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# **Chapter 6**

**Experimental**

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# 6 Experimental

## 6.1 About this chapter

1. General experimental details are listed in Section 6.2.
2. General procedures are used to describe similar reactions performed with various substrates or conditions. These are listed alphabetically in Section 6.3. Solvent amounts are expressed to form a total reaction volume of 10 ml and the final reaction concentration of the main substrate is expressed as concentration (conc.) in moles per litre (M). The amount of the main substrate is defined as one equivalent (1.0 eq.) and the mole amounts of other reagents are expressed in equivalents relative to the main substrate. The variables: temperature, time, reagents, reagent equivalents, solvents and purification methods are quoted as “specified” or as a range when they are not consistent between all procedures and are specified in Section 6.4.
3. Commercially available reagents that were not purchased were synthesised by the procedures in Section 6.4.1.
4. Experimental procedures for compounds described in Chapters 2 and 3 are listed chronologically in Section 6.4.2. Experimental procedures for compounds described in Chapter 4 are listed similarly in Section 6.4.3.
5. Compound names were generated using Name=Struct within ChemDraw 9.0 Ultra. Pictorial representations and references to atoms within discussion text is based on the numbering within the amino acid backbone as depicted in the Nomenclature section preceding this thesis.

## 6.2 General Details

1. Melting points were determined using a Reichert heating stage with microscope and are uncorrected.

2. Optical rotations were measured using an Optical Activity PolAAR 2001 Automatic polarimeter set at the 589.3 nm sodium D line, in a 0.25 dm cell, at the indicated temperature in the indicated solvent and concentration (c), reported as g solute / 100 ml. Specific rotations,  $\alpha_D$ , are quoted in  $10^{-1} \cdot \text{deg} \cdot \text{cm}^2 \cdot \text{g}^{-1}$ .

3. Infra-red absorption spectra were obtained using a Perkin Elmer 1600 series Fourier Transform Infra-Red (FTIR) spectrometer or a Shimadzu 8400 series FTIR spectrometer and were processed using Shimadzu IRsolution 1.04 software. Compounds were prepared as thin films between 0.5 cm sodium chloride plates seated on a custom made perch in the apparatus. Absorption maxima are expressed as wavenumbers ( $\text{cm}^{-1}$ ) and the appearance of bands are described by the abbreviations: br = broad, s = strong, m = medium, w = weak.

4.  $^1\text{H}$  Nuclear magnetic resonance spectra were recorded using a Bruker Avance 200 (200.13 MHz), or a Bruker Avance 300 (300.13 MHz) or a Bruker DPX 400 (400.21 MHz) spectrometer at 300 K unless otherwise specified and were processed using XWIN-NMR version 3.5. Samples were analysed as a solution in the specified solvent. Data are expressed as parts per million (ppm) downfield shift from tetramethylsilane ( $\delta_{\text{TMS}} = 0$ ) using either tetramethylsilane or residual chloroform solvent (7.26 ppm) as an internal reference and are reported as chemical shift ( $\delta$ ), relative integral, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, m = multiplet, q = quartet, quin = quintet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, ddt = doublet of doublets of triplets, dq = doublet of quartets, obs = obscured), coupling constant ( $J$  in Hz) and assignment. All coupling constants and multiplicities reported are apparent. The  $\blacklozenge$  denotes resonances from the minor diastereoisomer that differ from the major diastereoisomer in an inseparable mixture.

5.  $^{13}\text{C}$  Nuclear magnetic resonance spectra were recorded using a Bruker Avance 200 (50.0 MHz), or a Bruker Avance 300 (75.5 MHz) or a Bruker DPX 400

(100.6 MHz) spectrometer with complete proton decoupling at 300 K unless otherwise specified and were processed using XWIN-NMR version 3.5. Samples were analysed as a solution in the specified solvent. Data are expressed as parts per million (ppm) downfield shift from tetramethylsilane ( $\delta_{\text{TMS}} = 0$ ) using deuterated chloroform (77.0 ppm) as an internal reference and are reported as chemical shift ( $\delta$  in ppm). When coupling between a carbon and phosphorus was observed the data are reported as chemical shift ( $\delta$  in ppm), multiplicity (d = doublet), coupling constant ( $^xJ_{\text{PC}}$  in Hz, where x denotes the number of bonds between the coupled atoms) and assignment. All coupling constants and multiplicities are apparent.

6. Low resolution mass spectra were recorded by the Mass Spectrometry Unit at University of Sydney using positive electron impact (+EI) on a Finnigan Polaris Q ion trap mass spectrometer operated at 40 or 70 eV or using electrospray ionization (ESI) in positive (+ESI) or negative mode (-ESI) on a Finnigan LCQ ion trap mass spectrometer. High resolution mass spectra were recorded by the Mass Spectrometry Unit at University of Queensland using +EI on a Kratos MS25 RFA mass spectrometer operated at 70 eV in magnetic scan using perfluorokerosene (PFK) as standard or by the Mass Spectrometry Unit at Australian National University, Canberra using ESI on a 4.7T Bruker Apex II Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer or by the Mass Spectrometry Unit at University of New South Wales using ESI on a 7T Bruker Apex FTICR. Major fragments are quoted as mass to charge ratio (assignment where possible and relative intensity).

7. Analytical high performance liquid chromatography (HPLC) was carried out using a Waters Associates system consisting of a Millipore 510 pump, a Millipore U6K injector, a 2487 dual wavelength absorbance detector at 254 and 270 nm and a 410 differential refractometer. Data were acquired and processed using Empower software. Separation was carried out using the indicated solvents at a flow rate of 1 ml / min on a Jones Zorbax Sil-0201 analytical column with a length of 250 mm, an internal diameter of 4.6 mm and particle size of 5  $\mu\text{m}$ .

8. Preparative HPLC was carried out using a Waters Associates system consisting of a Model 510 pump, a Millipore U6K injector, a 490E programmable multi-wavelength detector at 254 nm and a Millipore R403 differential refractometer. Data were recorded and processed using Empower software.

Separation was carried out using the indicated solvents with a flow rate of 13.5 ml / min and pressure of 1000 psi on a RTI Zorbax Sil preparative column with a length of 250 mm, an internal diameter of 21.2 mm and particle size of 7  $\mu\text{m}$ . Retention time ( $t_R$ ) is reported as the time corresponding to the maximum absorbance for the peak detected at 254 nm.

9. Analytical thin layer chromatography (TLC) was performed using 0.2 mm thick, aluminium-backed, pre-coated silica gel plates (Merck Silicagel 60 F<sub>254</sub>). Compounds were visualised by short and long wavelength ultra-violet fluorescence and by staining with a mixture of phosphomolybdic acid and ceric sulfate in sulfuric acid or a solution of ninhydrin in sulfuric acid or an acidified ethanolic solution of anisaldehyde.

10. Flash chromatography was performed using Merck Silicagel 60 (230 – 400 mesh ASTM), under a positive pressure of nitrogen, with the indicated solvents. Solvent compositions were mixed volume per volume (v/v) as specified.

11. Evaporation or concentration under reduced pressure refers to evaporation using a rotary evaporator connected to a water aspirator. Removal of residual solvent when necessary was achieved by evacuation (0.1 – 0.01 mm Hg) with a high stage oil sealed vacuum pump.

12. All solvents and reagents were dried and purified when necessary according to procedures outlined by Perrin and Armarego<sup>63</sup> or Leonard, Lygo and Proctor.<sup>64</sup> Commercial *n*-butyl lithium in hexanes was titrated against 2-propanol in tetrahydrofuran using 2,2'-bipyridyl as an indicator. "Hexanes" refers to hexanes (b.p. 65 – 69 °C) and "brine" refers to saturated aqueous sodium chloride solution.

13. Moisture sensitive reactions were carried out in oven dried glassware under a dry inert atmosphere of nitrogen or argon. Powdered, 5 Å molecular sieves were activated in a muffle oven at 500 °C for 3 days and allowed to cool under desiccation before use. Reaction temperatures were controlled using dry ice : acetone (-78 °C), ice : water (0 – 5 °C) cooling baths or sand, oil heating baths (> room temperature).

## 6.3 General Procedures

### Alkene isomerisation:

To a solution of alkene (1.0 eq., conc. 0.040 – 0.080 M) in benzene (10 ml) was added thiophenol (0.48 – 1.0 eq.) and AIBN (0.10 eq.). The reaction was heated at 85 °C for time<sub>A</sub>, at room temperature for time<sub>B</sub> and was concentrated under reduced pressure to give the crude product. Purification was performed as specified.

### Asymmetric Aminohydroxylation:

A solution of sodium hydroxide (3.2 eq.) in water (5.0 ml) was added to a solution of *tert*-butyl carbamate (3.0 eq.) in propanol (2.0 ml) and 1,3-dichloro-5,5-dimethylhydantoin (2.0 eq.) was added. The suspension was stirred until clear and a solution of ligand (0.070 eq.) in propanol (1.5 ml) was added. A solution of alkene (1.0 eq., conc. 0.067 M) in propanol (1.5 ml) was added followed by potassium osmate(VI) dihydrate (0.050 eq.) and the reaction was stirred at room temperature for the specified time. A solution of sodium sulfite (sat. aq., 10 ml) was added and the reaction was stirred for 1 h. Brine (10 ml) was added and the crude product was extracted into ethyl acetate (3 x 20 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give crude product. The excess of *tert*-butyl carbamate was removed by sublimation under high vacuum. Purification was performed as specified.

### Asymmetric Dihydroxylation:

Potassium hexacyanoferrate(III) (3.0 eq.), potassium carbonate (3.2 eq.) and sodium hydrogen carbonate (3.2 eq.) were combined and added to a mixture of *tert*-butyl alcohol (4.5 ml) and water (5.0 ml). The mixture was stirred until homogeneous. Ligand (0.060 eq.) was added followed by potassium osmate(VI) dihydrate (0.010 eq.) and methanesulfonamide (3.2 eq.). The mixture was stirred until homogeneous and was cooled to 0 °C. The biphasic reaction mixture was added to a solution of alkene (1.0 eq., conc. 0.082 M) in *tert*-butyl alcohol (0.50 ml)

at room temperature. The reaction mixture was stirred at room temperature (~17 °C) for 17 h. Sodium sulfite solution (sat. aq., 20 ml) was added and the reaction was stirred for 2 h. The crude product was extracted into ethyl acetate (3 x 30 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

### **Bromine substitution:**

To a stirring suspension of alcohol (1.0 eq., conc. 0.55 M) in diethyl ether (5.0 ml) at 0 °C, was added drop-wise *via cannula* a solution of phosphorus tribromide (0.50 eq.) in diethyl ether (5.0 ml). The suspension was allowed to slowly warm to 20 °C over 1 h. Water (20 ml) was added and the crude product was extracted into dichloromethane (3 x 30 ml). The combined organic layers were washed with sodium hydrogen carbonate solution (sat. aq., 15 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give pure product which was used immediately in subsequent reactions.

### **Cross metathesis olefination:**

A solution of alkene (1.0 eq., conc. 0.10 M) in dichloromethane (3.0 ml) was transferred *via cannula*, to a stirring solution of tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride (0.080 eq.) and acrylate (2.4 eq.) in dichloromethane (5.0 ml), washing with dichloromethane (2 x 1.0 ml). The solution was heated at reflux under an atmosphere of nitrogen for the specified time, allowed to cool and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

### **Dess-Martin oxidation:**

Dess-Martin periodinane **172** (1.2 eq.) was added to a solution of alcohol (1.0 eq., conc. 0.10 M) in dichloromethane (10 ml). The white suspension was stirred at room temperature for the specified time. A mixture of sodium hydrogen carbonate solution (sat. aq., 10 ml) and sodium thiosulfate solution (sat. aq., 2.5 ml) was added and the reaction was stirred vigorously for 1 h. The crude

product was extracted into dichloromethane (3 x 25 ml) and the combined organic layers were washed with a mixture of sodium hydrogen carbonate solution (sat. aq., 5.0 ml) and sodium thiosulfate solution (sat. aq., 1.3 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give the crude product which was used without further purification in subsequent reactions. For the purpose of characterization, flash chromatographic purification was carried out where possible.

### **Ester reduction to alcohol:**

To a solution of ester (1.0 eq., conc. 0.10 M) in dichloromethane (10 ml) at  $-78\text{ }^\circ\text{C}$ , was added drop-wise a solution of diisobutylaluminium hydride (1.0 M in toluene, 2.5 eq.). The reaction was stirred at  $-78\text{ }^\circ\text{C}$  for the specified time. Methanol (0.50 ml) was added drop-wise. A solution of potassium sodium tartrate (sat. aq., 40 ml) was added and the crude product was extracted into dichloromethane (3 x 80 ml). The combined organic layers were washed with brine (40 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

### **Horner-Wadsworth-Emmons olefination:**

To a solution of phosphonate (1.5 eq.) in tetrahydrofuran (5.0 ml) at  $-78\text{ }^\circ\text{C}$ , was added a solution of base (0.50 – 1.6 M in specified solvent, 1.0 – 1.2 eq.). The reaction was stirred at  $-78\text{ }^\circ\text{C}$  for 30 min. A solution of aldehyde (1.0 eq., conc. 0.050 – 0.10 M) in tetrahydrofuran (5.0 ml) was added drop-wise, *via cannula*, and the reaction was stirred at room temperature for the specified time. Ammonium chloride solution (sat. aq., 5.0 ml) was added and the crude product was extracted into ethyl acetate (3 x 5.0 ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

## **Julia olefination:**

### ***Method 1 – Barbier conditions:***

A solution of sulfone (0.87 – 1.1 eq.) and aldehyde (1.0 eq., conc. 0.070 – 0.17 M) in the specified solvent (10 ml) under an atmosphere of argon, was cooled to the specified temperature (T). A solution of base (0.50 – 1.0 M in specified solvent, 1.0 – 1.5 eq.) was added drop-wise and the reaction was stirred at T for 45 min. The reaction was allowed to warm to room temperature and was stirred for the specified time. Ammonium chloride solution (sat. aq., 10 ml) was added and the crude product was extracted into ethyl acetate (3 x 20 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

### ***Method 2 – premetallation conditions:***

To a solution of sulfone (0.80 – 1.5 eq.) in the specified solvent (8.0 ml) at the specified temperature (T), was added drop-wise a solution of base (0.50 – 1.6 M in the specified solvent, 0.93 – 1.4 eq.). The reaction was stirred at T for time<sub>A</sub> and a solution of aldehyde (1.0 eq., conc. 0.080 – 0.15 M) in the specified solvent (2.0 ml) was added. The reaction was allowed to warm to room temperature and was stirred for time<sub>B</sub>. Ammonium chloride solution (sat. aq., 20 ml) was added and the crude product was extracted into ethyl acetate (3 x 30 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

## ***p*-methoxybenzoyl de-protection:**

### ***Method 1 – Using sodium methoxide:***

A solution of sodium methoxide (1.0 M, 0.060 – 1.9 eq.) was added drop-wise to a solution of *p*-methoxybenzoyl ester (1.0 eq., conc. 0.064 – 0.10 M) in dry methanol (10 ml). The reaction was stirred for the specified time at room temperature and ammonium chloride solution (sat. aq., 10 ml) was added. The crude product was extracted into ethyl acetate (3 x 30 ml). The combined organic

layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give crude product. Purification was performed as specified.

**Method 2 – Using caesium carbonate:**

Caesium carbonate (0.50 – 1.0 eq.) and *p*-methoxybenzoyl ester (1.0 eq., conc. 0.050 M) were combined and dissolved in dry methanol (10 ml). The reaction was stirred for the specified time at room temperature and ammonium chloride solution (sat. aq., 10 ml) was added. The crude product was extracted into ethyl acetate (3 x 30 ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give crude product. Purification was performed as specified.

**Mitsunobu reaction:**

To a solution of alcohol (1.0 eq., conc. 0.090 M) in tetrahydrofuran (10 ml) under a nitrogen atmosphere, was added thiazole (1.3 eq.) followed by triphenylphosphine (1.3 eq.). The solution was cooled to 0 °C and diisopropyl azodicarboxylate (1.8 eq.) was added drop-wise. The reaction was stirred at 0 °C for 40 min, allowed to warm to room temperature and stirred for the specified time. The reaction was diluted with ethyl acetate (50 ml) and brine (30 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (60 ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

**MTPA ester formation:**

**Method 1 – Using DCC:**

To a solution of 4-*N,N*-dimethylaminopyridine (0.30 eq.) and MTPA acid (2.1 eq.) in dichloromethane (5.0 ml) was added a solution of 1,3-dicyclohexylcarbodiimide (1.0 M in dichloromethane, 2.8 eq.). The reagent mixture was added *via cannula* to a solution of alcohol (1.0 eq., conc. 0.010 M) in dichloromethane (5.0 ml). The clear reaction was stirred under an atmosphere of nitrogen at room temperature for 2 h 15 min. The reaction became cloudy after

15 min. The suspension was filtered through a pad of celite washing with dichloromethane (3 x 15 ml). The filtrate was concentrated under reduced pressure to give the crude product. Purification was performed as specified.

**Method 2 – Via an acid chloride:**

To a solution of MTPA acid (1.0 eq.) in dichloromethane (5.0 ml) at 0 °C, was added oxalyl chloride (1.0 eq.) followed by *N,N*-dimethylformamide (1 drop). The reaction was allowed to warm to room temperature and was stirred for 30 min. The volatiles were removed from the reaction without exposing it to air and the crude acid chloride was dried under high vacuum for 20 min. The acid chloride was dissolved in dichloromethane (5.0 ml) and was added *via cannula* to a solution of alcohol (1.0 eq.), 4-*N,N*-dimethylaminopyridine (1.0 eq.) and diisopropylethylamine (2.0 eq.) in dichloromethane (5.0 ml). The reaction was stirred at room temperature for 15 h. Sodium hydrogen carbonate solution (sat. aq., 10 ml) was added and the crude product was extracted into dichloromethane (3 x 20 ml). The combined organic layers were washed with brine (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

**Phosponium salt formation:**

To a solution of halo-compound (1.0 eq., conc. 0.56 – 1.7 M) in the specified solvent (10 ml) was added triphenylphosphine (0.91 – 1.0 eq.). The mixture was heated at reflux for the specified time. The white suspension was allowed to cool to room temperature and to 0 °C on ice. The white precipitate was collected by filtration to give the crude product. Purification was performed as specified.

**Sulfide oxidation:**

To a suspension of thio-ether (1.0 eq., conc. 0.050 M) in absolute ethanol (10 ml) at 0 °C, was added drop-wise, a solution of ammonium molybdate tetrahydrate (0.10 eq.) in hydrogen peroxide (30% (w/w), 10 eq.). The reaction was allowed to warm to room temperature and was stirred for the specified time. Water (0.10 L) was added and the crude product was extracted into ethyl acetate (3 x 60 ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and

concentrated under reduced pressure to give the crude product. Purification was performed as specified.

**Wittig olefination:**

To a suspension of phosphonium salt (0.94 – 1.5 eq.) in the specified solvent (7.0 ml) at the specified temperature (T), was added drop-wise a solution of base (0.50 – 2.5 M in the specified solvent, 0.97 – 1.5 eq.). The reaction was allowed to warm to room temperature for time<sub>A</sub>. The reaction was cooled to T and a solution of aldehyde (1.0 eq., conc. 0.045 M) in the specified solvent (3.0 ml) was added. The reaction was allowed to warm to room temperature for time<sub>B</sub> and was quenched according to one of the following procedures:

Quench 1: The reaction was cooled to -78 °C and methanol (10 ml) was added. The solution was allowed to warm to room temperature, water (30 ml) was added and the crude product was extracted into chloroform (3 x 50 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give the crude product. Purification was performed as specified.

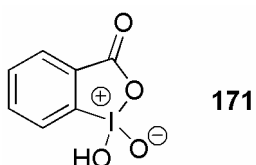
Quench 2: Ammonium chloride solution (sat. aq., 10 ml) was added and the crude product was extracted into ethyl acetate (3 x 50 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give the crude product.

Quench 3: Methanol (10 ml) was added followed by ammonium chloride solution (sat. aq., 10 ml) and the crude product was extracted into ethyl acetate (3 x 50 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give the crude product.

## 6.4 Specific Procedures

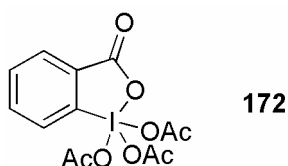
### 6.4.1 Reagents

#### 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide<sup>65</sup> **171**

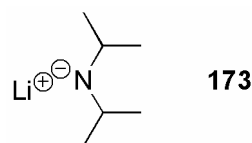


To a suspension of 2-iodobenzoic acid (20 g, 80 mmol) in dilute sulfuric acid (0.73 M, 0.17 L, 0.12 mol) at 55 °C, was added potassium bromate (18 g, 0.11 mol) over 1 h. Water (10 ml) was added and the reaction was heated to 70 °C for 4 h. The reaction was allowed to cool to room temperature and to 0 °C on ice for 30 min. The precipitate was collected, washed with water (3 x 100 ml) and absolute ethanol (3 x 15 ml) and dried overnight over potassium hydroxide under reduced pressure to give 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide **171** as an off-white powder (20 g, 71 mmol, 90%).

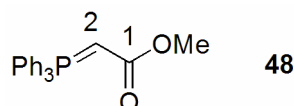
#### 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one<sup>66</sup> **172**



To a solution of *p*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol) in acetic anhydride (80 ml, 0.85 mol) was added 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide **171** (20 g, 71 mmol). The suspension was heated at 80 °C for 3 h, allowed to cool to room temperature and cooled on ice for 2 h 20 min. The white precipitate was collected, washed with diethyl ether (3 x 20 ml) and dried under reduced pressure to give 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one **172** as a white crystalline solid (16 g, 38 mmol, 54%): **m.p.** 133.5 – 134.5 °C (**lit.**<sup>65</sup> **m.p.** 133 – 134 °C).

**Lithium diisopropylamide<sup>67</sup> 173**

To a solution of diisopropylamine (0.23 ml, 1.6 mmol) in tetrahydrofuran (1.9 ml) at -78 °C, was added drop-wise a solution of *n*-butyl lithium (1.2 M in hexanes, 1.3 ml, 1.6 mmol). The reaction was stirred at -78 °C for 10 min and at 0 °C for 20 min. The solution of lithium diisopropylamide (0.50 M) was used immediately in subsequent reactions.

**(Carbomethoxymethylene)triphenylphosphorane<sup>68</sup> 48**

A solution of triphenylphosphine (9.1 g, 35 mmol) in ethyl acetate (10 ml) was added *via cannula*, to a solution of methyl bromoacetate (4.6 g, 30 mmol) in ethyl acetate (30 ml), washing with ethyl acetate (2 x 10 ml). The white suspension was stirred overnight at room temperature. The white precipitate was collected by filtration and washed with diethyl ether (2 x 15 ml) to give a white solid (12 g). The white solid was dissolved in dichloromethane (80 ml) and shaken vigorously with sodium hydroxide solution (5% aq., 45 ml). The organic layer was collected and the aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give (carbomethoxymethylene)triphenylphosphorane **48** as a pale-brown solid (9.7 g, 29 mmol, 97%): **m.p.** 163 – 165 °C. The reagent was used crude in subsequent reactions.

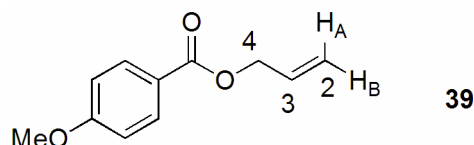
For the purpose of characterization, the sample was recrystallised (50% ethyl acetate : absolute ethanol) to give pure (carbomethoxymethylene)triphenylphosphorane **48** as an off-white crystalline solid: **R<sub>f</sub>** 0.09 (40% ethyl acetate : hexanes); **m.p.** 168.5 – 169.5 °C (*lit.*<sup>43</sup> **m.p.** 168 – 172 °C); **v<sub>max</sub>** (thin film) 1618 (s, C=O), 1124, 1103 (s, C-O) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.72 – 7.41 (15H, m, Ar-H), 3.52 (3H, s, C<sub>1</sub>-OMe), 2.93 (1H,

## Chapter 6

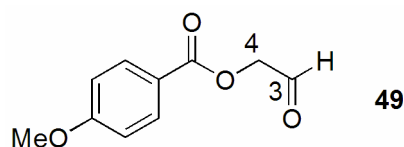
s, C<sub>2</sub>-H); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 171.4 (d, <sup>2</sup>J<sub>PC</sub> 12.4 Hz, C<sub>1</sub>), 132.8 (d, <sup>2</sup>J<sub>PC</sub> 10.0 Hz, *o*-Ar-C), 131.8, 128.6 (d, <sup>3</sup>J<sub>PC</sub> 12.2 Hz, *m*-Ar-C), 126.8, 49.6, 29.6 (d, <sup>1</sup>J<sub>PC</sub> 127.7 Hz, C<sub>2</sub>).

## 6.4.2 Experimental for Chapters 2, 3

### Allyl 4-methoxybenzoate<sup>28</sup> **39**

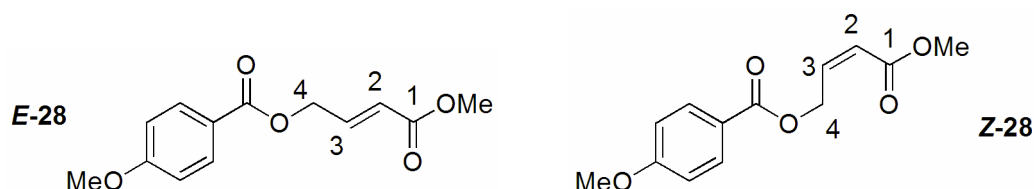


To a stirring solution of 4-methoxybenzoic acid (20 g, 0.13 mol) in dichloromethane (1.1 L) was added *N,N*-dimethylformamide (3.0 ml, 0.039 mol). The mixture was cooled to 0 °C and oxalyl chloride (12 ml, 0.14 mol) was added over 20 min. The white suspension was allowed to warm to room temperature and was stirred for 1 h 15 min. The clear solution was added *via cannula*, over 1 h, to a mixture of DMAP (3.3 g, 27 mmol), allyl alcohol (9.2 ml, 0.14 mol) and triethylamine (38 ml, 0.27 mol), washing with dichloromethane (2 x 10 ml). The orange solution was stirred at room temperature for 18 h. Sodium carbonate solution (sat. aq., 0.26 L) was added, the organic layer was collected and the aqueous layer was extracted with dichloromethane (3 x 0.20 L). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a viscous orange liquid (36 g). Flash chromatographic purification (20% ethyl acetate : hexanes) through a silica plug gave pure alkene, **39**, as a clear, colourless liquid (24 g, 0.12 mol, 95%): **R<sub>f</sub>** 0.37 (20% ethyl acetate : hexanes); **v<sub>max</sub>** (thin film) 1715 (s, C=O), 1648 (m, C=C), 1606, 1580, 1511 (s, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.94 – 7.86 (2H, m, Ar-H), 6.83 – 6.75 (2H, m, Ar-H), 5.92 (1H, ddt, *J* 17.2, 10.4, 5.6 Hz, C<sub>3</sub>-H), 5.28 (1H, dq, *J* 17.2, 1.5 Hz, C<sub>2</sub>-H<sub>A</sub>), 5.15 (1H, dq, *J* 10.4, 1.3 Hz, C<sub>2</sub>-H<sub>B</sub>), 4.68 (2H, dt, *J* 5.6, 1.4 Hz, C<sub>4</sub>-H<sub>2</sub>), 3.71 (3H, s, Ar-OCH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 166.0, 163.5, 132.6, 131.7, 122.6, 117.9, 113.7, 65.3, 55.4.

**2-Oxoethyl 4-methoxybenzoate<sup>61</sup> 49**

Water (0.11 L) was added to a solution of alkene **39** (22 g, 0.11 mol) in diethyl ether (0.33 L). Osmium tetroxide solution (4% wt aq., 7.2 ml, 1.1 mmol) was added and the biphasic reaction was stirred for 10 min. Sodium periodate (91 g, 0.42 mol) was added over 20 min and the reaction was stirred vigorously at room temperature for 15 h. Water (0.10 L) was added, to re-suspend the white solid, and the reaction was stirred vigorously at room temperature for 24 h. Water (0.50 L) was added, the organic layer was collected and the aqueous layer was extracted with ethyl acetate (3 x 0.50 L). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give crude aldehyde **49** as an olive green liquid (22 g) which was used without further purification in subsequent reactions.

For the purpose of characterization, flash chromatographic purification (40% ethyl acetate : hexanes) of a small amount of crude product gave pure aldehyde **49** as a clear colourless liquid:  $R_f$  0.18 (40% ethyl acetate : hexanes);  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.72 (1H, s, CHO), 8.09 – 8.02 (2H, m, Ar-H), 6.98 – 6.91 (2H, m, Ar-H), 4.85 (2H, s,  $\text{C}_4\text{-H}_2$ ), 3.87 (3H, s, Ar- $\text{OCH}_3$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 196.3, 165.7, 163.9, 132.0, 121.2, 113.8, 68.8, 55.5.

**(E)-4-Methoxy-4-oxobut-2-enyl 4-methoxybenzoate E-28****(Z)-4-Methoxy-4-oxobut-2-enyl 4-methoxybenzoate Z-28****Method 1 – Cross metathesis olefination:**

The general cross metathesis olefination procedure (see page 114) was followed using alkene **39** (0.50 g, 2.6 mmol) and methyl acrylate. Time = 1.5 days. The crude product was a viscous, dark-brown liquid (0.91 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure (*E*)-alkene **E-28** as a white crystalline solid (0.42 g, 1.7 mmol, 65%):  $R_f$  0.24 (20% ethyl acetate : hexanes), 0.45 (40% ethyl acetate : hexanes); **m.p.** 48.5 – 49.5 °C;  $\nu_{\max}$  (thin film) 1722, 1668 (s, C=O), 1607, 1581, 1512 (s, Ar(C=C))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.03 – 7.95 (2H, m, Ar-H), 7.03 (1H, dt,  $J$  15.8, 4.5 Hz,  $\text{C}_3\text{-H}$ ), 6.93 – 6.86 (2H, m, Ar-H), 6.09 (1H, dt,  $J$  15.8, 2.0 Hz,  $\text{C}_2\text{-H}$ ), 4.92 (2H, dd,  $J$  4.5, 2.0 Hz,  $\text{C}_4\text{-H}_2$ ), 3.82 (3H, s, Ar-OCH<sub>3</sub>), 3.72 (3H, s,  $\text{C}_1\text{-OCH}_3$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 166.1, 165.4, 163.6, 141.8, 131.6, 121.8, 121.5, 113.6, 62.5, 55.3, 51.5; **HRMS** (+EI) calc. for  $\text{C}_{13}\text{H}_{14}\text{O}_5$  250.0841, found 250.0841;  $m/z$  (+EI) 250 ( $\text{M}^+$ , 2%), 135 (100), 77 (16).

