379 ($[M+Na]^+$, 38), 357 ($[M+H]^+$, 85), 339 (12).

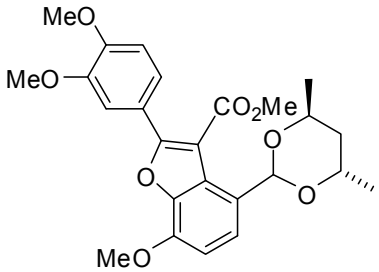
Methyl 2-(3',4'-dimethoxyphenyl)-4-formyl-7-methoxy-1-benzofuran-3-carboxylate (192)



192

To a solution of **182** (56.2 mg, 0.0145 mmol) in THF (2 mL) was added aqueous HCl (2M, 1 mL) and the resulting solution was stirred at rt for 1.5 h, before quenching by the addition of saturated aqueous $NaHCO_3$ solution (40 mL). This was then extracted with CH_2Cl_2 (3 × 40 mL), combined, dried over $MgSO_4$ and the solvent removed *in vacuo* to give the title compound **192** (47.6 mg, 98%) as a colourless oil that was used without further purification in the next step: $\mathbf{R_f}$ 0.51 (100% EtOAc); **IR** (thin film) 2951, 2840, 1729, 1681, 1619, 1570, 1514, 1401, 1288, 1025, 803 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (1H, s, C<u>H</u>O), 7.75 (1H, d, *J* = 8.4 Hz, Ar<u>H</u>), 7.60–7.49 (2H, m, 2 × Ar<u>H</u>), 6.95 (1H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.94 (1H, d, *J* = 8.3 Hz, Ar<u>H</u>), 4.12 (3H, s, OC<u>H</u>$_3$), 3.98 (3H, s, OC<u>H</u>$_3$), 3.97 (3H, s, OC<u>H</u>$_3$), 3.94 (3H, s, OC<u>H</u>$_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.8 (CH), 166.4 (C), 157.6 (C), 151.1 (C), 149.9 (C), 149.2 (C), 143.2 (C), 131.7 (CH), 127.2 (C), 123.3 (C), 121.8 (C), 121.3 (CH), 111.4 (CH), 110.9 (CH), 110.4 (C), 106.5 (CH), 56.6 (CH_3), 56.22 (CH_3), 56.15 (CH_3), 52.7 (CH_3) ppm; **MS** (+ESI) *m/z* 763 ([2M+Na]$^+$, 100%), 393 ([M+Na]$^+$, 29), 371 ([M+H]$^+$, 21), 339 (35).

Methyl 2-(3',4'-dimethoxyphenyl)-4-((4''*S*,6''*S*)-4'',6''-dimethyl-1'',3''-dioxan-2''-yl)-7-methoxy-1-benzofuran-3-carboxylate (193)

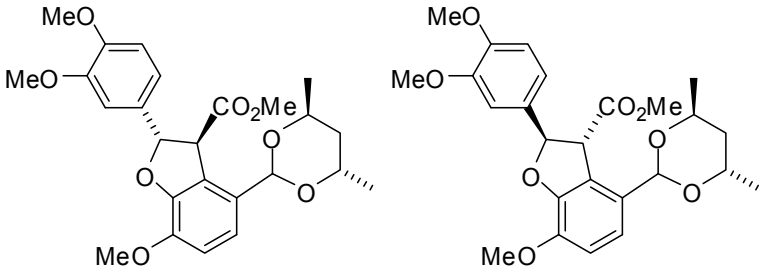


193

To a flask containing aldehyde **192** (38.2 mg, 0.103 mmol) and (2*S*,4*S*)-pentane-2,4-diol (43.0 mg, 0.413 mmol, 4.0 equiv.) was added CH_2Cl_2 (4.5 mL), followed by TMSCl (79 μL, 67 mg, 0.62 mmol, 6.0 equiv.) and the resulting solution stirred at reflux for 12 h before cooling to rt. The reaction was quenched by the addition of anhydrous K_2CO_3 (~50 mg) and left to stir for 2 h before being partitioned between pH 7 buffer solution (20 mL) and CH_2Cl_2 (20 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a light yellow film (52 mg). Purification by column chromatography on neutral alumina (10:90→20:80 EtOAc/hexanes) to afford the title compound **193** (34.7 mg, 74%) as a colourless film: $\mathbf{R_f}$ 0.09 (10:90 EtOAc/hexanes on neutral alumina tlc plates); **IR** (thin film) 2926, 2853, 1724, 1506, 1261, 1229, 1134, 1045 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J* = 8.4, 0.5 Hz, Ar<u>H</u>), 7.39–7.32 (2H, m, 2 × Ar<u>H</u>), 6.93 (1H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.83 (1H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.34 (1H, s, ArC<u>H</u>), 4.57–4.45 (1H, m, OC<u>H</u>(CH$_3$)CH$_2$), 4.25–4.14 (1H, m, OC<u>H</u>(CH$_3$)CH$_2$), 4.01 (3H, s, OCH$_3$), 3.95 (3H, s, OC<u>H</u>$_3$), 3.94 (3H, s, OC<u>H</u>$_3$), 3.88 (3H, s,

OC$\underline{H}_3$), 2.03–1.86 (1H, m, OCH(CH_3)C$\underline{H}_a$H$_b$CH(CH_3)O), 1.48–1.41 (1H, m, OCH(CH_3)CH$_a\underline{H}_b$CH(CH_3)O), 1.25 (6H, s, 2 × C$\underline{H}_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4 (C), 157.1 (C), 150.5 (C), 148.8 (C), 145.4 (C), 143.4 (C), 125.7 (C), 124.8 (C), 122.5 (C), 121.7 (CH), 121.5 (CH), 111.4 (CH), 110.9 (CH), 109.9 (C), 106.6 (CH), 90.7 (CH), 68.7 (CH), 67.3 (CH), 56.3 (CH_3), 56.2 (CH_3), 56.1 (CH_3), 52.2 (CH_3), 37.2 (CH_2), 22.0 (CH_3), 17.7 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{25}H_{28}O_8Na$ [M+Na]$^+$: 479.1676, found: 479.1680; **MS** (+ESI) *m/z* 935 ([2M+Na]$^+$, 100%), 479 ([M+Na]$^+$, 18), 457 ([M+H]$^+$, 90), 399 (3); **[α]$_D$** +28.4 ° (*c* 0.25, CH_2Cl_2).

Methyl 2-(3',4'-dimethoxyphenyl)-4-((4''*S*,6''*S*)-4'',6''-dimethyl-1'',3''-dioxan-2''-yl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-195)

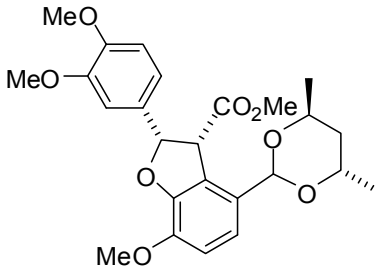


(20*S*,21*S*)-**195** (20*R*,21*R*)-**195**

To a solution of benzofuran **193** (29.7 mg, 0.0650 mmol) in MeOH (18 mL) was added Mg turnings (126 mg, 5.18 mmol, 80.0 equiv.) followed by a single crystal of iodine (*ca*. 10 mg) and the resulting mixture allowed to stir at rt for 15 h before concentrating *in vacuo*. The crude residue was partitioned between saturated aqueous NH_4Cl solution (50 mL) and CH_2Cl_2 (50 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a light yellow film (28.5 mg) that was purified by column chromatography (2:98:0.5 $Et_2O/CH_2Cl_2/NEt_3$) to afford the title compound *trans*-**195** (13.0 mg, 44%) and *cis*-**195** (8.6 mg, 29%).

Dihydrobenzofuran *trans*-195: pale yellow oil; **R$_f$** 0.21 (2:98:0.5 $Et_2O/CH_2Cl_2/NEt_3$); **IR** (thin film) 2926, 2853, 1627, 1594, 1517, 1282, 1264, 1159, 1133, 915, 804, 732 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) (some signals appeared doubled due to the presence of two diastereomers) δ 7.09–6.77 (2 × 5H, m, 2 × 5 × Ar$\underline{H}$), 5.81 (1 × 1H, s, ArC$\underline{H}$), 5.78 (1 × 1H, s, ArC$\underline{H}$), 5.77 (1 × 1H, d, *J* = 6.5 Hz, ArOC$\underline{H}$Ar), 5.73 (1 × 1H, d, *J* = 7.0 Hz, ArOC$\underline{H}$Ar), 4.59 (1 × 1H, d, *J* = 7.2 Hz, ArC$\underline{H}$CO$_2$CH$_3$), 4.57 (1 × 1H, d, *J* = 6.4 Hz, ArC$\underline{H}$CO$_2$CH$_3$), 4.47–4.38 (1 × 1H, m, OC$\underline{H}$CH$_3$), 4.37–4.27 (1 × 1H, m, OC$\underline{H}$CH$_3$), 4.15–4.06 (1 × 1H, m, OC$\underline{H}$CH$_3$), 4.05–3.96 (1 × 1H, m, OC$\underline{H}$CH$_3$), 3.88 (2 × 3H, s, 2 × OC$\underline{H}_3$), 3.86 (2 × 3H, s, 2 × OC$\underline{H}_3$), 3.85 (1 × 3H, s, OC$\underline{H}_3$), 3.84 (1 × 3H, s, OC$\underline{H}_3$), 3.76 (1 × 3H, s, OC$\underline{H}_3$), 3.75 (1 × 3H, s, OC$\underline{H}_3$), 1.99–1.86 (2 × 1H, m, 2 × OCH(CH_3)C$\underline{H}_a$H$_b$CH(CH_3)O), 1.44–1.37 (2 × 3H, m, 2 × C$\underline{H}_3$), 1.37–1.33 (2 × 1H, m, 2 × OCH(CH_3)CH$_a\underline{H}_b$CH(CH_3)O), 1.26–1.18 (2 × 3H, m, 2 × C$\underline{H}_3$) ppm; **^{13}C NMR** (100 MHz,

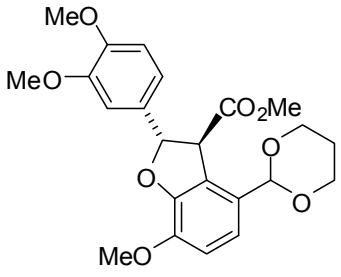
$CDCl_3$) (some signals appeared doubled due to the presence of two diastereomers) δ 172.75+172.67 (C), 149.3+149.31 (C), 149.31+149.29 (C), 149.02+148.98 (C), 145.01+144.97 (C), 133.23+132.9 (C), 128.68+128.53 (C), 123.36+123.10 (C), 119.84+119.70 (CH), 118.79+118.64 (CH), 112.25+112.22 (CH), 111.16+111.13 (CH), 109.20+109.09 (CH), 92.83+92.74 (CH), 88.29+88.06 (CH), 68.65 (2 × CH), 68.20+67.93 (CH), 57.26+57.049 (CH), 56.22 (2 × CH_3), 56.08 (2 × 2 × CH_3), 52.50+52.45 (CH_3), 36.78+36.69 (CH_2), 21.99+21.83 (CH_3), 17.23+17.04 (CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{25}H_{30}O_8Na$ $[M+Na]^+$: 481.1833, found: 481.1834; **MS** (+ESI) *m/z* 939 ($[2M+Na]^+$, 42), 481 ($[M+Na]^+$, 9), 459 ($[M+H]^+$, 100), 399 (4).



cis-**195**

Dihydrobenzofuran *cis*-195: yellow film; $\mathbf{R_f}$ 0.11 (2:98:0.5 Et_2O/CH_2Cl_2); ^{1}**H NMR** (200 MHz, $CDCl_3$) δ 7.08–6.76 (2 × 5H, m, 2 × 5 × ArH), 5.93 (2 × 1H, d, J = 9.5 Hz, 2 × ArOCHAr), 5.73 (2 × 1H, s, 2 × ArCH), 4.75 (2 × 1H, d, J = 9.4 Hz, 2 × $ArCHCO_2CH_3$), 4.46–4.33 (2 × 1H, m, 2 × $OCH(CH_3)CH_2$), 4.11–4.00 (2 × 1H, m, 2 × $OCH(CH_3)CH_2$), 3.91 (2 × 3H, s, 2 × OCH_3), 3.88 (2 × 6H, s, 2 × 2 × OCH_3), 3.25 (2 × 3H, s, 2 × OCH_3), 2.04–1.84 (2 × 1H, m, 2 × $OCH(CH_3)CH_aH_bCH(CH_3)O$), 1.58 (2 × 2 × 3H, s, 2 × 2 × CH_3), 1.47–1.34 (2 × 1H, m, 2 × $OCH(CH_3)CH_aH_bCH(CH_3)O$) ppm.

Methyl 2-(3',4'-dimethoxyphenyl)-4-(1'',3''-dioxan-2''-yl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-200)

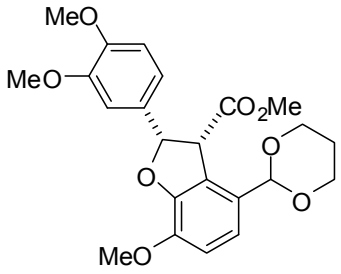


trans-**200**

To a flask containing benzofuran **182** (33.1 mg, 0.0773 mmol) and Mg turnings (37.0 mg, 1.55 mmol, 20 equiv.) was added MeOH (2.7 mL) followed by a crystal of iodine (*ca.* 10 mg) and stirred for ~5 min before the addition of THF (2.2 mL). The resulting mixture was stirred at rt for 16 h before a further portion of Mg turnings (37.0 mg, 1.55 mmol, 20 equiv.) was added and stirring continued for a further 7 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (50 mL) and diluted with

CH_2Cl_2 (50 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless film (32 mg) that was subjected to column chromatography (5:95:0.5 $Et_2O/CH_2Cl_2/NEt_3$) to afford the title compound *trans*-**200** (22.3 mg, 67%) and the diastereomeric counterpart *cis*-**200** (5.3 mg, 16%).

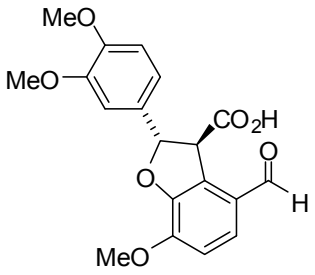
Dihydrobenzofuran *trans*-200: white foam; **m.p.** 52–55 °C; $\mathbf{R_f}$ 0.22 (5:95:0.5 $Et_2O/CH_2Cl_2/NEt_3$); **IR** (thin film) 2956, 2839, 1738, 1516, 1281, 1263, 1161, 1109, 1026 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (1H, d, J = 8.4 Hz, Ar<u>H</u>), 6.94–6.88 (2H, m, 2 × Ar<u>H</u>), 6.84 (1H, d, J = 8.8 Hz, Ar<u>H</u>), 6.82 (1H, d, J = 8.2 Hz, Ar<u>H</u>), 5.77 (1H, d, J = 7.1 Hz, ArOC<u>H</u>Ar), 5.45 (1H, s, ArC<u>H</u>), 4.55 (1H, d, J = 7.1 Hz, ArC<u>H</u>CO_2CH_3), 4.23–4.09 (2H, m, 2 × OC<u>H</u>$_a$H$_b$$CH_2$), 3.93–3.80 (2H, m, 2 × OCH$_a$<u>H</u>$_b$$CH_2$), 3.89 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.85 (3H, s, OC<u>H</u>$_3$), 3.76 (3H, s, OC<u>H</u>$_3$), 2.23–2.09 (1H, m, OCH_2C<u>H</u>$_a$H$_b$$CH_2O$), 1.42–1.34 (1H, m, OCH_2CH_a<u>H</u>$_b$$CH_2O$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7 (C), 149.4 (C), 149.3 (C), 148.9 (C), 145.1 (C), 132.8 (C), 128.0 (C), 123.3 (C), 119.4 (CH), 118.7 (CH), 112.2 (CH), 111.2 (CH), 109.2 (CH), 100.3 (CH), 88.2 (CH), 67.23 (CH_2), 67.17 (CH_2), 57.2, 56.2, 56.10, 56.10, 52.5 (1 × CH, 4 × CH_3), 25.7 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{23}H_{26}O_8Na$ $[M+Na]^+$: 453.1520, found: 453.1498; **MS** (+ESI) *m/z* 453 ($[M+Na]^+$, 18%), 431 ($[M+H]^+$, 100), 399 (35), 387 (25).



cis-**200**

Dihydrobenzofuran *cis*-200: colourless film; $\mathbf{R_f}$ 0.14 (5:95:0.5 $Et_2O/CH_2Cl_2/NEt_3$); **IR** (thin film) 2926, 2851, 1738, 1518, 1283, 1269, 1198, 1157, 1109, 1026 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.00–6.92 (3H, m, 3 × Ar<u>H</u>), 6.85–6.81 (2H, m, 2 × Ar<u>H</u>), 5.93 (1H, d, J = 9.5 Hz, ArOC<u>H</u>Ar), 5.39 (1H, s, ArC<u>H</u>), 4.73 (1H, d, J = 9.5 Hz, ArC<u>H</u>CO_2CH_3), 4.23–4.04 (2H, m, 2 × OC<u>H</u>$_a$H$_b$$CH_2$), 3.97–3.75 (2H, m, 2 × OCH$_a$<u>H</u>$_b$$CH_2$), 3.91 (3H, s, OCH_3), 3.87 (6H, s, 2 × CH_3), 3.26 (3H, s, OCH_3), 2.29–2.01 (1H, m, OCH_2C<u>H</u>$_a$H$_b$$CH_2O$), 1.40–1.32 (1H, m, OCH_2CH_a<u>H</u>$_b$$CH_2O$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6 (C), 149.5 (C), 148.9 (C), 148.7 (C), 145.3 (C), 128.9 (C), 127.9 (C), 124.6 (C), 119.8 (CH), 119.3 (CH), 112.0 (CH), 110.6 (CH), 109.8 (CH), 101.1 (CH), 87.3 (CH), 67.2 (CH_2), 67.1 (CH_2), 56.1, 56.0, 55.9, 54.6, 51.6 (1 × CH, 4 × CH_3), 25.6 (CH_2) ppm; **HRMS** (+ESI) Calc. for $C_{23}H_{26}O_8Na$ $[M+Na]^+$: 453.1520, found: 453.1515; **MS** (+ESI) *m/z* 883 ($[2M+Na]^+$, 55%), 453 ($[M+Na]^+$, 22), 431 ($[M+H]^+$, 100), 399 (20), 387 (12).

2-(3',4'-Dimethoxyphenyl)-4-formyl-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylic acid (*trans*-202)

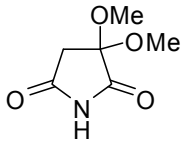


trans-**202**

To a flask containing ester *trans*-**200** (18.8 mg, 0.0437 mmol) and Me_3SnOH (40.0 mg, 0.218 mmol, 5.0 equiv.) was added 1,2-dichloroethane (2.2 mL) and the resulting solution heated at reflux for 5 d before a further portion of Me_3SnOH (40.0mg, 0.218 mmol, 5.0 equiv.) was added. After a further 24 h at reflux, the solution was cooled to rt and partitioned between HCl (1M, 20 mL) and EtOAc (20 mL). The organic phase was collected and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless film that contained ~1:1 acetal: aldehyde. This mixture was dissolved in THF (5 mL) and treated with aqueous HCl (2M, 1 mL) to drive the acetal hydrolysis to completion. After 10 min the solution was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL), combined, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound *trans*-**202** (13.6 mg, 87%) as a white solid: **m.p.** 105–108 °C; $\mathbf{R_f}$ 0.35 (10:90 Et_2O/CH_2Cl_2); **IR** (thin film) 3240, 2935, 2839, 1731, 1681, 1612, 1516, 1454, 1288, 1165, 1095, 1026, 941 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 9.81 (1H, s, C<u>H</u>O), 7.46 (1H, d, J = 8.3 Hz, Ar<u>H</u>), 7.02 (1H, d, J = 8.3 Hz, Ar<u>H</u>), 6.93–6.77 (3H, m, 3 × Ar<u>H</u>), 6.23 (1H, d, J = 5.2 Hz, ArOC<u>H</u>Ar), 4.69 (1H, d, J = 5.2 Hz, ArC<u>H</u>CO_2CH_3), 4.01 (3H, s, OC<u>H</u>$_3$), 3.85 (6H, s, 2 × OC<u>H</u>$_3$) ppm; ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 192.7 (CH), 173.5 (C), 150.6 (C), 150.0 (C), 149.5 (C), 149.4 (C), 132.4 (C), 130.2 (CH), 126.4 (C), 123.6 (C), 117.9 (CH), 112.2 (CH), 111.4 (CH), 108.9 (CH), 88.0 (CH), 56.60, 56.60, 56.13, 56.10 (1 × CH, 3 × CH_3) ppm; **HRMS** (+ESI) Calc. for $C_{19}H_{18}O_7Na$ $[M+Na]^+$: 381.0945, found: 381.0929; **MS** (+ESI) *m/z* 755 ($[2M+K]^+$, 95), 739 ($[2M+Na]^+$, 42), 397 ($[M+K]^+$, 100), 359 ($[M+H]^+$, 33), 341 (12).

8.8 Synthesis of Compounds from Chapter 7

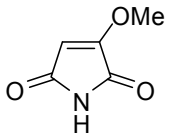
3,3-Dimethoxypyrrolidine-2,5-dione (217)



217

Bromine (4.0 mL, 12.4 g, 77.3 mmol, 1.5 equiv.) was added dropwise to a solution of maleimide (**216**) (5.00 g, 51.5 mmol, 1.0 equiv.) in MeOH (200 mL) at 0 °C. This was allowed to warm to rt and continued stirring for 16 h. The solvent was removed *in vacuo* and the crude residue redissolved in MeOH (75 mL) and the resulting solution transferred *via* cannula into an NaOMe solution, prepared by cautious addition of sodium metal (4.8 g, 206 mmol, 4.0 equiv.) to MeOH (200 mL) at rt. The resulting solution was then stirred for 20 h before concentration *in vacuo* to give a crude residue which was redissolved in EtOAc (100 mL). This was acidified with aqueous HCl (3 M, ~100 mL) then diluted with water (100 mL). The organic phase was isolated and the aqueous phase extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* gave the title compound **217** (7.90 g, 96%) as a light yellow solid whose spectral data were consistent with those previously reported.[138]

3-Methoxymaleimide (220a)



220a

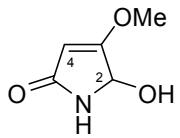
Procedure 1

To a solution of **217** (19.9 mg, 0.125 mmol) in PhMe (3.2 mL) was added *p*-TsOH (12.0 mg, 0.062 mmol, 0.5eq.). This was brought to reflux and PhMe was slowly distilled from the reaction mixture. To compensate for this, fresh PhMe was added at such a rate as to maintain constant volume. This process was continued for 1.5 h before allowing to cool to rt whereupon the solution was concentrated *in vacuo* and the resulting residue was subjected to column chromatography (50:50 EtOAc/hexanes) to afford the title compound **220a** (8.4 mg, 53%) as an off-white solid whose spectral data were consistent with those previously reported.[138]

Procedure 2

To a solution of **217** (7.79 g, 48.9 mmol) in PhMe (1.0 L) was added *p*-TsOH (810 mg, 4.25 mmol, 0.09 equiv.). This was brought to reflux and PhMe was slowly distilled from the reaction mixture. To compensate for this, fresh PhMe was added at such a rate as to maintain constant volume. This process was continued for 3 h before allowing to cool to rt and concentrated *in vacuo* to give the title compound **220a** (6.22 g, quant) as an off-white solid, contaminated with minor amounts of *p*-TsOH. This material was used without further purification in the subsequent step.

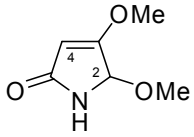
2-Hydroxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (222a)



222a

To a solution of **220a** (3.86 g, 30.4 mmol) in 2:1 THF (30 mL) and H_2O (15 mL) at 0 °C was added $NaBH_4$ (1.18 g, 30.4 mmol, 1.0 eq.) in four portions over 10 min. The resulting solution was allowed to stir at 0 °C for 30 min before being quenched by the addition of acetone (50 mL, bench grade). The resulting solution was concentrated *in vacuo* before being subjected to column chromatography (10:90, MeOH/CH_2Cl_2) to afford the title compound **222a** (3.40 g, 87%) as a white solid: **m.p.** 175–178 °C, lit.[139] m.p. 163 °C; $\mathbf{R_f}$ 0.24 (10:90 MeOH/CH_2Cl_2); **IR** (KBr disc) 3223, 3175, 2787, 1645, 1626, 1404, 1360, 1315, 1234, 1090, 991, 959, 800 cm^{-1}; ^{1}**H NMR** (300 MHz, DMSO-d_6) δ 7.73 (1H, br s, NH), 6.18 (1H, d, J = 8.5 Hz, OH), 5.21 (1H, dd, J = 8.5, 1.7 Hz, 2-CH), 4.97 (1H, d, J = 1.4 Hz, 4-CH), 3.74 (3H, s, OCH_3) ppm; ^{13}**C NMR** (75 MHz, DMSO-d_6) δ 176.5 (C), 172.4 (C), 93.6 (CH), 77.8 (CH), 58.8 (CH_3) ppm; **HRMS** (EI) Calcd. For $C_5H_7NO_3$ $[M]^{\bullet+}$: 129.0426, found : 129.0427; **MS** (EI) *m/z* 129 ($[M]^{\bullet+}$, 39%), 112 (16), 97 (34), 69 (100). Spectroscopic data matched that previously reported.[139]

2,3-Dimethoxy-1,2-dihydro-2*H*-pyrrol-5-one (232)

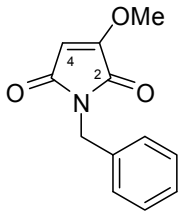


232

A solution of **222a** (500 mg, 3.87 mmol) in MeOH (20 mL) was cooled to 0 °C. To this solution was added anhydrous HCl in MeOH (1.0 mol L^{-1}, 775 μL, 0.775 mmol, 0.20 eq.), generated by adding trimethylsilyl chloride (256 μL, 2.00 mmol) to freshly distilled MeOH (2.00 mL). The resulting tetramate containing solution was allowed to stir whilst warming to rt. After 3.5 h at rt, the solvent was removed *in vacuo* to give the desired product **232** (554 mg, 100%) as a light yellow solid that could be

used without further purification. An analytically pure sample was obtained by subjecting this material to column chromatography (50:50:1 EtOAc/CH_2Cl_2/MeOH→50:50:5 EtOAc/CH_2Cl_2/MeOH) to afford a white solid: **m.p.** 105–106 °C; $\mathbf{R_f}$ 0.36 (5:95 MeOH/CH_2Cl_2); **IR** (KBr disc) 3246, 3092, 2943, 2846, 2752, 1701, 1666, 1632, 1456, 1420, 1367, 1342, 1240, 1207, 1097, 1078, 997, 955, 839 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.11 (1H, br s, NH), 5.33 (1H, d, J = 1.9 Hz, 2-CH), 5.08 (1H, d, J = 1.3 Hz, 4-CH), 3.85 (3H, s, OCH_3), 3.29 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6 (C), 173.4 (C), 95.0 (CH), 83.9 (CH), 58.7 (CH_3), 52.3 (CH_3) ppm; **HRMS** (+ESI) Calcd. For $C_6H_{10}NO_3$ $[M+H]^+$: 144.0655, found: 144.0656; **MS** (+ESI) *m/z* 144 ($[M+H]^+$, 100%), 112 (43). Spectroscopic data matched that previously reported.[139]

N-Benzyl-3-methoxymaleimide (220e)

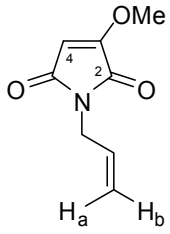


220e

Method A

To a solution of 3-methoxymaleimide (**220a**) (40.0 mg, 0.315 mmol) in MeCN (0.52 mL) was added K_2CO_3 (52.2 mg, 0.378 mmol, 1.2 equiv.) and then BnCl (72 μL, 0.63 mmol, 2.0 equiv.) dropwise. The mixture was heated to 50 °C for 40 h before cooling to rt and then concentrating *in vacuo*. The residue was partitioned between saturated aqueous NH_4Cl solution (10 mL), H_2O (10 mL) and EtOAc (20 mL). The organic phase was isolated and the aqueous phase extracted with EtOAc (2 × 20mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (40:60 EtOAc/hexanes) gave the title compound **220e** (67.6 mg, 99%) as a white solid: **m.p.** 68–69 °C; **IR** (thin film) 3117, 3032, 1709, 1639 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (5H, m, 5 × ArH), 5.39 (1H, s, 4-CH), 4.62 (2H, s, NCH_2Ph), 3.85 (3H, s, OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6 (C), 165.0 (C), 160.8 (C), 136.1 (C), 128.4 (CH), 128.0 (CH), 127.5 (CH), 96.2 (CH), 58.8 (CH_3), 40.9 (CH_2); **HRMS** (EI) calcd for $C_{12}H_{11}NO_3$ (M^+) 217.0739, found 217.0737; **MS** (+ESI) *m/z* 240 ($[M+Na]^+$, 100%) 218 ($[M+H]^+$, 83).

N-Allyl-3-methoxymaleimide (220d)

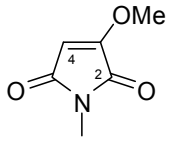


220d

Method B

To a mixture of 3-methoxymaleimide (**220a**) (63.5 mg, 0.500 mmol) and anhydrous CsF (228 mg, 1.50 mmol, 3.0 equiv.) was added DMF (1.67 mL), followed by allyl chloride (122 μL, 1.50 mmol, 3.0 equiv.). The mixture was heated at 30–38 °C for 24 h. The suspension was diluted with saturated aqueous $NaHCO_3$ solution (20 mL), H_2O (20 mL) and EtOAc (20 mL) and the organic phase isolated. The aqueous phase was extracted with EtOAc (4 × 20 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (40:60 EtOAc/hexanes) provided the title compound **220d** (70.0 mg, 84%) as a white solid: **m.p.** 61–63 °C; **IR** (thin film) 3111, 1705, 1626 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.80 (1H, ddt, J = 17.2, 15.7, 5.5 Hz, $NCH_2C\underline{H}=CH_2$), 5.43 (1H, s, 4-C$\underline{H}$), 5.21 (1H, ddd, J = 7.8, 1.5, 1.5 Hz, $\underline{H}_b$), 5.14 (1H, m, $\underline{H}_a$), 4.11 (2H, ddd, J = 5.6, 1.5 Hz, 1.5 Hz, $NC\underline{H}_2C$), 3.94 (3H, s, $OC\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6 (C), 165.1 (C), 160.9 (C), 131.5 (CH), 117.5 (CH_2), 96.2 (CH), 58.9 (CH_3), 39.6 (CH_2); **HRMS** (+ESI) calcd for $C_8H_9NO_3Na$ $[M+Na]^+$ 190.0475, found 190.0477; **MS** (+ESI) *m/z* 190 ($[M+Na]^+$, 50%), 168 ($[M+H]^+$, 100).

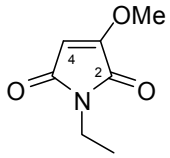
N-Methyl-3-methoxymaleimide (220b)



220b

The title compound **220b** was obtained using the procedure described for the preparation of **220e** (Method A) in acetone, using methyl iodide. Purification by column chromatography (40:60 EtOAc/hexanes) afforded **220b** (87%) as a white solid: **m.p.** 126–127 °C, lit.[152] m.p. 129–130 °C; **IR** (thin film) 3113, 1705, 1634 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.41 (1H, s, 4-C$\underline{H}$), 3.93 (3H, s, $OC\underline{H}_3$), 3.00 (3H, s, $NC\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.2 (C), 165.7 (C), 161.1 (C), 96.2 (CH), 58.9 (CH_3), 23.5 (CH_3). Physical and spectroscopic data matched that previously reported.[152]

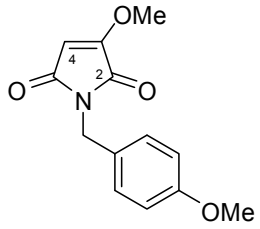
_N_-Ethyl-3-methoxymaleimide (220c)



220c

The title compound **220c** was obtained using the procedure described for the preparation of **220e** (Method A) in acetone, using ethyl iodide. Purification by column chromatography (40:60 EtOAc/hexanes) afforded **220c** (92%) as a white solid: **m.p.** 69–70 °C; **IR** (thin film) 3109, 1709, 1636 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.40 (1H, s, 4-C<u>H</u>), 3.93 (3H, s, OC<u>H</u>$_3$), 3.56 (2H, q, J = 7.2 Hz, NC<u>H</u>$_2$CH$_3$), 1.18 (3H, t, J = 7.2 Hz, NCH$_2$C<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.0 (C), 165.4 (C), 160.9 (C), 96.1 (CH), 58.8 (CH_3), 32.5 (CH_2), 13.9 (CH_3); **HRMS** (+ESI) calcd for $C_7H_{10}NO_3$ $[M+H]^+$ 156.0655, found 156.0654; **MS** (+ESI) m/z 156 ($[M+H]^+$, 100%).

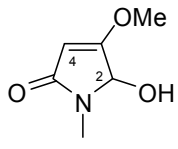
_N_-(4'-Methoxybenzyl)-3-methoxymaleimide (220f)



220f

The title compound **220f** was obtained using the procedure described for the preparation of **220e** (Method A) in acetone, using PMBCl. Purification by column chromatography (40:60 EtOAc/hexanes) afforded **220f** (91%) as a white solid: **m.p.** 104–105 °C; **IR** (thin film) 3101, 3013, 1713, 1636 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (2H, d, J = 8.7 Hz, Ar<u>H</u>), 6.83 (2H, d, J = 8.7 Hz, Ar<u>H</u>), 5.39 (1H, s, 4-C<u>H</u>), 4.59 (2H, s, NC<u>H</u>$_2$Ar), 3.90 (3H, s, OC<u>H</u>$_3$), 3.77 (3H, s, OC<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.8 (C), 165.3 (C), 161.0 (C), 159.2 (C), 129.9 (CH), 128.6 (C), 114.0 (CH), 96.3 (CH), 58.8 (CH_3), 55.2 (CH_3), 40.7 (CH_2); **HRMS** (+ESI) calcd for $C_{13}H_{13}NO_4Na$ $[M+Na]^+$ 270.0737, found 270.0736; **MS** (+ESI) m/z 270 ($[M+Na]^+$, 73%), 121 (100).

_N_-Methyl-2-hydroxy-3-methoxy-1,2-dihydro-2_H_-pyrrol-5-one (222b)

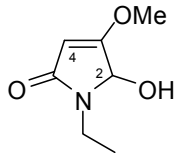


222b

The title compound **222b** was obtained from **220b** using the procedure described for the preparation of **222a**. Purification by column chromatography (5:95 acetone/EtOAc) afforded **222b** (87%) as a

colourless solid: **m.p.** 130–131 °C, lit.[153] m.p. 140–141 °C; **IR** (thin film) 3267, 3107, 1693, 1634 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.09 (1H, br d, *J* = ~8 Hz, 2-C<u>H</u>), 4.95 (1H, s, 4-C<u>H</u>), 4.30 (1H, br d, *J* = ~9 Hz, O<u>H</u>), 3.83 (3H, s, OC<u>H</u>$_3$), 2.90 (3H, s, NC<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7 (C), 170.8 (C), 93.2 (CH), 82.4 (CH), 58.4 (CH_3), 25.6 (CH_3); **HRMS** (+ESI) calcd for $C_6H_9NO_3Na$ $[M+Na]^+$ 166.0475, found 166.0475; **MS** (+ESI) *m/z* 166 ($[M+Na]^+$, 53%), 144 ($[M+H]^+$, 100).

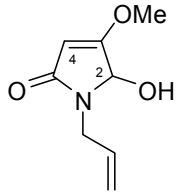
N-Ethyl-2-hydroxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (222c)



222c

The title compound **222c** was obtained from **220c** using the procedure described for the preparation of **222a**. Purification by column chromatography (5:95 acetone/EtOAc) afforded **222c** (84%) as a colourless solid: **m.p.** 79–83 °C; **IR** (thin film) 3337, 1653, 1637 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 5.21 (1H, d, *J* = 10.0 Hz, 2-C<u>H</u>), 4.98 (1H, s, 4-C<u>H</u>), 3.83 (3H, s, OC<u>H</u>$_3$), 3.59 (1H, dq, *J* = 14.5, 7.3 Hz, NC<u>H</u>$_a$H$_b$CH$_3$), 3.28 (1H, dq, *J* = 14.2, 7.1 Hz, NCH$_a$<u>H</u>$_b$CH$_3$), 2.64 (1H, d, *J* = 10.1 Hz, O<u>H</u>), 1.17 (3H, t, *J* = 7.2 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (C), 170.5 (C), 93.2 (CH), 80.3 (CH), 58.4 (CH_3), 33.5 (CH_2), 13.6 (CH_3); **HRMS** (+ESI) calcd for $C_7H_{11}NO_3Na$ $[M+Na]^+$ 180.0631, found 180.0629; **MS** (+ESI) *m/z* 180 ($[M+Na]^+$, 32%), 158 ($[M+H]^+$, 100).

N-Allyl-2-hydroxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (222d)

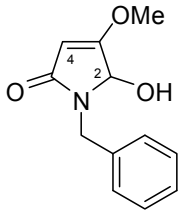


222d

The title compound **222d** was obtained from **220d** using the procedure described for the preparation of **222a**. Purification by column chromatography (5:95 acetone/EtOAc) afforded **222d** (85%) as a white solid: **m.p.** 70–71 °C; **IR** (thin film) 3275, 1666, 1636 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.77 (1H, dddd, *J* = 17.2, 11.6, 7.0, 4.6 Hz, NCH$_2$C<u>H</u>=CH$_2$), 5.21 (1H, br s, 2-C<u>H</u>), 5.16 (1H, m, CH=C<u>H</u>$_a$H$_b$), 5.15 (1H, m, CH=CH$_a$<u>H</u>$_b$), 5.09 (1H, br s, O<u>H</u>), 4.96 (1H, s, 4-C<u>H</u>), 4.23 (1H, app ddt, *J* = 15.8, 4.6, 1.6 Hz, NC<u>H</u>$_a$H$_b$CH=CH$_2$), 3.82 (3H, s, OC<u>H</u>$_3$), 3.70 (1H, app ddt, *J* = 15.8, 7.0, 1.0 Hz, NCH$_a$<u>H</u>$_b$CH=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (C), 170.6 (C), 133.0 (CH), 117.3 (CH_2), 92.9 (CH), 80.1 (CH), 58.4 (CH_3), 41.0 (CH_2); **HRMS** (+ESI) calcd for $C_8H_{11}NO_3Na$

$[M+Na]^+$ 192.0631, found 192.0637; **MS** (+ESI) *m/z* 192 ($[M+Na]^+$, 100%), 170 ($[M+H]^+$, 84), 152 (60).

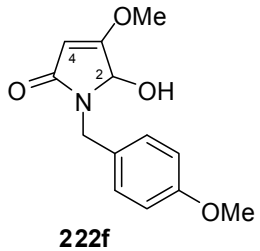
N-Benzyl-2-hydroxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (222e)



222e

The title compound **222e** was obtained from **220e** using the procedure described for the preparation of **222a**. Purification by column chromatography (5:95 $MeOH/CH_2Cl_2$) afforded the title compound **6e** (83%) as a white solid: **m.p.** 134–138 °C; **IR** (thin film) 3130, 3032, 1655, 1643 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (5H, m, 5 × ArH), 5.06 (1H, br d, *J* = 9 Hz, 2-CH), 5.00 (1H, s, 4-CH), 4.94 (1H, d, *J* = 15.1 Hz, NCH_aH_bPh), 4.17 (1H, d, *J* = 15.1 Hz, NCH_aH_bPh), 3.80 (3H, s, OCH_3), 3.68 (1H, br d, *J* = 9 Hz, OH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9 (C), 170.4 (C), 137.2 (C), 128.7 (CH), 128.2 (CH), 127.5 (CH), 93.2 (CH), 80.0 (CH), 58.4 (CH_3), 42.3 (CH_2); **HRMS** (ESI) calcd for $C_{12}H_{13}NO_3Na$ $[M+Na]^+$ 242.0788, found 242.0784; **MS** (ESI) *m/z* 242 ($[M+Na]^+$, 55%), 220 ($[M+H]^+$, 100), 202 (24). X-ray crystallographic data has been published.[154]

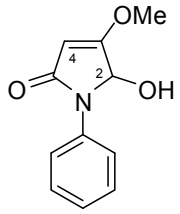
N-(4'-Methoxybenzyl)-2-hydroxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (222f)



222f

The title compound **222f** was obtained from **220f** using the procedure described for the preparation of **222a**. Purification by column chromatography (50:50 $EtOAc/CH_2Cl_2$) afforded the title compound **222f** (76%) as a white solid: **m.p.** 167–169 °C; **IR** (thin film) 3115, 1643 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.6 Hz, ArH), 6.84 (2H, d, *J* = 8.6 Hz, ArH), 5.04 (1H, d, *J* = 8.8 Hz, 2-CH), 5.00 (1H, s, 4-CH), 4.88 (1H, d, *J* = 14.9 Hz, NCH_aH_bAr), 4.12 (1H, d, *J* = 14.9 Hz, NCH_aH_bAr), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.13 (1H, br s, OH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.6 (C), 170.0 (C), 159.0 (C), 129.6 (CH), 129.4 (C), 114.1 (CH), 93.4 (CH), 80.0 (CH), 58.4 (CH_3), 55.3 (CH_3), 41.9 (CH_2); **HRMS** (+ESI) calcd for $C_{13}H_{15}NO_4Na$ $[M+Na]^+$ 272.0893, found 272.0883; **MS** (+ESI) *m/z* 272 ($[M+Na]^+$,100%), 250 ($[M+H]^+$, 48), 121 (25).

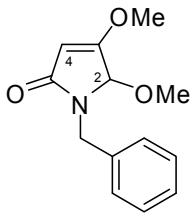
N-Phenyl-2-hydroxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (222g)



222g

The title compound **222g** was obtained from **220g** using the procedure described for the preparation of **222a**. Purification by column chromatography (40:60 hexane/EtOAc) afforded the title compound **222g** (70%) as a white solid: m.p 138–139 °C; **IR** (thin film) 3271, 1676, 1641 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67 (2H, dd, *J* = 8.7, 1.0 Hz, ArH), 7.33 (2H, app t, *J* = 7.5 Hz, ArH), 7.11 (1H, app t, *J* = 7.5 Hz, ArH), 5.67 (1H, br s, 2-CH), 4.89 (1H, s, 4-CH), 4.63 (1H, br s, OH), 3.70 (3H, s, OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.3 (C), 170.1 (C), 137.3 (C), 128.9 (CH), 124.3 (CH), 120.5 (CH), 93.9 (CH), 81.7 (CH), 58.5 (CH_3); **HRMS** (+ESI) calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0812, found 206.0811; **MS** (+ESI) *m/z* 228 ($[M+Na]^+$, 12%), 206 ($[M+H]^+$, 100), 188 (13), 174 (12).

N-Benzyl-2,3-dimethoxy-1,2-dihydro-2*H*-pyrrol-5-one (244)[†]



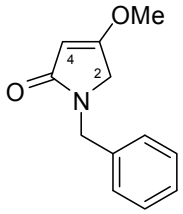
224

To a solution of **222e** (100 mg, 0.456 mmol) in MeOH (4.6 mL) at 0 °C was added TMSCl (174 μL, 1.37 mmol, 3.0 equiv.). The reaction was warmed to rt and allowed to stir for 21 h before being concentrated *in vacuo*. The residue was dissolved in EtOAc and the organic phase was washed with half-saturated aqueous $NaHCO_3$ solution, then saturated aqueous NaCl. The organic phase was dried over Na_2SO_4 then concentrated *in vacuo*. Purification of the residue by column chromatography (5:95 acetone/EtOAc) afforded the title compound **244** (94.8 mg, 89%) as a colourless oil: **IR** (thin film) 3107, 3028, 1703, 1634 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.24 (5H, m, 5 × ArH), 5.14 (1H, s, 2-CH), 5.04 (1H, s, 4-CH), 4.96 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 4.02 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 3.80 (3H, s, OCH_3), 3.11 (3H, s, OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.4 (C), 170.0 (C), 137.1 (C), 128.5 (CH), 128.3 (CH), 127.4 (CH), 95.2 (CH), 84.9 (CH), 58.2 (CH_3), 50.4

[†] Reaction and characterisation conducted by Dr Fatiah Issa

(CH_3), 42.5 (CH_2); **HRMS** (+ESI) calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125, found 234.1131; **MS** (+ESI) *m/z* 234 ($[M+H]^+$, 100%), 202 (13).