**Method 2 – Wittig olefination:**

(Carbomethoxymethylene)triphenylphosphine **48** (0.077 g, 0.23 mmol, 1.2 eq.) and purified aldehyde **49** (0.037 g, 0.19 mmol) were combined and dissolved in dichloromethane (0.72 ml). The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. Diethyl ether (6 x 60 ml) was added and the suspension was filtered. The filtrate was concentrated under reduced pressure to give a viscous yellow liquid (0.12 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E*)-alkene **E-28** to (*Z*)-alkene **Z-28** was determined to be 2 : 1 from integration of the  $\text{C}_2\text{-H}$  signals in the spectra:  $^1\text{H NMR}$

(200 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.09 (1H, dt,  $J$  15.8, 2.0 Hz, C<sub>2</sub>-H), 5.92 (1H, dt,  $J$  11.7, 2.3 Hz, C<sub>2</sub>-H). Flash chromatographic purification (30% ethyl acetate : hexanes) gave pure (*Z*)-alkene **Z-28** as a viscous clear, colourless liquid (0.011 g, 0.044 mmol, 23%) which solidified on sitting to give an off-white crystalline solid: **R<sub>f</sub>** 0.52 (40% ethyl acetate : hexanes); **m.p.** 47 – 52 °C; **v<sub>max</sub>** (thin film) 1717 (s, C=O), 1607, 1580, 1512 (m, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.05 – 7.98 (2H, m, Ar-H), 6.96 – 6.89 (2H, m, Ar-H), 6.39 (1H, dt,  $J$  11.6, 5.1 Hz, C<sub>3</sub>-H), 5.92 (1H, dt,  $J$  11.7, 2.3 Hz, C<sub>2</sub>-H), 5.40 (2H, dd,  $J$  5.1, 2.4 Hz, C<sub>4</sub>-H<sub>2</sub>), 3.87 (3H, s, Ar-OCH<sub>3</sub>), 3.76 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 166.2, 166.0, 163.5, 145.3, 131.7, 122.3, 120.2, 113.7, 62.8, 55.4, 51.5; **HRMS** (+EI) calc. for C<sub>13</sub>H<sub>14</sub>O<sub>5</sub> 250.0841, found 250.0838; **m/z** (+EI) 250 (M<sup>+</sup>, 2%), 135 (100), 99 (11), 77 (16).

A second fraction gave a mixture of (*E*)-alkene **E-28** and (*Z*)-alkene **Z-28** in a 4 : 1 ratio (determined by integration of the C<sub>2</sub>-H signals in the <sup>1</sup>H NMR spectra) as a viscous white liquid (0.027 g, 0.11 mmol, 57%).

### **Method 3 – Horner-Wadsworth-Emmons olefination:**

The general Horner Wadsworth Emmons olefination procedure (see page 115) was followed using methyl diethylphosphonoacetate, *n*-butyl lithium (1.6 M in hexanes, 1.0 eq.) and crude aldehyde **49** (22 g – assumed quantitative for previous step, 0.11 mol, 0.088 M). Time = 5 h. The crude product was a yellow liquid (42 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-28** to (*Z*)-alkene **Z-28** was determined to be 25 : 1 from integration of the C<sub>2</sub>-H signals in the spectra. Flash chromatographic purification (10% ethyl acetate : hexanes graded to 30% ethyl acetate : hexanes) gave pure (*E*)-alkene **E-28** as a white solid (26 g, 0.10 mol, 91% – over 2 steps).

A second fraction gave a mixture of (*E*)-alkene **E-28** and (*Z*)-alkene **Z-28** in a 1 : 3.7 ratio (determined by integration of the C<sub>2</sub>-H signals in the <sup>1</sup>H NMR spectra) as a viscous liquid (1.2 g, 4.8 mmol, 4%).

### **Method 4 – Alkene isomerisation:**

The general alkene isomerisation procedure (see page 113) was followed using a mixture of (*E*)-alkene **E-28** and (*Z*)-alkene **Z-28** in a 1 : 10 ratio (4.7 g, 19 mmol,

0.040 M) and thiophenol (0.48 eq.).  $\text{Time}_A = 20$  h,  $\text{time}_B = 20$  h. The crude product was a yellow liquid (5.0 g). The crude product was analysed by  $^1\text{H}$  NMR and the ratio of (*E*)-alkene **E-28** to (*Z*)-alkene **Z-28** was determined to be 18 : 1 from integration of the  $\text{C}_2\text{-H}$  signals in the spectra. Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure (*E*)-alkene **E-28** as a white solid (4.45 g, 18 mol, 95%).

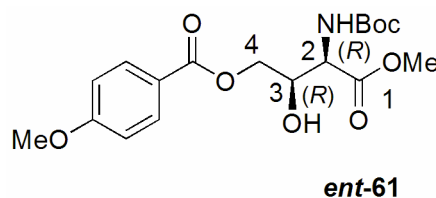
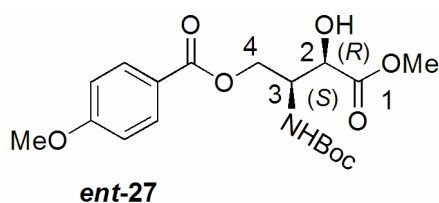
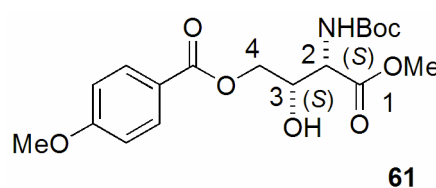
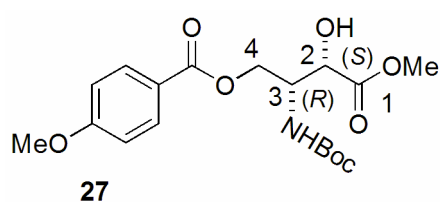
A second fraction gave a mixture of (*E*)-alkene **E-28** and (*Z*)-alkene **Z-28** as a viscous liquid (0.19 g, 0.76 mmol, 4%).

**(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxy-4-methoxy-4-oxobutyl 4-methoxybenzoate 27**

**(2*S*,3*S*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-4-methoxy-4-oxobutyl 4-methoxybenzoate 61**

**(2*S*,3*R*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxy-4-methoxy-4-oxobutyl 4-methoxybenzoate *ent*-27**

**(2*R*,3*R*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-4-methoxy-4-oxobutyl 4-methoxybenzoate *ent*-61**



#### **Method 1 – Using (DHQD)<sub>2</sub>PHAL ligand:**

The general AA procedure (see page 113) was followed using (DHQD)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-28** (9.3 g, 37 mmol). Time = 2 days. The crude product

was a beige residue (40 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave pure  $\beta$ -aminoalcohol **27** as a white crystalline solid (12 g, 31 mmol, 84%):  $R_f$  0.23 (40% ethyl acetate : hexanes); **m.p.** 80.0 – 82.0 °C;  $[\alpha]_D^{24}$  +37.3 (c 1.7, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (thin film) 3364 (br, m, O-H), 1715 (br, s, C=O), 1606, 1581, 1512 (m, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.00 – 7.97 (2H, m, Ar-H), 6.92 – 6.89 (2H, m, Ar-H), 4.94 (1H, br d,  $J$  8.9 Hz, N-H), 4.49 – 4.40 (4H, m, C<sub>2</sub>-H, C<sub>3</sub>-H, C<sub>4</sub>-H<sub>2</sub>), 3.86 (3H, s, Ar-OCH<sub>3</sub>), 3.81 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 1.39 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), OH not observed; **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 173.4, 166.0, 163.6, 155.2, 131.8, 122.1, 113.6, 80.0, 69.7, 63.2, 55.4, 53.0, 51.7, 28.2; **HRMS** (+ESI) calc. for C<sub>18</sub>H<sub>25</sub>NO<sub>8</sub>+Na 406.1478, found 406.1482;  **$m/z$**  (ESI) 789 ([2M+Na]<sup>+</sup>, 91%), 406 ([M+Na]<sup>+</sup>, 100).

#### **Method 2 – Using (DHQ)<sub>2</sub>PHAL ligand:**

The general AA procedure (see page 113) was followed using (DHQ)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-28** (0.10 g, 0.40 mmol). Time = 6 h. The crude product was a beige residue (0.40 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave pure  $\beta$ -aminoalcohol **ent-27** as a white crystalline solid (0.11 g, 0.28 mmol, 70%).

#### **Method 3 – Using (DHQD)<sub>2</sub>AQN ligand:**

The general AA procedure (see page 113) was followed using (DHQD)<sub>2</sub>AQN ligand and (*E*)-alkene **E-28** (0.10 g, 0.40 mmol). Time = 6 h. The crude product was a beige residue (0.41 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of **27** to **61** was determined to be 1 : 1.5 from integration of the N-H signals in the spectra: **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.48 (1H, br d,  $J$  8.6 Hz, N <sub>$\alpha$</sub> -H), 5.03 (1H, br d,  $J$  10.9 Hz, N <sub>$\beta$</sub> -H).

#### **Method 4 – Using (DHQ)<sub>2</sub>AQN ligand:**

The general AA procedure (see page 113) was followed using (DHQ)<sub>2</sub>AQN ligand and (*E*)-alkene **E-28** (0.10 g, 0.40 mmol). Time = 6 h. The crude product was a beige residue (0.42 g). The crude product was analysed by <sup>1</sup>H NMR and

the ratio of **ent-27** to **ent-61** was determined to be 1 : 1.2 from integration of the N-H signals in the spectra.

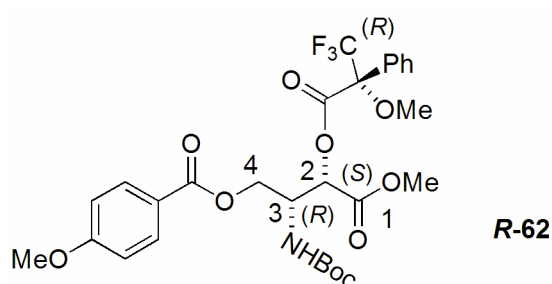
**Method 5 – Using (DHQD)<sub>2</sub>PYR ligand:**

The general AA procedure (see page 113) was followed using (DHQD)<sub>2</sub>PYR ligand and (*E*)-alkene **E-28** (0.10 g, 0.40 mmol). Time = 6 h. The crude product was a beige residue (0.40 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of **27** to **61** was determined to be 1.7 : 1 from integration of the N-H signals in the spectra.

**Method 6 – De-protection of by-product 69:**

To a solution of by-product **69** (3.6 g, 7.8 mmol) in methanol (50 ml) was added pyridinium *p*-toluenesulfonate (0.12 g, 0.48 mmol). The yellow solution was stirred at room temperature for 3 days and sodium hydrogen carbonate solution (sat. aq., 50 ml) was added. The organic layer was collected and the aqueous layer was extracted with ethyl acetate (3 x 150 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a viscous, orange liquid (4.2 g). Flash chromatographic purification (40% ethyl acetate : hexanes graded to 70% ethyl acetate : hexanes) gave β-aminoalcohol **27** as a viscous yellow liquid (2.9 g, 7.6 mmol, 97%) which appeared to be pure by <sup>1</sup>H NMR analysis.

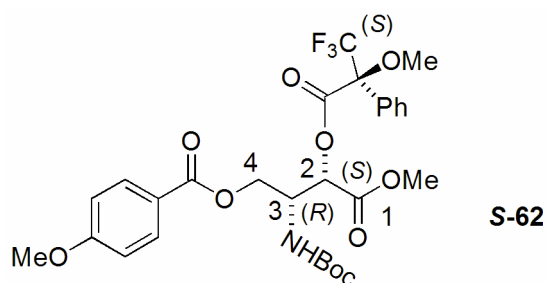
**(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-4-methoxy-4-oxo-3-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)butyl 4-methoxybenzoate *R*-62**



The general procedure for formation of MTPA esters *via* Method 1 (see page 117) was followed using (*R*)-MTPA acid and alcohol **27** (0.019 g, 0.051 mmol). The crude product was a white powder (0.081 g). Flash chromatographic

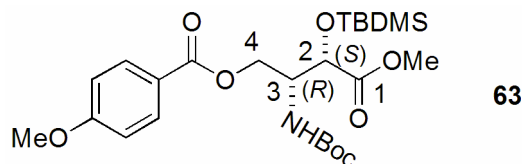
purification (40% ethyl acetate : hexanes) gave pure (*R*)-Mosher's ester **R-62** as a viscous, clear colourless liquid (0.030 g, 0.050 mmol, 98%): **R<sub>f</sub>** 0.39 (40% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 8.00 – 7.93 (2H, m, Ar-H), 7.57 – 7.53 (2H, m, MTPA-Ar-H), 7.46 – 7.33 (3H, m, MTPA-Ar-H), 6.96 – 6.89 (2H, m, Ar-H), 5.45 (1H, d, *J* 1.9 Hz, C<sub>2</sub>-H), 4.82 – 4.74 (2H, m, C<sub>3</sub>-H, N-H), 4.43 – 4.35 (1H, m, C<sub>4</sub>-H<sub>A</sub>), 4.17 – 4.10 (1H, m (obs), C<sub>4</sub>-H<sub>B</sub>), 3.86 (3H, s, Ar-OCH<sub>3</sub>), 3.77 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.55 (3H, d, *J* 1.0 Hz, MTPA-OCH<sub>3</sub>), 1.40 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>).

**(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-4-methoxy-4-oxo-3-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)butyl 4-methoxybenzoate **S-62****



The general procedure for formation of MTPA esters *via* Method 1 (see page 117) was followed using (*S*)-MTPA acid and alcohol **27** (0.020 g, 0.052 mmol). The crude product was a white powder (0.098 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave pure (*S*)-Mosher's ester **S-62** as a (0.030 g, 0.050 mmol, 96%): **R<sub>f</sub>** 0.43 (40% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.98 – 7.91 (2H, m, Ar-H), 7.62 – 7.54 (2H, m, MTPA-Ar-H), 7.43 – 7.34 (3H, m, MTPA-Ar-H), 6.96 – 6.89 (2H, m, Ar-H), 5.49 (1H, s, C<sub>2</sub>-H), 4.77 – 4.64 (2H, m, C<sub>3</sub>-H, N-H), 4.30 – 4.17 (1H, m, C<sub>4</sub>-H<sub>A</sub>), 3.88 – 3.84 (1H, m, C<sub>4</sub>-H<sub>B</sub>), 3.86 (3H, s, Ar-OCH<sub>3</sub>), 3.80 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.67 (3H, d, *J* 1.1 Hz, MTPA-OCH<sub>3</sub>), 1.40 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>).

**(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-4-methoxy-4-oxobutyl 4-methoxybenzoate **63****



**Method 1 – Using TBDMS-chloride:**

A solution of *tert*-butyldimethylsilyl chloride (0.23 g, 1.5 mmol) in dichloromethane (0.50 ml) was added to a suspension of  $\beta$ -aminoalcohol **27** (0.21 g, 0.55 mmol), DMAP (0.013 g, 0.11 mmol) and triethylamine (0.15 ml, 1.1 mmol) in dichloromethane (0.80 ml) *via cannula*. The reaction was stirred at room temperature, under an atmosphere of nitrogen, for 7 days. Water (30 ml) was added and the crude product was extracted into dichloromethane (3 x 30 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a viscous light-brown liquid (0.29 g). Flash chromatographic purification (20% ethyl acetate : hexanes graded to 40% ethyl acetate : hexanes) gave pure TBDMS protected  $\beta$ -aminoalcohol **63** as a viscous clear, colourless liquid (0.20 g, 0.40 mmol, 73%): **R<sub>f</sub>** 0.55 (40% ethyl acetate : hexanes); **[ $\alpha$ ]<sub>D</sub><sup>24</sup>** +28.8 (c 2.2, CH<sub>2</sub>Cl<sub>2</sub>); **v<sub>max</sub>** (thin film) 3445, 3364 (w, N-H), 1759, 1719, (s, C=O), 1606, 1581, 1512 (m, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.02 – 7.96 (2H, m, Ar-H), 6.93 – 6.90 (2H, m, Ar-H), 4.97 (1H, br d, *J* 9.4 Hz, N-H), 4.49 – 4.40 (2H, m, C<sub>2</sub>-H, C<sub>3</sub>-H), 4.35 (1H, dd, *J* 10.6, 6.0 Hz, C<sub>4</sub>-H<sub>A</sub>), 4.21 (1H, dd, *J* 10.5, 7.7 Hz, C<sub>4</sub>-H<sub>B</sub>), 3.86 (3H, s, Ar-OCH<sub>3</sub>), 3.72 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 1.41 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 0.91 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.10 (3H, s, Si-CH<sub>3</sub>), 0.03 (3H, s, Si-CH<sub>3</sub>); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 172.0, 165.8, 163.5, 155.2, 131.7, 122.2, 113.7, 79.8, 70.8, 62.9, 55.4, 52.4, 52.1, 28.2, 25.7, 18.3, -4.9, -5.6; **HRMS** (+ESI) calc. for C<sub>24</sub>H<sub>39</sub>NO<sub>8</sub>Si+Na 520.2343, found 520.2348; ***m/z*** (+ESI) 1017 ([2M+Na]<sup>+</sup>, 45%), 520 ([M+Na]<sup>+</sup>, 100).

A second fraction gave pure recovered- $\beta$ -aminoalcohol **27** as a white solid (0.021 g, 0.055 mmol, 10%).

**Method 2 – Using TBDMS-triflate:**

2,6-lutidine (0.22 ml, 1.9 mmol) was added to a solution of  $\beta$ -aminoalcohol **27** (0.36 g, 0.94 mmol), in dichloromethane (0.95 ml), under an atmosphere of nitrogen. The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and *tert*-butyldimethylsilyl triflate (0.32 ml, 1.4 mmol) was added drop-wise. The reaction was stirred at  $-78\text{ }^{\circ}\text{C}$  for 15 min and the resulting solid melted as the reaction was allowed to warm to room temperature. The reaction was stirred for 22 h. Water (15 ml) was added and the crude product was extracted into ethyl acetate (3 x 30 ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give a clear, colourless, viscous liquid (0.57 g). Flash chromatographic purification (20% ethyl acetate : hexanes graded to 40% ethyl acetate : hexanes) gave pure TBDMS protected  $\beta$ -aminoalcohol **63** as a viscous clear, colourless liquid (0.35 g, 0.70 mmol, 75%).

**(2*S*,3*R*)-Methyl 3-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldimethylsilyloxy)-4-hydroxybutanoate **64*******tert*-Butyl (3*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-5-oxo-tetrahydrofuran-3-ylcarbamate **65******Method 1 – Using sodium methoxide:**

The general *p*-methoxybenzoyl de-protection procedure *via* Method 1 (see page 116) was followed using sodium methoxide (1.9 eq.) and *p*-methoxybenzoyl ester **63** (0.11 g, 0.22 mmol, conc. 0.10 M). Time = 16 h. The crude product was a viscous yellow liquid (0.17 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave pure alcohol **64** as a viscous clear, colourless liquid (0.043 g, 0.12 mmol, 54%);  $R_f$  0.33 (40% ethyl acetate : hexanes);  $v_{\text{max}}$  (thin film) 3445 (br with a point, s, N-H and O-H), 1759, 1700, (br, s, C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.03 (1H, d,  $J$  8.8 Hz, N-H), 4.49 (1H, d,  $J$  2.5 Hz,  $\text{C}_2$ -H), 4.07

– 4.00 (1H, m, C<sub>3</sub>-H), 3.77 (1H, dd, *J* 10.8, 5.4 Hz, C<sub>4</sub>-H<sub>A</sub>), 3.73 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.59 (1H, dd, *J* 10.8, 7.0 Hz, C<sub>4</sub>-H<sub>B</sub>), 1.43 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 0.92 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.11 (3H, s, Si-CH<sub>3</sub>), 0.07 (3H, s, Si-CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 172.5, 155.9, 79.9, 71.0, 62.3, 54.9, 52.1, 28.3, 25.7, 18.3, -5.0, -5.6.

A second fraction gave an inseparable mixture of methyl 4-methoxybenzoate and recovered-*p*-methoxybenzoyl ester **63** (0.046 g) in a 1.3 : 1 ratio (determined by integration of the OCH<sub>3</sub> signals in the <sup>1</sup>H NMR spectra). From this, the amount of recovered-*p*-methoxybenzoyl ester **63** was determined to be (0.032 g, 0.064 mmol, 29%).

Alcohol **64** decomposed over time to give oxo-tetrahydrofuran **65** as a viscous clear, colourless liquid: *R<sub>f</sub>* 0.48 (40% ethyl acetate : hexanes); [*α*]<sub>D</sub><sup>21</sup> -44.1 (*c* 0.4, CH<sub>2</sub>Cl<sub>2</sub>); *v*<sub>max</sub> (thin film) 3354 (br, m, N-H), 1793 (br, s, C=O(lactone)), 1701 (br, s, C=O(carbamate)) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, 320 K, CDCl<sub>3</sub>) δ: 4.69 (1H, s, N-H), 4.55 – 4.42 (2H, m, CH), 4.20 – 4.03 (2H, m, CH), 1.46 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 0.93 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.2 (3H, s, Si-CH<sub>3</sub>), 0.17 (3H, s, Si-CH<sub>3</sub>); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ: 173.6, 154.8, 80.7, 71.7, 67.5, 55.7, 28.3, 25.6, 18.2, -4.6, -5.2; HRMS (+ESI) calc. for C<sub>15</sub>H<sub>29</sub>NO<sub>5</sub>Si+Na 354.1713, found 354.1716; *m/z* (+ESI) 685 ([2M+Na]<sup>+</sup>, 5%), 354 ([M+Na]<sup>+</sup>, 100).

### **Method 2 – Using caesium carbonate:**

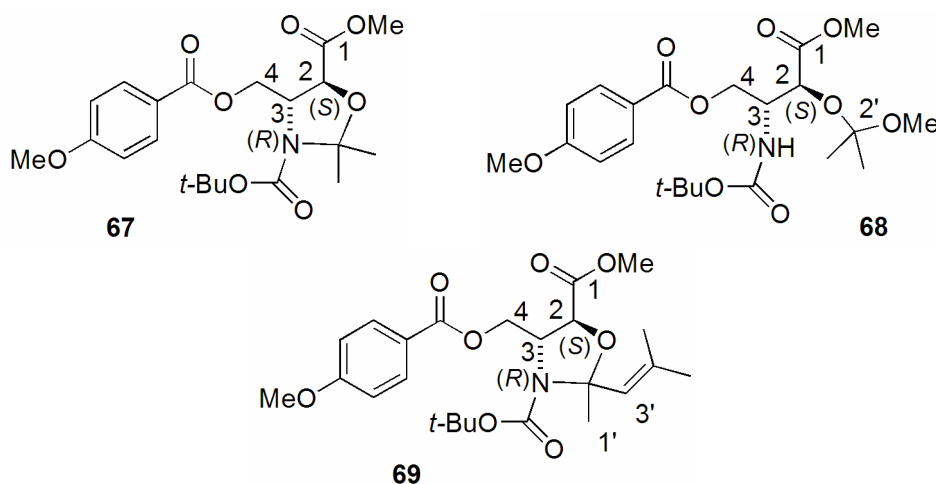
The general *p*-methoxybenzoyl de-protection procedure *via* Method 2 (see page 117) was followed using caesium carbonate (0.80 eq.) and *p*-methoxybenzoyl ester **63** (0.74 g, 1.5 mmol). Additional caesium carbonate (0.20 eq.) was added after 15 h. Time = 30 h. The crude product was a viscous yellow liquid (0.91 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure alcohol **64** as a viscous clear, colourless liquid (0.35 g, 0.96 mmol, 64%).

A second fraction gave an inseparable mixture of methyl 4-methoxybenzoate and recovered-*p*-methoxybenzoyl ester **63** as a white solid (0.18 g) in a 3.6 : 1 ratio (determined by integration of the OCH<sub>3</sub> signals in the <sup>1</sup>H NMR spectra). From this, the amount of recovered-*p*-methoxybenzoyl ester **63** was determined to be (0.082 g, 0.16 mmol, 11%).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4-methoxybenzoyloxy)methyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **67****

**(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-4-methoxy-3-(2-methoxypropan-2-yloxy)-4-oxobutyl 4-methoxybenzoate **68****

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4-methoxybenzoyloxy)methyl)-2-methyl-2-(2-methylprop-1-enyl)oxazolidine-3,5-dicarboxylate **69****



### **Method 1 – Using 2,2-dimethoxypropane and TsOH:**

To a solution of alcohol **27** (0.40 g, 0.94 mmol) in benzene (1.0 ml) was added 2,2-dimethoxypropane (0.39 ml, 3.2 mmol) followed by *p*-toluenesulfonic acid (0.076 g, 0.40 mmol). The solution was heated at 95 °C for 32 h adding additional aliquots of 2,2-dimethoxypropane (0.50 ml, 4.1 mmol) at 2h, 9h, 10h and 23h. The reaction was allowed to cool to room temperature and was poured into sodium hydrogen carbonate solution (sat. aq., 50 ml). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a viscous orange liquid (0.41 g). Flash chromatographic purification (20% ethyl acetate : hexanes graded to 40% ethyl acetate : hexanes) gave pure oxazolidine **67** as a viscous clear, colourless liquid (0.16 g, 0.37 mmol, 39%): *R<sub>f</sub>* 0.49 (40% ethyl acetate : hexanes); [ $\alpha$ ]<sub>D</sub><sup>19</sup> +4.8 (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>); *v*<sub>max</sub> (thin film) 1713 (br s, C=O), 1607, 1581, 1512 (m, Ar(C=C)) 1258 (br, s, N-CO-O) cm<sup>-1</sup>;

**<sup>1</sup>H NMR** (200 MHz, 340K, CDCl<sub>3</sub>) δ: 8.01 – 7.96 (2H, m, Ar-H), 6.93 – 6.88 (2H, m, Ar-H), 4.65 (1H, d, *J* 2.8 Hz, C<sub>2</sub>-H), 4.58 – 4.47 (3H, m, C<sub>3</sub>-H, C<sub>4</sub>-H<sub>2</sub>), 3.85 (3H, s, Ar-OCH<sub>3</sub>), 3.77 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 1.62 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.58 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.49 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, 340K, CDCl<sub>3</sub>) δ: 171.3, 165.8, 163.9, 151.5, 131.8, 122.6, 113.9, 96.8, 81.0, 76.3, 63.5, 59.1, 55.4, 52.3, 28.5, 27.5, 26.5; **HRMS** (+ESI) calc. for C<sub>21</sub>H<sub>29</sub>NO<sub>8</sub>+Na 446.1791, found 446.1779; ***m/z*** (+ESI) 869 ([2M+Na]<sup>+</sup>, 23%), 446 ([M+Na]<sup>+</sup>, 100), 390 (18), 346 (8).

A second fraction gave pure intermediate acetal **68** as a viscous clear colourless liquid (0.0070 g, 0.015 mmol, 1.6%): **R<sub>f</sub>** 0.38 (40% ethyl acetate : hexanes); **[α]<sub>D</sub><sup>21</sup>** +32.6 (*c* 3.6, CH<sub>2</sub>Cl<sub>2</sub>); **v<sub>max</sub>** (thin film) 3445, 3373 (br m, N-H), 1755, 1713, (s, C=O), 1607, 1581, 1514 (m, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 8.01 – 7.94 (2H, m, Ar-H), 6.92 – 6.88 (2H, m, Ar-H), 5.06 (1H, d, *J* 8.5 Hz, N-H), 4.53 – 4.52 (1H, m, C<sub>2</sub>-H), 4.38 – 4.22 (3H, m, C<sub>3</sub>-H, C<sub>4</sub>-H<sub>2</sub>), 3.84 (3H, s, Ar-OCH<sub>3</sub>), 3.70 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.19 (3H, s, C<sub>2</sub>'-OCH<sub>3</sub>), 1.40 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 1.37 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.32 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 171.8, 165.8, 163.5, 155.2, 131.7, 122.0, 113.6, 102.1, 79.8, 68.6, 63.0, 55.4, 52.1, 51.7, 50.0, 28.2, 24.5, 24.5; **HRMS** (+ESI) calc. for C<sub>22</sub>H<sub>33</sub>NO<sub>9</sub>+Na 478.2053, found 478.2041; ***m/z*** (+ESI) 933 ([2M+Na]<sup>+</sup>, 28%), 478 ([M+Na]<sup>+</sup>, 100), 406 (7), 350 (10).

A third fraction gave recovered-alcohol **27** as a white crystalline solid (0.16 g, 0.40 mmol, 43%).

### **Method 2 – Using 2-methoxypropene and TsOH:**

To a solution of alcohol **27** (1.8 g, 4.7 mmol) in benzene (20 ml) at 0 °C, was added 2-methoxypropene (1.5 ml, 16 mmol) followed by *p*-toluenesulfonic acid (0.20 g, 1.1 mmol). The resulting dark red solution was stirred at 0 °C for 2 h and an additional aliquot of 2-methoxypropene (1.6 ml, 17 mmol) was added. The reaction was allowed to warm to room temperature and was stirred for 5h adding additional aliquots of 2-methoxypropene (2.0 ml, 21 mmol) at 2h, 4h and an additional aliquot of *p*-toluenesulfonic acid (0.20 g, 1.1 mmol) at 3 h. Sodium hydrogen carbonate solution (sat. aq., 50 ml) was added, the organic layer was collected and the aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under

reduced pressure to give a viscous bright yellow liquid (3.9 g). Flash chromatographic purification (20% ethyl acetate : hexanes graded to 40% ethyl acetate : hexanes) gave pure oxazolidine **67** as a viscous clear, colourless liquid (1.2 g, 2.8 mmol, 60%).

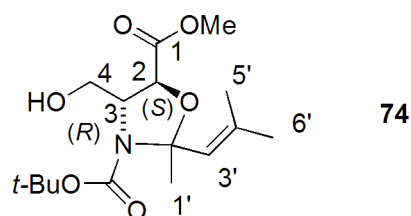
A second fraction gave recovered-alcohol **27** as a white crystalline solid (0.39 g, 1.0 mmol, 22%).

### **Method 3 – Using 2-methoxypropene and PPTS:**

To a solution of alcohol **27** (0.66 g, 1.7 mmol) in toluene (17 ml) was added 2-methoxypropene (3.3 ml, 34 mmol) followed by pyridinium *p*-toluenesulfonate (0.039 g, 0.16 mmol). The clear colourless solution was stirred at room temperature for 1 h, heated at 110 °C for 3 h and allowed to cool to room temperature. Sodium hydrogen carbonate solution (sat. aq., 100 ml) was added, the organic layer was collected and the aqueous layer was extracted with ethyl acetate (3 x 150 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a viscous yellow liquid (1.4 g). Flash chromatographic purification (5% ethyl acetate : hexanes graded to 40% ethyl acetate : hexanes) gave pure oxazolidine **67** as a viscous clear, colourless liquid (0.56 g, 1.3 mmol, 76%).