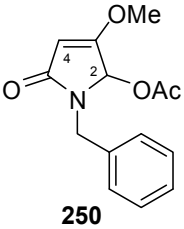
N-Benzyl-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (245)†



245

To a cooled (0 °C) suspension of **222e** (40.5 mg, 0.185 mmol, 1.0 equiv.) in CH_2Cl_2 (1.3 mL) was added triethylsilane (59 μL, 0.37 mmol, 2.0 equiv.), followed by $BF_3{\cdot}OEt_2$ (47.0 μL, 0.370 mmol, 2.0 equiv.). The mixture was slowly warmed to rt and stirred for 24 h. The solution was quenched with saturated aqueous K_2CO_3 solution and then the organic phase was isolated. The aqueous phase was extracted with CH_2Cl_2 (× 3) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (5:95 acetone/EtOAc) afforded the title compound **245** (36.1 mg, 96%) as a white solid: **m.p.** 44–45 °C; **IR** (thin film) 3028, 1674, 1624 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, 5 × ArH), 5.10 (1H, s, 4-CH), 4.57 (2H, s, NCH_2Ph), 3.76 (3H, s, OCH_3), 3.72 (2H, s, 2-CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.3 (C), 172.0 (C), 137.4 (C), 128.6 (CH), 127.8 (CH), 127.4 (CH), 94.1 (CH), 58.0 (CH_3), 49.8 (CH_2), 45.3 (CH_2); **HRMS** (+ESI) calcd for $C_{12}H_{13}NO_2Na$ $[M+Na]^+$ 226.0839, found 226.0836; **MS** (+ESI) *m/z* 226 ($[M+Na]^+$, 100%), 204 ($[M+H]^+$, 44).

N-Benzyl-2-acetoxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (250)†



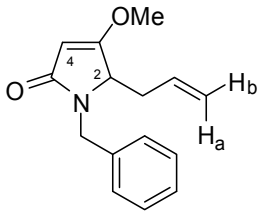
250

To a solution of **222e** (76.3 mg, 0.348 mmol, 1.0 equiv.) in pyridine (7.0 mL) at rt was added Ac_2O (329 μL, 3.48 mmol, 10 equiv.) followed by DMAP (4.3 mg, 0.0348 mmol, 0.1 equiv.). After stirring for 3 h, the reaction was quenched with water and extracted with Et_2O (× 5). The combined organic layers were dried over Na_2SO_4 then concentrated *in vacuo*. Purification *via* column chromatography (40:60 EtOAc/hexanes) afforded the title compound **250** (77.5 mg, 85%) as a white solid: **m.p.** 102–104 °C; **IR** (thin film) 3115, 1749, 1711, 1641 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30–7.23 (5H,

† Reaction and characterisation conducted by Dr Fatiah Issa

m, 5 × ArH), 6.42 (1H, s, 2-CH), 5.13 (1H, s, 4-CH), 4.59 (1H, d, J = 15.3 Hz, NCH_aH_bPh), 4.41 (1H, d, J = 15.3 Hz, NCH_aH_bPh), 3.80 (3H, s, OCH_3), 1.88 (3H, s, $O(CO)CH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2 (C), 170.5 (C), 170.2 (C), 137.2 (C), 128.4 (CH), 128.0 (CH), 127.3 (CH), 94.5 (CH), 79.2 (CH), 58.5 (CH_3), 43.8 (CH_2), 20.4 (CH_3); **HRMS** (+ESI) calcd for $C_{14}H_{15}NO_4Na$ $[M+Na]^+$ 284.0894, found 284.0897; **MS** (+ESI) *m/z* 284 ($[M+Na]^+$, 100%), 262($[M+H]^+$, 9), 202 (23).

N-Benzyl-2-allyl-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (246)[†]

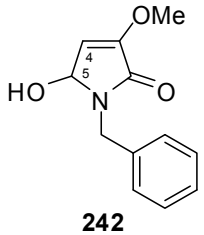


246

To a solution of **250** (20.5 mg, 0.0785 mmol, 1.0 equiv.) in CH_2Cl_2 (0.8 mL) at 0 °C, was added $BF_3{\cdot}OEt_2$ (39.8 μL, 0.314 mmol, 4.0 equiv.). After stirring at 0 °C for 10 min, allyltrimethylsilane (37.4 μL, 0.236 mmol, 3.0 equiv.) was added dropwise *via* syringe. The reaction was stirred at 0 °C for 7 h, then warmed to rt and stirred for a further 16 h. After pouring the mixture into water (1 mL), the organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (× 3). The combined organic phases were washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (40:60 acetone/hexanes) afforded the title compound **246** (17.9 mg, 94%) as a colourless oil: **IR** (thin film) 3076, 3028, 1680, 1626 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.21 (5H, m, 5 × ArH), 5.51 (1H, ddt, J = 17.1, 10.2, 7.1 Hz, $CH_2CH{=}CH_2$), 5.17 (1H, d, J = 15.4 Hz, NCH_aH_bPh), 5.10 (1H, s, 4-CH), 5.07 (1H, m, $CH{=}CH_2$), 5.06 (1H, m, $CH{=}CH_2$), 3.98 (1H, d, J = 15.4 Hz, NCH_aH_bPh), 3.87 (1H, t, J = 4.3 Hz, 2-CH), 3.76 (3H, s, OCH_3), 2.57–2.38 (2H, m, $CH_2CH{=}CH_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.3 (C), 171.7 (C), 137.6 (C), 131.0 (CH), 128.6 (CH), 127.9 (CH), 127.4 (CH), 118.8 (CH_2), 94.2 (CH), 58.5 (CH_3), 58.0 (CH), 43.2 (CH_2), 32.6 (CH_2); **HRMS** (+ESI) calcd for $C_{15}H_{17}NO_2Na$ $[M+Na]^+$ 266.1152, found 266.1152; **MS** (+ESI) *m/z* 266 ($[M+Na]^+$,76%), 244 ($[M+H]^+$, 100).

[†] Reaction and characterisation conducted by Dr Fatiah Issa

Reduction of 220e with DIBAL–H to give 242[†]



242

To a solution of **220e** (95.5 mg, 0.440 mmol, 1.0 equiv.) in THF (2.2 mL) at 0 °C was added DIBAL–H (1.0 M in heptane, 0.46 mL, 0.46 mmol, 1.05 equiv.) dropwise. The resultant brown solution was stirred at 0 °C for 4 h after which time the reaction was quenched with half-saturated aqueous $NaHCO_3$ solution, then diluted with H_2O and extracted with EtOAc (× 3). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a brown oil that was partially purified by column chromatography (10:90 acetone/EtOAc). This gave a mixture of **242** and **222e** that were separated by HPLC (2.5:97.5 *i*-PrOH/EtOAc at 13.5 mL min^{-1} on a preparative Zorbax Sil column) to afford the title compound **242** (**HPLC T_r** 12.5 min) and **222e** (**HPLC T_r** 14.0 min, spectroscopically identical to that obtained previously).

Title compound 242: white solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34–7.25 (5H, m, 5 × Ar<u>H</u>), 5.57 (1H, d, J = 2.1 Hz, 5-C<u>H</u>), 5.17 (1H, d, J = 1.9 Hz, 4-C<u>H</u>), 4.94 (1H, d, J = 14.8 Hz, NC<u>H</u>$_a$H$_b$Ph), 4.27 (1H, d, J = 14.9 Hz, NCH$_a$<u>H</u>$_b$Ph), 3.76 (3H, s, OC<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.2 (C), 153.0 (C), 136.8 (C), 128.7 (CH), 128.4 (CH), 127.6 (CH), 106.8 (CH), 78.9 (CH), 57.4 (CH_3), 42.9 (CH_2); **HRMS** (+ESI) calcd for $C_{12}H_{13}NO_3Na$ $[M+Na]^+$ 242.0788, found 242.0787; **MS** (+ESI) *m/z* 242 $[M+Na]^+$, 220 $[M+H]^+$, 202 $[M–OH]^+$.

[†] Reaction and characterisation conducted by Dr Fatiah Issa

REFERENCES

1. UNAIDS AIDS Epidemic Update: December 2006. http://data.unaids.org/pub/EpiReport/2006/2006_EpiUpdate_en.pdf (Accessed 15/09/2007),

2. Jaffe, H. *Science* **2004,** 305, (5688), 1243-1244.

3. Little, S. J.; Holte, S.; Routy, J.-P.; Daar, E. S.; Markowitz, M.; Collier, A. C.; Koup, R. A.; Mellors, J. W.; Connick, E.; Conway, B.; Kilby, M.; Wang, L.; Whitcomb, J. M.; Hellmann, N. S.; Richman, D. D. *N. Engl. J. Med.* **2002,** 347, (6), 385-394.

4. Hirsch, M. S. *N. Engl. J. Med.* **2002,** 347, (6), 438-439.

5. Johnson, A., A.; Marchand, C.; Pommier, Y. *Curr. Top. Med. Chem.* **2004,** 4, (10), 1059-1077.

6. Benjamin, C. L.; Garman, G. R.; Funston, J. H., *Human Biology*. McGraw-Hill: 1997; p 354-358.

7. Pommier, Y.; Johnson Allison, A.; Marchand, C. *Nat. Rev. Drug Discovery* **2005,** 4, (3), 236-248.

8. Drugs Used in the Treatment of HIV Infection. http://www.fda.gov/oashi/aids/virals.html (Accessed 28/09/07),

9. De Clercq, E. *Antiviral Res.* **1998,** 38, (3), 153-179.

10. De Clercq, E. *J. Med. Chem.* **2005,** 48, (5), 1297-1313.

11. Richman, D. D. *Nature* **2001,** 410, (6831), 995-1001.

12. Cohen, J. *Science* **2002,** 296, (5577), 2320-2324.

13. Fikkert, V.; Van Maele, B.; Vercammen, J.; Hantson, A.; Van Remoortel, B.; Michiels, M.; Gurnari, C.; Pannecouque, C.; De Maeyer, M.; Engelborghs, Y.; De Clercq, E.; Debyser, Z.; Witvrouw, M. *J. Virol.* **2003,** 77, (21), 11459-11470.

14. Witvrouw, M.; Van Maele, B.; Vercammen, J.; Hantson, A.; Engelborghs, Y.; De Clercq, E.; Pannecouque, C.; Debyser, Z. *Curr. Drug Metab.* **2004,** 5, (4), 291-304.

15. Hazuda, D. J.; Felock, P.; Witmer, M.; Wolfe, A.; Stillmock, K.; Grobler, J. A.; Espeseth, A.; Gabryelski, L.; Schleif, W.; Blau, C.; Miller, M. D. *Science* **2000,** 287, (5453), 646-650.

16. Hazuda, D. J.; Young, S. D.; Guare, J. P.; Anthony, N. J.; Gomez, R. P.; Wai, J. S.; Vacca, J. P.; Handt, L.; Motzel, S. L.; Klein, H. J.; Dornadula, G.; Danovich, R. M.; Witmer, M. V.; Wilson, K. A. A.; Tussey, L.; Schleif, W. A.; Gabryelski, L. S.; Jin, L.; Miller, M. D.; Casimiro, D. R.; Emini, E. A.; Shiver, J. W. *Science* **2004,** 305, (5683), 528-532.

17. Hadlington, S. *Chemistry World* **2007,** 4, (4), 14.

18. Release, G. P. Gilead Announces the Advancement of HIV Integrase Inhibitor GS 9137 to a Phase II Clinical Trial. http://www.gilead.com/pr_801963 (Accessed 25/9/07),

19. Release, G. P. Gilead Announces 24-Week Results from Phase II Study of Investigational HIV Integrase Inhibitor GS 9137. http://www.gilead.com/pr_969229 (Accessed 25/9/07),

20. Neamati, N.; Marchand, C.; Pommier, Y. *Adv. Pharmacol.* **2000,** 49, (HIV-1: Molecular Biology and Pathogenesis: Clinical Applications), 147-165.

21. Chiu, T. K.; Davies, D. R. *Curr. Top. Med. Chem.* **2004,** 4, (9), 965-977.

22. Maurin, C.; Bailly, F.; Cotelle, P. *Curr. Med. Chem.* **2003,** 10, (18), 1795-1810.

23. Engelman, A.; Bushman, F. D.; Craigie, R. *EMBO J.* **1993,** 12, (8), 3269-3275.

24. Zheng, R.; Jenkins, T. M.; Craigie, R. *Proc. Natl. Acad. Sci. U. S. A.* **1996,** 93, (24), 13659-13664.

25. Chen, J. C. H.; Krucinski, J.; Miercke, L. J. W.; Finer-Moore, J. S.; Tang, A. H.; Leavitt, A. D.; Stroud, R. M. *Proc. Natl. Acad. Sci. U. S. A.* **2000,** 97, (15), 8233-8238.

26. Marchand, C.; Johnson, A. A.; Karki, R. G.; Pais, G. C. G.; Zhang, X.; Cowansage, K.; Patel, T. A.; Nicklaus, M. C.; Burke, T. R., Jr.; Pommier, Y. *Mol. Pharmacol.* **2003,** 64, (3), 600-609.

27. Neamati, N.; Lin, Z.; Karki, R. G.; Orr, A.; Cowansage, K.; Strumberg, D.; Pais, G. C. G.; Voigt, J. H.; Nicklaus, M. C.; Winslow, H. E.; Zhao, H.; Turpin, J. A.; Yi, J.; Skalka, A. M.; Burke, T. R., Jr.; Pommier, Y. *J. Med. Chem.* **2002,** 45, (26), 5661-5670.

28. Dyda, F.; Hickman, A. B.; Jenkins, T. M.; Engelman, A.; Craigie, R.; Davies, D. R. *Science* **1994,** 266, (5193), 1981-1986.

29. Goldgur, Y.; Dyda, F.; Hickman, A. B.; Jenkins, T. M.; Craigie, R.; Davies, D. R. *Proc. Natl. Acad. Sci. U. S. A.* **1998,** 95, (16), 9150-9154.

30. Neamati, N. *Expert Opin. Ther. Pat.* **2002,** 12, (5), 709-724.

31. Craigie, R. *J. Biol. Chem.* **2001,** 276, (26), 23213-23216.

32. Craigie, R.; Mizuuchi, K.; Bushman, F. D.; Engelman, A. *Nucleic Acids Res.* **1991,** 19, (10), 2729-2734.

33. Makhija, M. T. *Curr. Med. Chem.* **2006,** 13, (20), 2429-2441.

34. Fesen, M. R.; Kohn, K. W.; Leteurtre, F.; Pommier, Y. *Proc. Natl. Acad. Sci. U. S. A.* **1993,** 90, (6), 2399-2403.

35. Burke, T. R., Jr.; Fesen, M.; Mazumder, A.; Yung, J.; Wang, J.; Carothers, A. M.; Grunberger, D.; Driscoll, J.; Pommier, Y.; Kohn, K. *J. Med. Chem.* **1995,** 38, (21), 4171.

36. LaFemina, R. L.; Graham, P. L.; LeGrow, K.; Hastings, J. C.; Wolfe, A.; Young, S. D.; Emini, E. A.; Hazuda, D. J. *Antimicrob. Agents Chemother.* **1995,** 39, (2), 320-324.

37. Zhao, H.; Neamati, N.; Mazumder, A.; Sunder, S.; Pommier, Y.; Burke, T. R. *J. Med. Chem.* **1997,** 40, (8), 1186-1194.

38. Dupont, R.; Jeanson, L.; Mouscadet, J.-F.; Cotelle, P. *Bioorg. Med. Chem. Lett.* **2001,** 11, (24), 3175-3178.

39. Dayam, R.; Deng, J.; Neamati, N. *Med. Res. Rev.* **2006,** 26, (3), 271-309.

40. Goldgur, Y.; Craigie, R.; Cohen, G. H.; Fujiwara, T.; Yoshinaga, T.; Fujishita, T.; Sugimoto, H.; Endo, T.; Murai, H.; Davies, D. R. *Proc. Natl. Acad. Sci. U. S. A.* **1999,** 96, (23), 13040-13043.

41. Nair, V.; Chi, G. *Rev. Med. Vir.* **2007,** 17, (4), 277-295.

42. Johnson, G.; Sunderwirth, S. G.; Gibian, H.; Coulter, A. W.; Gassner, F. X. *Phytochemistry* **1963,** 2, 145-150.

43. Kelley, C. J.; Mahajan, J. R.; Brooks, L. C.; Neubert, L. A.; Breneman, W. R.; Carmack, M. *J. Org. Chem.* **1975,** 40, (12), 1804-1815.

44. Gassner, F. X.; Hopwood, M. L.; Joechle, W.; Johnson, G.; Sunderwirth, S. G. *Proc. Soc. Exp. Biol. Med.* **1963,** 114, 20-25.

45. Wagner, H.; Wttmann, D.; Schaefer, W. *Tetrahedron Lett.* **1975**, (8), 547-550.

46. Zhou, L.; Zuo, Z.; Chow, M. S. S. *J. Clin. Pharmacol.* **2005,** 45, (12), 1345-1359.

47. Abd-Elazem, I. S.; Chen, H. S.; Bates, R. B.; Huang, R. C. C. *Antiviral Res.* **2002,** 55, (1), 91-106.

48. Jacobson, R. M.; Raths, R. A. *J. Org. Chem.* **1979,** 44, (22), 4013-4014.

49. O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005,** 127, (39), 13496-13497.

50. Minamikawa, J.; Brossi, A. *Tetrahedron Lett.* **1978**, (34), 3085-3086.

51. Singh, S. B.; Zink, D. L.; Goetz, M. A.; Dombrowski, A. W.; Polishook, J. D.; Hazuda, D. J. *Tetrahedron Lett.* **1998,** 39, (16), 2243-2246.

52. Singh, S. B.; Zink, D.; Polishook, J.; Valentino, D.; Shafiee, A.; Silverman, K.; Felock, P.; Teran, A.; Vilella, D.; Hazuda, D. J.; Lingham, R. B. *Tetrahedron Lett.* **1999,** 40, (50), 8775-8779.

53. Singh, S. B.; Jayasuriya, H.; Salituro, G. M.; Zink, D. L.; Shafiee, A.; Heimbuch, B.; Silverman, K. C.; Lingham, R. B.; Genilloud, O.; Teran, A.; Vilella, D.; Felock, P.; Hazuda, D. *J. Nat. Prod.* **2001,** 64, (7), 874-882.

54. Singh, S. B.; Zink, D. L.; Heimbach, B.; Genilloud, O.; Teran, A.; Silverman, K. C.; Lingham, R. B.; Felock, P.; Hazuda, D. J. *Org. Lett.* **2002,** 4, (7), 1123-1126.

55. Wang, L.; Floreancig, P. E. *Org. Lett.* **2004,** 6, (4), 1569-1572.

56. Dineen, T. A.; Roush, W. R. *Org. Lett.* **2005,** 7, (7), 1355-1358.

57. Bogucki, D. E.; Charlton, J. L. *Can. J. Chem.* **1997,** 75, (12), 1783-1794.

58. Reimann, E.; Maas, H. J.; Pflug, T. *Monatsh. Chem.* **1997,** 128, (10), 995-1008.

59. Reimann, E.; Pflug, T. *Monatsh. Chem.* **1998,** 129, (2), 187-193.

60. Wuensch, B.; Zott, M. *Liebigs Ann. Chem.* **1992**, (1), 39-45.

61. Markovich, K. M.; Tantishaiyakul, V.; Hamada, A.; Miller, D. D.; Romstedt, K. J.; Shams, G.; Shin, Y.; Fraundorfer, P. F.; Doyle, K.; Feller, D. R. *J. Med. Chem.* **1992,** 35, (3), 466-479.

62. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963,** 28, (12), 3313-3315.

63. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, (50), 4467-4470.

64. Li, J. J., *Name Reactions. A Collection of Detailed Reaction Mechanisms*. Springer Berlin Heidelberg New York: 2006.

65. Nicolaou, K. C.; Sorensen, E. J., *Classics in Total Synthesis*. VCH Publishers, Inc. NY USA: 1996; p 583.

66. Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000,** 2, (3), 297-299.

67. Cannizzaro, S. *Justus Liebigs Ann. Chem.* **1853,** 88, 129-130.

68. Zaugg, H. E. *J. Org. Chem.* **1976,** 41, (21), 3419-3421.

69. Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* **2003,** 44, (29), 5465-5468.

70. Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002,** 4, (15), 2607-2609.

71. Kondo, Y.; Sakamoto, T.; Yamanaka, H. *Heterocycles* **1989,** 29, (6), 1013-1016.

72. Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996,** 61, (26), 9280-9288.

73. Chaplin, J. H.; Flynn, B. L. *Chem. Comm.* **2001**, (17), 1594-1595.

74. Hu, Y.; Yang, Z. *Org. Lett.* **2001,** 3, (9), 1387-1390.

75. Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002,** 67, (7), 2365-2368.

76. Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004,** 6, (4), 457-460.

77. Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994,** 50, (41), 11803-11812.

78. Li, C. C.; Xie, Z. X.; Zhang, Y. D.; Chen, J. H.; Yang, Z. *J. Org. Chem.* **2003,** 68, (22), 8500-8504.

79. Lutjens, H.; Scammells, P. J. *Tetrahedron Lett.* **1998,** 39, (36), 6581-6584.

80. Lutjens, H.; Scammells, P. J. *Synlett* **1999**, (7), 1079-1081.

81. Kendall, P. M.; Johnson, J. V.; Cook, C. E. *J. Org. Chem.* **1979,** 44, (9), 1421.

82. Ronald, R. C.; Lansinger, J. M.; Lillie, T. S.; Wheeler, C. J. *J. Org. Chem.* **1982,** 47, (13), 2541.

83. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, (36), 3769-3772.

84. Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954,** 97, 1318-1330.

85. Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999,** 40, 8575-8578.

86. Wolkoff, P. *Can. J. Chem.* **1975,** 53, (9), 1333-1335.

87. Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997,** 119, (50), 12159-12169.

88. Bridges, A. J.; Lee, A.; Schwartz, C. E.; Towle, M. J.; Littlefield, B. A. *Bioorg. Med. Chem.* **1993,** 1, (6), 403-410.

89. Dodge, J. A.; Stocksdale, M. G.; Fahey, K. J.; Jones, C. D. *J. Org. Chem.* **1995,** 60, (3), 739-741.

90. Banwell, M. G.; Coster, M. J.; Edwards, A. J.; Karunaratne, O. P.; Smith, J. A.; Welling, L. L.; Willis, A. C. *Aust. J. Chem.* **2003,** 56, (6), 585-595.

91. Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, (16), 1327-1328.

92. Kende, A. S.; Rizzi, J. P. *Tetrahedron Lett.* **1981,** 22, (19), 1779-1782.

93. McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968,** 24, (5), 2289-2292.

94. Mewshaw, R. E.; Zhou, D.; Zhou, P.; Shi, X.; Hornby, G.; Spangler, T.; Scerni, R.; Smith, D.; Schechter, L. E.; Andree, T. H. *J. Med. Chem.* **2004,** 47, (15), 3823-3842.

95. Okamoto, A.; Tanabe, K.; Saito, I. *Org. Lett.* **2001,** 3, (6), 925-927.

96. Gonzalez-Gomez, J. C.; Uriarte, E. *Synlett* **2003**, (14), 2225-2227.

97. Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977,** 42, (5), 918-920.

98. Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002,** 67, (15), 5343-5351.

99. Tanaka, T.; Tasaki, T.; Aoyama, Y. *J. Am. Chem. Soc.* **2002,** 124, (42), 12453-12462.

100. Tyman, J. H. P. *J. Chem. Soc., Chem. Commun.* **1972**, (15), 914-915.

101. Schmid, C. R.; Beck, C. A.; Cronin, J. S.; Staszak, M. A. *Org. Process Res. Dev.* **2004,** 8, (4), 670-673.

102. Juhász, L.; Szilagyi, L.; Antus, S.; Visy, J.; Zsila, F.; Simonyi, M. *Tetrahedron* **2002,** 58, (21), 4261-4265.

103. Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986,** 27, (21), 2409-2410.

104. Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999,** 121, (40), 9473-9474.

105. Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003,** 125, (37), 11253-11258.

106. Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** 124, (12), 2892-2893.

107. Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003,** 5, (14), 2417-2420.

108. Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000,** 122, (28), 6797-6798.

109. Chan, T. H.; Brook, M. A.; Chaly, T. *Synthesis* **1983**, (3), 203-205.

110. Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*. Third John Wiley and Sons, Inc: 1999; p pp. 307.

111. Kumar, R.; Vandegraaff, N.; Mundy, L.; Burrell, C. J.; Li, P. *J. Virol. Methods* **2002,** 105, (2), 233-246.

112. Vandegraaff, N.; Kumar, R.; Burrell, C. J.; Li, P. *J. Virol.* **2001,** 75, (22), 11253-11260.

113. Vandegraaff, N.; Kumar, R.; Hocking, H.; Burke, T. R., Jr.; Mills, J.; Rhodes, D.; Burrell, C. J.; Li, P. *Antimicrob. Agents Chemother.* **2001,** 45, (9), 2510-2516.

114. Workcover: Work Involving Use of Carcinogenic Substances. http://www.workcover.nsw.gov.au/NR/rdonlyres/EF5C3917-ECF7-4E0E-A53D-0C63FA046FBE/0/guide_carcinog_subs_4073.pdf (Accessed 05/11/07),

115. Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, (2), 355-358.

116. Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1996,** 37, (30), 5229-5232.

117. Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A.; Pena, C.; Coba, M. P. *Tetrahedron* **1998,** 54, (43), 13023-13034.

118. Mascaretti, O. A.; Furlan, R. L. E. *Aldrichimica Acta* **1997,** 30, (2), 55-68.

119. Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005,** 44, (9), 1378-1382.

120. Gerstenberger, B. S.; Konopelski, J. P. *J. Org. Chem.* **2005,** 70, 1467-1470.

121. Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, (13), 2689-2693.

122. Pelter, A.; Ward, R. S.; Little, G. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, (10), 2775-2790.

123. Quinkert, G.; Schmalz, H.-G.; Dzierzynski, E. M.; Dürner, G.; Bats, J. W. *Angew. Chem., Int. Ed.* **1986,** 25, (11), 992-993.

124. Kozikowski, A. P.; Zhao, L.; Zhang, A.; Wang, C. Z.; Flippen-Anderson, J.; Johnson, K. M. *ChemMedChem* **2006,** 1, (1), 58-65.

125. Yang, D.; Ye, X.-Y.; Xu, M. *J. Org. Chem.* **2000,** 65, (7), 2208-2217.

126. Banwell, M. G.; Beck, D. A. S.; Smith, J. A. *Org. Biomol. Chem.* **2004,** 2, (2), 157-159.

127. Murthy, K. S. K.; Rey, A. W.; Tjepkema, M. *Tetrahedron Lett.* **2003,** 44, (28), 5355-5358.

128. Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007,** 9, (15), 2763-2766.

129. Otera, J. *Chem. Rev.* **1993,** 93, (4), 1449-1470.

130. Okawara, R.; Wads, M. *J. Organomet. Chem.* **1963,** 1, (1), 81-88.

131. Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986,** 27, (21), 2383-2386.

132. Otera, J.; Dan-Oh, N.; Nozaki, H. *J. Org. Chem.* **1991,** 56, 5307-5311.

133. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979,** 52, (7), 1989-1993.

134. Lepage, O.; Kattnig, E.; Fuerstner, A. *J. Am. Chem. Soc.* **2004,** 126, (49), 15970-15971.

135. Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990,** 1, (8), 477-511.

136. Saiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006,** 45, (31), 5194-5197.

137. Ley, S. V.; Trudell, M. L.; Wadsworth, D. J. *Tetrahedron* **1991,** 47, (38), 8285-8296.

138. Booker-Milburn, K. I.; Baker, J. R.; Bruce, I. *Org. Lett.* **2004,** 6, 1481-1484.

139. Farina, F.; Victoria Martin, M.; Carmen Paredes, M.; Carmen Ortega, M.; Tito, A. *Heterocycles* **1984,** 22, (8), 1733-1739.

140. Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974,** 30, (12), 1563-1572.

141. Wijnberg, J. B. P. A.; Speckamp, W. N.; Schoemaker, H. E. *Tetrahedron Lett.* **1974**, (46), 4073-4076.

142. Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978,** 34, (2), 179-187.

143. Mase, N.; Nishi, T.; Hiyoshi, M.; Ichihara, K.; Bessho, J.; Yoda, H.; Takabe, K. *J. Chem. Soc., Perkin Trans. 1* **2002**, (6), 707-709.

144. Bänziger, M.; McGarrity, J. F.; Meul, T. *J. Org. Chem.* **1993,** 58, (15), 4010-4012.

145. Huang, P.-Q.; Deng, J. *Synlett* **2004**, (2), 247-250.

146. Clark, J. H.; Miller, J. M. *J. Am. Chem. Soc.* **1977,** 99, (2), 498-504.

147. Sahoo, M. K.; Mhaske, S. B.; Argade, N. P. *Synthesis* **2003**, (3), 346-349.

148. Stachel, H.-D.; Schachtner, J.; Seidel, J. *Z. Naturforsch., B: Chem. Sci.* **1996,** 51, (3), 409-416.

149. Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1983,** 48, (14), 2420-2422.

150. Potgieter, M.; Wenteler, G. L.; Drewes, S. E. *Phytochemistry* **1988,** 27, (4), 1101-1104.

151. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987,** 109, (18), 5478-5486.

152. Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, (21), 2567-2579.

153. James, G. D.; Mills, S. D.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, (21), 2581-2584.

154. Issa, F.; Fischer, J.; Turner, P.; Coster, M. J. *J. Org. Chem.* **2006,** 71, (12), 4703-4705.

APPENDIX A

Permissions Granted for the reproduction of Figure 1

From: Yves Pommier [pommier@nih.gov]
Sent: Friday, 9 November 2007 9:57 AM
To: Josh Fischer
Subject: Re: Image Permission

Dear Josh,

Thanks for your interest.
I have not problem for you to use the figure.

Best wishes,

Yves P.

Yves Pommier, M.D., Ph.D.
Chief, Laboratory of Molecular Pharmacology
Center for Cancer Research, NCI
37 Convent Drive
Building 37, Room 5068
NIH
Bethesda,MD 20892-4255

Tel: 301-496-5944
Fax: 301-402-0752
email: pommier@nih.gov
videocalls for Mac users: yvespommier (iChat)
http://discover.nci.nih.gov/pommier/pommier.htm

Dear Dr. Pommier,
My name is Joshua Fischer and I am a chemistry graduate student at the University of Sydney, Australia. I am currently writing my PhD thesis, and was hoping to gain permission to reproduce the image "HIV replication and drug targets" (Figure 1, *Nature Rev. Drug Discov.*, **2005**, *4*, 236-248) in the introduction of my thesis, as a general schematic for the viral life cycle. This picture would, of course, be appropriately referenced and would be used solely for educational purposes with no profit accruing to me or any third party.
Thank-you for your time, and I look forward to hearing from you,
Joshua Fischer

Permissions granted for the reproduction of the Image in Figure 12

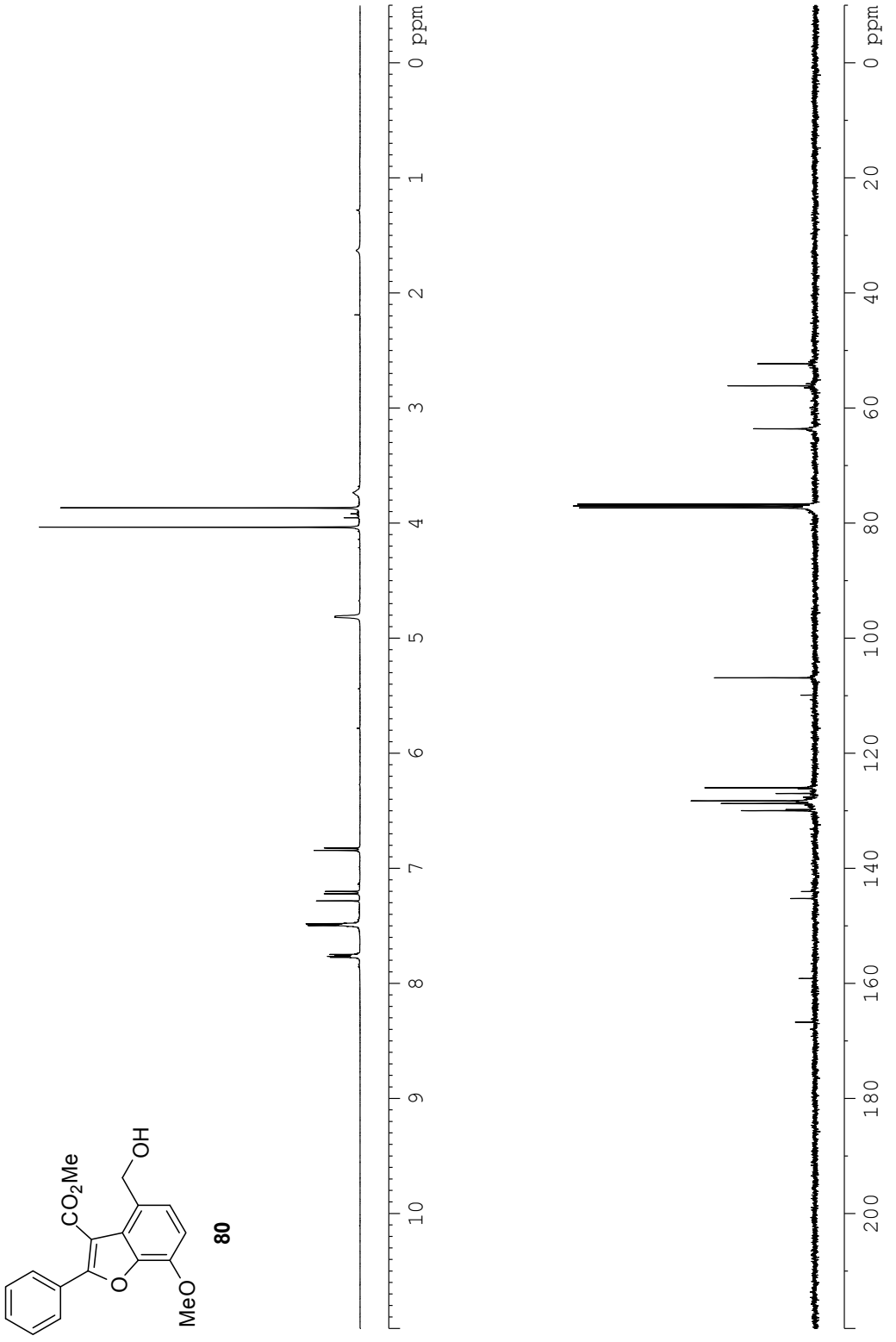
From: Ben Legler [blegler@u.washington.edu]
Sent: Wednesday, 10 October 2007 2:15 PM
To: Josh Fischer
Subject: Re: Image permission
Attachments: wtu000226.jpg

Joshua,
Sure, you may use the image in your thesis. I have attached the full-size image, 1704 by 2272 pixels, which should be adequate for a print size up to about 5x7 inches.
Ben

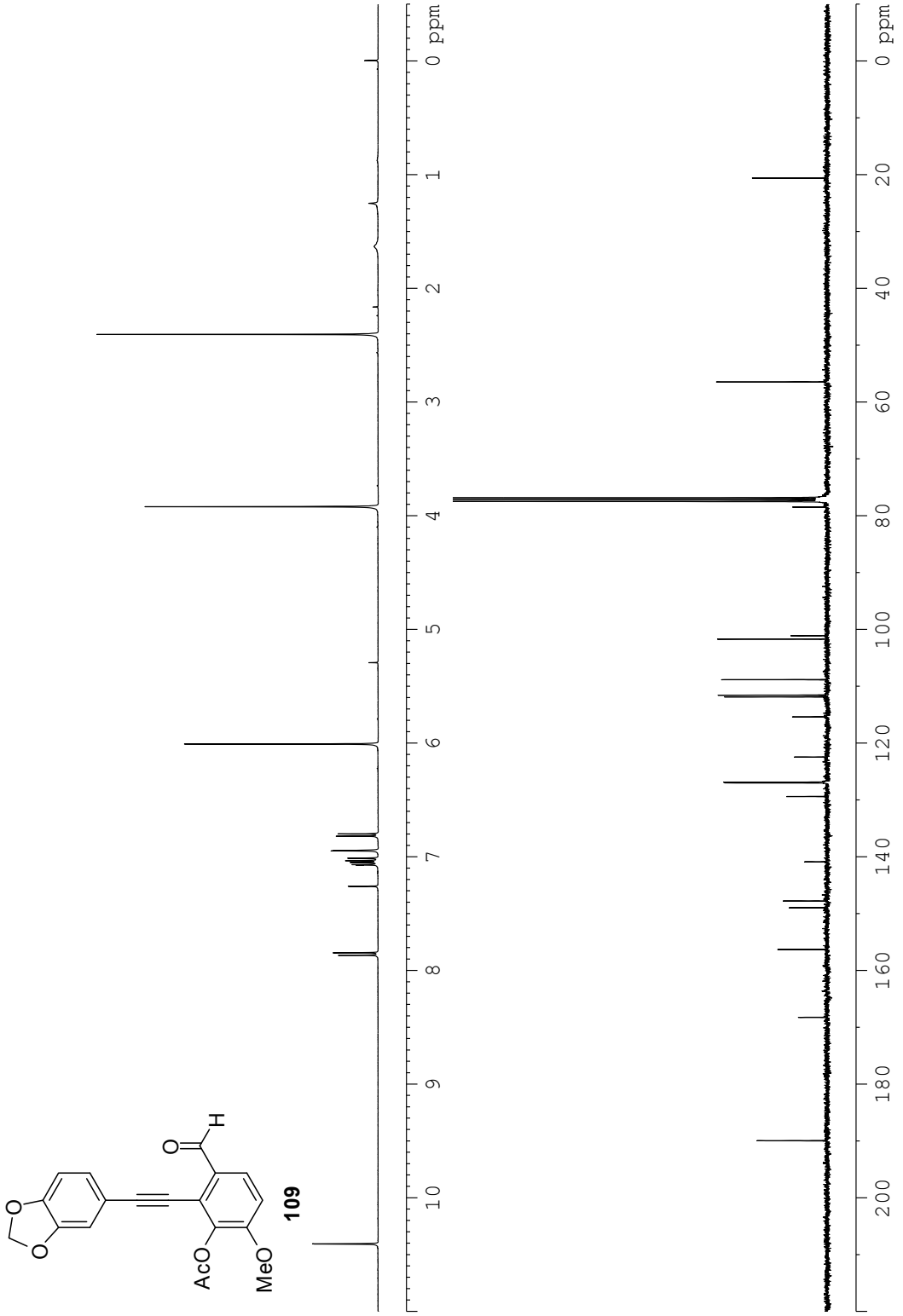
Dear Ben Legler,
My name is Joshua Fischer and I am a chemistry graduate student at the University of Sydney, Australia. I am currently writing my PhD thesis, and was hoping to gain permission to reproduce the picture of the Lithospermum ruderale taken by you shown on the website at
<http://biology.burke.washington.edu/herbarium/imagecollection/imagelarge.php?ImageNumber=226&TaxonID=2866&SourcePage=taxon&>
as a general picture of the plant in the introduction of my thesis.
This picture would, of course, be appropriately referenced and would be used solely for educational purposes with no profit accruing to me or any third party.
Thank-you for your time, and I look forward to hearing from you,
Joshua Fischer

APPENDIX B

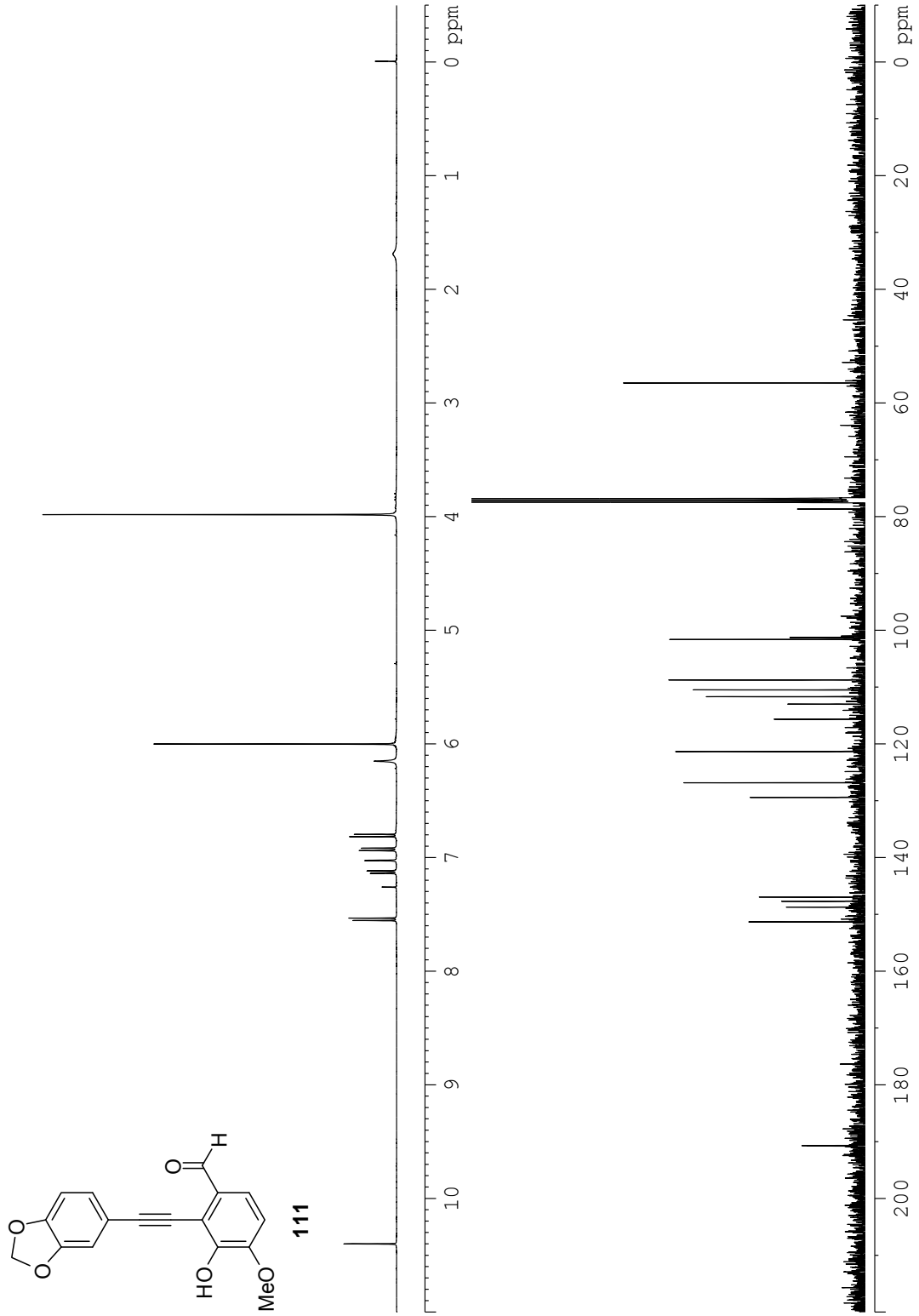
Methyl 4-(hydroxymethyl)-7-methoxy-2-phenyl-1-benzofuran-3-carboxylate (80)
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



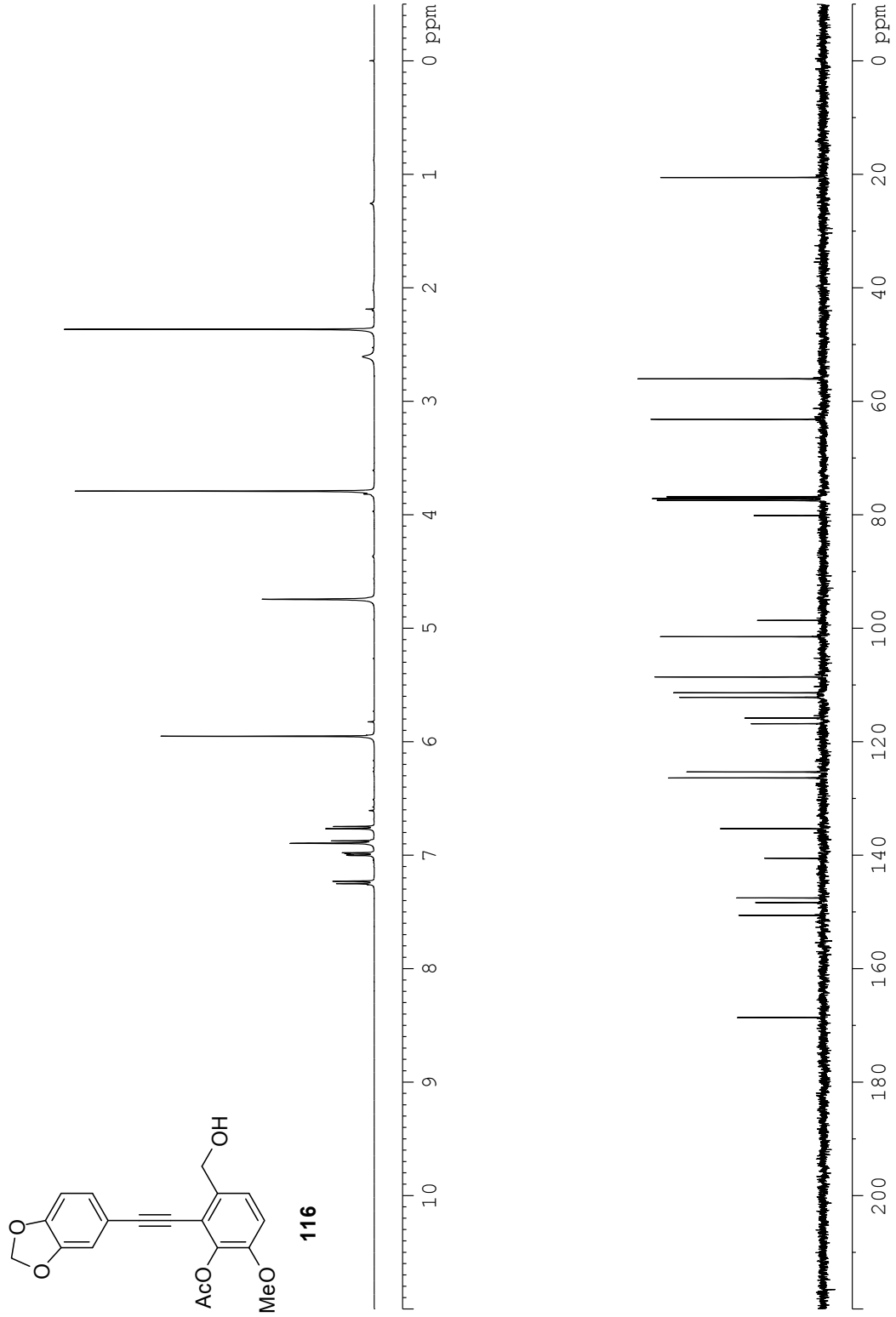
Methyl 4-(hydroxymethyl)-7-methoxy-2-phenyl-1-benzofuran-3-carboxylate (109)
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