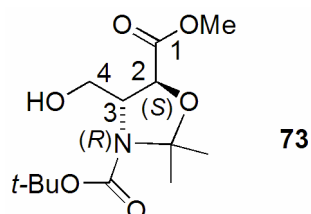
A second fraction gave pure by-product **69** as viscous clear colourless liquid (0.16 g, 0.35 mmol, 20%): **R<sub>f</sub>** 0.50 (40% ethyl acetate : hexanes); [ $\alpha$ ]<sub>D</sub><sup>21</sup> -68.9 (c 3.4, CH<sub>2</sub>Cl<sub>2</sub>); **v<sub>max</sub>** (thin film) 1701 (br, s, C=O), 1607, 1581, 1512 (m, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, 320K, CDCl<sub>3</sub>)  $\delta$ : 8.02 – 7.95 (2H, m, Ar-H), 6.94 – 6.87 (2H, m, Ar-H), 5.42 (1H, s, C<sub>3</sub>-H), 4.64 – 4.54 (4H, m, C<sub>2</sub>-H, C<sub>3</sub>-H, C<sub>4</sub>-H<sub>2</sub>), 3.85 (3H, s, Ar-OCH<sub>3</sub>), 3.70 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 1.79 – 1.79 (3H, m, C<sub>1</sub>-H<sub>3</sub>), 1.69 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>), 1.47 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, 320K, CDCl<sub>3</sub>)  $\delta$ : 170.4, 165.8, 163.6, 151.6, 137.3, 131.8, 126.2, 122.3, 113.7, 95.3, 80.7, 76.2, 62.9, 57.6, 55.4, 52.2, 28.4, 27.1, 26.7, 18.9; **HRMS** (+ESI) calc. for C<sub>24</sub>H<sub>33</sub>NO<sub>8</sub>+Na 486.2104, found 486.2110; **m/z** (+ESI) 949 ([2M+Na]<sup>+</sup>, 13%), 486 ([M+Na]<sup>+</sup>, 100); **m/z** (+EI) 348 (68%), 135 (100).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-(hydroxymethyl)-2-methyl-2-(2-methylprop-1-enyl)oxazolidine-3,5-dicarboxylate **74****



The general *p*-methoxybenzoyl de-protection procedure *via* Method 2 (see page 117) was followed using caesium carbonate (0.66 eq.) and *p*-methoxybenzoyl ester **69** (0.19 g, 0.41 mmol). Time = 4 h. The crude product was a viscous yellow liquid (0.24 g). Flash chromatographic purification (30% ethyl acetate : hexanes) gave pure alcohol **74** as a viscous, clear, colourless liquid (0.11 g, 0.33 mmol, 80%):  $R_f$  0.26 (40% ethyl acetate : hexanes);  $[\alpha]_D^{20}$  -65.3 (c 5.2, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{max}$  (thin film) 3466 (br m, O-H), 1742, 1697 (s, C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, 320K, CDCl<sub>3</sub>)  $\delta$ : 5.38 – 5.37 (1H, m, C<sub>3'</sub>-H), 4.46 (1H, d, *J* 5.8 Hz, C<sub>2</sub>-H), 4.33 – 4.25 (1H, m, C<sub>3</sub>-H), 3.87 – 3.77 (3H, m, C<sub>4</sub>-H<sub>2</sub>, OH), 3.75 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 1.77 (3H, d, *J* 1.2 Hz, C<sub>5'</sub>-H<sub>3</sub> or C<sub>6'</sub>-H<sub>3</sub>), 1.71 (3H, d, *J* 1.3 Hz, C<sub>5</sub>-H<sub>3</sub> or C<sub>6</sub>-H<sub>3</sub>), 1.64 (3H, s, C<sub>1</sub>-H<sub>3</sub>), 1.45 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (50 MHz, 320K, CDCl<sub>3</sub>)  $\delta$ : 170.2, 152.9, 137.6, 126.3, 94.8, 80.8, 75.4, 63.5, 61.1, 52.2, 28.3, 27.1, 26.6, 18.7. Significant decomposition occurred when analysed by mass spectroscopy.

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **73****



**Method 1 – Using sodium hydroxide:**

The general *p*-methoxybenzoyl de-protection procedure *via* Method 1 (see page 116) was followed using sodium methoxide (0.060 eq.) and *p*-methoxybenzoyl

ester **67** (0.77 g, 1.8 mmol, conc. 0.064 M). Time = 6 h 30 min. The crude product was a viscous cloudy, yellow liquid (1.1 g). Flash chromatographic purification (30% ethyl acetate : hexanes) gave pure alcohol **73** as a viscous, clear, colourless liquid (0.38 g, 1.3 mmol, 72%):  $R_f$  0.22 (40% ethyl acetate : hexanes);  $[\alpha]_D^{19} +13.5$  (c 0.7,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (thin film) 3460 (br m, O-H), 1742, 1697 (s, C=O)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz, 340K,  $\text{CDCl}_3$ )  $\delta$ : 4.46 (1H, d,  $J$  4.9 Hz,  $\text{C}_2\text{-H}$ ), 4.27 (1H, dt,  $J$  5.0, 4.9 Hz,  $\text{C}_3\text{-H}$ ), 3.86 – 3.78 (2H, m,  $\text{C}_4\text{-H}_2$ ), 3.80 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 1.62 (3H, s,  $\text{C}(\text{C}_A\text{H}_3)(\text{C}_B\text{H}_3)$ ), 1.57 (3H, s,  $\text{C}(\text{C}_A\text{H}_3)(\text{C}_B\text{H}_3)$ ), 1.50 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C NMR}$  (50 MHz, 340K,  $\text{CDCl}_3$ )  $\delta$ : 171.2, 152.9, 96.6, 81.3, 75.8, 64.1, 62.3, 52.3, 28.5, 27.4, 26.8; **HRMS** (+ESI) calc. for  $\text{C}_{13}\text{H}_{23}\text{NO}_6 + \text{Na}$  312.1423, found 312.1415;  $m/z$  (+ESI) 312 ( $[\text{M} + \text{Na}]^+$ , 100), 256 (12).

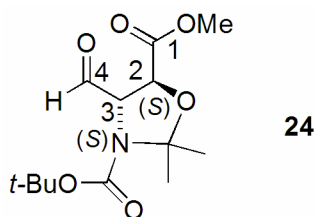
A second fraction gave a mixture of alcohol **73** and by-product alcohol **74** (0.056 g).

### Method 2 – Using caesium carbonate:

The general *p*-methoxybenzoyl de-protection procedure *via* Method 2 (see page 117) was followed using caesium carbonate (0.62 eq.) and *p*-methoxybenzoyl ester **67** (0.88 g, 2.1 mmol). Time = 16 h. The crude product was a viscous orange liquid (1.0 g). Flash chromatographic purification (30% ethyl acetate : hexanes) gave pure alcohol **73** as a viscous, clear, colourless liquid (0.49 g, 1.7 mmol, 81%).

A second fraction gave a mixture of alcohol **73** and by-product alcohol **74** (0.071 g).

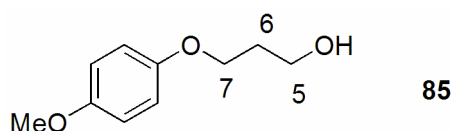
### (4*S*,5*S*)-3-*tert*-Butyl 5-methyl 4-formyl-2,2-dimethyloxazolidine-3,5-dicarboxylate **24**



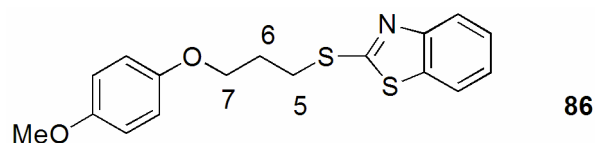
The general Dess-Martin oxidation procedure (see page 114) was followed using alcohol **73** (1.2 g, 4.1 mmol). Time = 1 h. The crude product was a cloudy,

yellow liquid (1.2 g). For the purpose of characterization, flash chromatographic purification (20% ethyl acetate : hexanes) of a small amount of crude product gave pure aldehyde **24** as a viscous, clear, colourless liquid:  $R_f$  0.40 – 0.15 (40% ethyl acetate : hexanes);  $\nu_{\max}$  (thin film) 1744, 1717, (s, C=O), 1367 (s, C-H(aldehyde))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz, 340K,  $\text{CDCl}_3$ )  $\delta$ : 9.59 (1H, s, CHO), 4.61 – 4.60 (2H, m,  $\text{C}_2\text{-H}$ ,  $\text{C}_3\text{-H}$ ), 3.77 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 1.60 (3H, s,  $\text{C}(\text{C}_A\text{H}_3)(\text{C}_B\text{H}_3)$ ), 1.55 (3H, s,  $\text{C}(\text{C}_A\text{H}_3)(\text{C}_B\text{H}_3)$ ), 1.43 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C NMR}$  (50 MHz, 340K,  $\text{CDCl}_3$ )  $\delta$ : 196.3, 169.9, 151.3, 97.0, 81.6, 73.6, 66.8, 52.5, 28.2, 26.6, 26.1; **HRMS** (+ESI) calc. for  $\text{C}_{13}\text{H}_{21}\text{NO}_6+\text{Na}$  310.1267, found 310.1265;  $m/z$  (+ESI) 902 ( $[\text{3M}+\text{Na}+\text{H}_2\text{O}]^+$ , 100%), 615 ( $[\text{2M}+\text{Na}+\text{H}_2\text{O}]^+$ , 70), 310 ( $[\text{M}+\text{Na}]^+$ , 14).

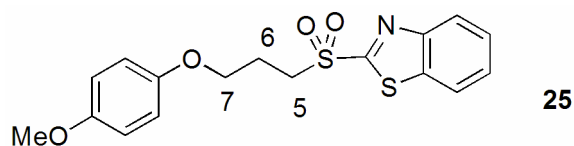
### 3-(4-Methoxyphenoxy)propan-1-ol<sup>69, 70</sup> **85**



To a solution of sodium metal (0.48 g, 20 mmol) in methanol (9.0 ml) was added drop-wise, a solution of 4-methoxyphenol (1.0 g, 8.1 mmol) in methanol (3.5 ml). The reaction was stirred for 10 min and 3-chloro-1-propanol (1.7 ml, 20 mmol) was added. The solution was stirred at room temperature for 1 h and was heated at reflux for 21 h. The solvent was removed under reduced pressure to give a pale brown residue. Diethyl ether (50 ml) and activated charcoal were added and the suspension was filtered through celite. The clear, colourless filtrate was concentrated under reduced pressure to give a viscous orange liquid (2.1 g). Flash chromatographic purification (30% ethyl acetate : hexanes) gave pure alcohol **85** as off-white flaky crystals (1.0 g, 5.5 mmol, 68%):  $R_f$  0.20 (40% ethyl acetate : hexanes); **m.p.** 62.5 – 63.5 °C (*lit.*<sup>69</sup> **m.p.** 65 – 66 °C);  $\nu_{\max}$  (thin film) 3269 (br, s, O-H), 1510 (s,  $\text{Ar}(\text{C}=\text{C})$ )  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.81 (4H, s, Ar-H), 4.01 (2H, t,  $J$  6.0 Hz,  $\text{C}_7\text{-H}_2$ ), 3.79 (2H, t,  $J$  6.0 Hz,  $\text{C}_5\text{-H}_2$ ), 3.73 (3H, s, Ar-OCH<sub>3</sub>), 2.76 (1H, br s, OH), 1.97 (2H, quin,  $J$  6.1 Hz,  $\text{C}_6\text{-H}_2$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 153.7, 152.8, 115.3, 114.5, 66.0, 59.9, 55.5, 31.9.

**2-(3-(4-Methoxyphenoxy)propylthio)benzo[d]thiazole 86**

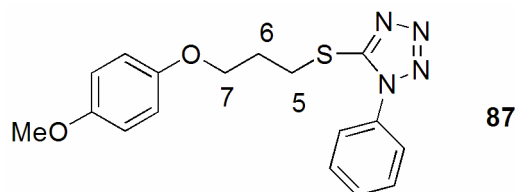
The general Mitsunobu reaction procedure (see page 117) was followed using alcohol **85** (0.10 g, 0.55 mmol) and 2-mercaptobenzothiazole. Time = 14 h 40 min. The crude product was a viscous yellow liquid (0.62 g). Flash chromatographic purification (10% ethyl acetate : hexanes graded to 20% ethyl acetate : hexanes) gave pure thio-ether **86** as a beige crystalline solid (0.15 g, 0.45 mmol, 82%):  $R_f$  0.37 (20% ethyl acetate : hexanes); **m.p.** 50.0 – 51.5 °C;  $\nu_{\max}$  (thin film) 1506 (s, Ar(C=C))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.95 – 7.69 (2H, m, BTA<sub>r</sub>-H), 7.48 – 7.25 (2H, m, BTA<sub>r</sub>-H), 6.87 – 6.80 (4H, m, Ar-H), 4.07 (2H, t,  $J$  5.9 Hz, C<sub>7</sub>-H), 3.76 (3H, s, Ar-OCH<sub>3</sub>), 3.54 (2H, t,  $J$  7.0 Hz, C<sub>5</sub>-H), 2.30 (2H, quin,  $J$  6.4 Hz, C<sub>6</sub>-H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 166.6, 153.9, 153.2, 152.8, 135.2, 126.0, 124.2, 121.5, 120.9, 115.4, 114.6, 66.5, 55.7, 30.2, 29.1; **HRMS** (+EI) calc. for  $\text{C}_{17}\text{H}_{17}\text{NO}_2\text{S}_2$  331.0701, found 331.0696;  $m/z$  (+EI) 331 ( $[\text{M}]^+$ , 10%), 284 (15), 281 (13), 211 (11), 210 (15), 209 (36), 208 (100), 180 (32), 167 (21), 136 (19), 109 (12).

**2-(3-(4-Methoxyphenoxy)propylsulfonyl)benzo[d]thiazole 25**

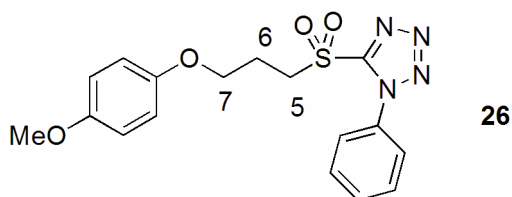
The general sulfide oxidation procedure (see page 118) was followed using thio-ether **86** (0.28 g, 0.84 mmol). Time = 30 h. The crude product was a pale brown crystalline solid (0.31 g). Flash chromatographic purification (20% ethyl acetate : hexanes graded to 30% ethyl acetate : hexanes) gave pure sulfone **25** as a bright-yellow crystalline solid (0.30 g, 0.83 mmol, 99%):  $R_f$  0.37 (40% ethyl acetate : hexanes); **m.p.** 84.0 – 85.0 °C;  $\nu_{\max}$  (thin film) 1508 (s, Ar(C=C)), 1327 (m, SO<sub>2</sub>), 1144 (s, SO<sub>2</sub>)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.21 – 8.18 (1H, m,

BTAr-H), 8.01 – 7.99 (1H, m, BTAr-H), 7.66 – 7.56 (2H, m, BTAr-H), 6.76 (4H, s, PMPAr-H), 4.03 (2H, t,  $J$  5.8 Hz, C<sub>7</sub>-H), 3.78 – 3.72 (2H, m, C<sub>5</sub>-H), 3.74 (3H, s, Ar-OCH<sub>3</sub>), 2.38 – 2.33 (2H, m, C<sub>6</sub>-H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 165.5, 154.0, 152.6, 152.3, 136.7, 128.0, 127.6, 125.4, 122.3, 115.4, 114.6, 65.8, 55.6, 51.9, 22.8; **HRMS** (+EI) calc. for C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub>S<sub>2</sub> 363.0599, found 363.0596; **m/z** (+EI) 363 ([M]<sup>+</sup>, 12%), 299 (10), 283 (17), 282 (17), 281 (57), 269 (19), 267 (22), 265 (21), 242 (15), 241 (15), 240 (100), 229 (16), 227 (30), 226 (10), 225 (40), 213 (11), 211 (50), 210 (19), 209 (78), 207 (17), 191 (11), 182 (42), 176 (13), 151 (15), 149 (12), 134 (16), 109 (16).

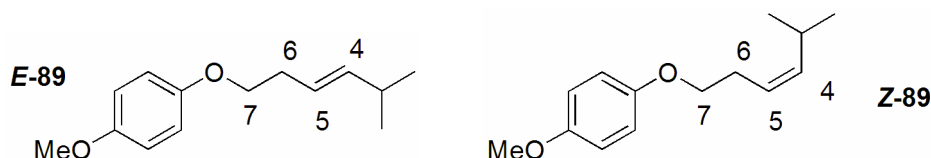
### 5-(3-(4-Methoxyphenoxy)propylthio)-1-phenyl-1H-tetrazole **87**



The general Mitsunobu reaction procedure (see page 117) was followed using alcohol **85** (1.0 g, 5.5 mmol) and 1-phenyl-1H-tetrazole-5-thiol. Time = 2 h 40 min. The crude product was a viscous cloudy yellow liquid (7.8 g). Flash chromatographic purification (15% ethyl acetate : hexanes) gave pure thio-ether **87** as an off-white crystalline solid (1.3 g, 3.8 mmol, 70%): **R<sub>f</sub>** 0.42 (40% ethyl acetate : hexanes); **m.p.** 101.0 – 102.5 °C; **v<sub>max</sub>** (thin film) 1597 (w, Ar(C=C)), 1508 (s, Ar(C=C)), 1501 (w, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.56 – 7.54 (5H, m, PTAr-H), 6.82 (4H, s, PMPAr-H), 4.04 (2H, t,  $J$  5.8 Hz, C<sub>7</sub>-H), 3.75 (3H, s, Ar-OCH<sub>3</sub>), 3.58 (2H, t,  $J$  7.0 Hz, C<sub>5</sub>-H), 2.38 – 2.26 (2H, m, C<sub>6</sub>-H); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 154.1, 153.9, 152.7, 133.6, 130.1, 129.7, 123.7, 115.4, 114.6, 66.2, 55.7, 30.0, 28.9; **HRMS** (+EI) calc. for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S 342.1150, found 342.1144; **m/z** (+EI) 342 ([M]<sup>+</sup>, 2%), 219 (66), 191 (10), 164 (12), 163 (100), 155 (15), 124 (12), 123 (16), 119 (38), 109 (19), 95 (13), 77 (19), 65 (16), 51 (11).

5-(3-(4-Methoxyphenoxy)propylsulfonyl)-1-phenyl-1H-tetrazole **26**

The general sulfide oxidation procedure (see page 118) was followed using thio-ether **87** (0.64 g, 1.9 mmol). Time = 20 h. The crude product was a viscous, cloudy yellow liquid (0.77 g). Flash chromatographic purification (crude product was absorbed onto silica (dichloromethane), 20% ethyl acetate : hexanes) gave pure sulfone **26** as a white crystalline solid (0.69 g, 1.8 mmol, 95%):  $R_f$  0.39 (40% ethyl acetate : hexanes); **m.p.** 82.5 – 83.0 °C;  $\nu_{max}$  (thin film) 1508 (s, Ar(C=C)), 1499 (m, Ar(C=C)), 1339, 1150 (m, SO<sub>2</sub>) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.71 – 7.60 (5H, m, PTA<sub>r</sub>-H), 6.83 (4H, s, PMPA<sub>r</sub>-H), 4.08 (2H, t,  $J$  5.7 Hz, C<sub>7</sub>-H), 4.00 – 3.95 (2H, m, C<sub>5</sub>-H) 3.77 (3H, s, Ar-OCH<sub>3</sub>), 2.48 – 2.39 (2H, m, C<sub>6</sub>-H); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 154.2, 153.4, 152.3, 133.0, 131.5, 129.7, 125.0, 115.5, 114.7, 65.7, 55.7, 53.3, 22.7; **HRMS** (+EI) calc. for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>S 374.1049, found 374.1043;  **$m/z$**  (+EI) 374 ([M]<sup>+</sup>, 15%), 281 (13), 251 (30), 225 (13), 223 (51), 211 (10), 209 (21), 159 (20), 137 (46), 132 (14), 131 (100), 124 (12), 123 (19), 118 (11), 117 (55), 109 (43), 107 (11), 95 (23), 94 (10), 92 (13), 91 (14), 81 (17), 79 (23), 77 (66), 65 (41), 63 (17).

**(E)-1-Methoxy-4-(5-methylhex-3-enyloxy)benzene E-89****(Z)-1-Methoxy-4-(5-methylhex-3-enyloxy)benzene Z-89****Method 1 – Julia olefination – premetallation with BT-sulfone:**

The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **25** (1.0 eq.), lithium diisopropylamide (0.50 M in tetrahydrofuran, 1.1 eq.) and isobutyraldehyde **88** (0.015 ml, 0.17 mmol, conc. 0.080 M). Solvent = tetrahydrofuran, T = -78 °C, time<sub>A</sub> = 15 min, time<sub>B</sub> = 15 h. The reaction was dark yellow in colour. The crude product was a bright yellow residue (0.040 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-89** to (*Z*)-alkene **Z-89** was determined to be 1 : 1 from integration of the C<sub>4</sub>-H and C<sub>5</sub>-H signals in the spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 5.53 (1H, dd, *J* 15.5, 6.1 Hz, **E-89**-C<sub>4</sub>-H), 5.42 (1H, dt, *J* 15.6, 6.3 Hz, **E-89**-C<sub>5</sub>-H), 5.38 - 5.27 (2H, m, **Z-89**-C<sub>4</sub>-H, **Z-89**-C<sub>5</sub>-H). Flash chromatographic purification (10% ethyl acetate : hexanes graded to 20% ethyl acetate : hexanes) gave an inseparable mixture of (*E*)-alkene **E-89** and (*Z*)-alkene **Z-89** as a viscous, clear colourless liquid (0.020 g, 0.091 mmol, 54%). For the purposes of characterisation a fraction containing a mixture of (*E*)-alkene **E-89** and (*Z*)-alkene **Z-89** in a 1.4 : 1 ratio was analysed: R<sub>f</sub> 0.34 (30% dichloromethane : hexanes); ν<sub>max</sub> (thin film) 1508 (s, Ar(C=C)) cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 6.83 (4H, s, Ar-H), 5.53 (1H, dd, *J* 15.5, 6.1 Hz, C<sub>4</sub>-H), 5.42 (1H, dt, *J* 15.6, 6.3 Hz, C<sub>5</sub>-H), 3.91 (2H, t, *J* 6.9 Hz, C<sub>7</sub>-H<sub>2</sub>), 3.77 (3H, s, Ar-OCH<sub>3</sub>), 2.44 (2H, q, *J* 6.7 Hz, C<sub>6</sub>-H<sub>2</sub>), 2.32 – 2.21 (1H, m, C<sub>3</sub>-H), 0.98 (6H, d, *J* 6.8 Hz, CH<sub>3</sub>); <sup>1</sup>H NMR♦ (300 MHz, CDCl<sub>3</sub>) δ: 5.38 – 5.27 (2H, m, C<sub>4</sub>-H, C<sub>5</sub>-H), 3.90 (2H, t, *J* 7.0 Hz, C<sub>7</sub>-H<sub>2</sub>), 2.69 – 2.58 (1H, m, C<sub>3</sub>-H), 2.52 (2H, q, *J* 6.5 Hz, C<sub>6</sub>-H<sub>2</sub>), 0.97 (6H, d, *J* 6.6 Hz, CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 153.8, 153.2, 153.1, 140.3, 140.2, 122.4, 122.3, 115.6, 115.5, 114.6, 68.6, 68.3, 55.7, 32.6, 31.1, 27.7, 26.7, 23.1, 22.5.

**Method 2 – Julia olefination – Barbier with BT-sulfone:**

The general Julia olefination procedure using Barbier conditions (see page 115) was followed using sulfone **25** (1.0 eq.), isobutyraldehyde **88** (0.015 ml, 0.17 mmol, conc. 0.085 M) and lithium diisopropylamide (0.50 M in tetrahydrofuran, 1.1 eq.). Solvent = tetrahydrofuran, T = -78 °C, time = 15 h. The crude product was a bright yellow residue (0.045 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-89** to (*Z*)-alkene **Z-89** was determined to be 1 : 1 from integration of the C<sub>4</sub>-H and C<sub>5</sub>-H signals in the spectra. Flash chromatographic purification (20% dichloromethane : hexanes) gave an inseparable mixture of (*E*)-alkene **E-89** and (*Z*)-alkene **Z-89** as a viscous, clear colourless liquid (0.026 g, 0.12 mmol, 71%).

**Method 3 – Julia olefination – premetallation with PT-sulfone:**

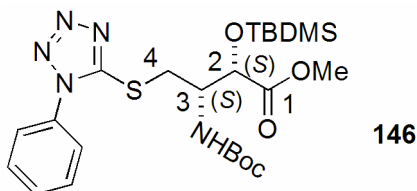
The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **26** (0.93 eq.), lithium diisopropylamide (0.50 M in tetrahydrofuran, 1.1 eq.) and isobutyraldehyde **88** (0.0040 ml, 0.044 mmol, conc. 0.15 M). Solvent = tetrahydrofuran, T = -78 °C, time<sub>A</sub> = 15 min, time<sub>B</sub> = 15 h. The crude product was a pale yellow solid (0.018 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-89** to (*Z*)-alkene **Z-89** was determined to be 2 : 1 from integration of the C<sub>4</sub>-H and C<sub>5</sub>-H signals in the spectra. Flash chromatographic purification (20% dichloromethane : hexanes) gave an inseparable mixture of (*E*)-alkene **E-89** and (*Z*)-alkene **Z-89** as a viscous, clear colourless liquid (0.0052 g, 0.024 mmol, 59%).

**Method 4 – Julia olefination – Barbier with PT-sulfone:**

The general Julia olefination procedure using Barbier conditions (see page 115) was followed using sulfone **26** (0.87 eq.), isobutyraldehyde **88** (0.0070 ml, 0.077 mmol, conc. 0.17 M) and lithium diisopropylamide (0.50 M in tetrahydrofuran, 1.0 eq.). Solvent = tetrahydrofuran, T = -78 °C, time = 15 h. The crude product was a pale yellow solid (0.030 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-89** to (*Z*)-alkene **Z-89** was determined to be 2 : 1 from integration of the C<sub>4</sub>-H and C<sub>5</sub>-H signals in the spectra. Flash chromatographic purification (20% dichloromethane : hexanes) gave an

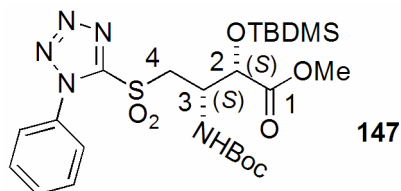
inseparable mixture of (*E*)-alkene **E-89** and (*Z*)-alkene **Z-89** as a viscous, clear colourless liquid (0.010 g, 0.045 mmol, 67%).

**(2*S*,3*S*)-Methyl 3-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldimethylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butanoate **146****



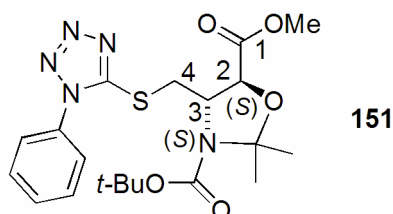
The general Mitsunobu reaction procedure (see page 117) was followed using alcohol **64** (0.15 g, 0.41 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol. Time = 3 h. The crude product was a viscous, bright yellow liquid (0.76 g). Flash chromatographic purification (15% ethyl acetate : hexanes graded to 20% ethyl acetate : hexanes) gave pure thio-ether **146** as a sticky white solid (0.19 g, 0.36 mmol, 88%);  $R_f$  0.48 (40% ethyl acetate : hexanes);  $[\alpha]_D^{20}$  +44.7 (*c* 4.2, CH<sub>2</sub>Cl<sub>2</sub>); **m.p.** 35.0 – 36.0 °C;  $\nu_{\max}$  (thin film) 3441 (br w, N-H), 1755, 1716, (br, s, C=O) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.56 – 7.52 (5H, m, Ph), 5.02 (1H, d, *J* 9.8 Hz, N-H), 4.49 – 4.33 (2H, m, C<sub>2</sub>-H, C<sub>3</sub>-H), 3.70 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.73 – 3.67 (1H, m, C<sub>4</sub>-H<sub>A</sub>), 3.44 – 3.36 (1H, m, C<sub>4</sub>-H<sub>B</sub>), 1.34 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 0.93 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.13 (3H, s, Si-CH<sub>3</sub>), 0.08 (3H, s, Si-CH<sub>3</sub>); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 171.4, 155.2, 153.9, 133.6, 130.1, 129.7, 124.1, 79.8, 72.9, 53.0, 52.2, 35.7, 28.1, 25.7, 18.3, -4.8, -5.5; **HRMS** (+ESI) calc. for C<sub>23</sub>H<sub>37</sub>N<sub>5</sub>O<sub>5</sub>SSi+Na 546.2182, found 546.2163; ***m/z*** (+ESI) 546 ([M+Na]<sup>+</sup>, 100%).

**(2*S*,3*S*)-Methyl 3-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldimethylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)butanoate **147****



The general sulfide oxidation procedure (see page 118) was followed using thio-ether **146** (0.034 g, 0.065 mmol). Time = 18 h. The crude product was a viscous, clear colourless liquid (0.099 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure sulfone **147** as a white crystalline solid (0.026 g, 0.047 mmol, 72%):  $R_f$  0.49 (40% ethyl acetate : hexanes);  $[\alpha]_D^{20}$  +16.7 ( $c$  0.9,  $\text{CH}_2\text{Cl}_2$ ); **m.p.** 94.5 – 96.0 °C;  $\nu_{\text{max}}$  (thin film) 3435 (br w, N-H), 1759, 1717, (s, C=O), 1348, 1155 (s,  $\text{SO}_2$ )  $\text{cm}^{-1}$ ;  **$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.70 – 7.54 (5H, m, Ph), 5.02 (1H, br d,  $J$  9.3 Hz, N-H), 4.72 – 4.59 (1H, m,  $\text{C}_3\text{-H}$ ), 4.49 (1H, d,  $J$  2.9 Hz,  $\text{C}_2\text{-H}$ ), 4.03 – 3.92 (2H, m,  $\text{C}_4\text{-H}_2$ ), 3.73 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 1.34 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ ), 0.94 (9H, s, Si- $\text{C}(\text{CH}_3)_3$ ), 0.14 (3H, s, Si- $\text{CH}_3$ ), 0.12 (3H, s, Si- $\text{CH}_3$ );  **$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.8, 154.5, 153.4, 133.0, 131.4, 129.6, 125.5, 80.5, 72.7, 56.8, 52.4, 49.2, 28.1, 25.7, 18.3, -4.9, -5.4; **HRMS** (+ESI) calc. for  $\text{C}_{23}\text{H}_{37}\text{N}_5\text{O}_7\text{SSi}+\text{Na}$  578.2081, found 578.2080;  **$m/z$**  (+ESI) 578 ( $[\text{M}+\text{Na}]^+$ , 100%), 456 (15).