2-(1',3'-Benzodioxol-5'-ylethynyl)-3-hydroxy-4-methoxybenzaldehyde (111)
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

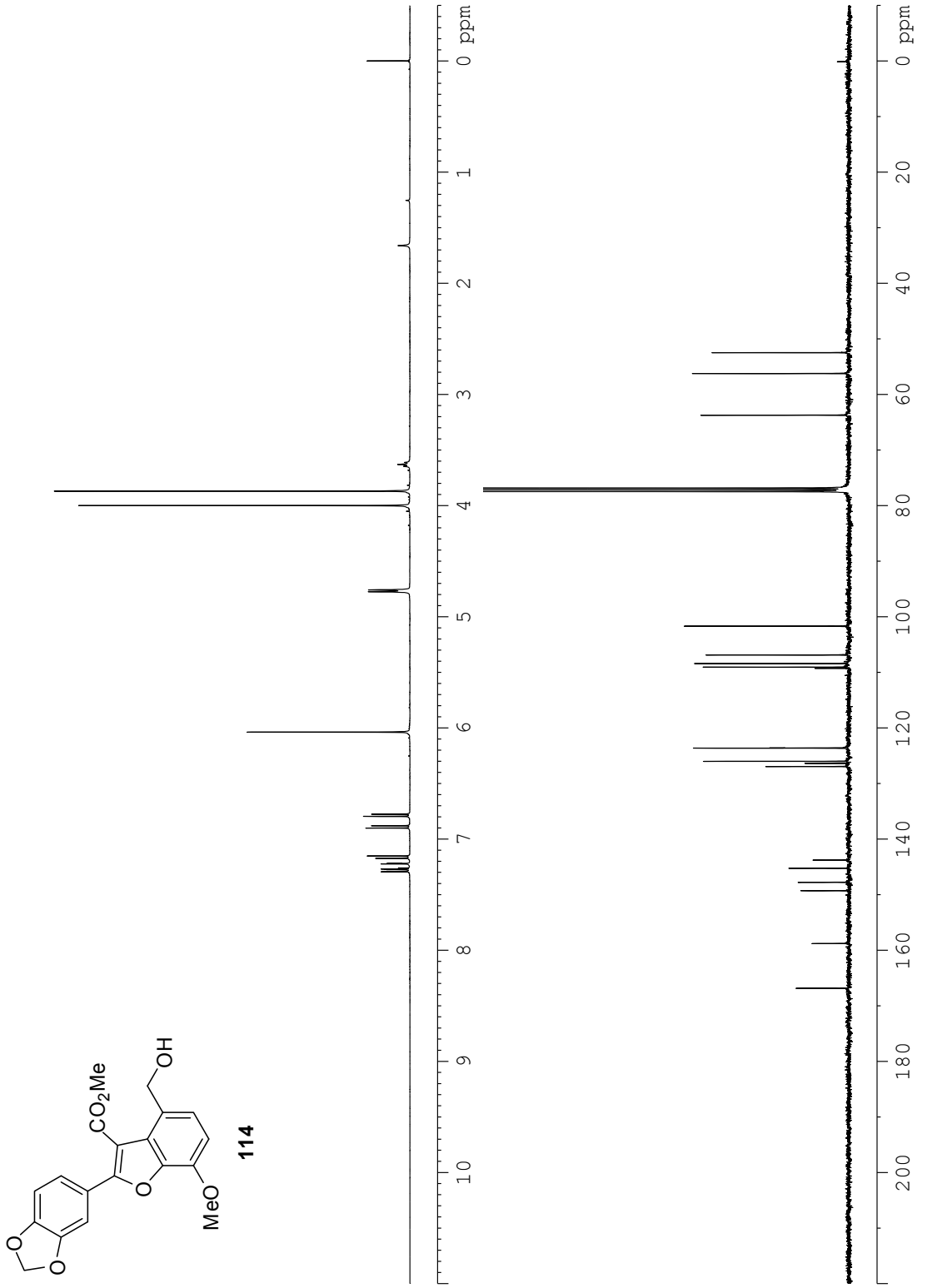


2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(hydroxymethyl)-6-methoxyphenyl acetate (116)
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

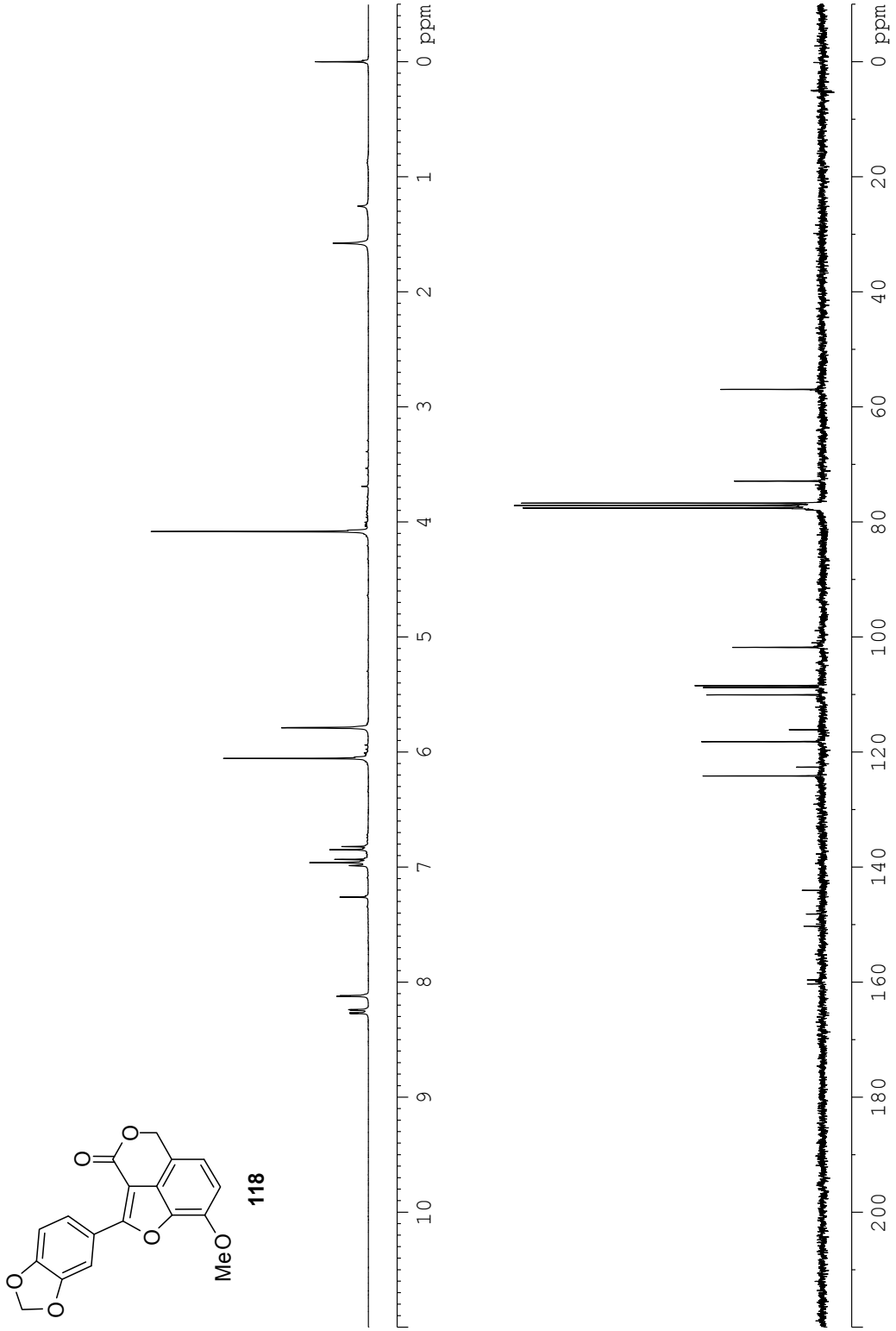


Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(hydroxymethyl)-7-methoxy-1-benzofuran-3-carboxylate (114)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

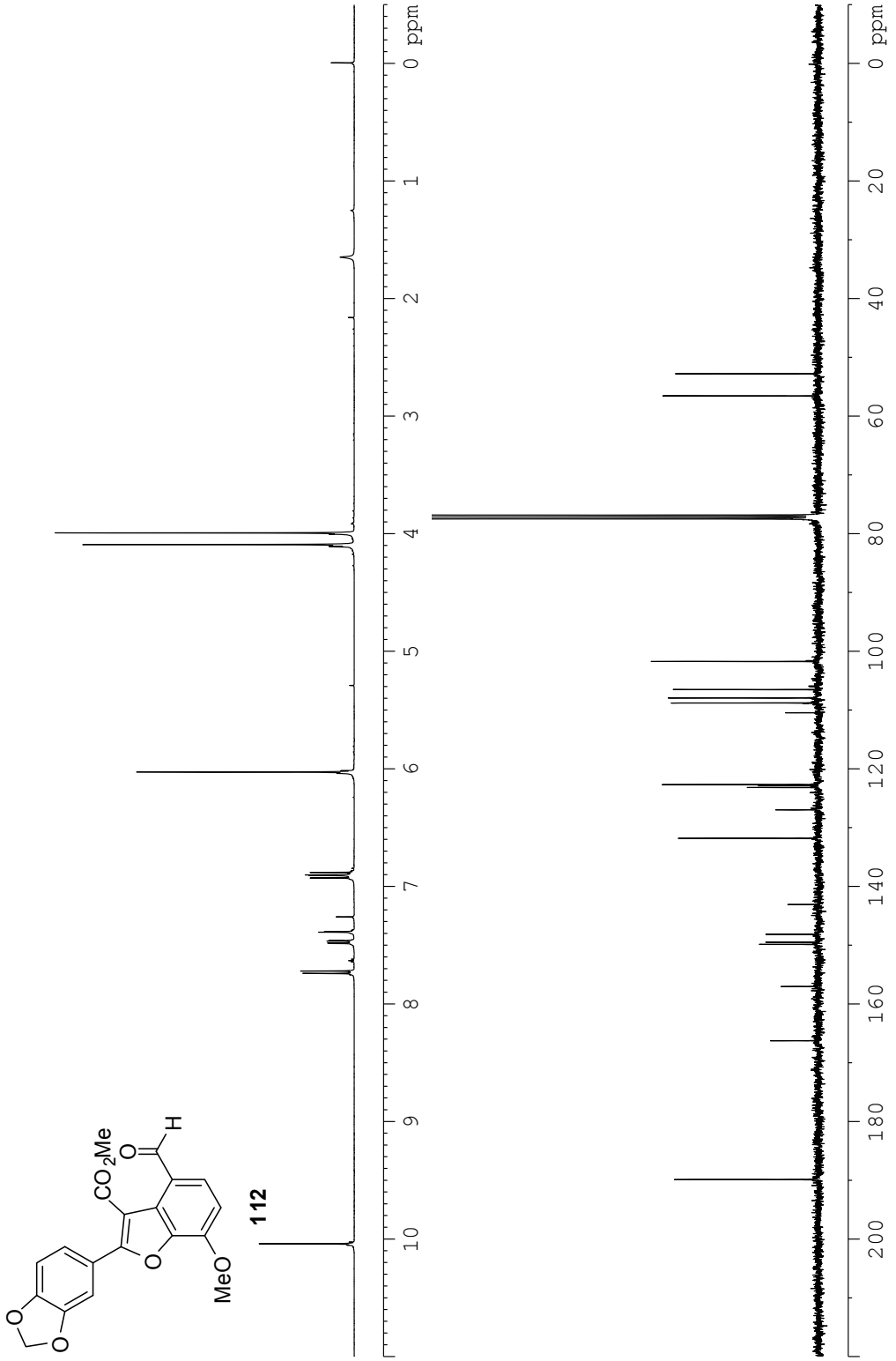


2-(1',3'-Benzodioxol-5'-yl)-8-methoxy-3*H*,5*H*-furo[4,3,2-*de*]isochromen-3-one (118)
^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$)



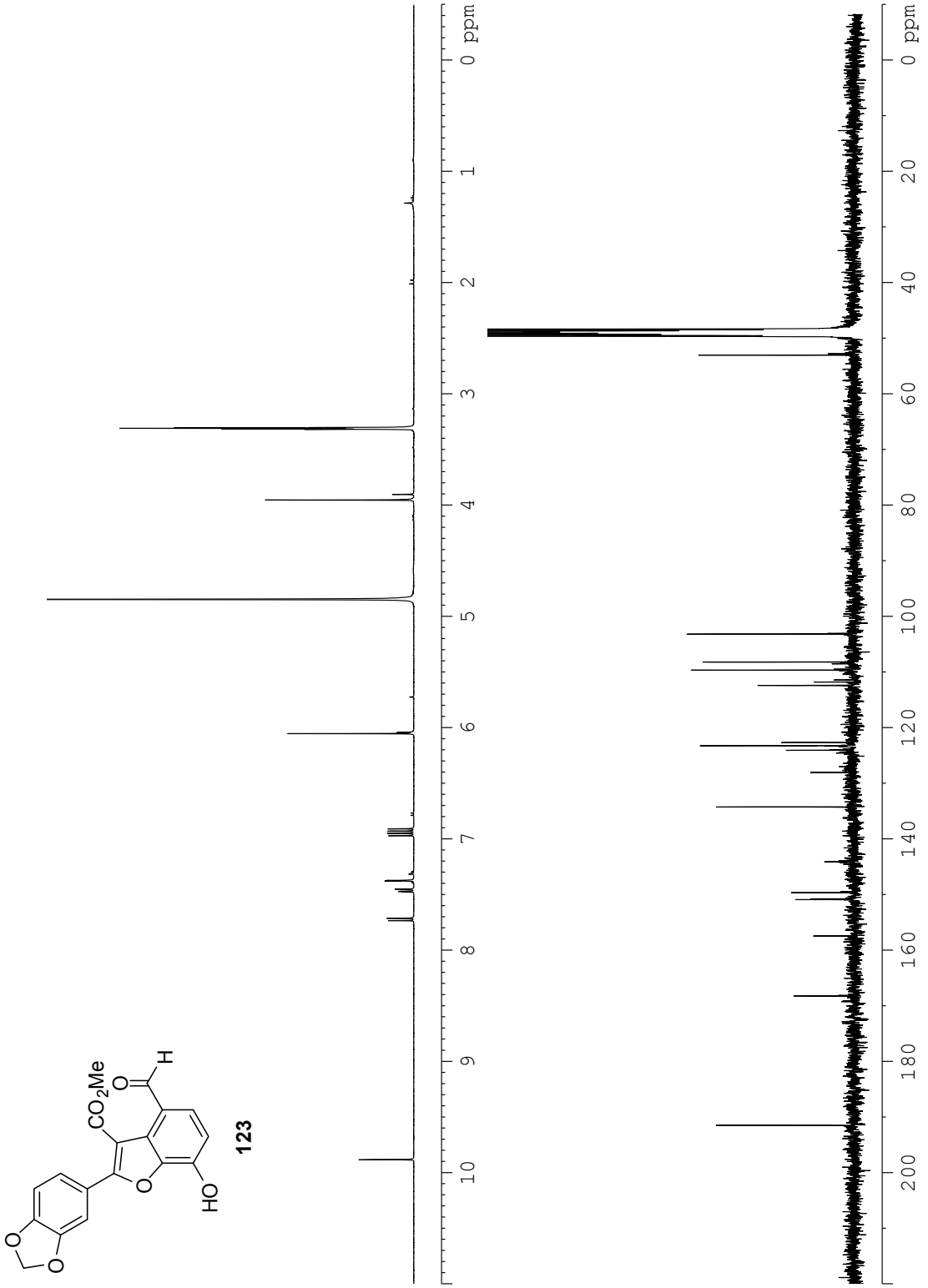
Methyl 2-(1',3'-benzodioxol-5'-yl)-4-formyl-7-methoxy-1-benzofuran-3-carboxylate (112)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



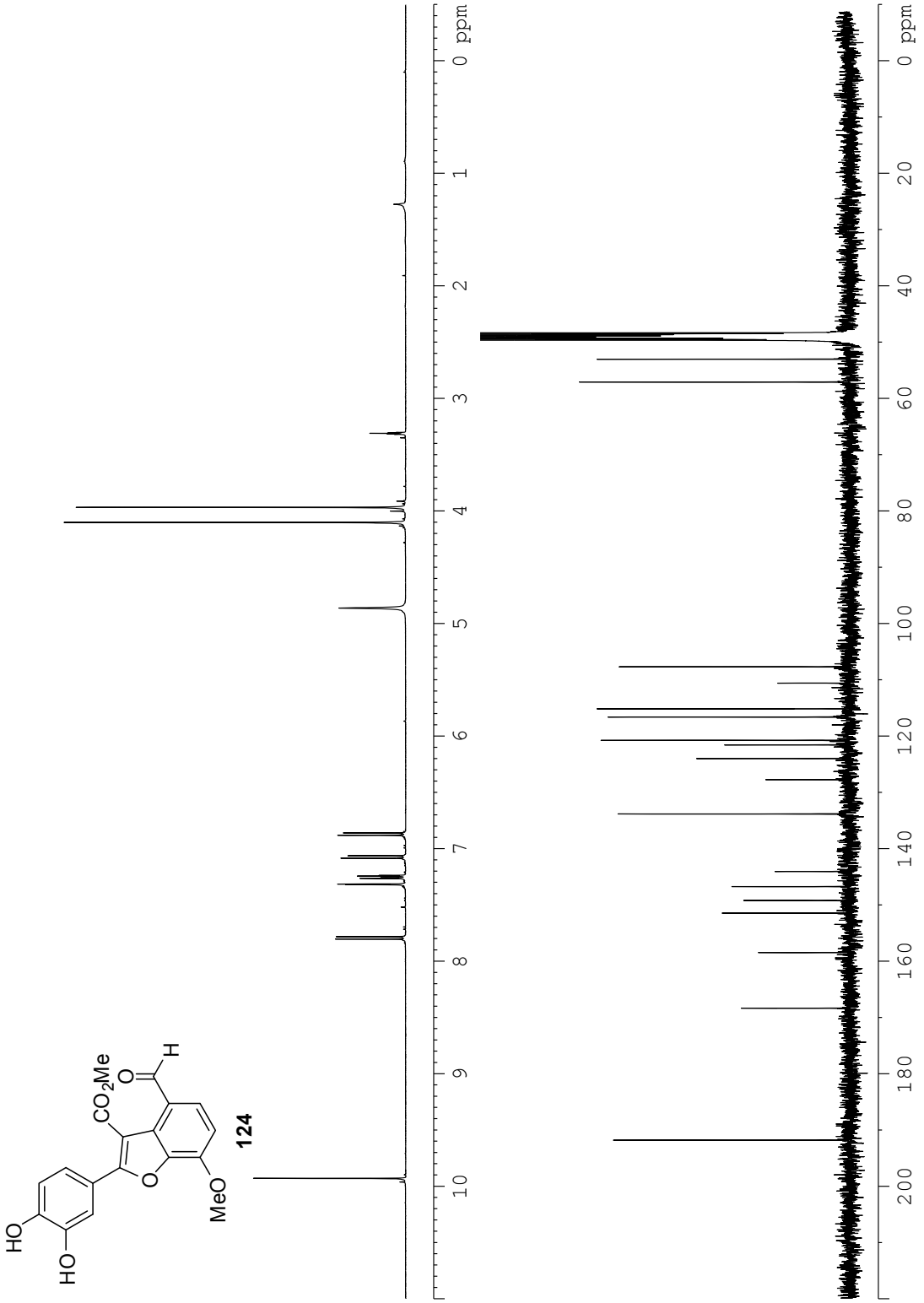
Methyl 2-(1',3'-benzodioxol-5'-yl)-4-formyl-7-hydroxy-1-benzofuran-3-carboxylate (123)

^{1}H NMR (400 MHz, CD_3OD), ^{13}C NMR (100 MHz, CD_3OD)



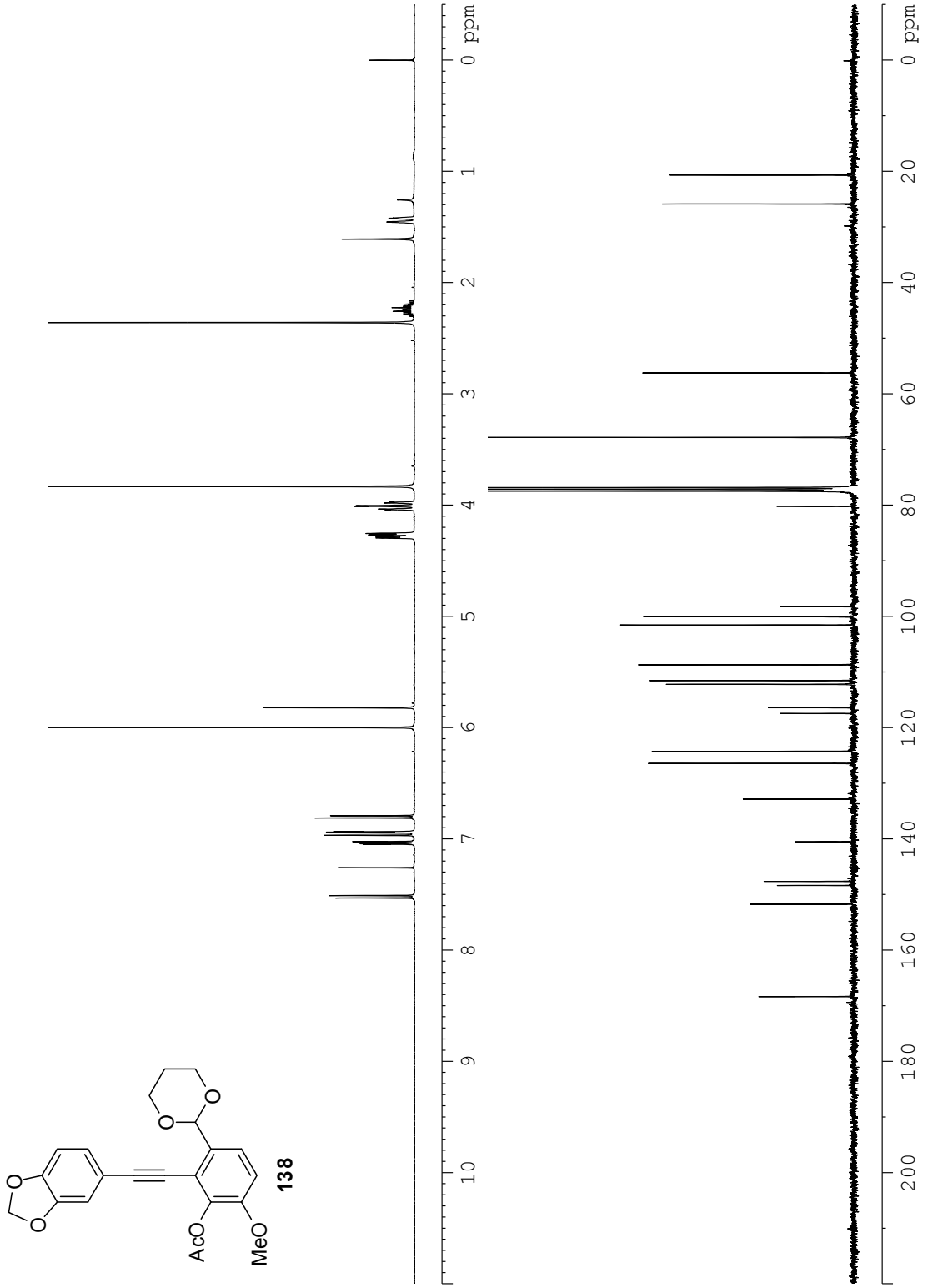
Methyl 2-(3',4'-dihydroxyphenyl)-4-formyl-7-methoxy-1-benzofuran-3-carboxylate (124)