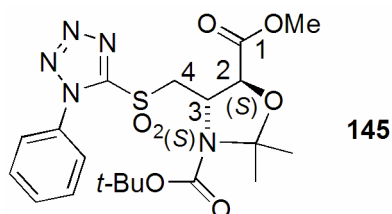
**(4*S*,5*S*)-3-*tert*-Butyl 5-methyl 2,2-dimethyl-4-((1-phenyl-1*H*-tetrazol-5-ylthio)methyl)oxazolidine-3,5-dicarboxylate **151****



The general Mitsunobu reaction procedure (see page 117) was followed using alcohol **73** (0.30 g, 1.0 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol. Time = 2 h. The crude product was a viscous, yellow liquid (1.4 g). Flash chromatographic

purification (10% ethyl acetate : hexanes graded to 15% ethyl acetate : hexanes) gave pure thio-ether **151** as a viscous, clear colourless liquid (0.36 g, 0.80 mmol, 80%):  $R_f$  0.45 (40% ethyl acetate : hexanes);  $[\alpha]_D^{19} +15.2$  ( $c$  1.7,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (thin film) 1750, 1699, (s,  $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.57 (5H, s, Ph), 4.69 – 4.66 (2H, m,  $\text{C}_2\text{-H}$ ,  $\text{C}_3\text{-H}$ ), 3.92 (2H, s,  $\text{C}_4\text{-H}_2$ ), 3.76 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 1.57 (6H, s,  $\text{C}(\text{CH}_3)_2$ ), 1.49 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C NMR}$  (50 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 170.9, 153.6, 151.6, 134.0, 130.2, 129.8, 124.1, 96.9, 81.4, 77.3, 59.2, 52.4, 36.0, 28.5, 27.8, 26.4; **HRMS** (+ESI) calc. for  $\text{C}_{20}\text{H}_{27}\text{N}_5\text{O}_5\text{S}+\text{Na}$  472.1631, found 472.1628;  $m/z$  (+ESI) 472 ( $[\text{M}+\text{Na}]^+$ , 100%).

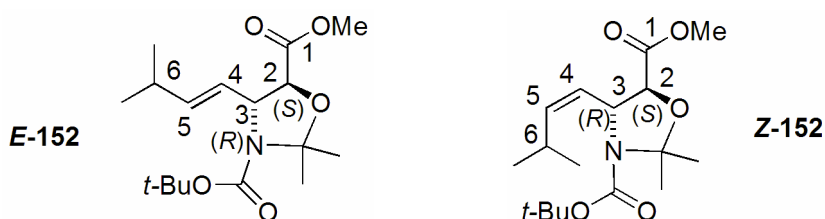
**(4S,5S)-3-tert-Butyl 5-methyl 2,2-dimethyl-4-((1-phenyl-1H-tetrazol-5-ylsulfonyl)methyl)oxazolidine-3,5-dicarboxylate 145**



The general sulfide oxidation procedure (see page 118) was followed using thio-ether **151** (0.36 g, 0.80 mmol). Time = 24 h. The crude product was a viscous, cloudy white liquid (0.43 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure sulfone **145** as a white crystalline solid (0.33 g, 0.69 mmol, 86%):  $R_f$  0.39 (40% ethyl acetate : hexanes);  $[\alpha]_D^{19} +4.7$  ( $c$  1.1,  $\text{CH}_2\text{Cl}_2$ ); **m.p.** 94.5 – 95.0 °C;  $\nu_{\text{max}}$  (thin film) 1744, 1701, (s,  $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 7.70 – 7.58 (5H, m, Ph), 5.0 (1H, d,  $J$  9.5 Hz,  $\text{C}_2\text{-H}$ ), 4.91 – 4.90 (1H, m,  $\text{C}_3\text{-H}$ ), 4.32 (1H, dd,  $J$  14.2, 2.5 Hz,  $\text{C}_4\text{-H}_A$ ), 3.96 (1H, dd,  $J$  14.2, 9.6 Hz,  $\text{C}_4\text{-H}_B$ ), 3.77 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 1.59 – 1.58 (6H, m,  $\text{C}(\text{CH}_3)_2$ ), 1.49 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C NMR}$  (50 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 170.2, 153.9, 151.0, 133.3, 131.5, 129.7, 125.5, 96.4, 82.1, 77.4, 57.7, 54.4, 52.6, 28.4, 28.0, 26.4; **HRMS** (+ESI) calc. for  $\text{C}_{20}\text{H}_{27}\text{N}_5\text{O}_7\text{S}+\text{Na}$  504.1529, found 504.1522;  $m/z$  (+ESI) 985 ( $[\text{2M}+\text{Na}]^+$ , 66%), 504 ( $[\text{M}+\text{Na}]^+$ , 100).

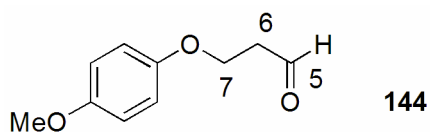
**(4*R*,5*S*,*E*)-3-*tert*-Butyl 5-methyl 2,2-dimethyl-4-(3-methylbut-1-enyl)oxazolidine-3,5-dicarboxylate *E*-152**

**(4*R*,5*S*,*Z*)-3-*tert*-Butyl 5-methyl 2,2-dimethyl-4-(3-methylbut-1-enyl)oxazolidine-3,5-dicarboxylate *Z*-152**



The general Julia olefination procedure using Barbier conditions (see page 115) was followed using sulfone **145** (1.0 eq.), isobutyraldehyde **88** (0.0070 ml, 0.077 mmol, conc. 0.075 M) and potassium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 1.5 eq.). Solvent = 1,2-dimethoxyethane, T = -60 °C, time = 15 h. The crude product was a viscous, pale-yellow liquid (0.050 g). Flash chromatographic purification (10% ethyl acetate : hexanes) gave an inseparable mixture of (*E*)-alkene **E-152** and (*Z*)-alkene **Z-152** in a 2 : 1 ratio (determined by integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra) contaminated with unknown impurities as a viscous, clear colourless liquid (0.0040 g, 0.012 mmol, 16%): **R<sub>f</sub>** 0.54 (40% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 5.66 (1H, dd, *J* 15.6, 6.2 Hz, C<sub>5</sub>-H), 5.38 (1H, dd, *J* 14.8, 8.1 Hz, C<sub>4</sub>-H), 4.59 – 4.57 (1H, m, C<sub>3</sub>-H), 4.34 (1H, d, *J* 3.5 Hz, C<sub>2</sub>-H), 3.79 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 2.37 – 2.27 (1H, m, C<sub>6</sub>-H), 1.63 (3H, s, NC(CH<sub>3</sub>)<sub>2</sub>O), 1.59 (3H, s, NC(CH<sub>3</sub>)<sub>2</sub>O), 1.56 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 1.01 (6H, dd, *J* 6.7, 0.9 Hz, C(CH<sub>3</sub>)<sub>2</sub>); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 5.60 – 5.25 (2H, m (obs), C<sub>5</sub>-H, C<sub>4</sub>-H), 4.99 – 4.95 (1H, m, C<sub>3</sub>-H), 4.28 (1H, d, *J* 3.8 Hz, C<sub>2</sub>-H), 3.75 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 2.77 – 2.68 (1H, m, C<sub>6</sub>-H).

A second fraction gave recovered-sulfone **145** as a white solid (0.021 g, 0.044 mmol, 58%).

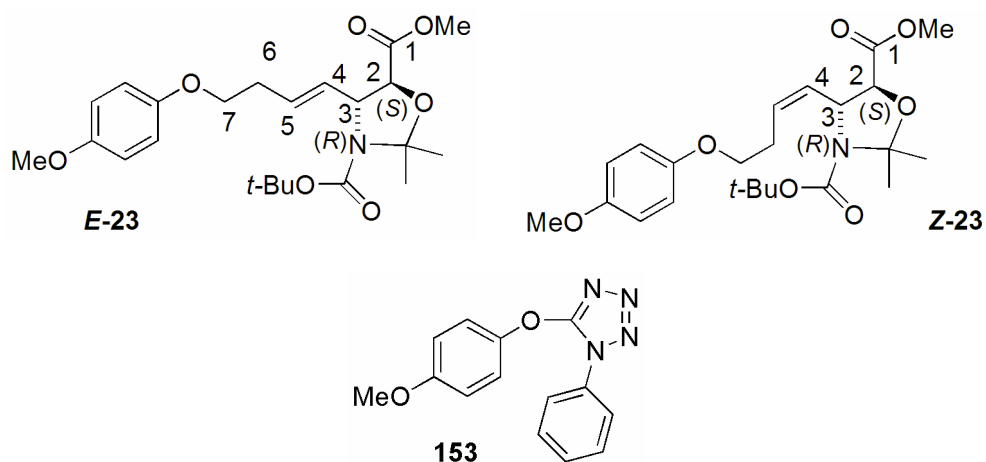
**3-(4-Methoxyphenoxy)propanal<sup>71</sup> 144**

The general Dess-Martin oxidation procedure (see page 114) was followed using alcohol **85** (0.90 g, 4.9 mmol). Time = 2 h 30 min. The crude product was pure aldehyde **144** as a fruity-smelling orange liquid (0.84 g, 4.7 mmol, 96%):  $R_f$  0.32 – 0.47 (40% ethyl acetate : hexanes);  $\nu_{\max}$  (thin film) 1724 (m, C=O), 1508 (s, Ar(C=C))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.74 – 9.72 (1H, m, CHO), 6.79 (4H, s, Ar-H), 4.15 (2H, t,  $J$  6.0 Hz,  $\text{C}_7\text{-H}_2$ ), 3.68 (3H, s, Ar-OCH<sub>3</sub>), 2.75 (2H, dt,  $J$  6.0, 1.4 Hz,  $\text{C}_6\text{-H}_2$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 200.9, 154.5, 153.0, 116.0, 115.0, 62.7, 55.9, 43.6.

**(4*R*,5*S*,*E*)-3-*tert*-Butyl 5-methyl 4-(4-(4-methoxyphenoxy)but-1-enyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *E*-23**

**(4*R*,5*S*,*Z*)-3-*tert*-Butyl 5-methyl 4-(4-(4-methoxyphenoxy)but-1-enyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *Z*-23**

**5-(4-Methoxyphenoxy)-1-phenyl-1*H*-tetrazole<sup>72, 73</sup> 153**



### **Method 1 – Julia olefination – Barbier:**

The general Julia olefination procedure using Barbier conditions (see page 115) was followed using sulfone **26** (1.1 eq.), crude aldehyde **24** (1.2 g – assumed quantitative for previous step, 4.0 mmol, conc. 0.10 M) and potassium bis(trimethylsilyl)amide (0.50 M in toluene, 1.5 eq.). Solvent = 1,2-dimethoxyethane, T = -60 °C, time = 1 h 15 min. The crude product was an orange residue (2.6 g). Flash chromatographic purification (5% ethyl acetate : 45% dichloromethane : hexanes) gave pure (*E*)-alkene **E-23** as a viscous, clear colourless liquid (0.53 g, 1.2 mmol, 30%):  $R_f$  0.21 (5% ethyl acetate : 45% DCM : hexanes);  $[\alpha]_D^{17} +46.7$  (c 4.0, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (thin film) 1759, 1735, 1701 (s, C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.68 (4H, s, Ar-H), 5.67 (1H, dt, *J* 15.3, 6.6 Hz, C<sub>5</sub>-H), 5.45 (1H, dd, *J* 15.3, 7.5 Hz, C<sub>4</sub>-H), 4.51 – 4.47 (1H, m, C<sub>3</sub>-H), 4.22 (1H, d, *J* 3.6 Hz, C<sub>2</sub>-H), 3.82 (2H, t, *J* 6.6 Hz, C<sub>7</sub>-H<sub>2</sub>), 3.64 (3H, s, Ar-OCH<sub>3</sub>), 3.62 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 2.39 (2H, q, *J* 6.5 Hz, C<sub>6</sub>-H<sub>2</sub>), 1.50 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.45 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.29 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (50 MHz,

CDCl<sub>3</sub>)  $\delta$ : 171.1, 153.8, 152.9, 151.4, 130.5, 129.6, 115.5, 114.6, 96.1, 80.2, 78.6, 67.7, 61.7, 55.6, 52.4, 32.1, 28.3, 27.3, 26.4; **HRMS** (+ESI) calc. for C<sub>23</sub>H<sub>33</sub>NO<sub>7</sub>+Na 458.2155, found 458.2140; **m/z** (+ESI) 500 (15) 458 ([M+Na]<sup>+</sup>, 100), 402 (18), 358 (4), 336 (9).

A second fraction gave a mixture of (*E*)-alkene **E-23** and (*Z*)-alkene **Z-23** in a 1.1 : 1 ratio (determined by integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra) as a viscous, yellow liquid (0.68 g, 1.6 mmol, 40 %).

For the purposes of characterization, flash chromatographic purification (15% ethyl acetate : hexanes) of the mixed fraction gave pure (*Z*)-alkene **Z-23** as a viscous, clear, pale yellow liquid: **R<sub>f</sub>** 0.22 (5% ethyl acetate : 45% DCM : hexanes); **[ $\alpha$ ]<sub>D</sub><sup>17</sup>** +105.5 (*c* 0.7, CH<sub>2</sub>Cl<sub>2</sub>); **v<sub>max</sub>** (thin film) 1759, 1738, 1697 (s, C=O) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, 320 K, CDCl<sub>3</sub>)  $\delta$ : 6.83 (4H, s, Ar-H), 5.69 (1H, dt, *J* 7.2, 4.9 Hz, C<sub>5</sub>-H), 5.53 (1H, dd, *J* 7.1, 6.2 Hz, C<sub>4</sub>-H), 4.98 (1H, dd, *J* 6.0, 2.6 Hz, C<sub>3</sub>-H), 4.33 (1H, d, *J* 2.8 Hz, C<sub>2</sub>-H), 4.00 – 3.94 (2H, m, C<sub>7</sub>-H<sub>2</sub>), 3.77 (6H, s, 2 x OMe), 2.67 – 2.63 (2H, m, C<sub>6</sub>-H<sub>2</sub>), 1.64 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.61 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.45 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); **<sup>13</sup>C NMR** (75 MHz, 320 K, CDCl<sub>3</sub>)  $\delta$ : 170.9, 154.1, 153.2, 151.6, 131.3, 128.5, 115.7, 114.8, 96.3, 80.4, 79.2, 68.0, 57.5, 55.8, 52.4, 28.5, 27.9, 27.4, 26.6.

### **Method 2 – Julia olefination – Barbier – reversed system:**

The general Julia olefination procedure using Barbier conditions (see page 115) was followed using sulfone **145** (1.0 eq.), crude aldehyde **144** (0.021 g – assumed quantitative for previous step, 0.12 mmol, conc. 0.080 M) and potassium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 1.5 eq.). Solvent = 1,2-dimethoxyethane, T = -60 °C, time = 1 h 15 min. Flash chromatographic purification (20% ethyl acetate : hexanes) gave by-product **153** as a viscous, clear colourless liquid (0.014 g, 0.052 mmol, 43%): **R<sub>f</sub>** 0.47 (40% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.84 – 7.78 (2H, m, PT-Ar-H), 7.63 – 7.50 (3H, m, PT-Ar-H), 7.36 – 7.28 (2H, m, Ar-H), 6.99 – 6.91 (2H, m, Ar-H), 3.83 (3H, s, Ar-OCH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 157.8, 147.1, 139.3, 129.7, 129.4, 122.1, 120.6, 114.9, 55.7.

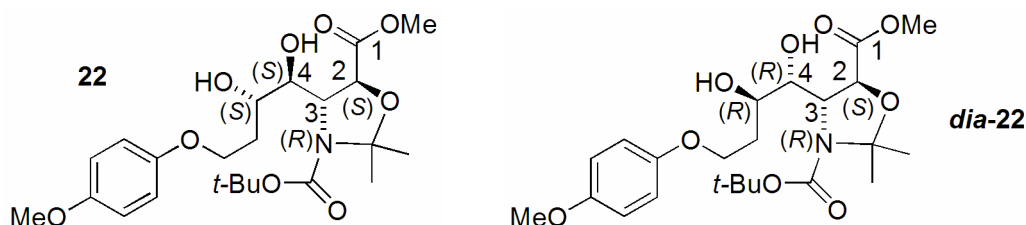
A second fraction gave recovered-sulfone **145** as a white crystalline solid (0.010 g, 0.021 mmol, 18%).

**Method 3 – Alkene isomerisation:**

The general *Z* to *E* isomerisation procedure (see page 113) was followed using a mixture of (*E*)-alkene **E-23** and (*Z*)-alkene **Z-23** in a 1 : 8 ratio (0.44 g, 1.0 mmol, 0.080 M) and thiophenol (1.0 eq.). Time<sub>A</sub> = 10 days. An additional aliquot of AIBN (0.10 eq.) was added every day. Time<sub>B</sub> = 2 h. The crude product was an oily residue (0.99 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-23** to (*Z*)-alkene **Z-23** was determined to be 6.5 : 1 from integration of the C<sub>4</sub>-H signals in the spectra. Flash chromatographic purification (5% ethyl acetate : 45% dichloromethane : hexanes) gave a mixture of (*E*)-alkene **E-23** and (*Z*)-alkene **Z-23** as a viscous, clear, colourless liquid (0.43 g, 0.99 mmol, 98%).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((1*S*,2*S*)-1,2-dihydroxy-4-(4-methoxyphenoxy)butyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **22****

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((1*R*,2*R*)-1,2-dihydroxy-4-(4-methoxyphenoxy)butyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *dia*-**22****

**Method 1 – No ligand:**

To a solution of alkene **E-23** (0.010 g, 0.023 mmol) in tetrahydrofuran (0.070 ml) and water (0.010 ml), was added a solution of osmium tetroxide (2.5%(w/w) in *tert*-butyl alcohol, 0.030 ml, 0.0024 mmol). To the grey reaction mixture was added a solution of 4-methylmorpholine *N*-oxide (0.0090 g, 0.077 mmol) in water (0.015 ml). The reaction was stirred at room temperature (~ 28 °C) for 2 h. Sodium sulfite solution (sat. aq., 10 ml) was added, the reaction was stirred for 1 h and the crude product was extracted into ethyl acetate (3 x 50 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a yellow residue (0.052 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of diol **22** to diol *dia*-**22** was determined to be 2 : 1 from

integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the spectra: **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ: 4.79 (1H, s, **22**-C<sub>2</sub>-H), 4.67 (1H, dd, *J* 7.9, 2.0 Hz, **dia-22**-C<sub>3</sub>-H), 4.57 (1H, d, *J* 2.2 Hz, **dia-22**-C<sub>2</sub>-H), 4.35 (1H, d, *J* 9.1 Hz, **22**-C<sub>3</sub>-H). Flash chromatographic purification (40% ethyl acetate : hexanes) gave an inseparable mixture of diol **22** and diol **dia-22** as a viscous, pale yellow liquid (0.0051 g, 0.011 mmol, 48%).

### **Method 2 – DHQ-IND ligand:**

The general AD procedure (see page 113) was followed using DHQ-IND ligand and alkene **E-23** (0.23 g, 0.53 mmol). The reaction was stirred at room temperature (approx. 17 °C) for 10 h and was heated at 27 °C for 4 h. The crude product was an orange residue (0.51 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave an inseparable mixture of diol **22** and diol **dia-22** in a 7.4 : 1 ratio (determined by integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra) as a viscous, clear, pale yellow liquid (0.21 g, 0.45 mmol, 85%). Data for the major isomer only are quoted where appropriate: **R<sub>f</sub>** 0.17 (40% ethyl acetate : hexanes); **[α]<sub>D</sub><sup>21</sup>** +9.6 (*c* 3.4, CH<sub>2</sub>Cl<sub>2</sub>); **v<sub>max</sub>** (thin film) 3427 (s, O-H), 1759, 1740, 1666 (s, C=O) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ: 6.80 (4H, s, Ar-H), 4.79 (1H, s, C<sub>2</sub>-H), 4.35 (1H, d, *J* 9.1 Hz, C<sub>3</sub>-H), 4.24 (1H, s, C<sub>5</sub>-OH), 4.13 – 4.01 (2H, m, C<sub>7</sub>-H<sub>2</sub>), 3.90 – 3.86 (1H, m, C<sub>5</sub>-H), 3.78 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.75 (3H, s, Ar-OCH<sub>3</sub>), 3.36 (1H, br d, *J* 9.5 Hz, C<sub>4</sub>-H), 2.63 (1H, s, C<sub>4</sub>-OH), 2.16 – 2.07 (1H, m, C<sub>6</sub>-H<sub>A</sub>), 1.99 – 1.90 (1H, m, C<sub>6</sub>-H<sub>B</sub>), 1.61 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.48 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.47 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ: 171.8, 153.8, 153.7, 153.0, 115.5, 114.6, 96.2, 82.1, 76.6, 74.4, 65.6, 65.3, 61.6, 55.7, 52.5, 32.4, 28.6, 28.3, 27.2; **HRMS** (+ESI) calc. for C<sub>23</sub>H<sub>35</sub>NO<sub>9</sub>+Na 492.2210, found 492.2203; ***m/z*** (+ESI) 961 ([2M+Na]<sup>+</sup>, 30%), 492 ([M+Na]<sup>+</sup>, 100), 463 (9), 370 (15), 103 (9).

### **Method 3 – DHQD-IND ligand:**

The general AD procedure (see page 113) was followed using DHQD-IND ligand and alkene **E-23** (0.020 g, 0.046 mmol). The crude product was a brown residue (0.015 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave an inseparable mixture of diol **22** and diol **dia-22** in a 1 : 5.1 ratio (determined by integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra) as

a viscous, clear, pale yellow liquid (0.0042 g, 0.0089 mmol, 19%). Data for the major isomer only are quoted:  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.83 (4H, s, Ar-H), 4.67 (1H, dd,  $J$  7.9, 2.2 Hz,  $\text{C}_3\text{-H}$ ), 4.56 (1H, d,  $J$  2.2 Hz,  $\text{C}_2\text{-H}$ ), 4.17 – 4.07 (2H, m,  $\text{C}_7\text{-H}_2$ ), 4.02 – 3.92 (1H, m,  $\text{C}_5\text{-H}$ ), 3.79 (3H, s, OMe), 3.77 (3H, s, OMe), 3.68 (1H, t,  $J$  7.0 Hz,  $\text{C}_4\text{-H}$ ), 2.16 – 1.94 (2H, m,  $\text{C}_6\text{-H}_2$ ), 1.64 (3H, s,  $\text{C}(\text{C}_\text{A}\text{H}_3)(\text{C}_\text{B}\text{H}_3)$ ), 1.61 (3H, s,  $\text{C}(\text{C}_\text{A}\text{H}_3)(\text{C}_\text{B}\text{H}_3)$ ), 1.49 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ ).

**Method 4 – DHQ-CLB ligand:**

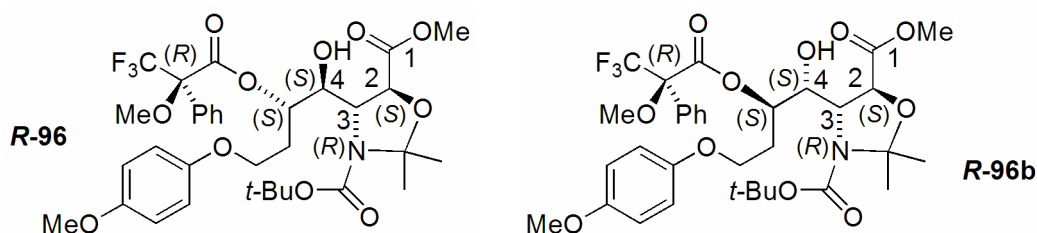
The general AD procedure (see page 113) was followed using DHQ-CLB ligand and alkene **E-23** (0.020 g, 0.046 mmol). The crude product was an off-white solid (0.037 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave an inseparable mixture of diol **22** and diol **dia-22** in a 3.3 : 1 ratio (determined by integration of the  $\text{C}_2\text{-H}$  and  $\text{C}_3\text{-H}$  signals in the  $^1\text{H NMR}$  spectra) as a viscous, clear, pale yellow liquid (0.0023 g, 0.0049 mmol, 11%).

**Method 5 – DHQD-CLB ligand:**

The general AD procedure (see page 113) was followed using DHQD-CLB ligand and alkene **E-23** (0.020 g, 0.046 mmol). The crude product was an off-white solid (0.036 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave an inseparable mixture of diol **22** and diol **dia-22** in a 1 : 2.5 ratio (determined by integration of the  $\text{C}_2\text{-H}$  and  $\text{C}_3\text{-H}$  signals in the  $^1\text{H NMR}$  spectra) as a viscous, clear, pale yellow liquid (0.0010 g, 0.0021 mmol, 5%).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((1*S*,2*S*)-1-hydroxy-4-(4-methoxyphenoxy)-2-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)butyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *R*-96**

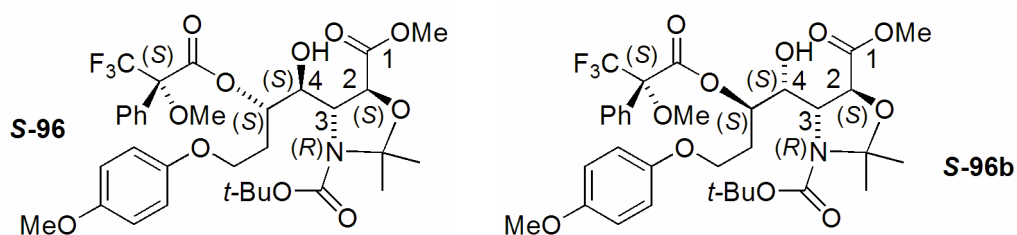
**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((1*R*,2*R*)-1-hydroxy-4-(4-methoxyphenoxy)-2-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)butyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *R*-96b**



The general procedure for formation of MTPA esters *via* Method 2 (see page 117) was followed using (*R*)-MTPA acid and a mixture of diol **22** and diol **dia-22** (**22** : **dia-22** = 3.3 : 1, 0.0093 g, 0.020 mmol). The crude product was an off-white powder (0.012 g). Flash chromatographic purification (30% ethyl acetate : hexanes) gave a mixture of (*R*)-Mosher's ester **R-96** and (*R*)-Mosher's ester **R-96b** in a 1.8 : 1 ratio (determined by integration of the C<sub>5</sub>-H signals in the <sup>1</sup>H NMR spectra) as a viscous, clear colourless liquid (0.023 g, 0.0034 mmol, 37%). NMR data were assigned using COSY NMR correlations and that corresponding to ester **R-96** (the major product) is quoted first: **R<sub>f</sub>** 0.42 (40% ethyl acetate : hexanes); <sup>1</sup>H NMR (200 MHz, 340 K, CDCl<sub>3</sub>) δ: 7.66 – 7.57 (2H, m, MTPA-Ar-H), 7.40 – 7.33 (3H, m, MTPA-Ar-H), 6.81 (4H, s, Ar-H), 5.37 – 5.27 (1H, m, C<sub>5</sub>-H), 4.85 (1H, d, *J* 2.8 Hz, C<sub>2</sub>-H), 4.46 (1H, t, *J* 2.9 Hz, C<sub>3</sub>-H), 4.20 – 4.12 (1H, m, C<sub>4</sub>-H), 4.09 – 3.95 (2H, m, C<sub>7</sub>-H<sub>2</sub>), 3.77 (6H, s, Ar-OCH<sub>3</sub>, C<sub>1</sub>-OCH<sub>3</sub>), 3.57 – 3.57 (3H, m, MTPA-OCH<sub>3</sub>), 2.42 – 2.29 (1H, m, C<sub>6</sub>-H<sub>A</sub>), 2.21 – 2.11 (1H, m (obs), C<sub>6</sub>-H<sub>B</sub>), 1.50 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>), 1.48 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); <sup>1</sup>H NMR♦ (200 MHz, 340 K, CDCl<sub>3</sub>) δ: 6.80 (4H, s, Ar-H), 5.53 - 5.49 (1H, m, C<sub>5</sub>-H), 4.72 (1H, d, *J* 6.3 Hz, C<sub>4</sub>-H), 4.67 - 4.64 (1H, m, C<sub>3</sub>-H), 4.52 - 4.51 (1H, m, C<sub>2</sub>-H).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((1*S*,2*S*)-1-hydroxy-4-(4-methoxyphenoxy)-2-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)butyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **S-96****

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((1*R*,2*R*)-1-hydroxy-4-(4-methoxyphenoxy)-2-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)butyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **S-96b****

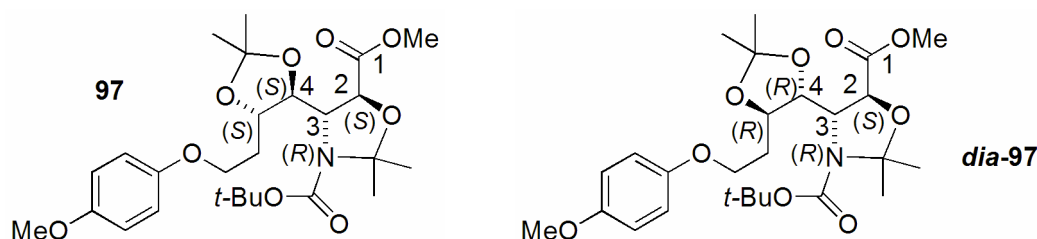


The general procedure for formation of MTPA esters *via* Method 1 (see page 117) was followed using (*S*)-MTPA acid and a mixture of diol **22** and diol **dia-22** (**22** : **dia-22** = 5 : 1, 1.4 mg, 3.0  $\mu$ mol). A second addition of (*S*)-MTPA acid (0.012 g, 0.051 mmol, 17 eq.) followed by a solution of 1,3-dicyclohexylcarbodiimide (1.0 M in dichloromethane, 8.0  $\mu$ l, 2.8 eq.) was made after 2 h 30 min. The crude product was an off-white powder (0.014 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave a mixture of (*S*)-Mosher's ester **S-96** and (*S*)-Mosher's ester **S-96b** in a 2.4 : 1 ratio (determined by integration of the C<sub>5</sub>-H and C<sub>2</sub>-H signals in the <sup>1</sup>H NMR spectra) with some impurities as a viscous, clear colourless liquid (0.6 mg, 0.9  $\mu$ mol, 30%). NMR data were assigned using COSY NMR correlations and that corresponding to ester **S-96** (the major product) only is quoted first: **R<sub>f</sub>** 0.40 (40% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, 340 K, CDCl<sub>3</sub>)  $\delta$ : 7.59 – 7.54 (2H, m (obs), MTPA-Ar-H), 7.44 – 7.34 (3H, m (obs), MTPA-Ar-H), 6.85 – 6.76 (4H, m, Ar-H), 5.39 – 5.29 (1H, m, C<sub>5</sub>-H), 4.84 (1H, d, *J* 2.9 Hz, C<sub>2</sub>-H), 4.50 (1H, t, *J* 3.0 Hz, C<sub>3</sub>-H), 4.17 (1H, dd, *J* 7.1, 3.1 Hz, C<sub>4</sub>-H), 3.95 – 3.81 (2H, m, C<sub>7</sub>-H<sub>2</sub>), 3.77 (6H, s, Ar-OCH<sub>3</sub>, C<sub>1</sub>-OCH<sub>3</sub>), 3.59 – 3.59 (3H, m (obs), MTPA-OCH<sub>3</sub>), 2.36 – 2.22 (1H, m, C<sub>6</sub>-H<sub>A</sub>), 2.15 – 1.98 (1H, m, C<sub>6</sub>-H<sub>B</sub>), 1.61 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>), 1.58 (3H, s, C(CH<sub>3</sub>)<sub>2</sub>), 1.49 (9H, s (obs), BOC C(CH<sub>3</sub>)<sub>3</sub>);

$^1\text{H NMR}$  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 5.43 – 5.37 (1H, m,  $\text{C}_5\text{-H}$ ), 4.67 (1H, dd,  $J$  6.3, 2.3 Hz,  $\text{C}_4\text{-H}$ ), 4.44 – 4.38 (1H, m,  $\text{C}_3\text{-H}$ ).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*S*,5*S*)-5-(2-(4-methoxyphenoxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **97****

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*R*,5*R*)-5-(2-(4-methoxyphenoxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *dia*-**97****

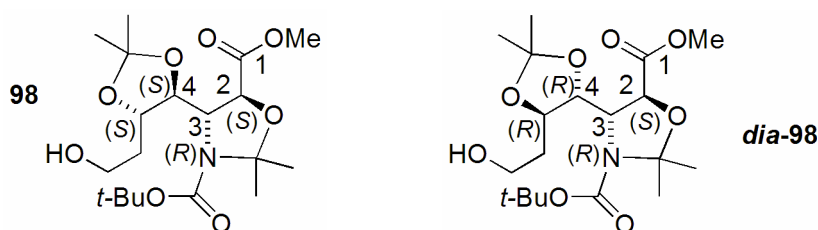


To a solution of diol **22** and diol *dia*-**22** (**22** : *dia*-**22** = 7 : 1, 0.053 g, 0.11 mmol) in dichloromethane (1.0 ml) was added 2,2-dimethoxypropane (0.028 ml, 0.23 mmol) followed by (1*S*)-(+)-10-camphorsulfonic acid (0.0053 g, 0.023 mmol). The reaction was stirred at room temperature for 10 min. An additional aliquot of 2,2-dimethoxypropane (0.050 ml, 0.41 mmol) was added and the reaction was stirred for 25 min. A solution of sodium hydrogen carbonate (sat. aq., 10 ml) was added and the crude product was extracted into dichloromethane (3 x 20 ml). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give a pale yellow residue (0.063 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave an inseparable mixture of acetal **97** and acetal *dia*-**97** in a 7 : 1 ratio (determined by integration of the  $\text{C}_2\text{-H}$  signals in the  $^1\text{H NMR}$  spectra:  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.70 (1H, d,  $J$  1.6 Hz, **97**- $\text{C}_2\text{-H}$ ), 4.64 (1H, d,  $J$  2.8 Hz, *dia*-**97**- $\text{C}_2\text{-H}$ ) as a viscous, clear, colourless liquid (0.057 g, 0.11 mmol, 99%). Data for the major isomer only are quoted where appropriate:  $R_f$  0.50 (40% ethyl acetate : hexanes);  $[\alpha]_D^{23}$  +0.8 ( $c$  6.4,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (thin film) 1759, 1738, 1704 (s,  $\text{C}=\text{O}$ ), 1510 (Ar( $\text{C}=\text{C}$ ))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 6.88 – 6.77 (4H, m, Ar-H), 4.72 (1H, d,  $J$  2.2 Hz,  $\text{C}_2\text{-H}$ ), 4.47 (1H, dd,  $J$  4.9, 2.2 Hz,  $\text{C}_3\text{-H}$ ), 4.19 – 3.98 (4H, m,  $\text{C}_5\text{-H}$ ,  $\text{C}_7\text{-H}_2$ ,  $\text{C}_4\text{-H}$ ), 3.75 (3H, s, Ar- $\text{OCH}_3$ ), 3.74 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 2.19 – 1.89 (2H, m,  $\text{C}_6\text{-H}_2$ ), 1.63 (3H, s,

NC(CH<sub>3</sub>)<sub>2</sub>O), 1.59 (3H, s, NC(CH<sub>3</sub>)<sub>2</sub>O), 1.49 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 1.41 (3H, s, OC(CH<sub>3</sub>)<sub>2</sub>O), 1.4 (3H, s, OC(CH<sub>3</sub>)<sub>2</sub>O); <sup>13</sup>C NMR (50 MHz, 340 K, CDCl<sub>3</sub>) δ: 172.0, 154.2, 153.4, 151.8, 115.9, 114.9, 109.0, 96.8, 80.9, 80.7, 75.8, 75.1, 65.8, 61.2, 55.8, 52.2, 33.6, 28.4, 27.7, 27.4, 27.2, 27.1; HRMS (+ESI) calc. for C<sub>26</sub>H<sub>39</sub>NO<sub>9</sub>+Na 532.2523, found 532.2494; *m/z* (+ESI) 532 ([M+Na]<sup>+</sup>, 100%), 410 (18).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*S*,5*S*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **98****

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*R*,5*R*)-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *dia*-**98****

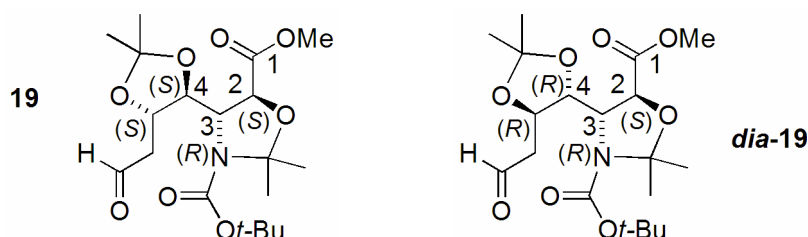


To a solution of acetal **97** and acetal *dia*-**97** (**97** : *dia*-**97** = 7 : 1, 0.065 g, 0.13 mmol) in acetonitrile (1.3 ml) at 0 °C, was added drop-wise a solution of ammonium cerium(IV) nitrate (0.16 g, 0.29 mmol) in water (1.3 ml). The solution was stirred at 0 °C for 18 min. The reaction was diluted with chloroform (20 ml) and water (10 ml) and the layers were separated. The aqueous layer was extracted with chloroform (2 x 20 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a viscous yellow liquid (0.078 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave an inseparable mixture of alcohol **98** and alcohol *dia*-**98** in a 7 : 1 ratio (determined by integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 4.70 (1H, d, *J* 2.2 Hz, **98**-C<sub>2</sub>-H), 4.66 – 4.61 (2H, m, *dia*-**98**-C<sub>2</sub>-H, *dia*-**98**-C<sub>3</sub>-H)) as a clear, viscous, pale yellow liquid (0.049 g, 0.12 mmol, 92%). Data for the major isomer only are quoted where appropriate: *R*<sub>f</sub> 0.23 (40% ethyl acetate : hexanes); [α]<sub>D</sub><sup>23</sup> -5.9 (*c* 0.7, CH<sub>2</sub>Cl<sub>2</sub>); *v*<sub>max</sub> (thin film) 3458 (br, s, O-H), 1760, 1734, 1690 (br, s, C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, 320 K,

CDCl<sub>3</sub>)  $\delta$ : 4.70 (1H, d,  $J$  2.1 Hz, C<sub>2</sub>-H), 4.44 – 4.42 (1H, m, C<sub>3</sub>-H), 4.21 – 4.08 (1H, m, C<sub>5</sub>-H), 3.96 (1H, dd,  $J$  8.3, 5.2 Hz, C<sub>4</sub>-H), 3.82 – 3.78 (2H, m, C<sub>7</sub>-H), 3.77 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 2.10 (1H, s, C<sub>7</sub>-OH), 1.93 – 1.78 (2H, m, C<sub>6</sub>-H), 1.60 (3H, s, NC(CH<sub>3</sub>)<sub>2</sub>O), 1.56 (3H, s, NC(CH<sub>3</sub>)<sub>2</sub>O), 1.47 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 1.40 (6H, s, OC(CH<sub>3</sub>)<sub>2</sub>O); <sup>13</sup>C NMR (50 MHz, 320 K, CDCl<sub>3</sub>)  $\delta$ : 172.1, 151.9, 109.1, 96.7, 81.1, 80.4, 77.6, 75.0, 60.9, 60.6, 52.4, 35.5, 28.4, 27.7, 27.3, 27.1, 27.0; HRMS (+ESI) calc. for C<sub>19</sub>H<sub>33</sub>NO<sub>8</sub>+Na 426.2104, found 426.2095;  $m/z$  (+ESI) 426 ([M+Na]<sup>+</sup>, 100%), 387 (55).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*S*,5*S*)-2,2-dimethyl-5-(2-oxoethyl)-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **19****

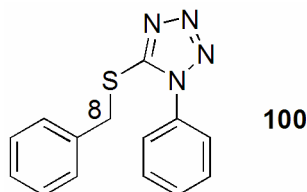
**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*R*,5*R*)-2,2-dimethyl-5-(2-oxoethyl)-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *dia*-**19****



The general Dess-Martin oxidation procedure (see page 114) was followed using alcohol **98** and alcohol *dia*-**98** (**98** : *dia*-**98** = 7 : 1, 0.11 g, 0.27 mmol). Time = 45 min. The crude product was a cloudy yellow residue (0.11 g). For the purpose of characterization, flash chromatographic purification (20% ethyl acetate : hexanes) of a small amount of crude product gave an inseparable mixture of aldehyde **19** and aldehyde *dia*-**19** in a 7 : 1 ratio (determined by integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.73 (1H, d,  $J$  2.0 Hz, **19** C<sub>2</sub>-H), 4.68 – 4.65 (2H, m, *dia*-**19** C<sub>2</sub>-H, C<sub>3</sub>-H)) as a viscous, clear, colourless liquid. Data for the major isomer only are quoted where appropriate:  $R_f$  0.32 to 0.50 (40% ethyl acetate : hexanes);  $[\alpha]_D^{26}$  -5.9 (c 1.2, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (thin film) 1763, 1732, 1693 (s, C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, 320 K, CDCl<sub>3</sub>)  $\delta$ : 9.80 (1H, t,  $J$  2.1 Hz, CHO), 4.73 (1H, d,  $J$  2.0 Hz, C<sub>2</sub>-H), 4.51 – 4.47 (2H, m, C<sub>3</sub>-H, C<sub>5</sub>-H), 3.94 (1H, dd,  $J$  8.1, 6.0 Hz, C<sub>4</sub>-H), 3.79 (3H, s,

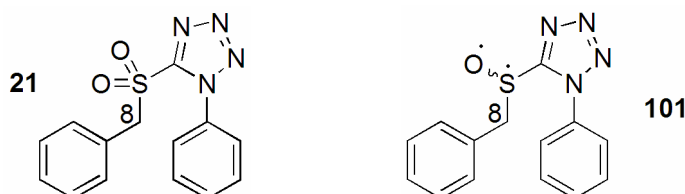
C<sub>1</sub>-OCH<sub>3</sub>), 2.67 – 2.61 (2H, m, C<sub>6</sub>-H<sub>2</sub>), 1.61 (3H, s, NC(CH<sub>3</sub>)<sub>2</sub>O), 1.56 (3H, s, NC(CH<sub>3</sub>)<sub>2</sub>O), 1.48 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 1.42 (3H, s, OC(CH<sub>3</sub>)<sub>2</sub>O), 1.40 (3H, s, OC(CH<sub>3</sub>)<sub>2</sub>O); <sup>13</sup>C NMR (50 MHz, 320 K, CDCl<sub>3</sub>) δ: 199.4, 171.9, 151.9, 109.5, 96.7, 81.3, 80.3, 75.2, 73.7, 61.0, 52.5, 46.7, 28.4, 27.9, 27.2, 26.9.

### 5-(Benzylthio)-1-phenyl-1*H*-tetrazole<sup>74</sup> **100**



The general Mitsunobu reaction procedure (see page 117) was followed using benzyl alcohol (1.0 ml, 9.7 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol. Time = 1 h. The crude product was a bright yellow liquid (11 g). Flash chromatographic purification (70% dichloromethane : hexanes graded to 80% dichloromethane : hexanes) gave pure thio-ether **100** as a clear colourless liquid which crystallised on standing to a white crystalline solid (1.6 g, 6.0 mmol, 62%): **R<sub>f</sub>** 0.49 (40% ethyl acetate : hexanes); **m.p.** 69.5 – 70.5 °C; **v<sub>max</sub>** (thin film) 3061, 3028 (w, Ar(C-H)), 1597 (m, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.44 (5H, s, Ph), 7.36 – 7.21 (5H, m, Ph), 4.55 (2H, s, C<sub>8</sub>H<sub>2</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 153.9, 135.2, 133.6, 130.1, 129.7, 129.2, 128.8, 128.1, 123.8, 37.6; **HRMS** (+EI) calc. for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>S 268.0783, found 268.0789; **m/z** (+EI) 268 ([M]<sup>+</sup>, 19%), 240 (13), 239 (24), 207 (40), 194 (11), 167 (34), 131 (25), 123 (12), 121 (15), 118 (25), 91 (100), 77 (27), 65 (60), 63 (20), 51 (29).

**5-(Benzylsulfonyl)-1-phenyl-1H-tetrazole<sup>75</sup> **21****  
**Sulfoxide **101****



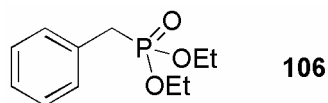
**Method 1 – Sulfide starting material:**

The general sulfide oxidation procedure (see page 118) was followed using thio-ether **100** (0.69 g, 2.6 mmol). Time = 4 h. The crude product was an off-white crystalline solid (1.1 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure sulfone **21** as a white crystalline solid (0.53 g, 1.8 mmol, 69%):  $R_f$  0.48 (40% ethyl acetate : hexanes); **m.p.** 163.5 – 164.5 °C;  $\nu_{max}$  (thin film) 3068, 3059 (w, Ar(C-H)), 1346, 1155 (m, SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.57 – 7.30 (10H, m, Ph), 4.97 (2H, s, C<sub>8</sub>H<sub>2</sub>); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 152.9, 132.8, 131.6, 131.3, 129.8, 129.3, 129.1, 125.3, 124.7, 62.3; **HRMS** (+EI) calc. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>N<sub>4</sub>S 300.0681, found 300.0679; **m/z** (+EI) 300 ([M]<sup>+</sup>, 1%), 91 (100), 65 (38).

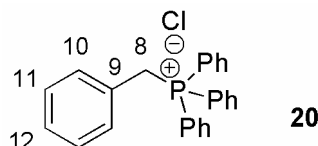
A second fraction gave sulfoxide **101** as a viscous, clear colourless liquid (0.20 g, 0.70 mmol, 27%):  $R_f$  0.32 (40% ethyl acetate : hexanes); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.48 – 7.08 (10H, m, 2 x Ph), 4.83 (1H, d, *J* 12.6 Hz, C<sub>8</sub>H<sub>A</sub>), 4.65 (1H, d, *J* 12.8 Hz, C<sub>8</sub>H<sub>B</sub>).

**Method 2 – Sulfoxide starting material:**

The general sulfide oxidation procedure (see page 118) was followed using sulfoxide **101** (0.20 g, 0.70 mmol). Time = 14 h. The crude product was an off-white crystalline solid (0.25 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure sulfone **21** as a white crystalline solid (0.20 g, 0.67 mmol, 96%).

**Diethyl benzylphosphonate<sup>76</sup> 106**

Benzyl bromide (10 ml, 84 mmol) was added drop-wise to stirring triethyl phosphite (16 ml, 93 mmol) at room temperature. The reaction was stirred at room temperature for 45 min, heated at 150 °C for 4 h and allowed to cool to room temperature. The excess of unreacted triethyl phosphite was removed under high vacuum (~ 2 mmHg) to give a clear colourless liquid. Fractional distillation under high vacuum gave pure diethyl benzylphosphonate **106** as a clear colourless liquid (13 g, 57 mmol, 68%, b.p. 135 – 137 °C) which was used without further purification in subsequent reactions. For the purposes of characterisation, flash chromatographic purification (40% ethyl acetate : hexanes graded to 100% ethyl acetate) of a small amount of the distilled product gave diethyl benzylphosphonate **106** as a clear colourless liquid:  $R_f$  0.08 (40% ethyl acetate : hexanes);  $v_{max}$  (thin film) 1250 (br, s,  $R(R'O)_2P=O$ ), 1032, 962 (P-O-C)  $cm^{-1}$ ;  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 7.12 – 6.99 (5H, m, Ph), 3.88 – 3.70 (4H, m,  $OCH_2CH_3$ ), 2.92 (2H, d,  $^2J_{PH}$  21.6 Hz,  $PhCH_2$ ), 1.00 (6H, t,  $J$  7.0 Hz,  $OCH_2CH_3$ );  $^{13}C$  NMR (50 MHz,  $CDCl_3$ )  $\delta$ : 130.9 (d,  $^2J_{PC}$  9.0 Hz, Ph(quat)), 129.0 (d,  $^3J_{PC}$  6.5 Hz, Ph(o)), 127.7 (d,  $^4J_{PC}$  2.7 Hz, Ph(m)), 126.0 (d,  $^5J_{PC}$  3.3 Hz, Ph(p)), 61.2 (d,  $^2J_{PC}$  6.7 Hz,  $OCH_2CH_3$ ), 32.9 (d,  $^1J_{PC}$  138.0 Hz,  $PhCH_2$ ), 15.6 (d,  $^3J_{PC}$  5.9 Hz,  $OCH_2CH_3$ ).

**Benzyltriphenylphosphonium chloride<sup>77</sup> 20**

The general procedure for formation of phosphonium salts (see page 118) was followed using benzyl chloride (11 ml, 96 mmol, 0.76 M) and triphenylphosphine (1.0 eq.). Solvent = acetonitrile, time = 2 h. The crude product was a white crystalline solid (25 g) which was recrystallised (absolute ethanol) to give benzyltriphenylphosphonium chloride **20** as a white crystalline solid (25 g, 64 mmol, 67%):  $R_f$  baseline (40% ethyl acetate : hexanes); **m.p.** > 195 °C (lit.<sup>77</sup>

**m.p.** > 300 °C);  $\nu_{\max}$  (thin film) 1587, 1492, 1482 (s, Ar(C-C))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.65 – 7.43 (15H, m, Ar-H), 7.18 – 6.93 (5H, m, Ar-H), 5.25 (2H, d,  $^2J_{\text{PH}}$  14.5 Hz,  $\text{C}_8\text{-H}_2$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 134.7 (d,  $^4J_{\text{PC}}$  2.0 Hz, *p*-Ar-C), 134.0 (d,  $^3J_{\text{PC}}$  9.7 Hz, *m*-Ar-C), 131.1 (d,  $^3J_{\text{PC}}$  5.3 Hz,  $\text{C}_{10}$ ), 129.8 (d,  $^2J_{\text{PC}}$  12.5 Hz, *o*-Ar-C), 128.4 (d,  $^4J_{\text{PC}}$  2.8 Hz,  $\text{C}_{11}$ ), 128.0 (d,  $^5J_{\text{PC}}$  3.9 Hz,  $\text{C}_{12}$ ), 127.0 (d,  $^2J_{\text{PC}}$  8.5 Hz,  $\text{C}_9$ ), 117.4 (d,  $^1J_{\text{PC}}$  85.7 Hz, *q*-Ar-C), 30.3 (d,  $^1J_{\text{PC}}$  46.9 Hz,  $\text{C}_8\text{H}_2$ ).

**(*E*)-(3-Methylbut-1-enyl)benzene**<sup>78,79</sup> ***E*-102**

**(*Z*)-(3-Methylbut-1-enyl)benzene**<sup>78</sup> ***Z*-102**



#### **Method 1 – Horner-Wadsworth-Emmons olefination with *n*-BuLi:**

The general Horner-Wadsworth-Emmons procedure (see page 115) was followed using diethyl benzylphosphonate **106**, *n*-butyl lithium solution (1.6 M in hexanes, 1.2 eq.) and isobutyraldehyde **88** (0.033 ml, 0.36 mmol, conc. 0.065 M). Time = 17 h. The crude product was a clear colourless liquid (0.099 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E*)-alkene ***E*-102** to (*Z*)-alkene ***Z*-102** to unreacted phosphonate **106** was determined to be 24 : 1 : 170 from integration of the  $\text{C}_7\text{-H}$  and  $\text{C}_8\text{-H}$  signals in the spectra:  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.29 (1H, d,  $J$  16.0 Hz, ***E*-102**- $\text{C}_8\text{-H}$ ) with 6.24 (1H, d,  $J$  11.4 Hz, ***Z*-102**- $\text{C}_8\text{-H}$ ), 6.12 (1H, dd,  $J$  15.9, 6.3 Hz, ***E*-102**- $\text{C}_7\text{-H}$ ), 5.41 (1H, dd,  $J$  11.6, 10.2 Hz, ***Z*-102**- $\text{C}_7\text{-H}$ ), 3.09 (2H, d,  $^2J_{\text{PH}}$  21.6 Hz, **106**- $\text{C}_8\text{-H}_2$ ). Flash chromatographic purification (100% hexanes) gave pure (*E*)-alkene ***E*-102** as a clear colourless liquid (0.010 g, 0.068 mmol, 19%):  $R_f$  0.62 (10% ethyl acetate : hexanes);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.29 – 7.18 (4H, m, *o*-Ar-H, *m*-Ar-H), 7.13 – 7.11 (1H, m, *p*-Ar-H), 6.27 (1H, d,  $J$  16.0 Hz,  $\text{C}_8\text{-H}$ ), 6.12 (1H, dd,  $J$  16.0, 6.6 Hz,  $\text{C}_7\text{-H}$ ), 2.45 – 2.34 (1H, m,  $\text{C}_6\text{-H}$ ), 1.02 (6H, d,  $J$  6.8 Hz,  $\text{C}(\text{CH}_3)_2$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 138.0, 138.0, 128.4, 126.8, 126.7, 126.5, 125.9, 31.5, 22.4.

**Method 2 – Horner-Wadsworth-Emmons olefination with KHMDS:**

The general Horner-Wadsworth-Emmons procedure (see page 115) was followed using diethyl benzylphosphonate **106**, potassium bis(trimethylsilyl)amide (0.50 M in hexanes, 1.2 eq.) and isobutyraldehyde **88** (0.091 ml, 0.99 mmol, conc. 0.050 M). Time = 16 h. The crude product was a clear colourless liquid (0.49 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-102** to (*Z*)-alkene **Z-102** : unreacted phosphonate **106** was determined to be 4.4 : 1 : 3.1 from integration of the C<sub>7</sub>-H and C<sub>8</sub>-H signals in the spectra.

**Method 3 – Julia olefination – premetallation with *n*-BuLi:**

The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **21** (0.80 eq.), *n*-butyl lithium solution (1.0 M in hexanes, 0.93 eq.) and isobutyraldehyde **88** (0.013 ml, 0.14 mmol, conc. 0.10 M). Solvent = tetrahydrofuran, T = -78 °C, time<sub>A</sub> = 15 min, time<sub>B</sub> = 30 min. The reaction was pale yellow in colour. The crude product was a off-white residue (0.11 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-102** to (*Z*)-alkene **Z-102** was determined to be 1 : 4 from integration of the C<sub>7</sub>-H and C<sub>8</sub>-H signals in the spectra.

**Method 4 – Julia olefination – premetallation with KHMDS:**

The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **21** (0.84 eq.), potassium bis(trimethylsilyl)amide (0.50 M in hexanes, 1.0 eq.) and isobutyraldehyde **88** (0.0051 ml, 0.056 mmol, conc. 0.10 M). Solvent = tetrahydrofuran, T = -78 °C, time<sub>A</sub> = 15 min, time<sub>B</sub> = 30 min. The crude product was an off-white solid (0.074 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-102** to (*Z*)-alkene **Z-102** was determined to be 1 : 2 from integration of the C<sub>7</sub>-H and C<sub>8</sub>-H signals in the spectra.

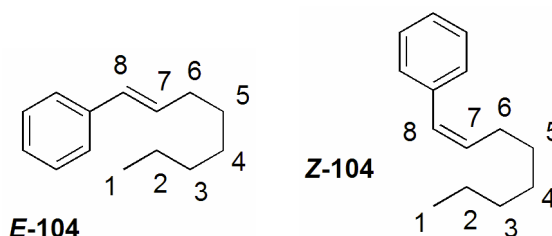
**Method 5 – Wittig olefination:**

The general Wittig olefination procedure (see page 119) was followed using benzyltriphenylphosphonium chloride **20** (1.5 eq.), *n*-butyl lithium (1.6 M in hexanes, 1.2 eq.) and isobutyraldehyde **88** (0.027 ml, 0.30 mmol). Solvent =

tetrahydrofuran,  $T = -78\text{ }^{\circ}\text{C}$ ,  $\text{time}_A = 4\text{ h}$ ,  $\text{time}_B = 16\text{ h}$ , quench = 1. The crude product was a pale pink crystalline solid (0.22 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E*)-alkene **E-102** to (*Z*)-alkene **Z-102** to unreacted phosphonium salt was determined to be 4 : 1 : 4 from integration of the  $\text{C}_7\text{-H}$  and  $\text{C}_8\text{-H}$  signals in the spectra. Flash chromatographic purification (2% ethyl acetate : hexanes) gave an inseparable mixture of (*E*)-alkene **E-102** and (*Z*)-alkene **Z-102** as a clear colourless liquid (0.026 g, 0.18 mmol, 60%).

(*E*)-Oct-1-enylbenzene<sup>80</sup> **E-104**

(*Z*)-Oct-1-enylbenzene **Z-104**



#### Method 1 – Wittig olefination with *n*-BuLi:

The general Wittig olefination procedure (see page 119) was followed using benzyltriphenylphosphonium chloride **20** (1.0 eq.), *n*-butyl lithium (2.5 M in hexanes, 0.98 eq.) and heptaldehyde **103** (0.071 ml, 0.51 mmol). Solvent = benzene,  $T = 0\text{ }^{\circ}\text{C}$ ,  $\text{time}_A = 20\text{ min}$ ,  $\text{time}_B = 1\text{ h } 30\text{ min}$ , quench = 3. The crude product was a white oily solid (0.36 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E*)-alkene **E-104** to (*Z*)-alkene **Z-104** to unreacted phosphonium salt **20** was determined to be 3 : 1 : 1.3 from integration of the  $\text{C}_7\text{-H}$  and  $\text{C}_8\text{-H}$  signals in the spectra:  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.29 (1H, dt,  $J$  15.8, 6.4 Hz, **E-104**- $\text{C}_7\text{-H}$ ), 5.74 (1H, dt,  $J$  11.7, 7.3 Hz, **Z-104**- $\text{C}_7\text{-H}$ ), 5.25 (2H, d,  $^2J_{\text{PH}}$  14.5 Hz, **20**- $\text{C}_8\text{-H}_2$ ). Flash chromatographic purification (100% hexanes) gave an inseparable mixture of (*E*)-alkene **E-104** and (*Z*)-alkene **Z-104** as a clear colourless liquid (0.055 g, 0.29 mmol, 58%). For the purposes of characterisation a fraction containing a mixture of (*E*)-alkene **E-104** and (*Z*)-alkene **Z-104** in a 2.5 : 1 ratio was analysed:  $R_f$  0.47 (100% hexanes);  $\nu_{\text{max}}$  (thin film) 962 (s, trans C=C), 692 (s, cis C=C)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.44 – 7.21 (5H, m, Ph), 6.45

(1H, d, *J* 16.0 Hz, C<sub>8</sub>-H), 6.29 (1H, dt, *J* 15.8, 6.4 Hz, C<sub>7</sub>-H), 2.28 (2H, q, *J* 6.8 Hz, C<sub>6</sub>-H<sub>2</sub>), 1.57 – 1.36 (8H, m, C<sub>5</sub>-H<sub>2</sub>, C<sub>4</sub>-H<sub>2</sub>, C<sub>3</sub>-H<sub>2</sub>, C<sub>2</sub>-H<sub>2</sub>), 1.00 – 0.92 (3H, m, CH<sub>3</sub>); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 6.52 – 6.44 (1H, m, C<sub>8</sub>-H), 5.74 (1H, dt, *J* 11.7, 7.3 Hz, C<sub>7</sub>-H), 2.40 (2H, dq, *J* 7.3, 1.6 Hz, C<sub>6</sub>-H<sub>2</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 138.0, 137.8, 133.3, 131.2, 129.7, 128.7, 128.7, 128.4, 128.1, 126.7, 126.4, 125.9, 33.0, 31.8, 30.0, 29.4, 29.0, 28.9, 28.6, 22.6, 14.1.

#### **Method 2 – Wittig olefination with KHMDS:**

The general Wittig olefination procedure (see page 119) was followed using benzyltriphenylphosphonium chloride **20** (0.97 eq.), potassium bis(trimethylsilyl)amide (0.50 M in hexanes, 0.97 eq.) and heptaldehyde **103** (0.040 ml, 0.29 mmol). Solvent = benzene, T = 0 °C, time<sub>A</sub> = 15 min, time<sub>B</sub> = 50 min, quench = 3. The crude product was a white oily solid (0.24 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-104** to (*Z*)-alkene **Z-104** to unreacted phosphonium salt was determined to be 3 : 1 : 0.5 from integration of the C<sub>7</sub>-H and C<sub>8</sub>-H signals in the spectra. Flash chromatographic purification (100% hexanes) gave an inseparable mixture of (*E*)-alkene **E-104** and (*Z*)-alkene **Z-104** as a clear colourless liquid (0.040 g, 0.21 mmol, 75%).

#### **Method 3 – Julia olefination – premetallation with *n*-BuLi:**

The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **21** (1.2 eq.), *n*-butyl lithium solution (1.6 M in hexanes, 1.1 eq.) and heptaldehyde **103** (0.017 ml, 0.12 mmol, conc. 0.080 M). Solvent = tetrahydrofuran, T = -78 °C, time<sub>A</sub> = 15 min, time<sub>B</sub> = 35 min. The reaction turned from bright yellow to a clear colourless solution on addition of heptaldehyde. The crude product was an off-white residue (0.056 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-104** to (*Z*)-alkene **Z-104** was determined to be 1 : 1.6 from integration of the C<sub>7</sub>-H signals in the spectra.

#### **Method 4 – Julia olefination – premetallation with KHMDS:**

The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **21** (1.2 eq.), potassium bis(trimethylsilyl)amide (0.50 M in hexanes, 1.1 eq.) and heptaldehyde **103** (0.021 ml, 0.15 mmol, conc. 0.080 M).

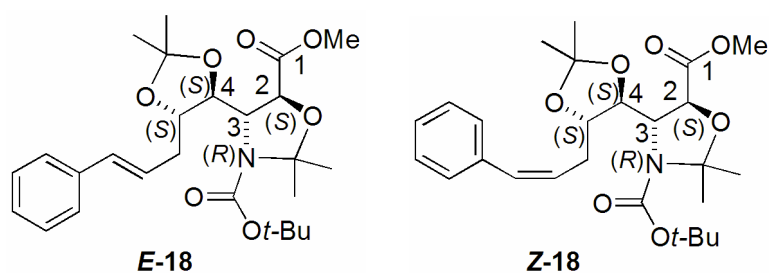
Solvent = tetrahydrofuran,  $T = -78\text{ }^{\circ}\text{C}$ ,  $\text{time}_A = 15\text{ min}$ ,  $\text{time}_B = 35\text{ min}$ . The reaction turned from bright yellow to pale yellow on addition of heptaldehyde. The crude product was an off-white residue (0.12 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E*)-alkene **E-104** to (*Z*)-alkene **Z-104** was determined to be 1 : 2.1 from integration of the  $\text{C}_7\text{-H}$  signals in the spectra.