^{1}H NMR (400 MHz, CD_3OD), ^{13}C NMR (100 MHz, CD_3OD)

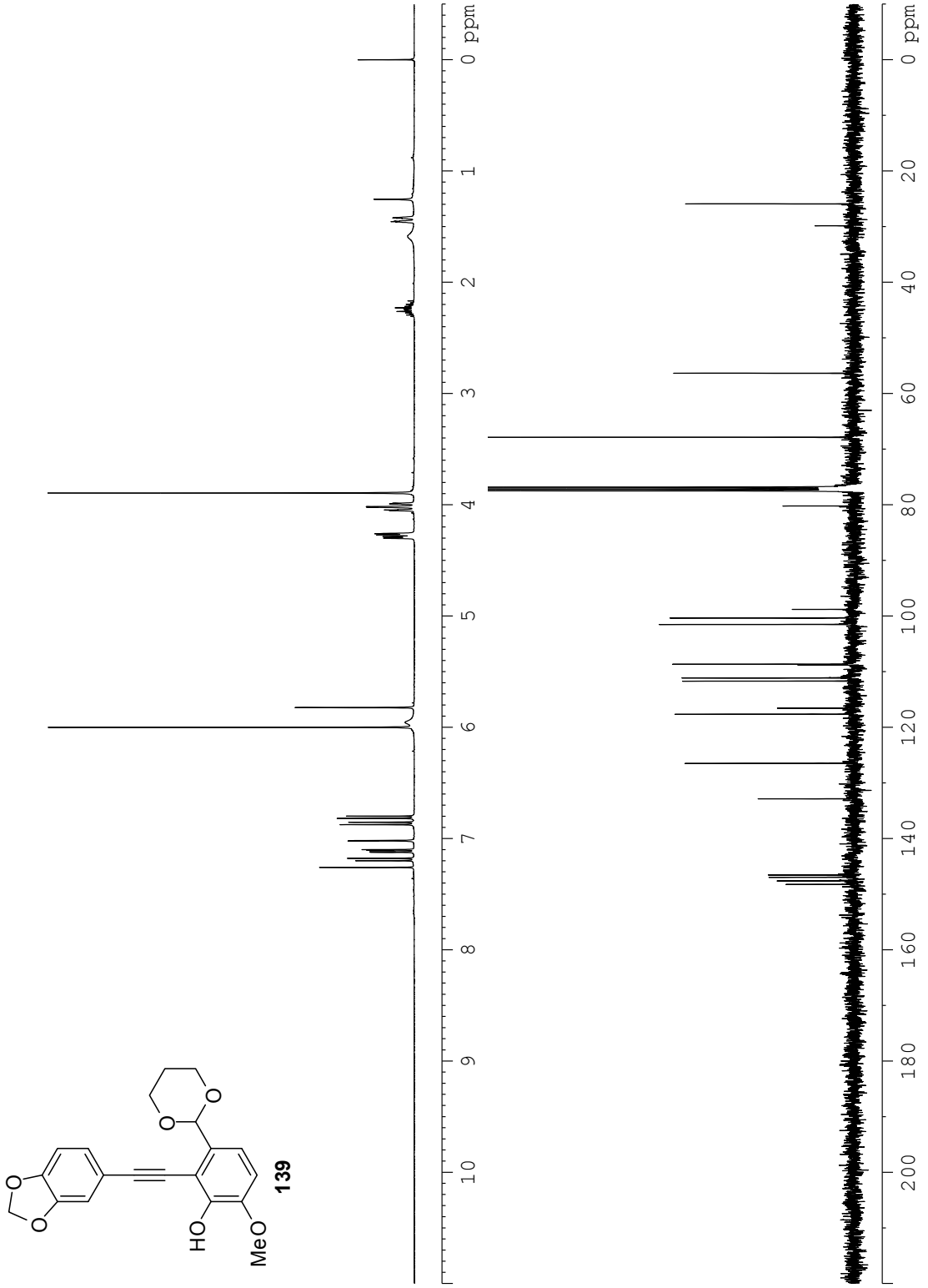


2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenyl acetate (138)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

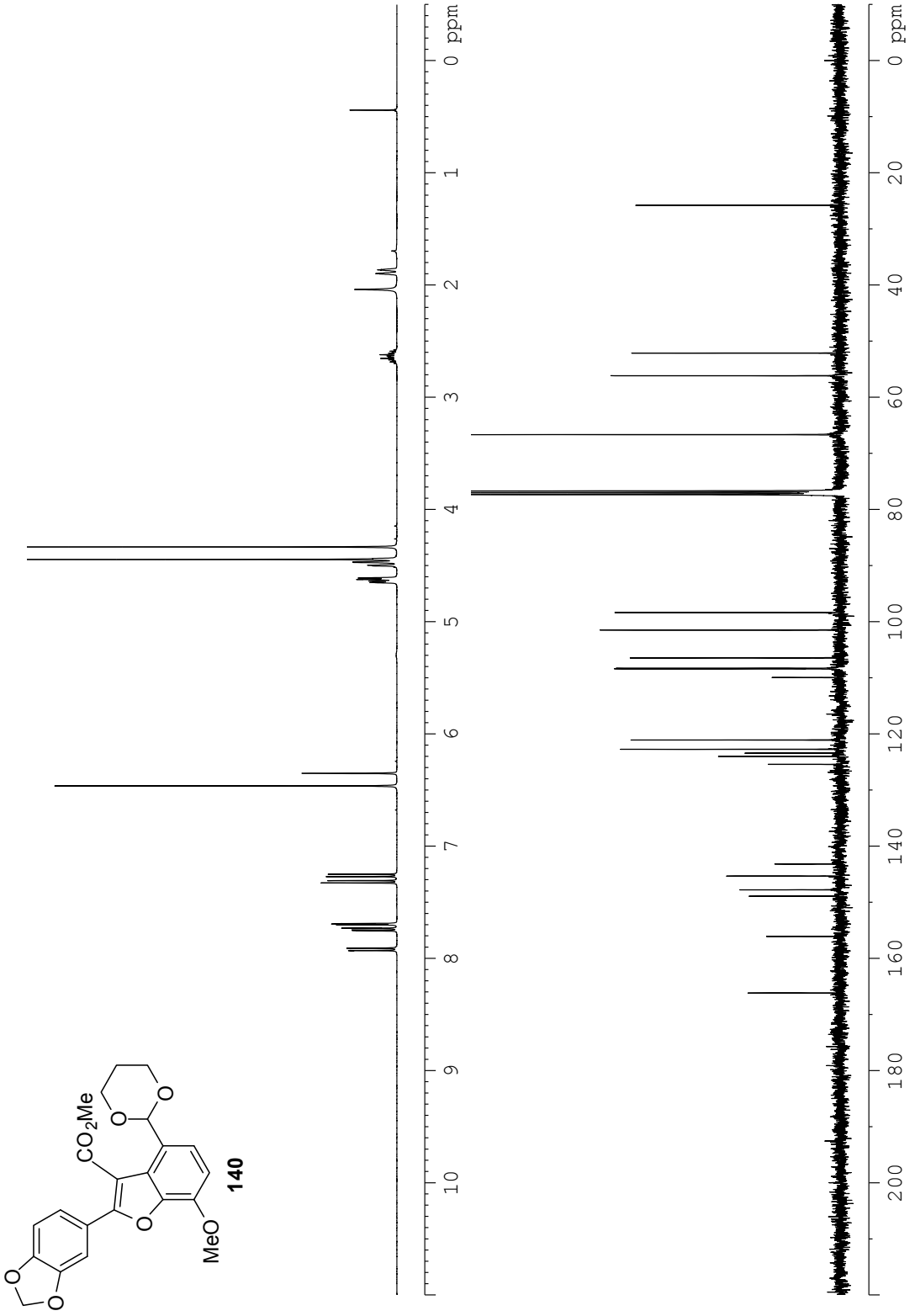


2-(1',3'-Benzodioxol-5'-ylethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenol (139)
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



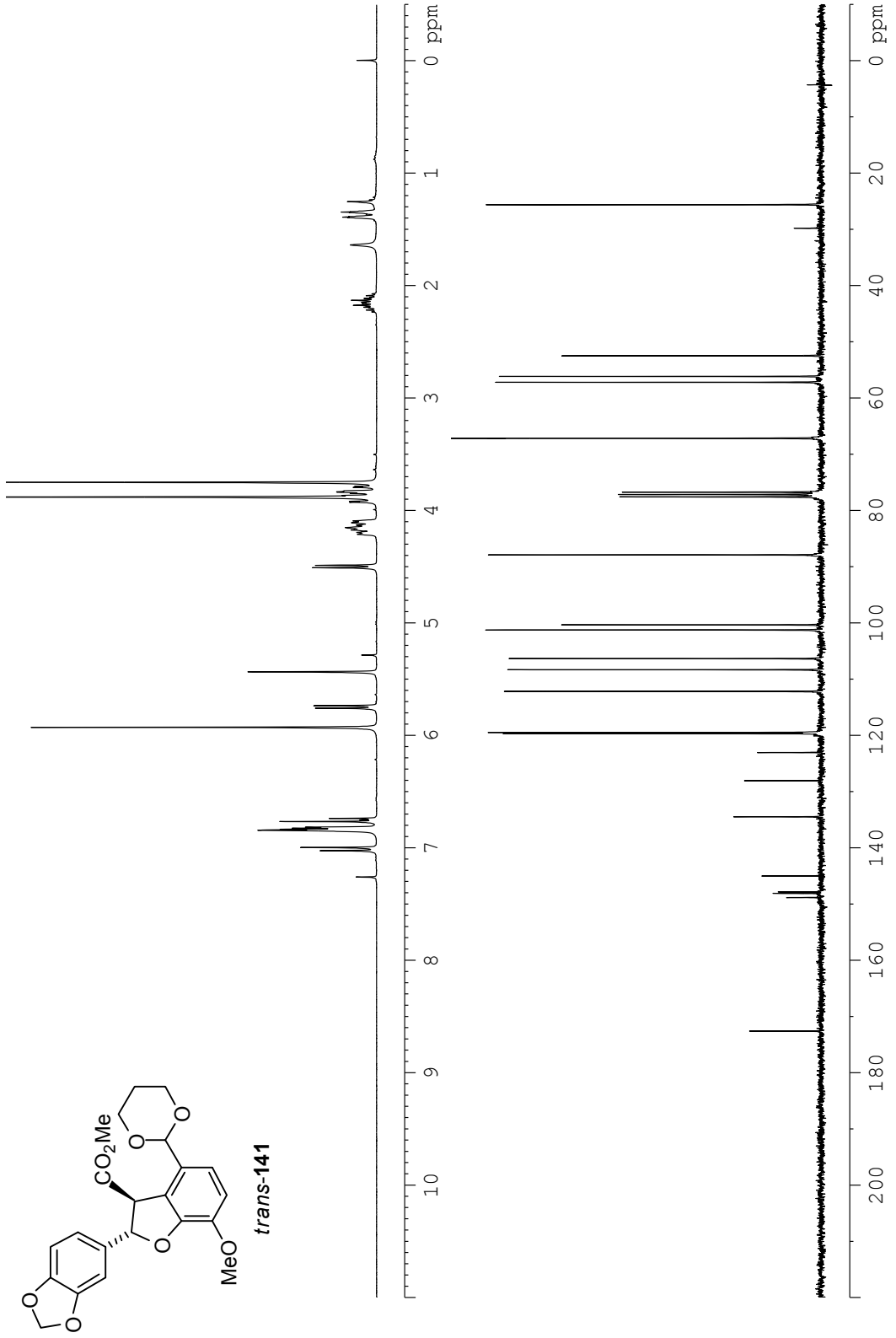
Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(1'',3''-dioxan-2''-yl)-7-methoxybenzofuran-3-carboxylate (140)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



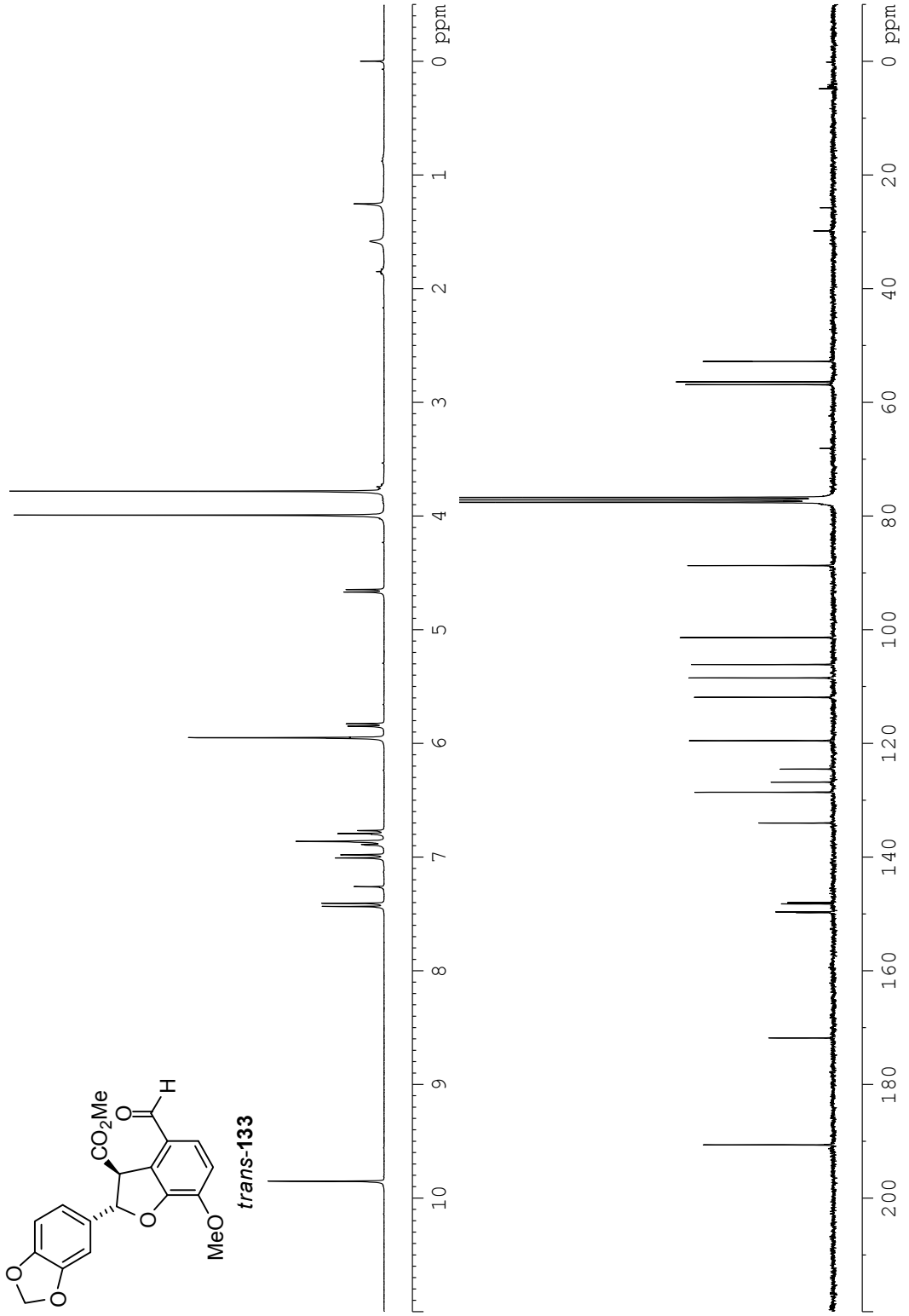
Methyl 2-(1',3'-benzodioxol-5'-yl)-4-(1'',3''-dioxan-2''-yl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-141)

^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$)



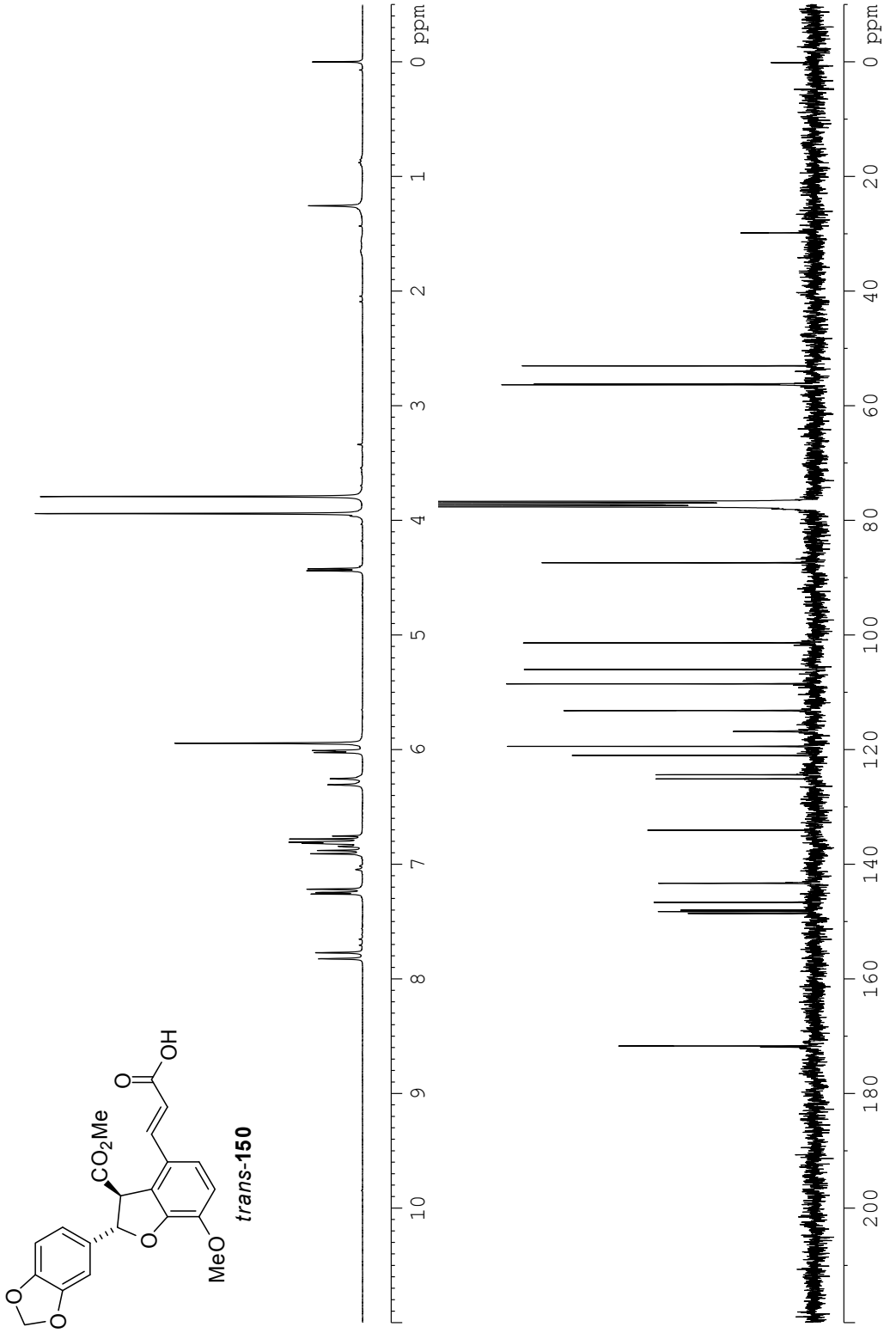
Methyl 2-(1',3'-benzodioxol-5'-yl)-4-formyl-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-133)

^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$)