#### Method 5 – Horner-Wadsworth-Emmons olefination:

The general Horner-Wadsworth-Emmons procedure (see page 115) was followed using diethyl benzylphosphonate **106**, potassium bis(trimethylsilyl)amide (0.50 M in hexanes, 1.2 eq.) and heptaldehyde **103** (0.14 ml, 0.99 mmol, conc. 0.050 M). Time = 16 h. The crude product was a viscous yellow liquid (0.48 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E*)-alkene **E-104** to (*Z*)-alkene **Z-104** : unreacted phosphonate was determined to be 3.2 : 1 : 32 from integration of the  $\text{C}_7\text{-H}$  and  $\text{C}_8\text{-H}$  signals in the spectra:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.22 (2H, d,  $^2J_{\text{PH}} 21.6\text{ Hz}$ , **106**- $\text{C}_8\text{-H}_2$ ).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*S*,5*S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate E-18**

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*S*,5*S*)-2,2-dimethyl-5-((*Z*)-3-phenylallyl)-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate Z-18**



The general Wittig olefination procedure (see page 119) was followed using benzyltriphenylphosphonium chloride **20** (0.96 eq.), potassium bis(trimethylsilyl)amide (0.50 M in toluene, 1.0 eq.) and a crude mixture of aldehyde **19** and aldehyde *dia*-**19** (**19** : *dia*-**19** = 7 : 1, 0.11 g – assumed quantitative for previous step, 0.27 mmol). Solvent = benzene,  $T = 0\text{ }^{\circ}\text{C}$ ,  $\text{time}_A = 15\text{ min}$ ,  $\text{time}_B = 1\text{ h}$ , quench = 3. The crude product was an orange residue

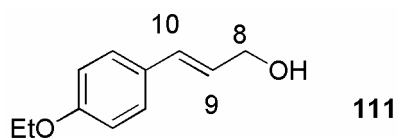
(0.24 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E*)-alkene **E-18** to (*Z*)-alkene **Z-18** to unreacted phosphonium salt **20** was determined to be 3.5 : 1 : 0.75 from integration of the  $\text{C}_7\text{-H}$  and  $\text{C}_8\text{-H}$  signals in the spectra:  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.53 – 6.47 (1H, m, **Z-18-C**<sub>8</sub>-H) with 6.43 (1H, d, *J* 16.0 Hz, **E-18-C**<sub>8</sub>-H), 6.22 (1H, dt, *J* 15.7, 6.8 Hz, **E-18-C**<sub>7</sub>-H), 5.75 (1H, dt, *J* 11.7, 7.0 Hz, **Z-18-C**<sub>7</sub>-H), 5.33 (2H, d,  $^2J_{\text{PH}}$  14.4 Hz, **20-C**<sub>8</sub>-H<sub>2</sub>). Flash chromatographic purification (20% ethyl acetate : hexanes) gave an inseparable mixture of (*E*)-alkene **E-18** and (*Z*)-alkene **Z-18** as a viscous, clear colourless liquid (0.096 g, 0.20 mmol, 77% - from alcohol **98**):  $R_f$  0.43 (40% ethyl acetate : hexanes), 0.19 (20% ethyl acetate : hexanes);  $[\alpha]_D^{19}$  -2.2 (*c* 1.7,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (thin film) 1763 (m), 1740 (m), 1701 (s, C=O)  $\text{cm}^{-1}$ ; **HRMS** (+ESI) calc. for  $\text{C}_{26}\text{H}_{37}\text{O}_7\text{N}+\text{Na}$  498.2468, found 498.2458;  $m/z$  (+ESI) 498 ( $[\text{M}+\text{Na}]^+$ , 100%), 442 (24).

For the purposes of characterisation, preparative HPLC purification (RTI Zorbax Sil, 7.5% ethyl acetate : hexanes) gave pure (*E*)-alkene **E-18** ( $t_R \sim 31.5$  min) as a viscous, clear, colourless liquid (0.038 g, 0.080 mmol, 30%):  $[\alpha]_D^{21}$  -3.1 (*c* 3.8,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H NMR}$  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 7.36 – 7.12 (5H, m, Ph), 6.49 (1H, d, *J* 15.9 Hz,  $\text{C}_8\text{-H}$ ), 6.26 (1H, dt, *J* 15.9, 6.8 Hz,  $\text{C}_7\text{-H}$ ), 4.71 (1H, d, *J* 2.1 Hz,  $\text{C}_2\text{-H}$ ), 4.47 (1H, dd, *J* 5.2, 2.1 Hz,  $\text{C}_3\text{-H}$ ), 4.19 – 4.10 (1H, m,  $\text{C}_5\text{-H}$ ), 4.01 (1H, dd, *J* 7.9, 5.2 Hz,  $\text{C}_4\text{-H}$ ), 3.73 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 2.65 – 2.39 (2H, m,  $\text{C}_6\text{-H}_2$ ), 1.61 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.56 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.49 (9H, s,  $\text{BOC C}(\text{CH}_3)_3$ ), 1.41 (6H, s,  $\text{OC}(\text{CH}_3)_2\text{O}$ );  $^{13}\text{C NMR}$  (50 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 172.1, 151.9, 137.7, 133.0, 128.5, 127.1, 126.3, 125.6, 109.0, 96.8, 80.9, 80.1, 78.4, 75.2, 61.4, 52.2, 36.6, 28.5, 27.7, 27.4, 27.2.

A second fraction gave pure (*Z*)-alkene **Z-18** ( $t_R \sim 28.5$  min) as a viscous, clear, colourless liquid (0.0080 g, 0.017 mmol, 6.3%):  $[\alpha]_D^{21}$  +3.7 (*c* 0.8,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H NMR}$  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 7.30 – 7.16 (5H, m, Ph), 6.58 – 6.52 (1H, m,  $\text{C}_8\text{-H}$ ), 5.79 (1H, dt, *J* 11.7, 7.0 Hz,  $\text{C}_7\text{-H}$ ), 4.68 (1H, d, *J* 2.1 Hz,  $\text{C}_2\text{-H}$ ), 4.44 (1H, m,  $\text{C}_3\text{-H}$ ), 4.22 – 4.10 (1H, m,  $\text{C}_5\text{-H}$ ), 3.97 (1H, dd, *J* 7.8, 5.5 Hz,  $\text{C}_4\text{-H}$ ), 3.73 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 2.66 – 2.59 (2H, m,  $\text{C}_6\text{-H}_2$ ), 1.58 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.48 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.42 (12H, s,  $\text{BOC C}(\text{CH}_3)_3$ ,  $\text{OC}(\text{CH}_3)_2\text{O}$ ), 1.40 (3H, s,  $\text{OC}(\text{CH}_3)_2\text{O}$ );  $^{13}\text{C NMR}$  (50 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 172.1, 151.8, 137.5, 131.4, 128.9, 128.2, 127.2, 126.8, 109.1, 96.8, 80.9, 80.4, 78.3, 75.3, 61.5, 52.2, 32.5, 28.4, 27.6, 27.4, 27.2, 27.0.

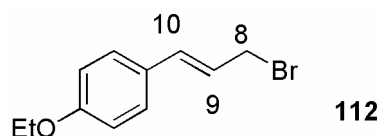
A third fraction gave a mixture of (*E*)-alkene **E-18** and (*Z*)-alkene **Z-18** as a viscous, clear, colourless liquid (0.017 g, 0.036 mmol, 13%).

**(*E*)-3-(4-Ethoxyphenyl)prop-2-en-1-ol<sup>81</sup> 111**

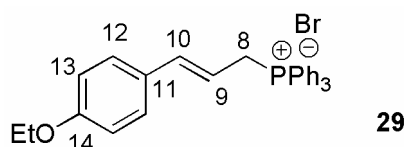


The general procedure for ester reduction (see page 115) was followed using ethyl *trans*-4-ethoxycinnamate (0.10 g, 0.45 mmol) and diisobutylaluminium hydride (1.0 M in toluene, 2.5 eq.). Time = 35 min. The crude product was a white, crystalline solid (0.12 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave pure alcohol **111** (0.080 g, 0.45 mmol, 99%) as a white crystalline solid: **R<sub>f</sub>** 0.25 (40% ethyl acetate : hexanes); **m.p.** 87.0 – 88.0 °C (**lit.**<sup>81</sup> **m.p.** 90 – 91 °C); **v<sub>max</sub>** (thin film) 3369 (br s, O-H), 1512 (m, Ar(C=C)), 972 (m, *trans* C=C) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.32 – 7.25 (2H, m, Ar-H), 6.86 – 6.79 (2H, m, Ar-H), 6.52 (1H, d, *J* 15.9 Hz, C<sub>10</sub>-H), 6.20 (1H, dt, *J* 15.9, 5.9 Hz, C<sub>9</sub>-H), 4.26 (2H, d, *J* 5.6 Hz, C<sub>8</sub>-H<sub>2</sub>), 4.01 (2H, q, *J* 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.00 (1H, s, OH), 1.40 (3H, t, *J* 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 158.6, 130.8, 129.3, 127.6, 126.1, 114.5, 63.7, 63.4, 14.7.

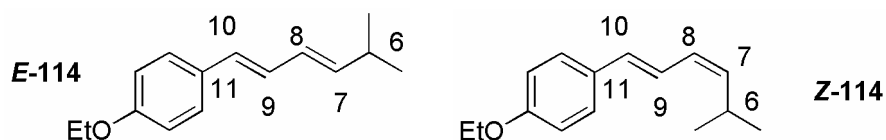
**(*E*)-1-(3-Bromoprop-1-enyl)-4-ethoxybenzene 112**



The general procedure for bromine substitution (see page 114) was followed using alcohol **111** (0.83 g, 4.7 mmol). The crude product was pure bromide **112** as a pale yellow crystalline solid (1.0 g, 4.1 mmol, 87%): **v<sub>max</sub>** (thin film) 1607, 1510 (s, Ar(C=C)), 1047 (s, C-Br), 970 (s, *trans* C=C) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.33 – 7.24 (2H, m, Ar-H), 6.89 – 6.80 (2H, m, Ar-H), 6.58 (1H, d, *J* 15.6 Hz, C<sub>10</sub>-H), 6.24 (1H, dt, *J* 15.5, 7.8 Hz, C<sub>9</sub>-H), 4.15 (2H, d, *J* 7.8 Hz, C<sub>8</sub>-H), 4.02 (2H, q, *J* 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.40 (3H, t, *J* 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 159.2, 134.2, 128.3, 128.0, 122.8, 114.6, 63.4, 34.2, 14.7.

**(E)-3-(4-Ethoxyphenyl)allyl)triphenylphosphonium bromide 29**

The general procedure for formation of phosphonium salts (see page 118) was followed using bromo-compound **112** (0.85 g, 3.5 mmol, 0.58 M) and triphenylphosphine (0.97 eq.). Solvent = benzene, time = 17 h. The crude product was washed with diethyl ether (3 x 5 ml) and dried under reduced pressure to give pure phosphonium salt **29** as a white powder (1.5 g, 3.0 mmol, 86%): **R<sub>f</sub>** baseline (40% ethyl acetate : hexanes); **m.p.** 98 – 99 °C; **v<sub>max</sub>** (thin film) 1605, 1510 (s, Ar(C=C)), 1250 (s), 1043 (m, ArC-O-AlC), 723 (s, P-C) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.92 – 7.63 (15H, m, Ar-H), 7.13 (2H, d, *J* 8.4 Hz, 2 x C<sub>12</sub>-H), 6.76 (2H, d, *J* 8.5 Hz, 2 x C<sub>13</sub>-H), 6.76 – 6.66 (1H, m, C<sub>10</sub>-H), 5.90 – 5.72 (1H, m, C<sub>9</sub>-H), 4.93 (2H, dd, *J* 15.0, 7.4 Hz, C<sub>8</sub>-H<sub>2</sub>), 3.99 (2H, q, *J* 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.38 (3H, t, *J* 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 159.3, 139.8 (d, <sup>3</sup>*J*<sub>PC</sub> 13.5 Hz, C<sub>10</sub>), 135.0 (d, <sup>4</sup>*J*<sub>PC</sub> 2.3 Hz, *p*-Ar-C), 134.1 (d, <sup>2</sup>*J*<sub>PC</sub> 9.7 Hz, *o*-Ar-C), 130.4 (d, <sup>3</sup>*J*<sub>PC</sub> 12.5 Hz, *m*-Ar-C), 128.5 (d, <sup>4</sup>*J*<sub>PC</sub> 3.6 Hz, C<sub>11</sub>), 127.9, 118.2 (d, <sup>1</sup>*J*<sub>PC</sub> 85.4 Hz, *q*-Ar-C), 114.6, 110.8 (d, <sup>2</sup>*J*<sub>PC</sub> 11.0 Hz, C<sub>9</sub>), 63.5, 28.4 (d, <sup>1</sup>*J*<sub>PC</sub> 48.7 Hz, C<sub>8</sub>), 14.8; **HRMS** (+ESI) calc. for C<sub>29</sub>H<sub>28</sub>OP 423.1878, found 423.1873; **m/z** (+ESI) 423 ([M-Br]<sup>+</sup>, 34%), 161 (78), 133 (100) 105 (19); (-ESI) 81 (Br(81), 83%), 79 (Br(79), 100).

**1-Ethoxy-4-((1E,3E)-5-methylhexa-1,3-dienyl)benzene E-114****1-Ethoxy-4-((1E,3Z)-5-methylhexa-1,3-dienyl)benzene Z-114****Method 1 – Wittig olefination with *n*-BuLi:**

The general Wittig olefination procedure (see page 119) was followed using phosphonium salt **29** (1.0 eq.), *n*-butyl lithium (2.5 M in hexanes, 1.1 eq.) and

isobutyraldehyde **88** (0.014 ml, 0.15 mmol). Solvent = benzene,  $T = 0\text{ }^{\circ}\text{C}$ ,  $\text{time}_A = 30\text{ min}$ ,  $\text{time}_B = 1\text{ h}$ , quench = 3. The crude product was a viscous, clear colourless liquid (0.14 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E,E*)-diene **E-114** to (*E,Z*)-diene **Z-114** was determined to be 2 : 1 from integration of the  $\text{C}_7\text{-H}$  signals in the spectra:  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.67 (1H, dd,  $J$  15.2, 6.7 Hz, (*E,E*)- $\text{C}_7\text{-H}$ ), 5.22 (1H, t,  $J$  10.2 Hz, (*E,Z*)- $\text{C}_7\text{-H}$ ). Flash chromatographic purification (10% ethyl acetate : hexanes) gave an inseparable mixture of (*E,E*)-diene **E-114** and (*E,Z*)-diene **Z-114** as a viscous clear colourless liquid (0.026 g, 0.12 mmol, 80%). For the purposes of characterisation a fraction containing a mixture of (*E,E*)-diene **E-114** and (*E,Z*)-diene **Z-114** in a 1.7 : 1 ratio was analysed:  $R_f$  0.48 (10% ethyl acetate : hexanes);  $\nu_{\text{max}}$  (thin film) 1605, 1510 (s,  $\text{Ar}(\text{C}=\text{C})$ )  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.28 – 7.18 (2H, m, Ar-H), 6.80 – 6.71 (2H, m, Ar-H), 6.55 (1H, dd,  $J$  15.6, 10.0 Hz,  $\text{C}_9\text{-H}$ ), 6.32 (1H, d,  $J$  15.6 Hz,  $\text{C}_{10}\text{-H}$ ), 6.07 (1H, ddd,  $J$  15.2, 10.0, 1.1 Hz,  $\text{C}_8\text{-H}$ ), 5.67 (1H, dd,  $J$  15.2, 6.7 Hz,  $\text{C}_7\text{-H}$ ), 3.95 (2H, q,  $J$  7.0 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.40 – 2.19 (1H, m,  $\text{C}_6\text{-H}$ ), 1.33 (3H, t,  $J$  7.0 Hz,  $\text{OCH}_2\text{CH}_3$ ), 0.97 (6H, d,  $J$  6.8 Hz,  $\text{C}(\text{CH}_3)_2$ );  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.92 – 6.80 (1H, m,  $\text{C}_9\text{-H}$ ), 6.38 (1H, d,  $J$  15.4 Hz,  $\text{C}_{10}\text{-H}$ ), 5.94 (1H, t,  $J$  10.9 Hz,  $\text{C}_8\text{-H}$ ), 5.22 (1H, t,  $J$  10.2 Hz,  $\text{C}_7\text{-H}$ ), 3.96 (2H, q,  $J$  7.0 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.91 – 2.73 (1H, m,  $\text{C}_6\text{-H}$ ), 0.96 (6H, d,  $J$  6.6 Hz,  $\text{C}(\text{CH}_3)_2$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 158.5, 158.3, 141.6, 139.4, 131.6, 130.4, 129.7, 127.7, 127.5, 127.5, 127.2, 126.6, 114.6, 63.4, 31.2, 27.3, 23.2, 22.4, 14.8;  $m/z$  (+EI, 40 eV) 648 ( $[\text{3M}]^+$ , 48), 591 (12), 535 (10), 479 (10), 432 ( $[\text{2M}]^+$ , 4), 423 (10), 292 (22), 217 ( $[\text{M}+\text{H}]^+$ , 21), 216 ( $[\text{M}]^+$ , 90), 201 (48), 173 (63), 145 (88), 107 (34), 85 (51), 71 (66), 57 (100). The isomers were not separated and COSY NMR was used to assign the isomers.

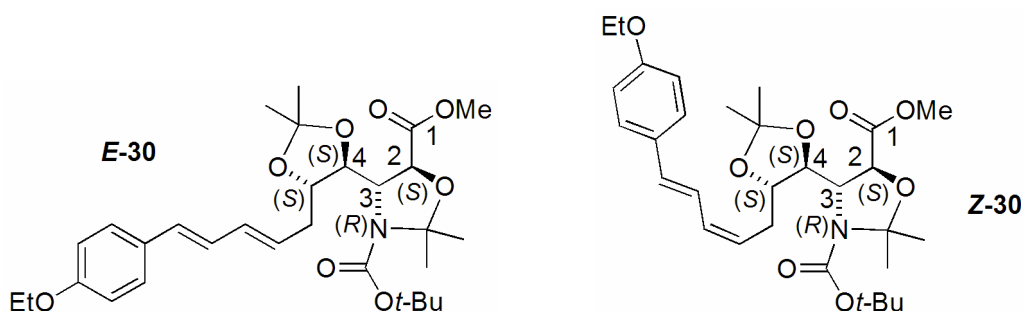
### **Method 2 – Wittig olefination with KHMDS:**

The general Wittig olefination procedure (see page 119) was followed using phosphonium salt **29** (0.94 eq.), potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.0 eq.) and isobutyraldehyde **88** (0.015 ml, 0.17 mmol). Solvent = benzene,  $T = 0\text{ }^{\circ}\text{C}$ ,  $\text{time}_A = 15\text{ min}$ ,  $\text{time}_B = 2\text{ h}$ , quench = 3. The crude product was a bright yellow residue (0.067 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E,E*)-diene **E-114** to (*E,Z*)-diene **Z-114** was determined to be 2.5 : 1 from integration of the  $\text{C}_7\text{-H}$  signals in the spectra. Flash

chromatographic purification (10% ethyl acetate : hexanes) gave an inseparable mixture of (*E,E*)-diene **E-114** and (*E,Z*)-diene **Z-114** as a viscous clear colourless liquid (0.026 g, 0.12 mmol, 75%).

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*S*,5*S*)-5-((2*E*,4*E*)-5-(4-ethoxyphenyl)penta-2,4-dienyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **E-30****

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((4*S*,5*S*)-5-((2*Z*,4*E*)-5-(4-ethoxyphenyl)penta-2,4-dienyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **Z-30****



The general Wittig olefination procedure (see page 119) was followed using phosphonium salt **29** (1.0 eq.), potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.0 eq.) and a crude mixture of aldehyde **19** and aldehyde **dia-19** (**19** : **dia-19** = 7 : 1, 0.065 g – assumed quantitative for previous step, 0.16 mmol). Solvent = benzene,  $T = 0\text{ }^{\circ}\text{C}$ ,  $\text{time}_A = 10\text{ min}$ ,  $\text{time}_B = 25\text{ min}$ , quench = 3. The crude product was an orange residue (0.14 g). The crude product was analysed by  $^1\text{H NMR}$  and the ratio of (*E,E*)-diene **E-30** to (*E,Z*)-diene **Z-30** was determined to be 2.7 : 1 from integration of the  $\text{C}_7\text{-H}$  signals in the spectra:  $^1\text{H NMR}$  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 5.79 (1H, dt,  $J$  14.8, 7.3 Hz, **E-30-C<sub>7</sub>-H), 5.56 (1H, dt,  $J$  10.9, 7.5 Hz, **Z-30-C<sub>7</sub>-H). Flash chromatographic purification (15% ethyl acetate : hexanes) gave an inseparable mixture of (*E,E*)-diene **E-30** and (*E,Z*)-diene **Z-30** as a viscous clear colourless liquid (0.056 g, 0.10 mmol, 63% - from alcohol **98**). For the purposes of characterisation a fraction containing a mixture of (*E,E*)-diene **E-30** and (*E,Z*)-diene **Z-30** in a 3.2 : 1 ratio was analysed:  $R_f$  0.30 (20% ethyl acetate : hexanes), 0.11 (10% ethyl acetate : hexanes);  $[\alpha]_D^{17} +4.7$  ( $c$  1.4,  $\text{CH}_2\text{Cl}_2$ );****

$\nu_{\text{max}}$  (thin film) 1763 (m), 1740 (m), 1701 (s, C=O), 1605, 1510 (s, Ar(C=C)), 1250, 1175, 1089 (C-O-C)  $\text{cm}^{-1}$ ; **HRMS** (+ESI) calc. for  $\text{C}_{30}\text{H}_{43}\text{O}_8\text{N}+\text{Na}$  568.2886, found 568.2871; **m/z** (+ESI) 584 ( $[\text{M}+\text{K}]^+$ , 28%), 568 ( $[\text{M}+\text{Na}]^+$ , 100), 512 (43).

Preparative HPLC purification (RTI Zorbax Sil, 10% ethyl acetate : hexanes) gave pure (*E,E*)-diene **E-30** ( $t_{\text{R}} \sim 33.0$  min) as a viscous, clear, colourless liquid (0.020 g, 0.037 mmol, 23%):  $[\alpha]_{\text{D}}^{18} -1.8$  ( $c$  1.8,  $\text{CH}_2\text{Cl}_2$ );  **$^1\text{H NMR}$**  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 7.29 – 7.21 (2H, m, Ar-H), 6.85 – 6.78 (2H, m, Ar-H), 6.61 (1H, dd,  $J$  15.5, 10.0 Hz,  $\text{C}_9\text{-H}$ ), 6.39 (1H, d,  $J$  15.6 Hz,  $\text{C}_{10}\text{-H}$ ), 6.26 (1H, dd,  $J$  15.1, 10.0 Hz,  $\text{C}_8\text{-H}$ ), 5.79 (1H, dt,  $J$  14.8, 7.3 Hz,  $\text{C}_7\text{-H}$ ), 4.70 (1H, d,  $J$  2.1 Hz,  $\text{C}_2\text{-H}$ ), 4.45 (1H, dd,  $J$  5.1, 2.0 Hz,  $\text{C}_3\text{-H}$ ), 4.11 – 3.94 (4H, m,  $\text{C}_5\text{-H}$ ,  $\text{C}_4\text{-H}$ ,  $\text{OCH}_2\text{CH}_3$ ), 3.76 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 2.52 – 2.31 (2H, m,  $\text{C}_6\text{-H}_2$ ), 1.61 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.57 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.50 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ ), 1.42 – 1.35 (9H, m,  $\text{OC}(\text{CH}_3)_2\text{O}$ ,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C NMR}$**  (50 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 172.1, 158.7, 151.9, 133.7, 130.9, 130.5, 128.4, 127.5, 127.1, 115.0, 109.0, 96.8, 80.9, 80.1, 78.4, 75.3, 63.7, 61.4, 52.2, 36.5, 28.5, 27.7, 27.4, 27.2, 27.1, 14.8.

A second fraction gave pure (*E,Z*)-diene **Z-30** ( $t_{\text{R}} \sim 29.0$  min) as a viscous, clear, colourless liquid (0.0067 g, 0.012 mmol, 7.5%):  $[\alpha]_{\text{D}}^{18} +10.3$  ( $c$  0.57,  $\text{CH}_2\text{Cl}_2$ );  **$^1\text{H NMR}$**  (200 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 7.36 – 7.32 (2H, m, Ar-H), 6.97 – 6.81 (3H, m,  $\text{C}_9\text{-H}$ , Ar-H), 6.49 (1H, d,  $J$  15.9 Hz,  $\text{C}_{10}\text{-H}$ ), 6.26 (1H, t,  $J$  11.0 Hz,  $\text{C}_8\text{-H}$ ), 5.56 (1H, dt,  $J$  10.9, 7.5 Hz,  $\text{C}_7\text{-H}$ ), 4.72 (1H, d,  $J$  2.2 Hz,  $\text{C}_2\text{-H}$ ), 4.49 (1H, dd,  $J$  4.6, 1.9 Hz,  $\text{C}_3\text{-H}$ ), 4.15 – 4.00 (4H, m,  $\text{C}_5\text{-H}$ ,  $\text{C}_4\text{-H}$ ,  $\text{OCH}_2\text{CH}_3$ ), 3.75 (3H, s,  $\text{C}_1\text{-OCH}_3$ ), 2.61 (2H, t,  $J$  6.2 Hz,  $\text{C}_6\text{-H}_2$ ), 1.63 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.58 (3H, s,  $\text{NC}(\text{CH}_3)_2\text{O}$ ), 1.50 (9H, s, BOC  $\text{C}(\text{CH}_3)_3$ ), 1.44 – 1.37 (9H, m,  $\text{OC}(\text{CH}_3)_2\text{O}$ ,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C NMR}$**  (50 MHz, 340 K,  $\text{CDCl}_3$ )  $\delta$ : 172.2, 158.1, 151.9, 132.9, 131.5, 130.5, 127.8, 125.6, 122.5, 115.0, 109.1, 96.9, 80.9, 80.3, 78.4, 75.2, 63.7, 61.5, 52.3, 31.8, 28.5, 27.8, 27.5, 27.2, 14.8.

A third fraction gave impure (*E,E*)-diene **E-30** as a viscous, clear colourless liquid (0.0037 g, 0.0068 mmol, 4.3%).

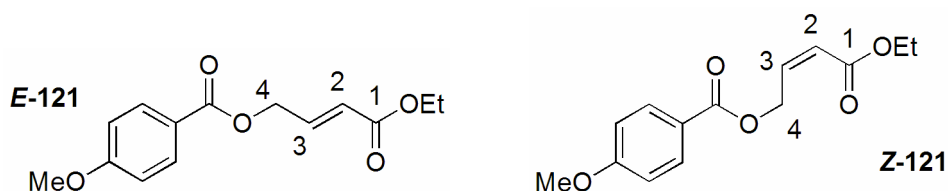
A fourth fraction gave impure (*E,Z*)-diene **Z-30** as a viscous, clear colourless liquid (0.0042 g, 0.0077 mmol, 4.8%).

## 6.4.3 Experimental for Chapter 4

Preliminary studies into using these compounds in the syntheses were made. When these approaches were abandoned some compounds are listed with incomplete characterisation data.

**(*E*)-4-Ethoxy-4-oxobut-2-enyl 4-methoxybenzoate**<sup>61</sup> ***E*-121**

**(*Z*)-4-Ethoxy-4-oxobut-2-enyl 4-methoxybenzoate**<sup>61</sup> ***Z*-121**



The general cross metathesis olefination procedure (see page 114) was followed using alkene **39** (0.33 g, 1.7 mmol) and ethyl acrylate. Time = 20 h. The crude product was a viscous, dark-brown liquid (0.70 g). Flash chromatographic purification (10% ethyl acetate : hexanes) gave pure (*E*)-alkene ***E*-121** as a viscous, clear, colourless liquid (0.35 g, 1.3 mmol, 78%): **R<sub>f</sub>** 0.55 (55% ethyl acetate : hexanes); **v<sub>max</sub>** (thin film) 1720 (br, s, C=O), 1605, 1582, 1512 (s, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 8.04 – 7.97 (2H, m, Ar-H), 7.03 (1H, dt, *J* 15.8, 4.5 Hz, C<sub>3</sub>-H), 6.95 – 6.88 (2H, m, Ar-H), 6.09 (1H, dt, *J* 15.8, 2.0 Hz, C<sub>2</sub>-H), 4.94 (2H, dd, *J* 4.5, 2.0 Hz, C<sub>4</sub>-H<sub>2</sub>), 4.19 (2H, q, *J* 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.84 (3H, s, Ar-OCH<sub>3</sub>), 1.27 (3H, t, *J* 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 165.8, 165.5, 163.6, 141.5, 131.7, 122.0, 121.8, 113.7, 62.6, 60.5, 55.4, 14.1.

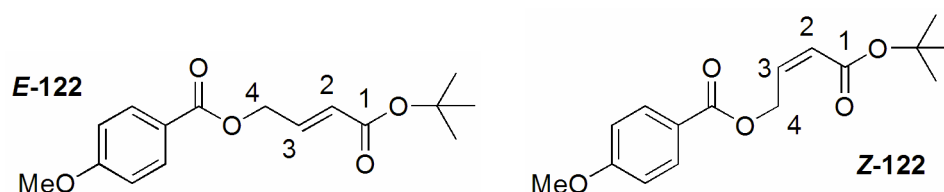
A second fraction gave pure (*Z*)-alkene ***Z*-121** as a white crystalline solid (0.007 g, 0.026 mmol, 2%): **R<sub>f</sub>** 0.58 (55% ethyl acetate : hexanes); **m.p.** 82.0 – 83.5 °C; **v<sub>max</sub>** (thin film) 1697 (s, C=O), 1601, 1578, 1514 (s, Ar(C=C)) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 8.05 – 7.98 (2H, m, Ar-H), 6.96 – 6.89 (2H, m, Ar-H), 6.38 (1H, dt, *J* 11.6, 5.1 Hz, C<sub>3</sub>-H), 5.90 (1H, dt, *J* 11.6, 2.3 Hz, C<sub>2</sub>-H), 5.41 (2H, dd, *J* 5.1, 2.3 Hz, C<sub>4</sub>-H<sub>2</sub>), 4.22 (2H, q, *J* 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.87 (3H, s, Ar-OCH<sub>3</sub>),

1.31 (3H, t,  $J$  7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 166.0, 165.8, 163.5, 145.0, 131.7, 122.3, 120.7, 113.7, 62.9, 60.5, 55.4, 14.2.

A third fraction gave a mixture of (*E*)-alkene **E-121** and (*Z*)-alkene **Z-121** in a 1 : 5.8 ratio (determined by integration of the C<sub>2</sub>-H and C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra) as a white crystalline solid (0.025 g, 0.095 mmol, 6%).

**(*E*)-4-*tert*-Butoxy-4-oxobut-2-enyl 4-methoxybenzoate **E-122****

**(*Z*)-4-*tert*-Butoxy-4-oxobut-2-enyl 4-methoxybenzoate **Z-122****



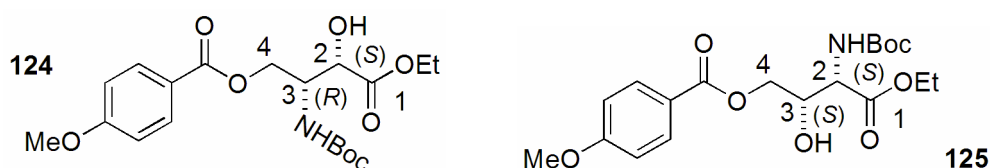
The general cross metathesis olefination procedure (see page 114) was followed using alkene **39** (0.48 g, 2.5 mmol) and *tert*-butyl acrylate. Time = 20 h. The crude product was a viscous, dark-brown liquid (1.0 g). Flash chromatographic purification (10% ethyl acetate : hexanes) gave pure (*E*)-alkene **E-122** as a viscous, clear, colourless liquid (0.56 g, 1.9 mmol, 77%):  $R_f$  0.51 (40% ethyl acetate : hexanes);  $\nu_{\max}$  (thin film) 1710 (br, s, C=O), 1605, 1582, 1510 (s, Ar(C=C)) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.07 – 7.99 (2H, m, Ar-H), 7.00 – 6.88 (3H, m, Ar-H, C<sub>3</sub>-H), 6.02 (1H, dt,  $J$  15.7, 1.9 Hz, C<sub>2</sub>-H), 4.94 (2H, dd,  $J$  4.6, 1.9 Hz, C<sub>4</sub>-H<sub>2</sub>), 3.87 (3H, s, Ar-OCH<sub>3</sub>), 1.49 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 165.6, 165.2, 163.6, 140.2, 131.8, 124.0, 122.0, 113.7, 80.7, 62.8, 55.4, 28.1; HRMS (+ESI) calc. for C<sub>16</sub>H<sub>20</sub>O<sub>5</sub>+Na 315.1208, found 315.1204;  $m/z$  (+EI) 236 (6%), 152 (18), 135 (100), 77 (14);  $m/z$  (+ESI) 315 ([M+Na]<sup>+</sup>, 100).

A second fraction gave pure (*Z*)-alkene **Z-122** as an off-white crystalline solid (0.053 g, 0.18 mmol, 7%):  $R_f$  0.52 (40% ethyl acetate : hexanes); **m.p.** 64.0 – 65.0 °C;  $\nu_{\max}$  (thin film) 1705 (s, C=O), 1605, 1582, 1510 (w, Ar(C=C)) cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.05 – 7.99 (2H, m, Ar-H), 6.96 – 6.90 (2H, m, Ar-H), 6.28 (1H, dt,  $J$  11.7, 5.0 Hz, C<sub>3</sub>-H), 5.81 (1H, dt,  $J$  11.7, 2.3 Hz, C<sub>2</sub>-H), 5.37 (2H, dd,  $J$  5.0, 2.4 Hz, C<sub>4</sub>-H<sub>2</sub>), 3.87 (3H, s, Ar-OCH<sub>3</sub>), 1.51 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR

(50 MHz, CDCl<sub>3</sub>)  $\delta$ : 166.1, 165.2, 163.5, 143.5, 131.7, 122.6, 122.4, 113.6, 81.0, 62.9, 55.4, 28.2.

**(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxy-4-ethoxy-4-oxobutyl 4-methoxybenzoate<sup>61</sup> **124****

**(2*S*,3*S*)-3-(*tert*-Butoxycarbonylamino)-4-ethoxy-2-hydroxy-4-oxobutyl 4-methoxybenzoate<sup>61</sup> **125****



**Method 1 – Using (DHQD)<sub>2</sub>PHAL ligand:**

The general AA procedure (see page 113) was followed using (DHQD)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-121** (0.066 g, 0.25 mmol). Time = 19 h. The crude product was a beige residue (0.26 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of **124** to **125** was determined to be 5.6 : 1 from integration of the N-H signals in the spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.36 – 5.25 (1H, m, N <sub>$\alpha$</sub> -H), 5.07 (1H, d, *J* 9.5 Hz, N <sub>$\beta$</sub> -H).  $\beta$ -aminoalcohol **124**: R<sub>f</sub> 0.33 (40% ethyl acetate : hexanes).

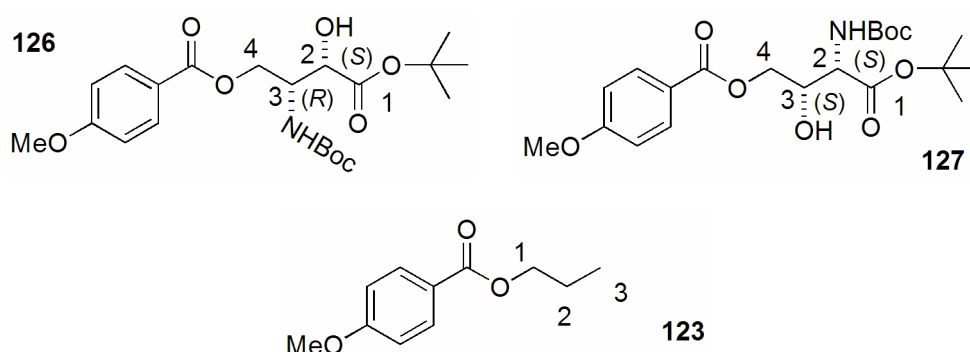
**Method 2 – Using (DHQ)<sub>2</sub>PHAL ligand:**

The general AA procedure (see page 113) was followed using (DHQ)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-121** (0.041 g, 0.15 mmol). Time = 19 h. The crude product was a beige residue (0.13 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of **124** to **125** was determined to be 5.9 : 1 from integration of the N-H signals in the spectra.

**(2*R*,3*S*)-4-*tert*-Butoxy-2-(*tert*-butoxycarbonylamino)-3-hydroxy-4-oxobutyl 4-methoxybenzoate **126****

**(2*S*,3*S*)-4-*tert*-Butoxy-3-(*tert*-butoxycarbonylamino)-2-hydroxy-4-oxobutyl 4-methoxybenzoate **127****

***n*-Propyl 4-methoxybenzoate<sup>82</sup> **123****



**Method 1 – Using (DHQD)<sub>2</sub>PHAL ligand:**

The general AA procedure (see page 113) was followed using (DHQD)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-122** (0.048 g, 0.16 mmol). Time = 1 day, 4 h. The crude product was a beige residue (0.11 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave by-product **123** as a viscous, clear, colourless liquid (0.014 g, 0.072 mmol, 45%):  $R_f$  0.64 (40% ethyl acetate : hexanes);  $\nu_{max}$  (thin film) 1709 (s, C=O), 1607, 1512 (m, Ar(C=C)), 1275, 1256 (s, C-O)  $cm^{-1}$ ;  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 8.04 – 7.97 (2H, m, Ar-H), 6.95 – 6.88 (2H, m, Ar-H), 4.25 (2H, t,  $J$  6.6 Hz, C<sub>1</sub>-H<sub>2</sub>), 3.86 (3H, s, Ar-OCH<sub>3</sub>), 1.83 – 1.73 (2H, m, C<sub>2</sub>-H<sub>2</sub>), 1.02 (2H, t,  $J$  7.4 Hz, CH<sub>3</sub>);  $^{13}C$  NMR (50 MHz,  $CDCl_3$ )  $\delta$ : 166.5, 163.3, 131.5, 123.0, 113.6, 66.2, 55.4, 22.2, 10.5.

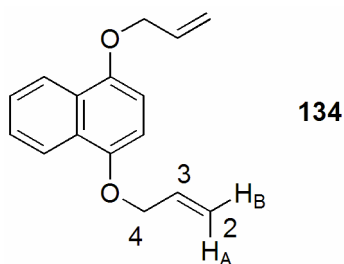
A second fraction gave an inseparable mixture of  $\alpha$ -aminoalcohol **127** and  $\beta$ -aminoalcohol **126** in a 8.4 : 1 ratio (determined by integration of the N-H signals in the  $^1H$  NMR spectra:  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$ : 5.31 (1H, br d,  $J$  13.0 Hz, N $_{\alpha}$ -H), 4.85 (1H, br d,  $J$  10.3 Hz, N $_{\beta}$ -H)) as a pale orange film (0.001 g, 0.0024 mmol, 1%) – see Method 3 for characterisation data.

**Method 2 – Using (DHQ)<sub>2</sub>PHAL ligand:**

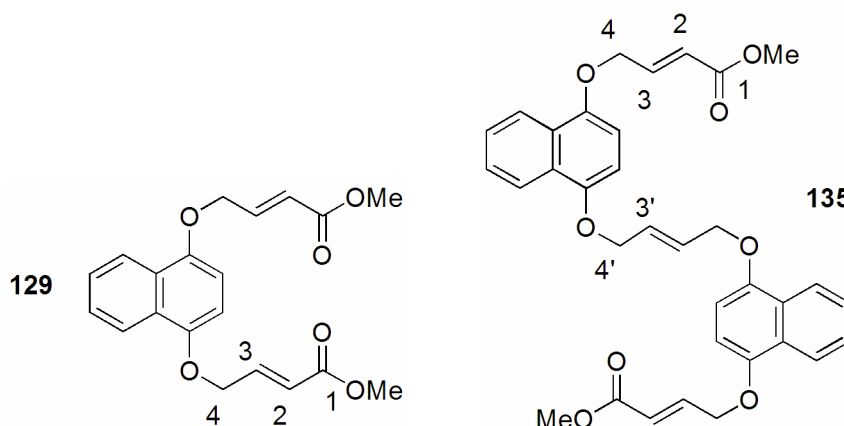
The general AA procedure (see page 113) was followed using (DHQ)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-122** (0.021 g, 0.070 mmol). Time = 1 day, 4 h. The crude product was a beige residue (0.080 g). The crude product was analysed by <sup>1</sup>H NMR and by-product **123** was identified as the major product.

**Method 3 – Using DHQD-CLB ligand:**

The general AA procedure (see page 113) was followed using DHQD-CLB ligand and (*E*)-alkene **E-122** (0.054 g, 0.18 mmol). Time = 16 h. The crude product was a beige residue (0.21 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of β-aminoalcohol **126** to α-aminoalcohol **127** was determined to be 1.8 : 1 from integration of the N-H signals in the spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 5.45 (1H, d, *J* 9.0 Hz, N<sub>α</sub>-H), 4.98 (1H, d, *J* 9.9 Hz, N<sub>β</sub>-H). Flash chromatographic purification (30% ethyl acetate : hexanes) gave a mixture of β-aminoalcohol **126** and α-aminoalcohol **127** as viscous, clear, colourless liquid (0.050 g, 0.12 mmol, 67%): **R<sub>f</sub>**(β-aminoalcohol **126**) 0.33 (40% ethyl acetate : hexanes); **R<sub>f</sub>**(α-aminoalcohol **127**) 0.30 (40% ethyl acetate : hexanes); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 7.98 (2H, d, *J* 8.9 Hz, Ar-H), 6.87 (2H, d, *J* 8.8 Hz, Ar-H), 4.98 (1H, d, *J* 9.9 Hz, N-H), 4.62 – 4.42 (4H, m, C<sub>2</sub>-H, C<sub>3</sub>-H, C<sub>4</sub>-H<sub>2</sub>), 3.83 (3H, s, Ar-OCH<sub>3</sub>), 1.47 (9H, s, COOC(CH<sub>3</sub>)<sub>3</sub>), 1.43 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 7.99 (2H, d, *J* 9.0 Hz, Ar-H), 6.89 (2H, d, *J* 8.9 Hz, Ar-H), 5.45 (1H, d, *J* 9.0 Hz, N-H), 3.83 (3H, s, Ar-OCH<sub>3</sub>), 1.46 (9H, s, COOC(CH<sub>3</sub>)<sub>3</sub>); **HRMS** (+ESI) calc. for C<sub>21</sub>H<sub>31</sub>NO<sub>8</sub>+Na 448.1947, found 448.1941; **m/z** (+ESI) 448 ([M+Na]<sup>+</sup>, 100%), 392 (24), 336 (16).

**1,4-Bis(allyloxy)naphthalene 134**

A solution of 1,4-naphthoquinone (6.0 g, 0.038 mol) in dichloromethane (0.19 L) and diethyl ether (0.58 L) was shaken vigorously with a freshly prepared solution of sodium dithionite (50 g, 0.29 mol) in water (0.77 ml) for 10 min. The organic layer was separated, washed with brine (0.10 L), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give crude 1,4-naphthalenediol as a pale brown solid. The 1,4-naphthalenediol was dissolved in acetone (45 ml) and added to a suspension of potassium carbonate (31 g, 0.22 mol) and allyl bromide (11 ml, 0.13 mol) in acetone (30 ml). The red solution was heated at reflux (70 °C) for 6.5 h and allowed to cool to room temperature. The reaction was filtered, washing with ether (0.10 L) and concentrated under reduced pressure to give a viscous orange liquid (11 g). Flash chromatographic purification (20% dichloromethane : hexanes) gave bis-alkene **134** as a lime green solid (8.8 g, 0.037 mol, 97%):  $R_f$  0.30 (20% dichloromethane : hexanes);  $\nu_{\text{max}}$  (thin film) 1648, 1628, 1596 (m, Ar(C=C))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.38 – 8.29 (2H, m, Ar-H), 7.60 – 7.52 (2H, m, Ar-H), 6.71 (2H, s, Ar-H), 6.22 (2H, ddt,  $J$  17.3, 10.4, 5.2 Hz,  $\text{C}_3\text{-H}$ ), 5.56 (2H, dq,  $J$  17.3, 1.6 Hz,  $\text{C}_2\text{-H}_A$ ), 5.37 (2H, dq,  $J$  10.5, 1.5 Hz,  $\text{C}_2\text{-H}_B$ ), 4.69 (4H, dt,  $J$  5.1, 1.5 Hz,  $\text{C}_4\text{-H}_2$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 148.5, 133.6, 126.6, 125.8, 121.9, 117.1, 104.7, 69.3; **HRMS** (+EI) calc. for  $\text{C}_{16}\text{H}_{16}\text{O}_2$  240.1150, found 240.1154;  $m/z$  (+EI) 241 ( $[\text{M}+\text{H}]^+$ , 19%), 240 ( $[\text{M}]^+$ , 67), 200 (33), 199 (100), 181 (33), 159 (15), 130 (14), 115 (11), 114 (19), 104 (17), 102 (17), 77 (12), 76 (17).

**(2*E*,2'*E*)-Dimethyl 4,4'-(naphthalene-1,4-diylbis(oxy))dibut-2-enoate 129****(2*E*,2'*E*)-Dimethyl 4,4'-(4,4'-(*E*)-but-2-ene-1,4-diylbis(oxy))bis(naphthalene-4,1-diyl))bis(oxy)dibut-2-enoate 135**

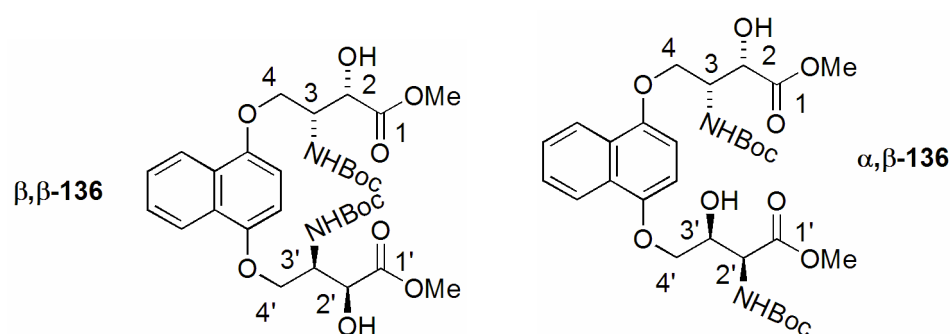
The general cross metathesis olefination procedure (see page 114) was followed using bis-alkene **134** (0.50 g, 2.1 mmol) and methyl acrylate (4.0 eq.). The reaction was kept in the dark. Time = 4.5 h. The crude product was a viscous, dark-brown liquid (0.86 g). Flash chromatographic purification (30% ethyl acetate : hexanes) was performed immediately and gave pure bis-(*E*)-alkene **129** as a grey solid (0.34 g, 0.95 mmol, 46%):  $R_f$  0.43 (50% ethyl acetate : hexanes);  $\nu_{\max}$  (thin film) 1724 (s, C=O), 1666, 1629, 1596 (m, Ar(C=C))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.29 – 8.23 (2H, m, Ar-H), 7.57 – 7.49 (2H, m, Ar-H), 7.19 (2H, dt,  $J$  15.8, 4.0 Hz,  $\text{C}_3\text{-H}$ ), 6.64 (2H, s, Ar-H), 6.34 (2H, dt,  $J$  15.8, 2.0 Hz,  $\text{C}_2\text{-H}$ ), 4.82 (4H, dd,  $J$  3.9, 2.1 Hz,  $\text{C}_4\text{-H}_2$ ), 3.78 (6H, s,  $\text{C}_1\text{-OCH}_3$ );  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 166.5, 148.2, 142.9, 126.4, 126.3, 121.8, 121.4, 104.5, 67.0, 51.7; **HRMS** (+EI) calc. for  $\text{C}_{20}\text{H}_{20}\text{O}_6$  356.1260, found 356.1254;  $m/z$  (+EI) 356 ( $[\text{M}]^+$ , 28%), 283 (12), 258 (14), 257 (46), 225 (18), 197 (18), 159 (12), 130 (11), 114 (10), 104 (12), 102 (11), 100 (21), 99 (100), 76 (10), 71 (49), 68 (33), 59 (17).

A second fraction gave dimer **135** as a blue solid (0.13 g, 0.23 mmol, 22%):  $R_f$  0.36 (50% ethyl acetate : hexanes);  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.31 – 8.24 (4H, m, Ar-H), 7.58 – 7.50 (4H, m, Ar-H), 7.20 (2H, dt, partially obscured,  $J$  15.8, 3.9 Hz,  $\text{C}_3\text{-H}$ ), 6.76 – 6.63 (4H, m, Ar-H), 6.44 – 6.28 (4H, m,  $\text{C}_2\text{-H}$ ,  $\text{C}_3'\text{-H}$ ), 4.85 – 4.67 (8H, m,  $\text{C}_4\text{-H}_2$ ,  $\text{C}_4'\text{-H}_2$ ), 3.79 (6H, s,  $\text{C}_1\text{-OCH}_3$ );  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ :

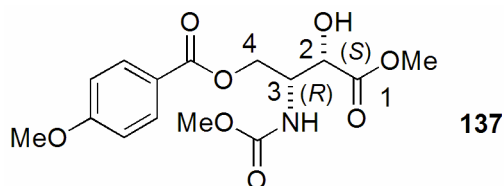
166.6, 148.8, 147.9, 143.1, 128.3, 126.7, 126.4, 126.1, 122.0, 121.7, 121.4, 104.8, 104.7, 68.4, 67.0, 51.7.

**(2*S*,2'*S*,3*R*,3'*R*)-Dimethyl 4,4'-(naphthalene-1,4-diylbis(oxy))bis(3-(*tert*-butoxycarbonylamino)-2-hydroxybutanoate)  $\beta,\beta$ -136**

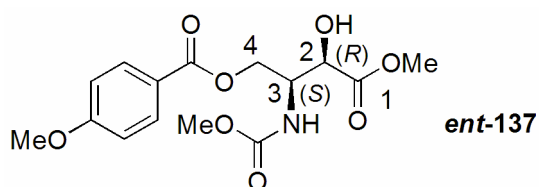
**(2*S*,3*R*)-Methyl 3-(*tert*-butoxycarbonylamino)-4-(4-((2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-hydroxy-4-methoxy-4-oxobutoxy)naphthalen-1-yloxy)-2-hydroxybutanoate  $\alpha,\beta$ -136**



The general AA procedure (see page 113) was followed using sodium hydroxide (10 eq.) in water (2.0 ml), *tert*-butyl carbamate (9.5 eq.) in propanol (2.5 ml), 1,3-dichloro-5,5-dimethylhydantoin (3.4 eq.), (DHQD)<sub>2</sub>PHAL (0.22 eq.), bis-(*E*)-alkene **129** (1 eq., conc. 0.033 M, 0.064 g, 0.18 mmol) in propanol (1.0 ml), potassium osmate(VI) dihydrate (0.15 eq.). Time = 4 h. The crude product was a brown crystalline solid (0.41 g). Flash chromatographic purification (50% ethyl acetate : hexanes graded to 90% ethyl acetate : hexanes) gave an inseparable mixture of products:  $R_f$  0.52 (90% ethyl acetate : hexanes). The mixture was analysed by <sup>1</sup>H NMR and the ratio of  $\beta,\beta$ -136 to  $\alpha,\beta$ -136 was determined to be 1 : 1.4 from integration of the N-H signals in the spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.48 (1H, br d, *J* 7.2 Hz, N <sub>$\alpha$</sub> -H), 5.06 (1.4H, br d, *J* 9.8 Hz, N <sub>$\beta$</sub> -H).

**(2*R*,3*S*)-3-Hydroxy-4-methoxy-2-(methoxycarbonylamino)-4-oxobutyl 4-methoxybenzoate 137**

The general AA procedure (see page 113) was followed using (DHQD)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-28** (0.90 g, 3.6 mmol) with the exception that methyl carbamate was used instead of *tert*-butyl carbamate. Time = 16 h. The crude product was a viscous yellow liquid (3.3 g). Flash chromatographic purification (30% ethyl acetate : hexanes graded to 40% ethyl acetate : hexanes) gave pure β-aminoalcohol **137** as a viscous clear colourless liquid (0.83 g, 2.4 mmol, 67%): **R<sub>f</sub>** 0.12 (40% ethyl acetate : hexanes); **[α]<sub>D</sub><sup>26</sup>** +57.5 (c 0.08, CH<sub>2</sub>Cl<sub>2</sub>); **v<sub>max</sub>** (thin film) 3358 (br, m, O-H, N-H), 1720 (br, s, C=O), 1607, 1582, 1514 (m, Ar(C=C)); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 8.02 – 7.95 (2H, m, Ar-H), 6.96 – 6.88 (2H, m, Ar-H), 5.13 (1H, br d, *J* 8.6 Hz, N-H), 4.56 – 4.32 (4H, m, C<sub>2</sub>-H, C<sub>3</sub>-H, C<sub>4</sub>-H<sub>2</sub>), 3.86 (3H, s, Ar-OCH<sub>3</sub>), 3.81 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.64 (3H, s, N-CO<sub>2</sub>Me), 3.24 (1H, d, *J* 3.9 Hz, O-H); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 173.7, 166.4, 164.1, 156.9, 132.2, 122.4, 114.1, 69.9, 63.4, 55.9, 53.6, 52.8, 52.6; **HRMS** (+ESI) calc. for C<sub>15</sub>H<sub>19</sub>NO<sub>8</sub>+Na 364.1008, found 364.1005; ***m/z*** (+ESI) 705 ([2M+Na]<sup>+</sup>, 34%), 364 ([M+Na]<sup>+</sup>, 100).

**(2*S*,3*R*)-3-Hydroxy-4-methoxy-2-(methoxycarbonylamino)-4-oxobutyl 4-methoxybenzoate *ent*-137**

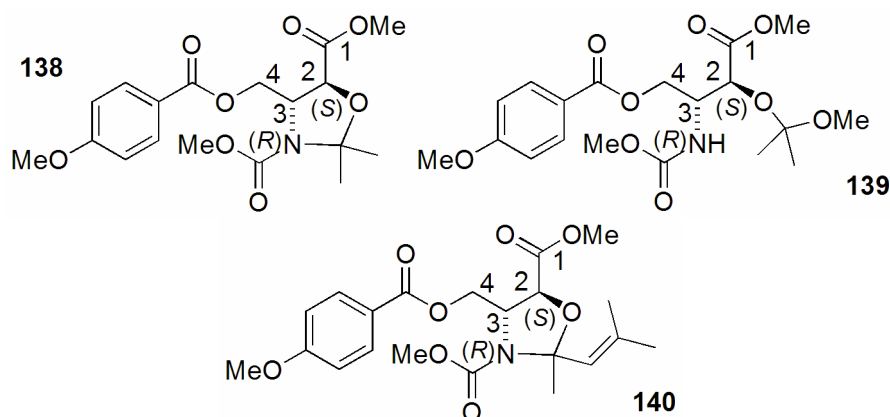
The general AA procedure (see page 113) was followed using (DHQ)<sub>2</sub>PHAL ligand and (*E*)-alkene **E-28** (0.071 g, 0.28 mmol) with the exception that methyl carbamate was used instead of *tert*-butyl carbamate. Time = 16 h. The crude product was a yellow residue (0.25 g). Flash chromatographic purification

(40% ethyl acetate : hexanes) gave pure  $\beta$ -aminoalcohol **ent-137** as a viscous clear colourless liquid (0.042 g, 0.12 mmol, 43%):  $[\alpha]_D^{20}$  -40.8 (*c* 3.2, CH<sub>2</sub>Cl<sub>2</sub>).

**(4*R*,5*S*)-Dimethyl 4-((4-methoxybenzoyloxy)methyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate 138**

**(2*R*,3*S*)-4-Methoxy-2-(methoxycarbonylamino)-3-(2-methoxypropan-2-yloxy)-4-oxobutyl 4-methoxybenzoate 139**

**(4*R*,5*S*)-Dimethyl 4-((4-methoxybenzoyloxy)methyl)-2-methyl-2-(2-methylprop-1-enyl)oxazolidine-3,5-dicarboxylate 140**



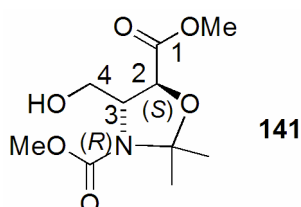
To a solution of alcohol **137** (0.66 g, 1.9 mmol) in toluene (20 ml) was added 2-methoxypropene (3.7 ml, 39 mmol) followed by pyridinium *p*-toluenesulfonate (0.044 g, 0.18 mmol). The clear colourless solution was heated at 110 °C for 5 h while additional aliquots of 2-methoxypropene (3.7 ml, 39 mmol) were added at 3.5 h and 4.5 h. Sodium hydrogen carbonate solution (sat. aq., 20 ml) was added, the organic layer was collected and the aqueous layer was extracted with ethyl acetate (3 x 40 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a viscous yellow liquid (2.0 g). Flash chromatographic purification (20% ethyl acetate : hexanes graded to 40% ethyl acetate : hexanes) gave pure oxazolidine **138** as a viscous clear, colourless liquid (0.38 g, 1.0 mmol, 53%): *R<sub>f</sub>* 0.28 (40% ethyl acetate : hexanes); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.01 – 7.94 (2H, m, Ar-H), 6.92 – 6.86 (2H, m, Ar-H), 4.68 – 4.63 (2H, m, C<sub>2</sub>-H, C<sub>3</sub>-H), 4.50 – 4.41 (2H, m, C<sub>4</sub>-H<sub>2</sub>), 3.83 (3H, s, Ar-OCH<sub>3</sub>), 3.78

(3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.69 (3H, s, NCO<sub>2</sub>CH<sub>3</sub>), 1.60 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.59 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)); **HRMS** (+ESI) calc. for C<sub>18</sub>H<sub>23</sub>NO<sub>8</sub>+Na 404.1321, found 404.1318; **m/z** (+ESI) 785 ([2M+Na]<sup>+</sup>, 100%), 404 ([M+Na]<sup>+</sup>, 56).

A second fraction gave by-product **140** (0.21 g, 0.49 mmol, 26%): **R<sub>f</sub>** 0.36 (40% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 8.02 – 7.93 (2H, m, Ar-H), 6.94 – 6.87 (2H, m, Ar-H), 5.43 (1H, br s, C<sub>3</sub>-H), 4.76 – 4.70 (1H, m, C<sub>3</sub>-H), 4.65 – 4.60 (1H, m, C<sub>2</sub>-H), 4.49 – 4.39 (2H, m, C<sub>4</sub>-H<sub>2</sub>), 3.84 (3H, s, Ar-OCH<sub>3</sub>), 3.71 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.69 (3H, s, NCO<sub>2</sub>CH<sub>3</sub>), 1.80 (3H, d, *J* 1.2 Hz, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.72 (3H, s, C<sub>1</sub>-H<sub>3</sub>), 1.67 (3H, d, *J* 1.3 Hz, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)); **HRMS** (+ESI) calc. for C<sub>21</sub>H<sub>27</sub>NO<sub>8</sub>+Na 444.1634, found 444.1629; **m/z** (+ESI) 444.1 ([M+Na]<sup>+</sup>, 100%).

A third fraction gave intermediate **139** (0.050 g, 0.12 mmol, 6.3%): **R<sub>f</sub>** 0.13 (40% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 8.01 – 7.94 (2H, m, Ar-H), 6.95 – 6.88 (2H, m, Ar-H), 5.30 – 5.27 (1H, m, N-H), 4.52 (1H, s, C<sub>2</sub>-H), 4.44 – 4.20 (3H, m, C<sub>3</sub>-H, C<sub>4</sub>-H<sub>2</sub>), 3.85 (3H, s, Ar-OCH<sub>3</sub>), 3.71 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.65 (3H, s, NCO<sub>2</sub>CH<sub>3</sub>), 3.20 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 1.37 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.33 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)).

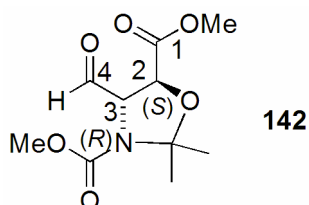
#### (4*R*,5*S*)-Dimethyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate **141**



The general *p*-methoxybenzoyl de-protection procedure *via* Method 2 (see page 117) was followed using caesium carbonate (0.60 eq.) and *p*-methoxybenzoyl ester **138** (0.34 g, 0.89 mmol). Time = 14 h. The crude product was a viscous yellow liquid (0.46 g). Flash chromatographic purification (60% ethyl acetate : hexanes) gave pure alcohol **141** as a viscous clear, colourless liquid (0.16 g, 0.65 mmol, 73%): **R<sub>f</sub>** 0.22 (60% ethyl acetate : hexanes); **[α]<sub>D</sub><sup>19</sup>** +9.6 (*c* 1.2, CH<sub>2</sub>Cl<sub>2</sub>); **v<sub>max</sub>** (thin film) 3474 (br s, O-H), 1742, 1674 (br, s, C=O) cm<sup>-1</sup>; **<sup>1</sup>H NMR** (200 MHz, 320K, CDCl<sub>3</sub>) δ: 4.57 (1H, d, *J* 4.1 Hz, C<sub>2</sub>-H), 4.35 – 4.28 (1H, m, C<sub>3</sub>-H), 3.86 – 3.80 (2H, m, C<sub>4</sub>-H<sub>2</sub>), 3.79 (3H, s, Ar-OCH<sub>3</sub>), 3.73 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 1.61 (3H, s,

$C(C_AH_3)(C_BH_3)$ ), 1.57 (3H, s,  $C(C_AH_3)(C_BH_3)$ );  $^{13}C$  NMR (50 MHz, 320K,  $CDCl_3$ )  $\delta$ : 171.1, 153.5, 96.7, 75.7, 63.0, 61.8 (br), 52.4, 27.1, 26.4; **HRMS** (+ESI) calc. for  $C_{10}H_{17}NO_6+Na$  270.0954, found 270.0940; **m/z** (+ESI) 517 ( $[2M+Na]^+$ , 42), 440 (25), 391 (22), 270 ( $[M+Na]^+$ , 100), 208 (29), 190 (20), 176 (17).