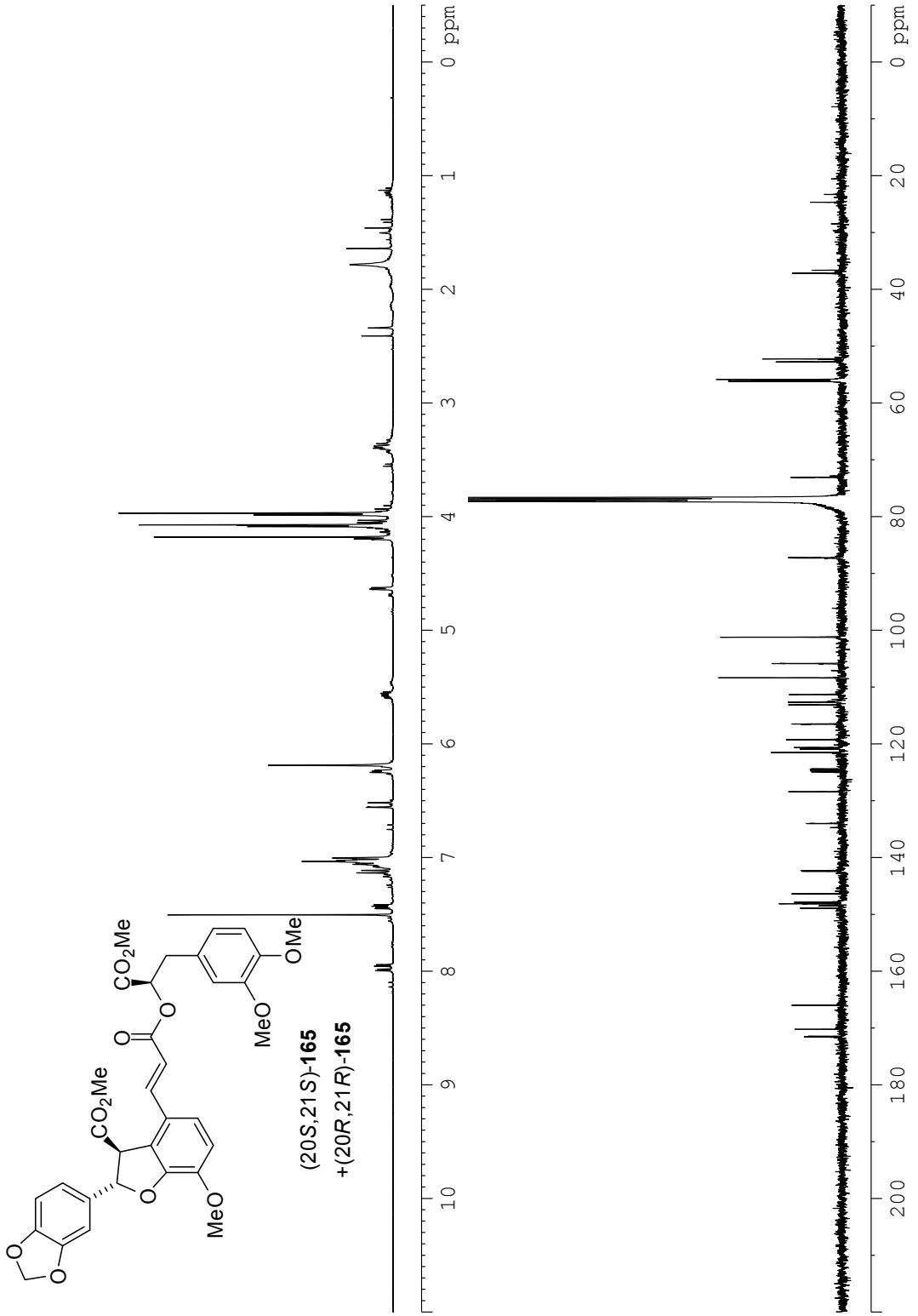
(2*E*)-3-[2'-(1'',3''-benzodioxol-5''-yl)-7'-methoxy-3'-(methoxycarbonyl)-2',3'-dihydro-1'-benzofuran-4'-yl]prop-2-enoic acid (*trans*-150)

^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$)



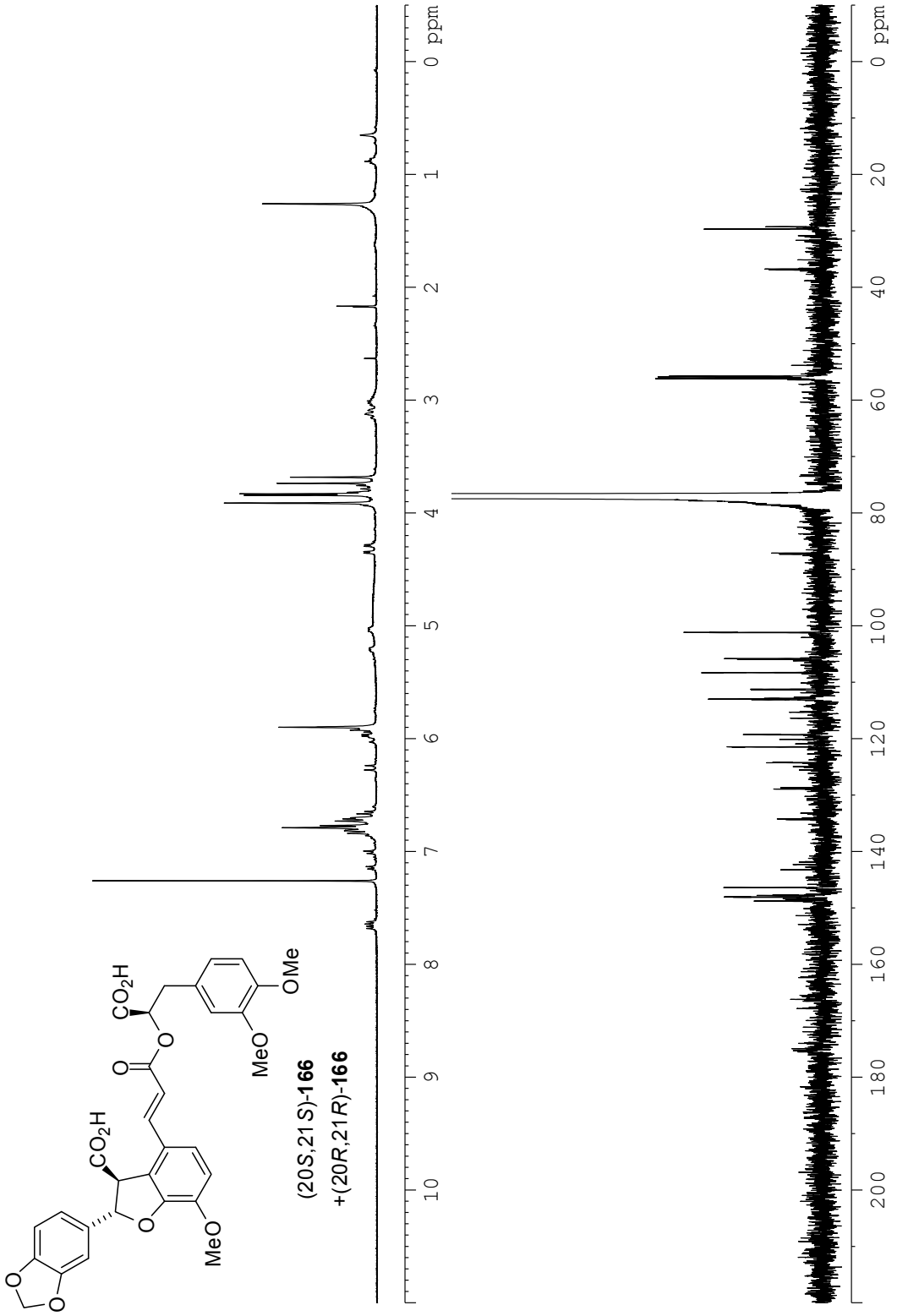
(20*R*,21*R*)-165 and (20*S*,21*S*)-165

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

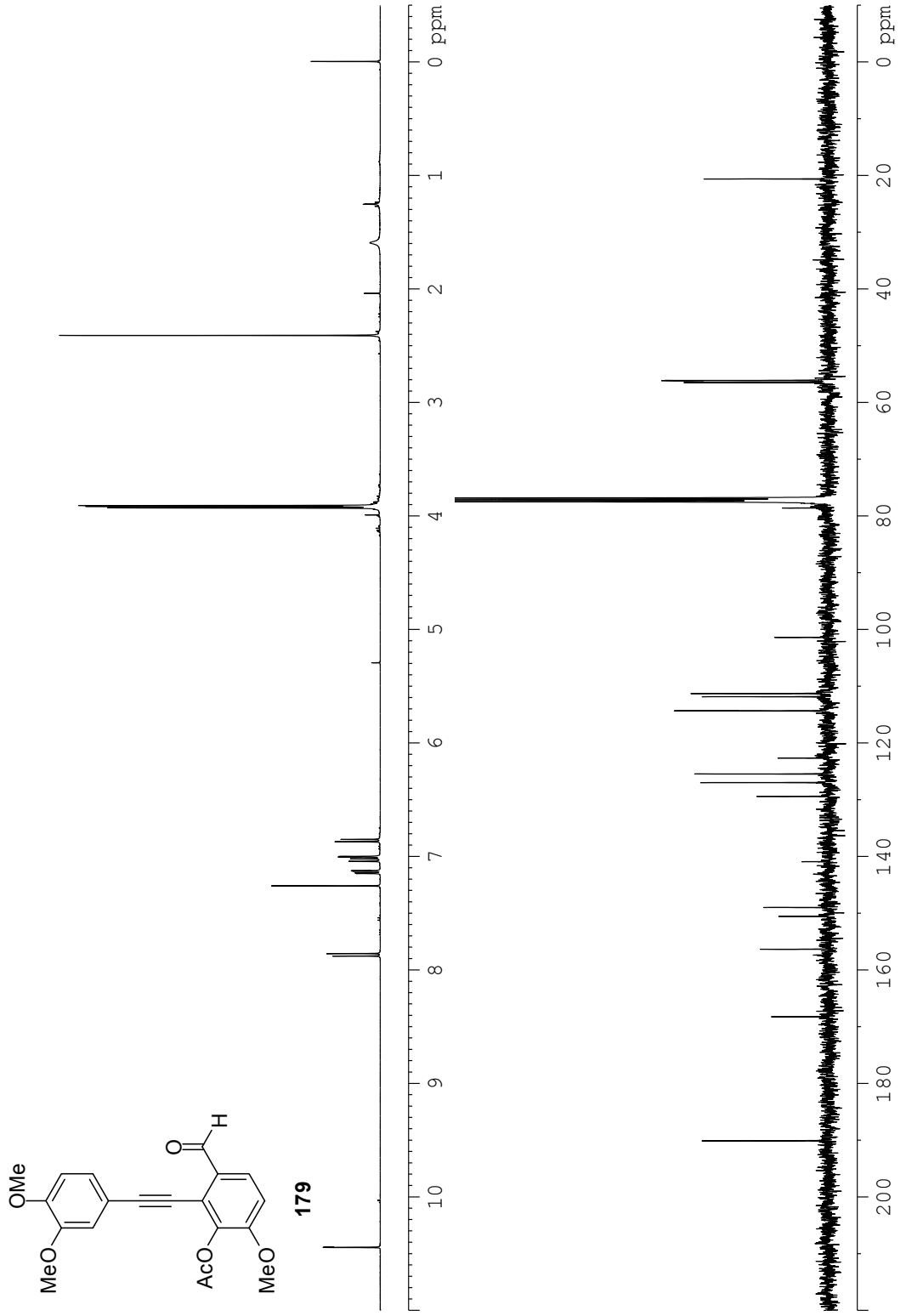


(20*R*,21*R*)-166 and (20*S*,21*S*)-166

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

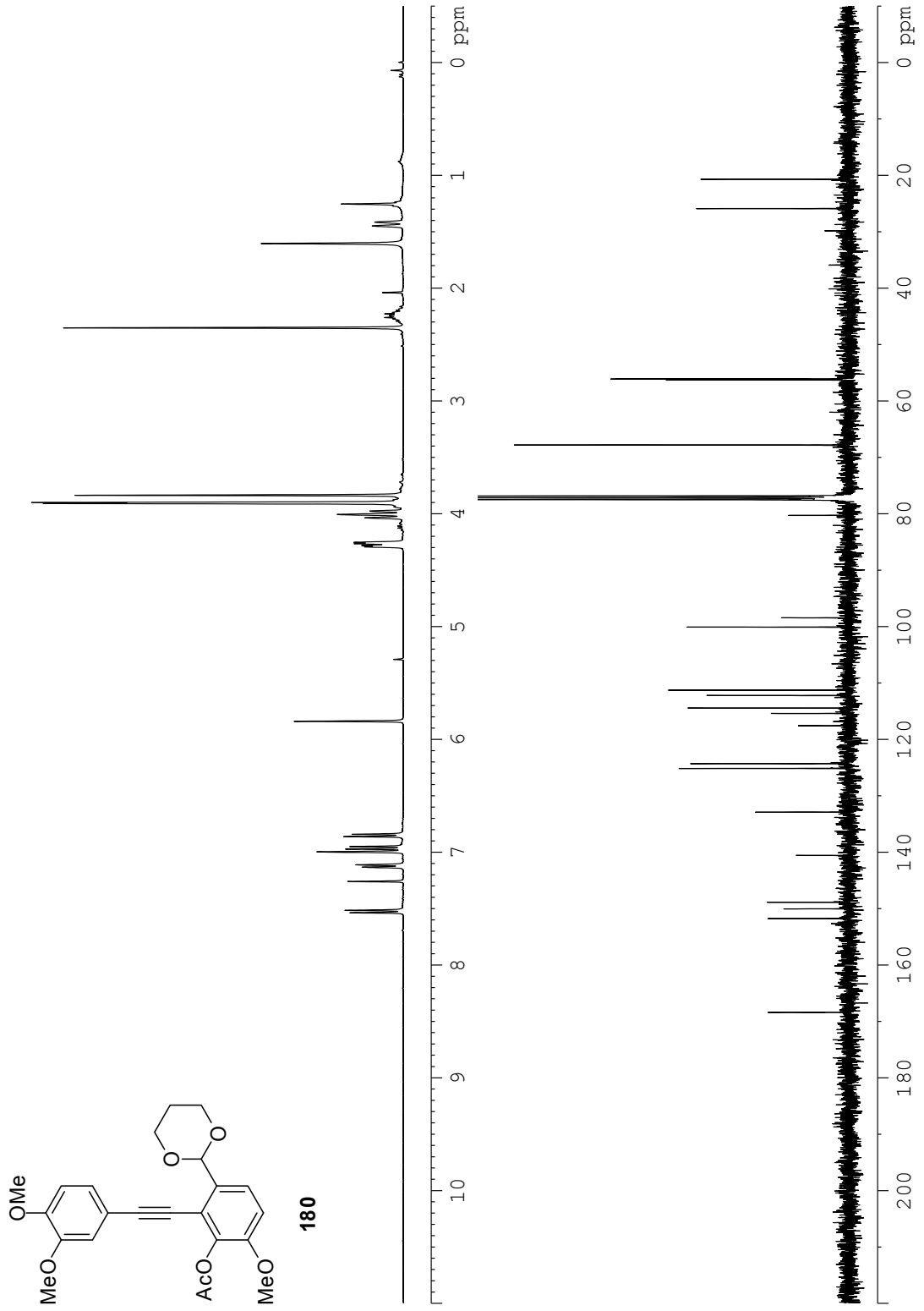


2-((3',4'-Dimethoxyphenyl)ethynyl)-3-acetoxy-4-methoxybenzaldehyde (179)
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

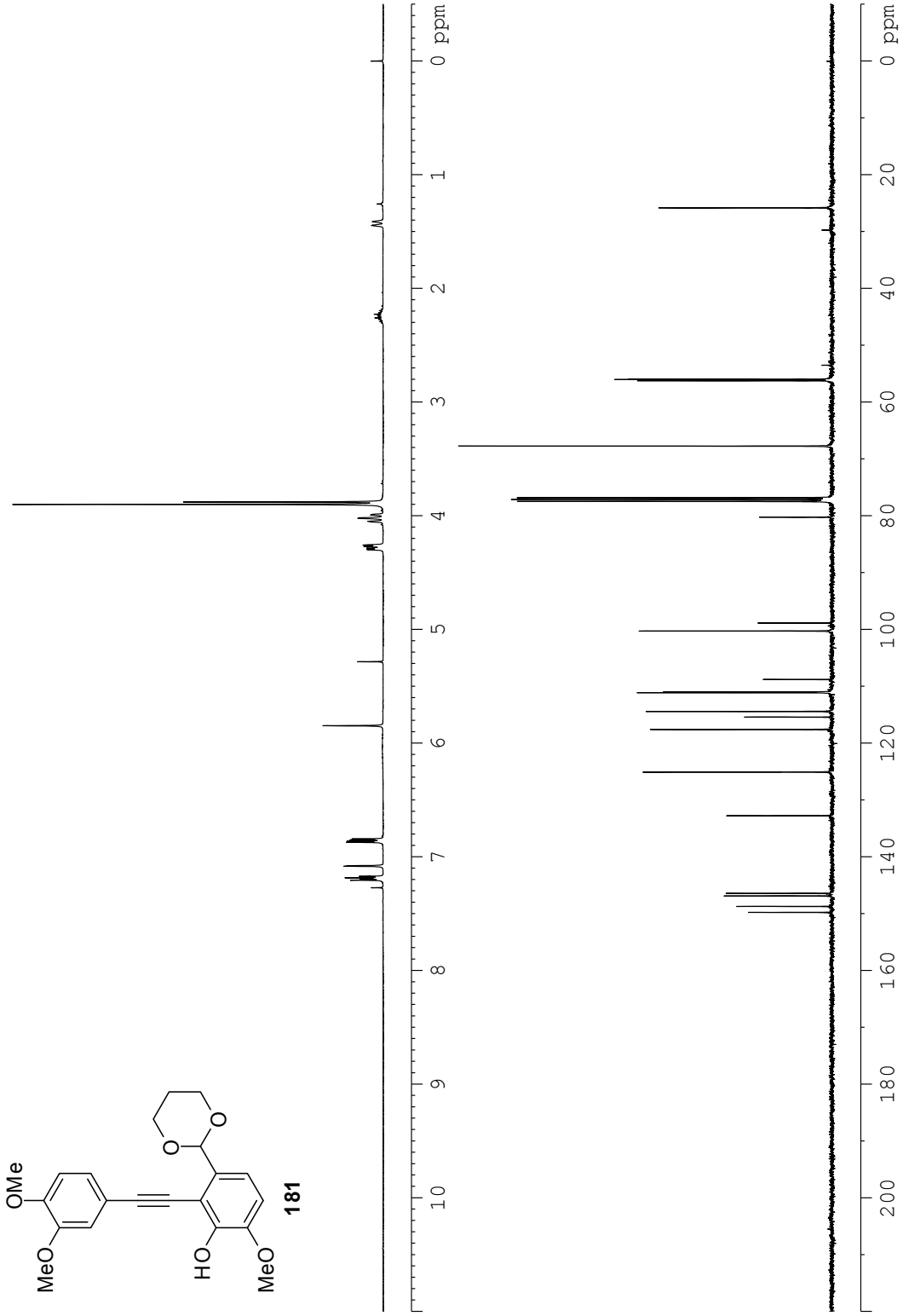


2-((3',4'-Dimethoxyphenyl)ethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenyl acetate (180)

^{1}H NMR (400 MHz, CDCl3), ^{13}C NMR (100 MHz, $CDCl_3$)

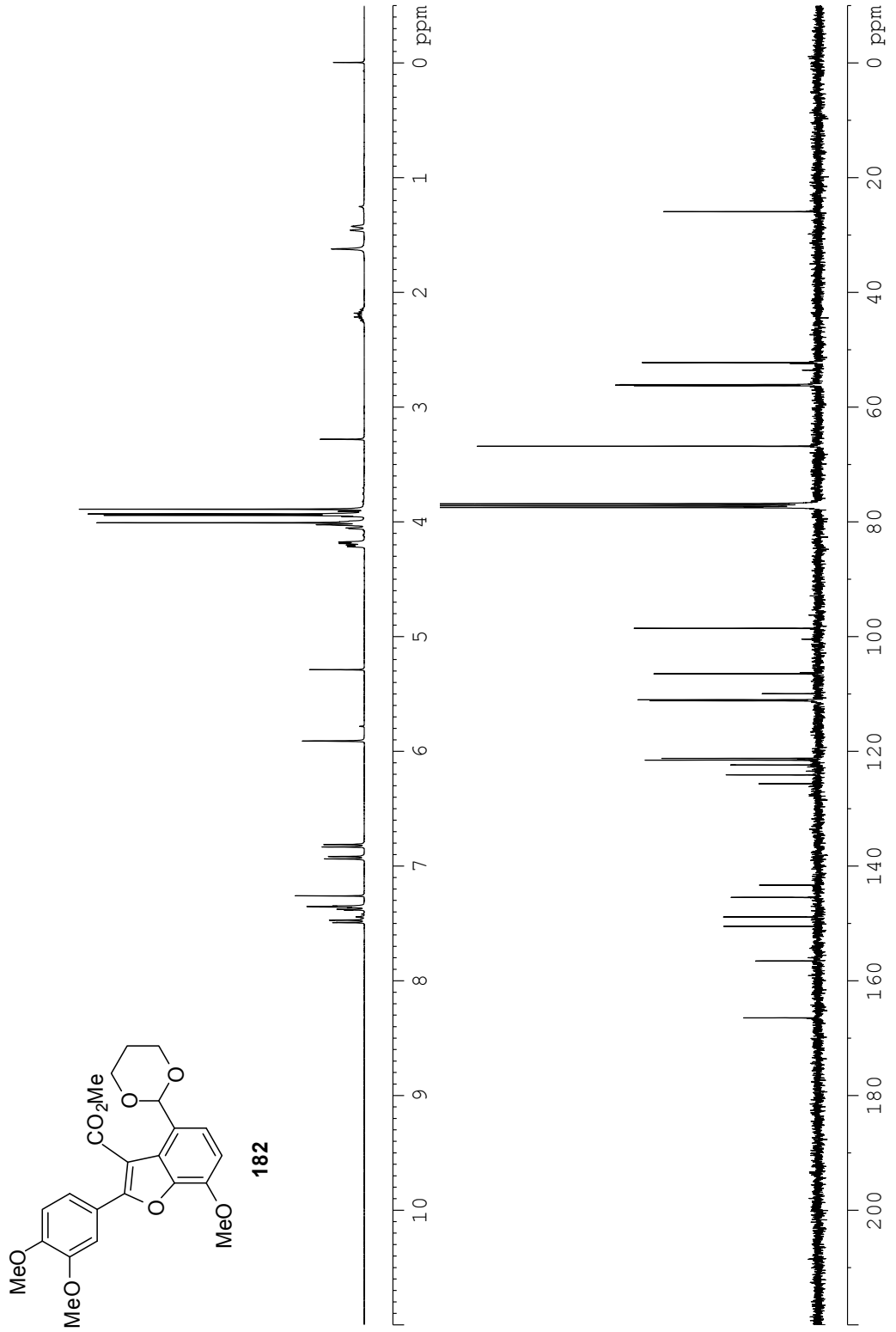


2-((3',4'-Dimethoxyphenyl)ethynyl)-3-(1'',3''-dioxan-2''-yl)-6-methoxyphenol (181)
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



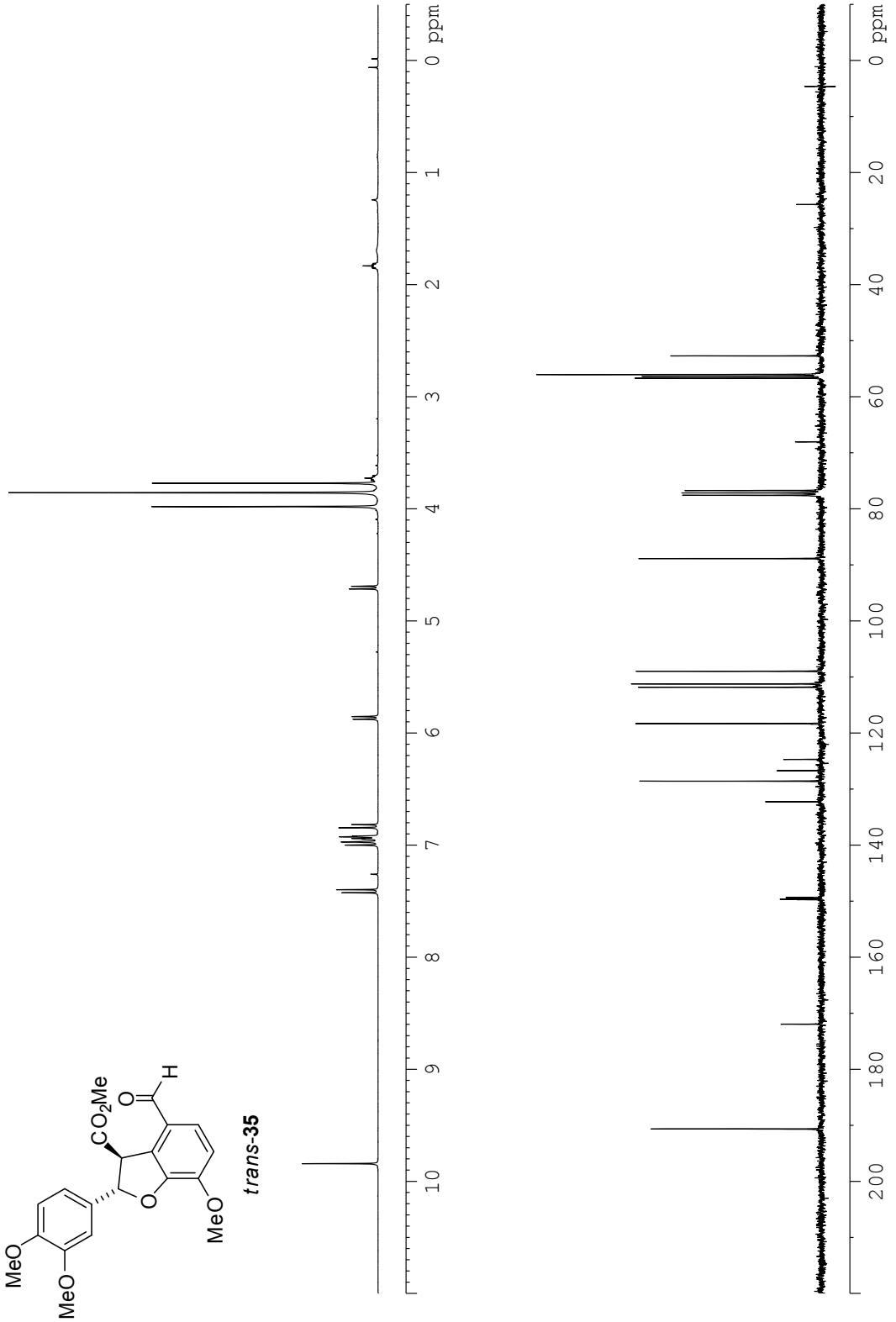
Methyl 2-(3',4'-dimethoxyphenyl)-4-(1'',3''-dioxan-2''-yl)-7-methoxybenzofuran-3-carboxylate (182)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



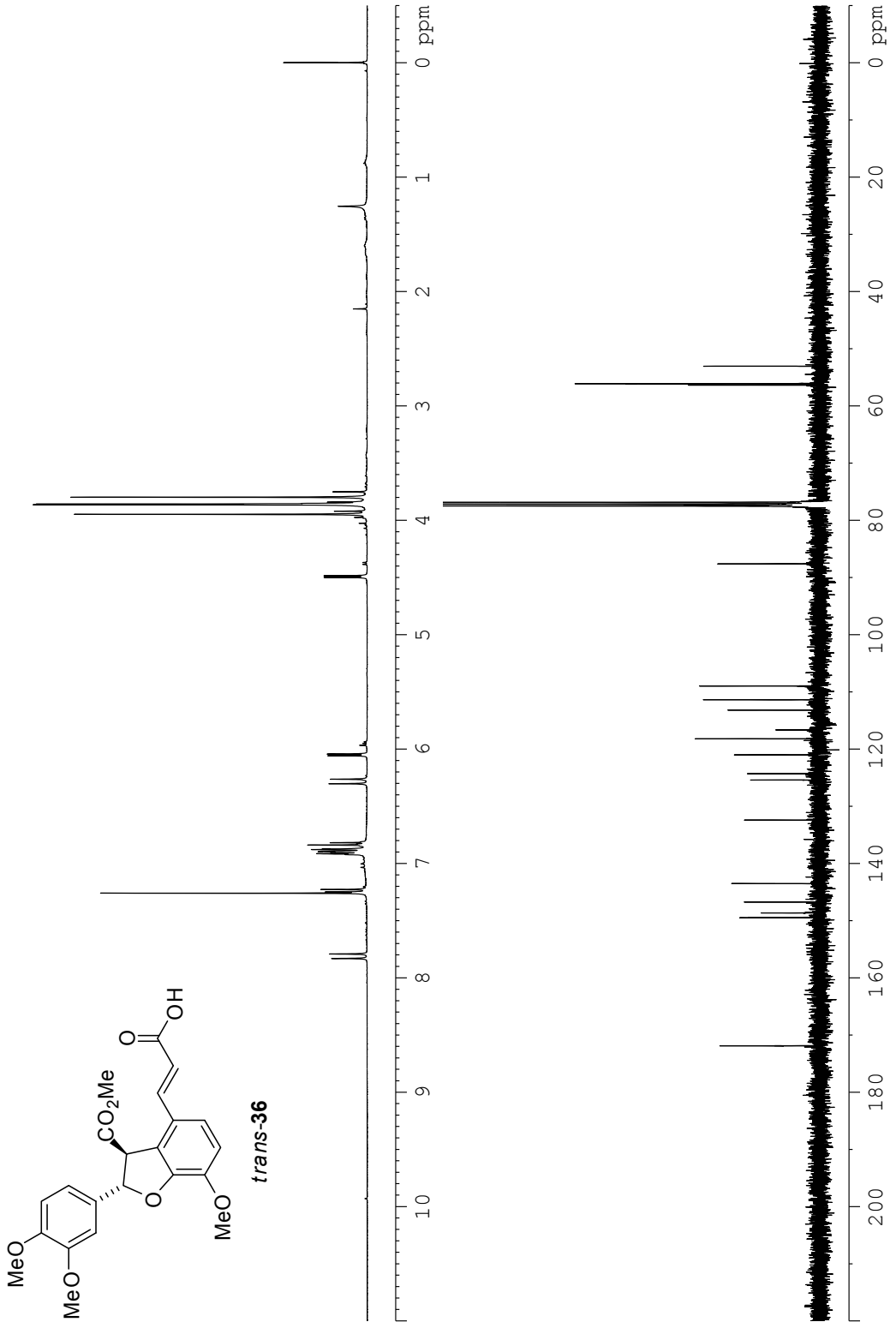
Methyl 2-(3',4'-dimethoxyphenyl)-4-formyl-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-35)

^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$)



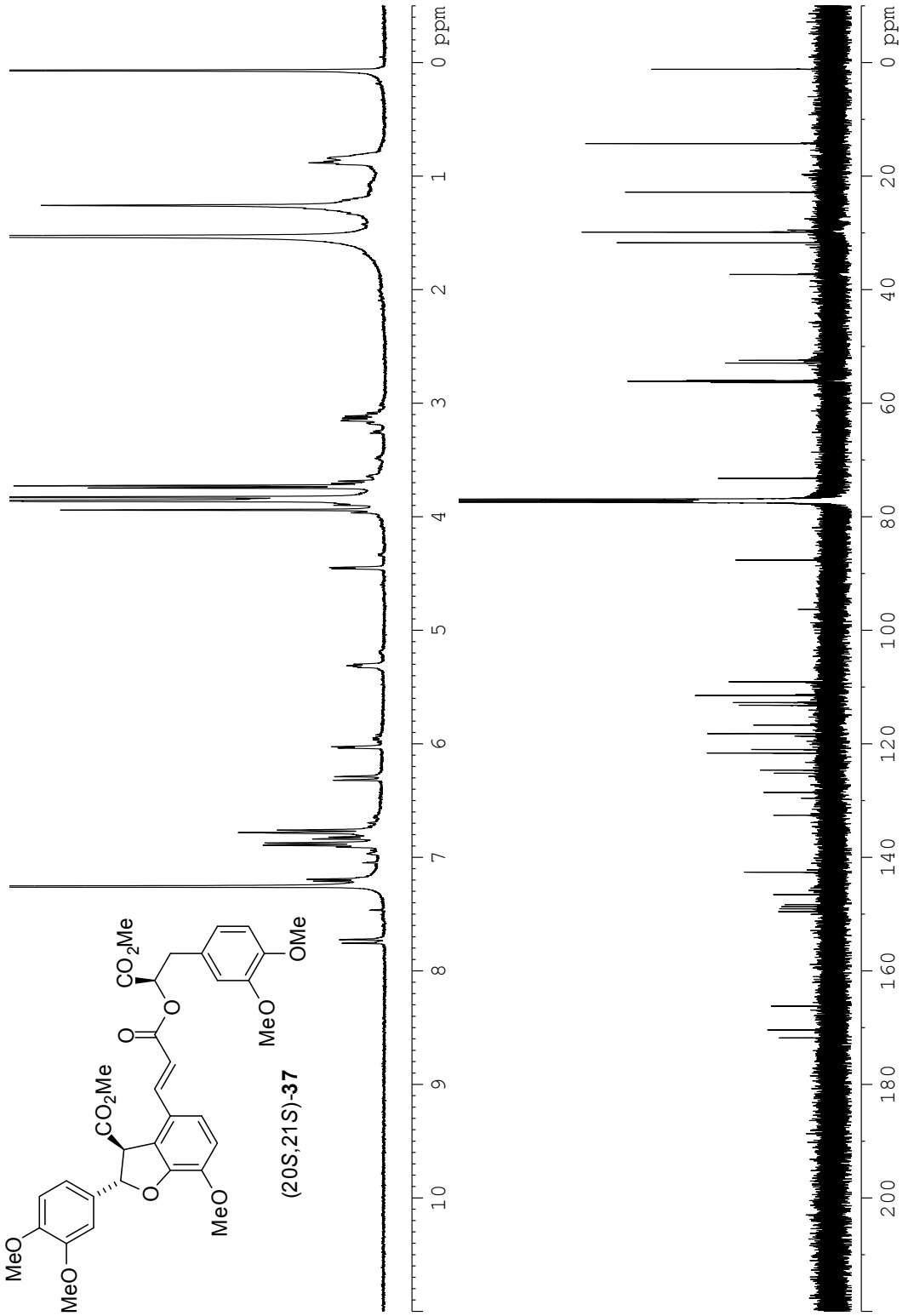
(2*E*)-3-[2'-(3'',4''-Dimethoxyphenyl)-7'-methoxy-3'-(methoxycarbonyl)-2',3'-dihydro-1'-benzofuran-4'-yl]prop-2-enoic acid (*trans*-36)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



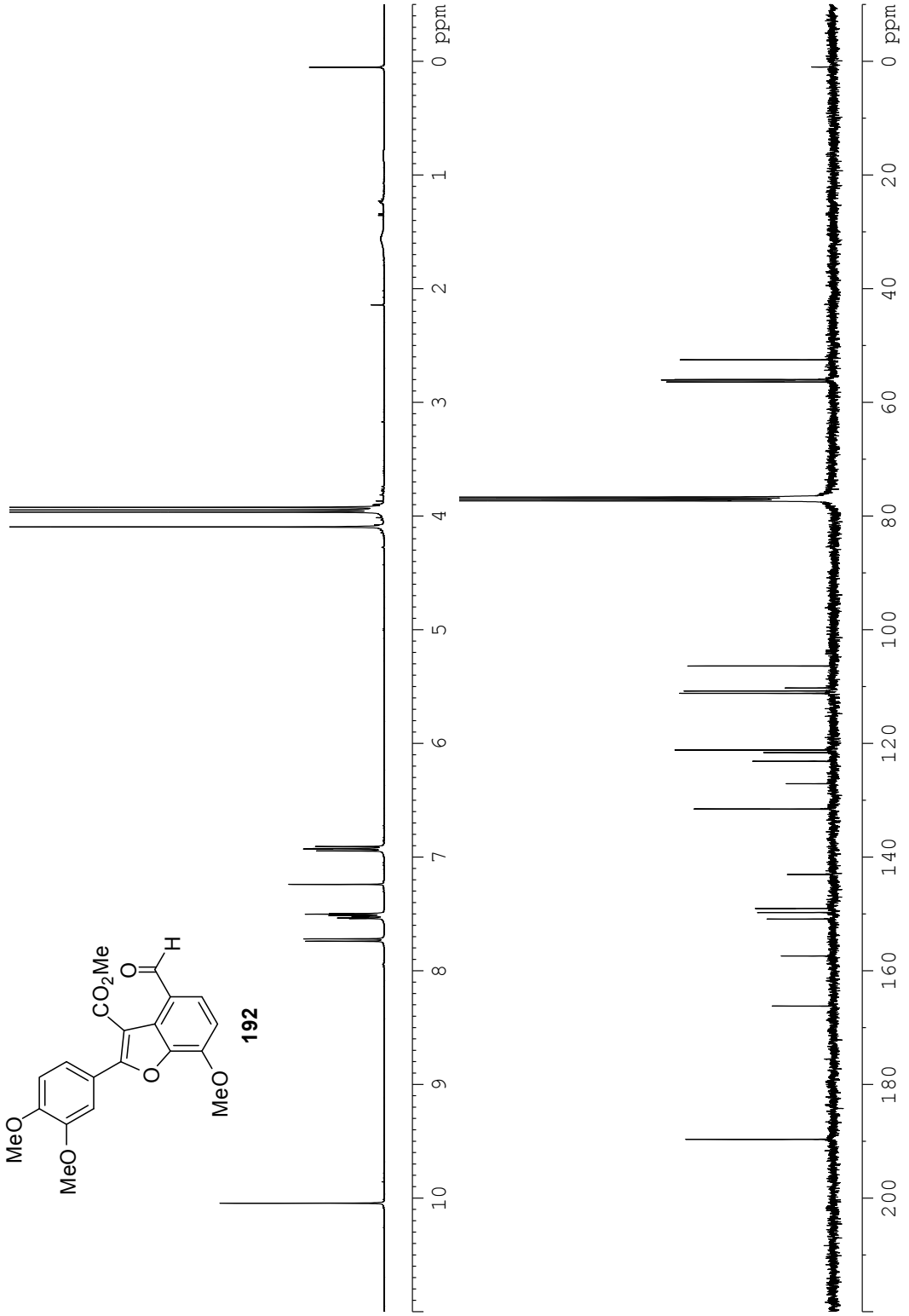
Heptamethyl lithospermate (20*S*,21*S*)-37

^{1}H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (126 MHz, $CDCl_3$)



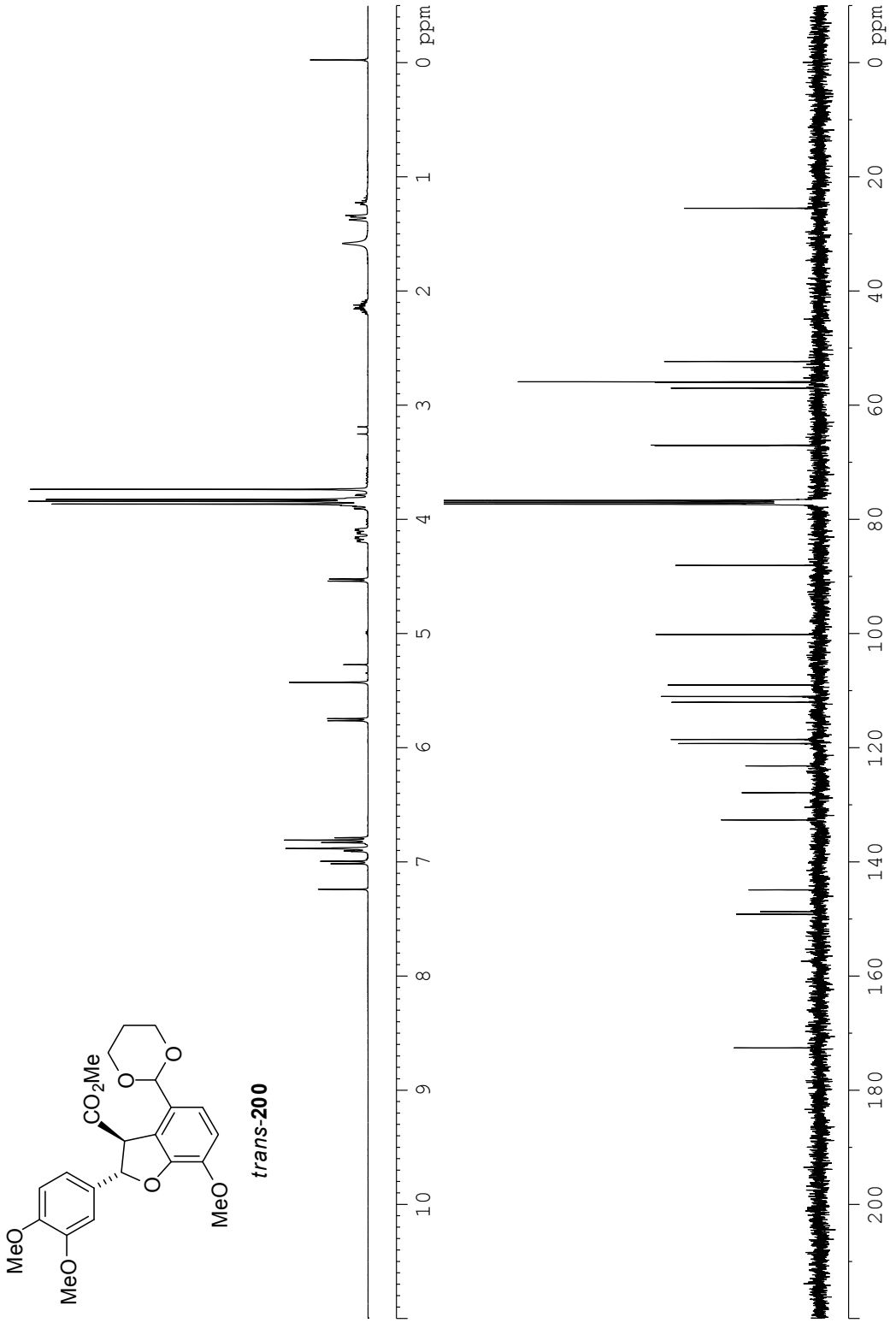
Methyl 2-(3',4'-dimethoxyphenyl)-4-formyl-7-methoxy-1-benzofuran-3-carboxylate (192)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



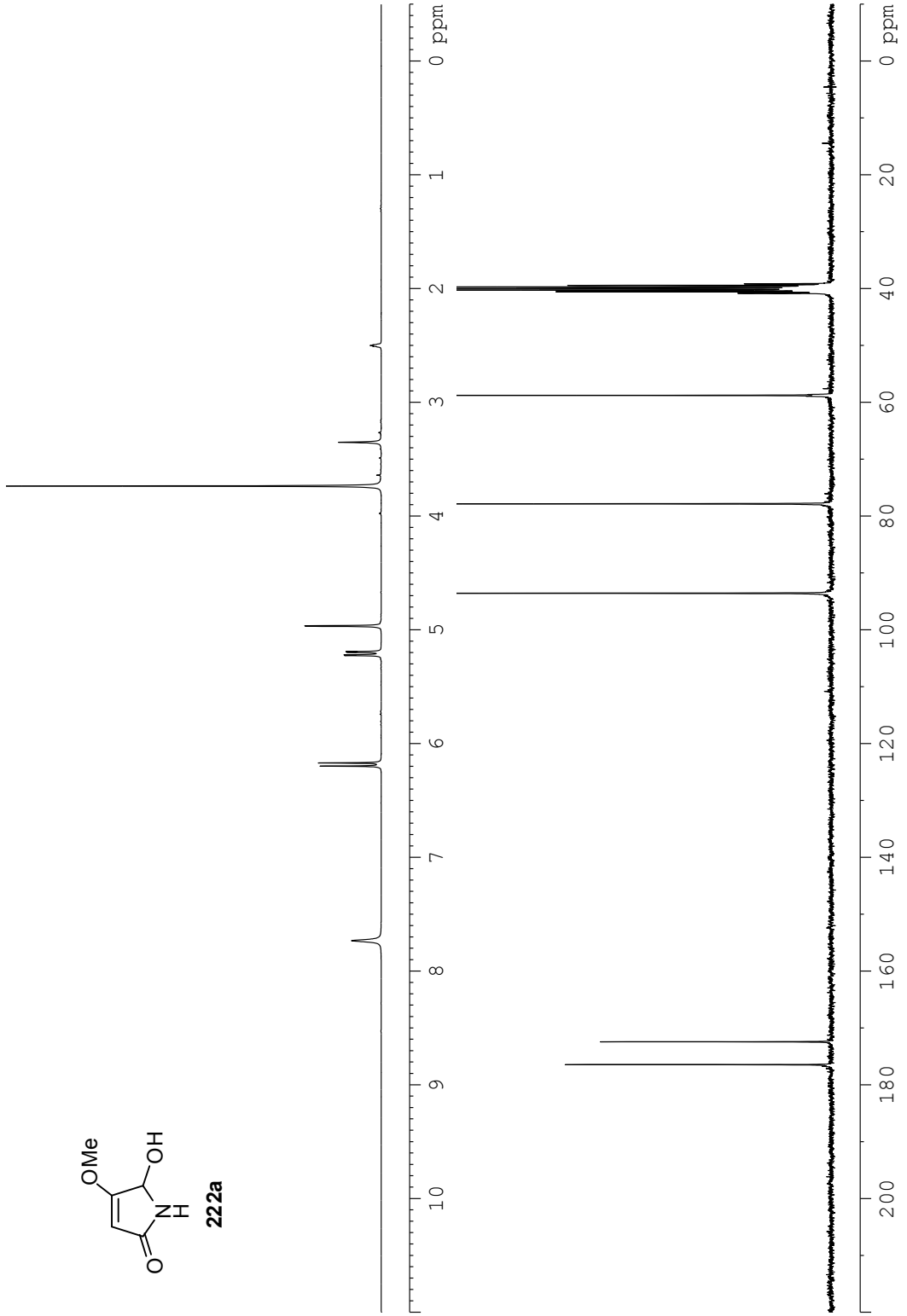
Methyl 2-(3',4'-dimethoxyphenyl)-4-(1'',3''-dioxan-2''-yl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (*trans*-200)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)



2-Hydroxy-3-methoxy-1,2-dihydro-2*H*-pyrrol-5-one (222a)

^{1}H NMR (300 MHz, DMSO-d_6), ^{13}C NMR (75 MHz, DMSO-d_6)



2,3-Dimethoxy-1,2-dihydro-2*H*-pyrrol-5-one (232)

^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)