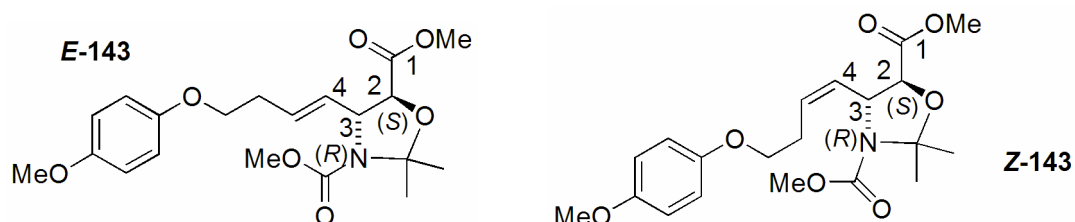
**(4S,5S)-Dimethyl 4-formyl-2,2-dimethyloxazolidine-3,5-dicarboxylate 142**



The general Dess-Martin oxidation procedure (see page 114) was followed using alcohol **141** (0.14 g, 0.57 mmol). Time = 1 h. The crude product was a cloudy, oily residue (0.19 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave pure aldehyde **142** as a viscous, clear, colourless liquid (0.12 g, 0.49 mmol, 86%):  $R_f$  0.16 – 0.31 (60% ethyl acetate : hexanes);  $^1H$  NMR (200 MHz, 320K,  $CDCl_3$ )  $\delta$ : 9.62 (1H, s, CHO), 4.74 – 4.68 (2H, m,  $C_2$ -H,  $C_3$ -H), 3.79 (3H, s,  $C_1$ -OCH<sub>3</sub>), 3.7 (3H, s, NCO<sub>2</sub>Me), 1.62 (3H, s,  $C(C_AH_3)(C_BH_3)$ ), 1.57 (3H, s,  $C(C_AH_3)(C_BH_3)$ );  $^{13}C$  NMR (50 MHz, 320K,  $CDCl_3$ )  $\delta$ : 196.3, 169.9, 169.9, 97.4, 73.8, 66.7, 52.7, 52.7, 26.5, 25.9.

**(4R,5S,E)-Dimethyl 4-(4-(4-methoxyphenoxy)but-1-enyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate E-143**

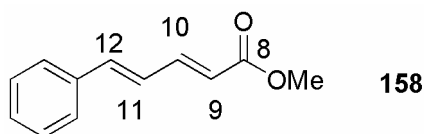
**(4R,5S,Z)-Dimethyl 4-(4-(4-methoxyphenoxy)but-1-enyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate Z-143**



The general Julia olefination procedure using Barbier conditions (see page 115) was followed using sulfone **26** (1.0 eq.), purified aldehyde **142** (0.055 g,

0.22 mmol, conc. 0.070 M) and potassium bis(trimethylsilyl)amide (0.50 M in toluene, 1.5 eq.). Solvent = 1,2-dimethoxyethane, T = -60 °C, time = 1 h. The crude product was a clear oily residue (0.10 g). Flash chromatographic purification (40% ethyl acetate : hexanes) gave an inseparable mixture of (*E*)-alkene **E-143** and (*Z*)-alkene **Z-143** in a 2.4 : 1 ratio (determined by integration of the C<sub>3</sub>-H signals in the <sup>1</sup>H NMR spectra) contaminated with unknown impurities as a viscous, clear colourless liquid (0.052 g, 0.13 mmol, 59%). It was estimated from integration of the <sup>1</sup>H NMR of the purified product that the purity was 80%. From this it was estimated that the overall yield of alkene products was 47%. Data for the alkenes only are quoted where appropriate where unobscured by impurities: **R<sub>f</sub>** 0.22 (5% ethyl acetate : 45% dichloromethane : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 6.81 (4H, s, Ar-H), 5.81 (1H, dt, *J* 15.3, 6.7 Hz, C<sub>5</sub>-H), 5.59 (1H, dd, *J* 15.3, 7.5 Hz, C<sub>4</sub>-H), 4.71 (1H, dd, *J* 7.2, 3.0 Hz, C<sub>3</sub>-H), 4.39 (1H, d, *J* 3.4 Hz, C<sub>2</sub>-H), 3.95 (2H, t, *J* 6.4 Hz, C<sub>7</sub>-H), 3.77 (3H, s, Ar-OCH<sub>3</sub>), 3.75 (6H, s, C<sub>1</sub>-OCH<sub>3</sub>, NCO<sub>2</sub>CH<sub>3</sub>), 2.51 (1H, q, *J* 6.3 Hz, C<sub>6</sub>-H), 1.63 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.59 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 6.81 (4H, s, Ar-H), 5.81 – 5.69 (1H, m (obs), C<sub>5</sub>-H), 5.61 – 5.47 (1H, m (obs), C<sub>4</sub>-H), 5.06 (1H, dd, *J* 9.4, 3.4 Hz, C<sub>3</sub>-H), 4.37 (1H, d, *J* 3.4 Hz, C<sub>2</sub>-H), 4.00 – 3.93 (2H, m (obs), C<sub>7</sub>-H), 2.66 (1H, q, *J* 6.7 Hz, C<sub>6</sub>-H); **HRMS** (+ESI) calc. for C<sub>20</sub>H<sub>27</sub>NO<sub>7</sub>+Na 416.1685, found 416.1680; **m/z** (+ESI) 416 ([M+Na]<sup>+</sup>, 100%), 402 (28).

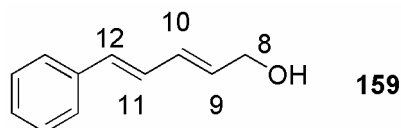
**(2*E*,4*E*)-Methyl 5-phenylpenta-2,4-dienoate**<sup>83, 84</sup> **158**



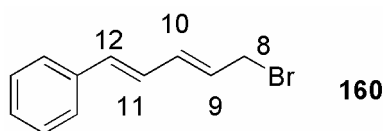
To a solution of methyl diethylphosphonoacetate (1.2 ml, 6.5 mmol) in tetrahydrofuran (40 ml) at -78 °C, was added drop-wise a solution of *n*-butyl lithium (1.5 M in hexanes, 5.3 ml, 8.0 mmol). The reaction was stirred at -78 °C for 35 min and a solution of *trans*-cinnamaldehyde (1.0 ml, 7.9 mmol) in tetrahydrofuran (30 ml) was added *via cannula*, washing with tetrahydrofuran (2 x 5 ml). The reaction was slowly allowed to warm to room temperature over 3 h 20 min. A solution of ammonium chloride (sat. aq., 20 ml) was added and the crude product was extracted into ethyl acetate (3 x 60 ml). The combined organic

layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give a yellow crystalline solid (1.9 g). The crude product was recrystallised from hexanes to give pure (*E,E*)-diene **158** as a pale-yellow crystalline solid (1.1 g, 5.8 mmol, 89%):  $R_f$  0.38 (20% ethyl acetate : hexanes); **m.p.** 67.0 – 68.0 °C (*lit.*<sup>83</sup> **m.p.** 67.0 – 68.0 °C, *lit.*<sup>84</sup> **m.p.** 71 °C);  $\nu_{\text{max}}$  (thin film) 1713 (s, C=O  $\alpha,\beta$ -unsaturated ester), 1628, 1614, 1593 (m, Ar(C-C))  $\text{cm}^{-1}$ ;  **$^1\text{H NMR}$**  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.56 – 7.31 (6H, m, Ar-H,  $\text{C}_{10}$ -H), 7.00 – 6.82 (2H, m,  $\text{C}_{11}$ -H,  $\text{C}_{12}$ -H), 6.04 (1H, d,  $J$  15.3 Hz,  $\text{C}_9$ -H), 3.81 (3H, s,  $\text{C}_1$ - $\text{OCH}_3$ );  **$^{13}\text{C NMR}$**  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 167.4, 144.8, 140.5, 135.9, 129.0, 128.7, 127.1, 126.1, 120.7, 51.5.

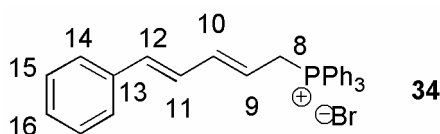
**(2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-ol**<sup>83, 85, 86, 87</sup> **159**



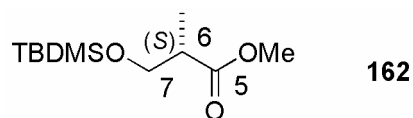
The general procedure for ester reduction (see page 115) was followed using (*E,E*)-diene **158** (0.17 g, 0.90 mmol) and diisobutylaluminium hydride (1.0 M in toluene, 2.5 eq.). Time = 1 h 10 min. The crude product was a yellow crystalline solid (0.21 g). Flash chromatographic purification (30% ethyl acetate : hexanes) gave pure alcohol **159** (0.11 g, 0.69 mmol, 77%) as a white powder:  $R_f$  0.33 (40% ethyl acetate : hexanes); **m.p.** 71.0 – 72.0 °C (*lit.*<sup>83</sup> **m.p.** 79.5 – 81.5 °C, *lit.*<sup>85</sup> **m.p.** 73 – 78 °C, *lit.*<sup>86</sup> **m.p.** 67 – 69 °C);  $\nu_{\text{max}}$  (thin film) 3301 (br s, O-H), 991, 982 (s, HC=CH), 743, 690 (s, Ar(C-H))  $\text{cm}^{-1}$ ;  **$^1\text{H NMR}$**  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.40 – 7.16 (5H, m, Ph), 6.78 (1H, dd,  $J$  15.5, 10.3 Hz,  $\text{C}_{11}$ -H), 6.53 (1H, d,  $J$  15.6 Hz,  $\text{C}_{12}$ -H), 6.40 (1H, ddt,  $J$  15.1, 10.3, 1.4 Hz,  $\text{C}_{10}$ -H), 5.94 (1H, dt,  $J$  15.1, 5.8 Hz,  $\text{C}_9$ -H), 4.22 (2H, d,  $J$  5.7 Hz,  $\text{C}_8$ - $\text{H}_2$ ), 1.91 (1H, s, OH);  **$^{13}\text{C NMR}$**  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 137.1, 132.7, 132.5, 131.5, 128.6, 128.1, 127.6, 126.3, 63.3.

**((1*E*,3*E*)-5-Bromopenta-1,3-dienyl)benzene<sup>83</sup> **160****

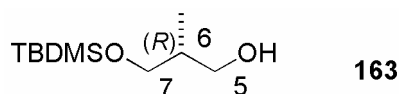
The general procedure for bromine substitution (see page 114) was followed using alcohol **159** (1.1 g, 6.9 mmol). The crude product was pure bromide **160** as a pale yellow solid (1.5 g, 6.7 mmol, 97%):  $\nu_{\max}$  (thin film) 995 (s, HC=CH), 756, 694 (s, Ar(C-H))  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.34 – 7.10 (5H, m, Ph), 6.66 (1H, dd,  $J$  15.6, 10.1 Hz, C<sub>11</sub>-H), 6.48 (1H, d,  $J$  15.5 Hz, C<sub>12</sub>-H), 6.34 (1H, ddt,  $J$  14.8, 10.1, 0.8 Hz, C<sub>10</sub>-H), 5.88 (1H, dt,  $J$  15.1, 7.7 Hz, C<sub>9</sub>-H), 3.99 (2H, dd,  $J$  8.0, 0.7 Hz, C<sub>8</sub>-H<sub>2</sub>);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 136.7, 135.1, 134.4, 128.9, 128.6, 127.9, 127.2, 126.5, 33.4.

**Triphenyl((2*E*,4*E*)-5-phenylpenta-2,4-dienyl)phosphonium bromide<sup>85</sup> **34****

The general procedure for formation of phosphonium salts (see page 118) was followed using bromo-compound **160** (1.5 g, 6.7 mmol, 0.56 M) and triphenylphosphine (0.97 eq.). Solvent = benzene, time = 3 days. The crude product was washed with diethyl ether (3 x 10 ml) and dried under reduced pressure to give pure phosphonium salt **34** as an off-white solid (2.9 g, 6.0 mmol, 92%):  $R_f$  baseline (40% ethyl acetate : hexanes); **m.p.** 212 – 215 °C (*lit.*<sup>88</sup> **m.p.** 229 – 230 °C, *lit.*<sup>85</sup> **m.p.** 236 – 240 °C);  $\nu_{\max}$  (thin film) 1587, 1485 (w, Ar(C=C)), 997, 924 (s, HC=CH), 723 (br, s, P-C)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.81 – 7.57 (15H, m, Ar-H), 7.31 – 7.12 (5H, m, Ar-H), 6.68 – 6.33 (3H, m, C<sub>12</sub>-H, C<sub>11</sub>-H, C<sub>10</sub>-H), 5.63 – 5.46 (1H, m, C<sub>9</sub>-H), 4.78 (2H, dd,  $J$  15.7, 7.5 Hz, C<sub>8</sub>-H<sub>2</sub>);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : 140.2 (d,  $^3J_{\text{PC}}$  13.7 Hz, C<sub>10</sub>), 136.1, 134.7 (d,  $^4J_{\text{PC}}$  2.0 Hz, *p*-Ar-H), 134.4 (d,  $^5J_{\text{PC}}$  4.7 Hz, C<sub>12</sub>), 133.6 (d,  $^2J_{\text{PC}}$  9.7 Hz, *o*-Ar-H), 130.0 (d,  $^3J_{\text{PC}}$  12.5 Hz, *m*-Ar-H), 128.3, 127.7, 126.7 (d,  $^4J_{\text{PC}}$  5.3 Hz, C<sub>11</sub>), 126.2, 117.6 (d,  $^1J_{\text{PC}}$  85.5 Hz, *q*-Ar-H), 116.4 (d,  $^2J_{\text{PC}}$  11.5 Hz, C<sub>9</sub>), 28.1 (d,  $^1J_{\text{PC}}$  49.6 Hz, C<sub>8</sub>).

**(S)-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate**<sup>89,90</sup> **162**

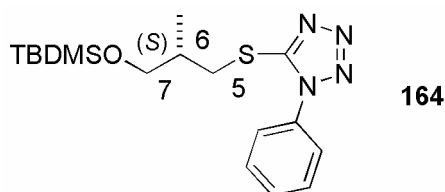
To a solution of (+)-methyl (S)-3-hydroxy-2-methylpropanoate (5.0 ml, 45 mmol) in dichloromethane (45 ml) was added *tert*-butyldimethylsilyl chloride (14 g, 93 mmol). The reaction was cooled to 0 °C and imidazole (6.2 g, 91 mmol) was added over 30 min. The reaction was allowed to warm to room temperature and was stirred for 2 h. Water (40 ml) was added and the organic layer was collected. The aqueous layer was extracted with dichloromethane (2 x 50 ml). The combined organic layers were washed with brine (20 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure to give a clear, colourless liquid (18 g). Flash chromatographic purification (10% ethyl acetate : hexanes) gave pure ether **162** (10 g, 43 mmol, 96%) as a clear colourless liquid: **R<sub>f</sub>** 0.44 (20% ethyl acetate : hexanes); **[α]<sub>D</sub><sup>22</sup>** +23.2 (*c* 0.48, CH<sub>2</sub>Cl<sub>2</sub>), (**lit.**<sup>89</sup> **[α]<sub>D</sub><sup>20</sup>** +20.7 (*c* 1, CCl<sub>4</sub>), **lit.**<sup>90</sup> **[α]<sub>D</sub><sup>24</sup>** +18.8 (*c* 2.04, CHCl<sub>3</sub>); **v<sub>max</sub>** (thin film) 1740 (C=O), 1258 (Si-CH<sub>3</sub>), 1095, 837 (Si-O-C), 777 (Si-CH<sub>3</sub>); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 3.76 (1H, dd, *J* 9.7, 6.9 Hz, C<sub>7</sub>-H<sub>A</sub>), 3.65 (3H, s, OMe), 3.63 (1H, dd, *J* 9.7, 6.0 Hz, C<sub>7</sub>-H<sub>B</sub>), 2.72 – 2.54 (1H, m, C<sub>6</sub>-H), 1.12 (3H, d, *J* 7.0 Hz, CH<sub>3</sub>), 0.85 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.02 (6H, s, Si-CH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 175.4, 65.2, 51.4, 42.5, 25.7, 18.2, 13.4, -5.6.

**(R)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-1-ol**<sup>90</sup> **163**

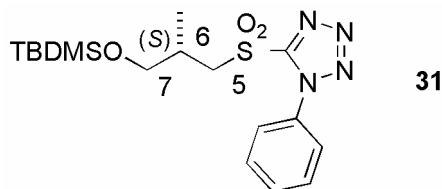
The general procedure for ester reduction (see page 115) was followed using ester **162** (10 g, 43 mmol) and diisobutylaluminium hydride (1.0 M in hexanes, 3.0 eq.). Time = 3 h. The crude product was a clear, colourless liquid (52 g). Flash chromatographic purification (10% ethyl acetate : hexanes graded to 20% ethyl acetate : hexanes) gave pure alcohol **163** (7.4 g, 36 mmol, 84%) as a clear, colourless liquid: **R<sub>f</sub>** 0.26 (20% ethyl acetate : hexanes); **[α]<sub>D</sub><sup>25</sup>** +7.9 (*c* 1.16, CH<sub>2</sub>Cl<sub>2</sub>), (**lit.**<sup>90</sup> **[α]<sub>D</sub><sup>24</sup>** +10.9 (*c* 2.13, CHCl<sub>3</sub>); **v<sub>max</sub>** (thin film) 3356 (br, s, O-H), 1258

(Si-CH<sub>3</sub>), 1090, 1040, 837 (Si-O-C), 775 (Si-CH<sub>3</sub>); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 3.76 – 3.68 (1H, m, C<sub>7</sub>-H<sub>A</sub>), 3.64 – 3.59 (2H, m, C<sub>5</sub>-H<sub>2</sub>), 3.53 (1H, dd, *J* 9.9, 7.8 Hz, C<sub>7</sub>-H<sub>B</sub>), 2.86 (1H, t, *J* 5.2 Hz, OH), 2.04 – 1.83 (1H, m, C<sub>6</sub>-H), 0.89 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.83 (3H, d, *J* 6.9 Hz, CH<sub>3</sub>), 0.06 (6H, s, Si-CH<sub>3</sub>); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ: 68.6, 68.2, 37.0, 25.8, 18.2, 13.1, -5.6.

**(S)-5-(3-(*tert*-Butyldimethylsilyloxy)-2-methylpropylthio)-1-phenyl-1*H*-tetrazole<sup>91</sup> **164****



The general Mitsunobu reaction procedure (see page 117) was followed using alcohol **163** (3.5 g, 17 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol. Time = 18 h. The crude product was a cloudy yellow liquid (21 g). Flash chromatographic purification (60% dichloromethane : hexanes) gave pure thio-ether **164** as a clear colourless liquid (5.9 g, 16 mmol, 94%): *R<sub>f</sub>* 0.44 (60% dichloromethane : hexanes);  $[\alpha]_D^{22}$  -2.1 (*c* 3.04, CH<sub>2</sub>Cl<sub>2</sub>), (*ent*-**164** lit.<sup>91</sup>  $[\alpha]_D^{20}$  +2.2 (*c* 3.43, CHCl<sub>3</sub>)); *v*<sub>max</sub> (thin film) 1597 (m), 1501 (s, Ar(C=C)), 1250 (Si-CH<sub>3</sub>), 1088, 837 (Si-O-C), 777 (Si-CH<sub>3</sub>); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 7.60 – 7.52 (5H, m, Ph), 3.64 (1H, dd, *J* 10.0, 4.9 Hz, C<sub>7</sub>-H<sub>A</sub>), 3.51 (1H, dd, *J* 10.0, 5.6 Hz, C<sub>7</sub>-H<sub>B</sub>), 3.50 (1H, dd, *J* 13.1, 6.9 Hz, C<sub>5</sub>-H<sub>A</sub>), 3.36 (1H, dd, *J* 12.8, 6.6 Hz, C<sub>5</sub>-H<sub>B</sub>), 2.24 – 2.03 (1H, m, C<sub>6</sub>-H), 1.04 (3H, d, *J* 6.8 Hz, C<sub>6</sub>-CH<sub>3</sub>), 0.87 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.03 (6H, s, 2 x Si-CH<sub>3</sub>); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ: 154.9, 133.8, 130.0, 129.7, 123.9, 66.3, 36.9, 35.6, 25.8, 18.2, 16.2, -5.5; HRMS (+ESI) calc. for C<sub>17</sub>H<sub>28</sub>N<sub>4</sub>OSSi+Na 387.1651, found 387.1640; *m/z* (+ESI) 387 ([M+Na]<sup>+</sup>, 99%), 365 ([M+H]<sup>+</sup>, 100).

**(S)-5-(3-(*tert*-Butyldimethylsilyloxy)-2-methylpropylsulfonyl)-1-phenyl-1*H*-tetrazole<sup>91</sup> **31****

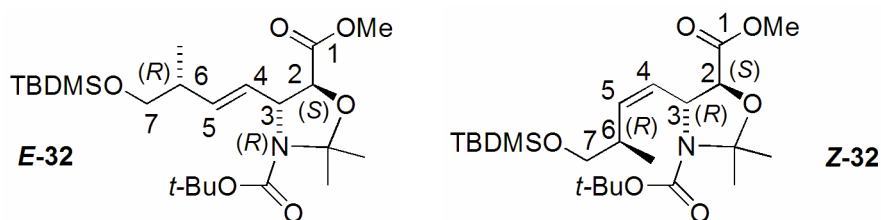
The general sulfide oxidation procedure (see page 118) was followed using thio-ether **164** (4.4 g, 12 mmol) with the exception that potassium dihydrogen phosphate (4 eq.) was added to the reaction before the molybdate catalyst. Time = 21 h. The crude product was a clear colourless liquid (4.5 g). Flash chromatographic purification (20% ethyl acetate : hexanes) gave pure sulfone **31** as a clear colourless liquid (4.3 g, 11 mmol, 92%):  $R_f$  0.34 (60% dichloromethane : hexanes);  $[\alpha]_D^{23}$  +2.1 (c 1.33, CH<sub>2</sub>Cl<sub>2</sub>), (*ent*-**31** lit.<sup>91</sup>  $[\alpha]_D^{20}$  -5.5 (c 6.23, CHCl<sub>3</sub>));  $\nu_{max}$  (thin film) 1595 (w), 1499 (s, Ar(C=C)), 1337, 1153 (s, R-SO<sub>2</sub>-R), 1252 (s, Si-CH<sub>3</sub>), 1105, 839 (s, Si-O-C), 777, 762 (s, Si-CH<sub>3</sub>); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.73 – 7.56 (5H, m, Ar-H), 4.04 (1H, dd,  $J$  14.6, 4.9 Hz, C<sub>5</sub>-H<sub>A</sub>), 3.72 (1H, dd,  $J$  10.0, 4.6 Hz, C<sub>7</sub>-H<sub>A</sub>), 3.55 (1H, dd,  $J$  14.6, 7.7 Hz, C<sub>5</sub>-H<sub>B</sub>), 3.50 (1H, dd,  $J$  9.9, 5.7 Hz, C<sub>7</sub>-H<sub>B</sub>), 2.58 – 2.36 (1H, m, C<sub>6</sub>-H), 1.16 (3H, d,  $J$  6.8 Hz, C<sub>6</sub>-CH<sub>3</sub>), 0.89 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.05 (6H, s, 2 x Si-CH<sub>3</sub>); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>)  $\delta$ : 154.0, 133.1, 131.4, 129.7, 125.2, 66.1, 58.6, 31.2, 25.8, 18.2, 16.8, -5.5, -5.5; **HRMS** (+ESI) calc. for C<sub>17</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub>SSi+Na 419.1549, found 419.1555;  $m/z$  (+ESI) 815 ([2M+Na]<sup>+</sup>, 42%), 614 (48), 419 ([M+Na]<sup>+</sup>, 100), 397 ([M+H]<sup>+</sup>, 51).

**(*R,E*)-tert-Butyl(2,5-dimethylhex-3-enyloxy)dimethylsilane *E*-165****(*R,Z*)-tert-Butyl(2,5-dimethylhex-3-enyloxy)dimethylsilane *Z*-165**

The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **31** (1.5 eq.), potassium bis(trimethylsilyl)amide (0.50 M in toluene, 1.4 eq.) and isobutyraldehyde **88** (0.018 ml, 0.20 mmol, conc. 0.13 M). Solvent = 1,2-dimethoxyethane, T = -60 °C, time<sub>A</sub> = 1 h, time<sub>B</sub> = 19 h. The crude product was a viscous, off-white liquid (0.19 g). The crude product was analysed by <sup>1</sup>H NMR and the ratio of (*E*)-alkene **E-165** to (*Z*)-alkene **Z-165** was determined to be 1.9 : 1 from integration of the C<sub>4</sub>-H signals in the spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 5.25 (1H, dd, *J* 15.6, 6.3 Hz, **E-165**-C<sub>4</sub>-H), 4.75 (1H, dd, *J* 8.6, 7.1 Hz, **Z-165**-C<sub>4</sub>-H). Flash chromatographic purification (5% ethyl acetate : hexanes graded to 10% ethyl acetate : hexanes) gave pure (*E*)-alkene **E-165** as a viscous clear colourless liquid (0.020 g, 0.082 mmol, 41%): *R*<sub>f</sub> 0.71 (10% ethyl acetate : hexanes); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 5.41 (1H, dd, *J* 15.8, 6.0 Hz, C<sub>5</sub>-H), 5.25 (1H, dd, *J* 15.6, 6.3 Hz, C<sub>4</sub>-H), 3.47 (1H, dd, *J* 9.7, 6.2 Hz, C<sub>7</sub>-H<sub>A</sub>), 3.35 (1H, dd, *J* 9.7, 7.1 Hz, C<sub>7</sub>-H<sub>B</sub>), 2.34 – 2.14 (2H, m, C<sub>6</sub>-H, C<sub>3</sub>-H), 0.96 (9H, d, *J* 6.7 Hz, 3 x CH<sub>3</sub>), 0.89 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.03 (6H, s, 2 x Si-CH<sub>3</sub>); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ: 137.3, 129.7, 68.4, 39.2, 31.1, 25.9, 22.6, 18.4, 16.8, -5.3.

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((*R*,*E*)-4-(*tert*-butyldimethylsilyloxy)-3-methylbut-1-enyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *E*-32**

**(4*R*,5*S*)-3-*tert*-Butyl 5-methyl 4-((*R*,*Z*)-4-(*tert*-butyldimethylsilyloxy)-3-methylbut-1-enyl)-2,2-dimethyloxazolidine-3,5-dicarboxylate *Z*-32**



The general Julia olefination procedure *via* premetallation (see page 116) was followed using sulfone **31** (1.5 eq.), potassium bis(trimethylsilyl)amide (0.50 M in toluene, 1.4 eq.) and aldehyde **24** (0.28 g, 0.97 mmol, conc. 0.10 M). Solvent = 1,2-dimethoxyethane, T = -60 °C, time<sub>A</sub> = 1 h, time<sub>B</sub> = 22 h. The crude product was a viscous, yellow liquid (0.85 g). Flash chromatographic purification (10% ethyl acetate : hexanes graded to 20% ethyl acetate : hexanes) gave a mixture of (*E*)-alkene **E-32** and (*Z*)-alkene **Z-32** in a 1 : 1.5 ratio (determined by integration of the C<sub>2</sub>-H signals in the <sup>1</sup>H NMR spectra: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 4.34 (1H, d, *J* 3.3 Hz, **E-32**-C<sub>2</sub>-H), 4.30 (1H, d, *J* 3.7 Hz, **Z-32**-C<sub>2</sub>-H)) as a clear colourless liquid (0.17 g, 0.37 mmol, 38%).

For characterisation purposes flash chromatographic purification (10% ethyl acetate : hexanes) gave a mixture of (*E*)-alkene **E-32** and (*Z*)-alkene **Z-32** in a 2.5 : 1 ratio (determined by integration of the C<sub>2</sub>-H signals in the <sup>1</sup>H NMR spectra) as a viscous clear colourless liquid (0.023 g, 0.050 mmol, 5%). Data for the (*E*)-alkene only are quoted where appropriate: **R<sub>f</sub>** 0.44 (20% ethyl acetate : hexanes); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 5.63 (1H, dd, *J* 15.4, 6.8 Hz, C<sub>5</sub>-H), 5.47 (1H, dd, *J* 15.6, 7.0 Hz, C<sub>4</sub>-H), 4.63 – 4.55 (1H, m, C<sub>3</sub>-H), 4.34 (1H, d, *J* 3.3 Hz, C<sub>2</sub>-H), 3.78 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.53 – 3.33 (2H, m (obs), C<sub>7</sub>-H<sub>2</sub>), 2.40 – 2.27 (1H, m, C<sub>6</sub>-H), 1.62 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.58 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.43 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 1.00 (3H, d, *J* 6.8 Hz, C<sub>6</sub>-CH<sub>3</sub>), 0.88 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.03 (6H, s, 2 x Si-CH<sub>3</sub>).

A second fraction gave pure (*Z*)-alkene **Z-32** as a viscous clear colourless liquid (0.033 g, 0.072 mmol, 7%): **R<sub>f</sub>** 0.47 (20% ethyl acetate : hexanes); **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 5.48 – 5.33 (2H, m, C<sub>5</sub>-H, C<sub>4</sub>-H), 4.94 (1H, dd, *J* 7.7, 3.7 Hz, C<sub>3</sub>-H), 4.30 (1H, d, *J* 3.7 Hz, C<sub>2</sub>-H), 3.79 (3H, s, C<sub>1</sub>-OCH<sub>3</sub>), 3.64 (1H, dd, *J* 9.6, 4.4 Hz, C<sub>7</sub>-H<sub>A</sub>), 3.38 (1H, dd, *J* 9.5, 7.3 Hz, C<sub>7</sub>-H<sub>B</sub>), 2.77 (1H, br s, C<sub>6</sub>-H), 1.63 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.59 (3H, s, C(C<sub>A</sub>H<sub>3</sub>)(C<sub>B</sub>H<sub>3</sub>)), 1.44 (9H, s, BOC C(CH<sub>3</sub>)<sub>3</sub>), 0.99 (3H, d, *J* 6.7 Hz, C<sub>6</sub>-CH<sub>3</sub>), 0.89 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.04 (6H, s, 2 x Si-CH<sub>3</sub>).

A third fraction gave a mixture of (*E*)-alkene **E-32** and (*Z*)-alkene **Z-32** (0.11 g, 0.24 mmol, 25%). The sample decomposed before mass spectroscopy with hydrolysis of the TBDMS group: **HRMS** (+ESI) calc. for C<sub>17</sub>H<sub>29</sub>NO<sub>6</sub>+Na 366.1893, found 366.1876; ***m/z*** (+ESI) 366 ([M+Na]<sup>+</sup>, 100%), 310 (7), 266 (35).