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Synthesis of enantiopure cyclopropyl esters from (-)-levoglucosenone.

K. P. Stockton and B. W. Greatrex

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The biorenewable chiral synthon (-)-levoglucosenone has been converted to enantiopure cyclopropyl esters using the base-promoted carbocyclisation of 4,5-epoxyvalerates. This protocol was applied to the asymmetric synthesis of the GABA_A receptor agonist (1*R*,2*R*)-*trans*-2-aminomethylcyclopropanecarboxylic acid ((-)-TAMP) and its enantiomer. The process was also extended to generate 1,1,2- and 1,2,3-trisubstituted cyclopropanes resulting in a formal synthesis of the selective glutamate receptor antagonist PCCG-4.

Introduction

The cellulose pyrolysis product (-)-levoglucosenone (**1**) has long been recognised as a versatile and potentially useful chiral synthon.^{1,2} Availability has been an issue and recent improvements in the production of **1** have only now made its use in industry feasible.³ Consequently, we have begun to develop methods for the conversion of **1** into new chiral materials,⁴ and now disclose a general route to substituted enantiopure cyclopropyl esters.

Cyclopropyl rings are commonly encountered in synthetic bioactives due to their rigid bond angles which restrict conformational freedom and promote selective interactions with biological targets.⁵ An example of such a bioactive is *trans*-(aminomethyl)cyclopropanecarboxylic acid ((-)-TAMP, (**R,R**)-**2**), which is a partial agonist of the GABA_A (K_D 55 μ M) and ρ_2 GABA_C (K_D 2.6 μ M) receptors.⁶ The enantiomer (**S,S**)-**2** is also a partial agonist but has lower activity (K_D 31 μ M) at the ρ_2 GABA_C receptors. Duke et al. suggested that the ability of the *cis*- and *trans*-cyclopropyl isomers to selectively bind to γ -aminobutyric acid (GABA) receptors was a function of their rigid mimicry of the folded and extended conformations of GABA.⁷ Other CNS active cyclopropane derivatives include the serotonin-norepinephrine reuptake inhibitor milnacipran **3**,⁸ and the glutamate receptor antagonist PCCG-4 **4** (Figure 1).⁹

A variety of techniques^{5,10-12} have been developed for the synthesis of cyclopropyl acids and derivatives of amino acids as they are particularly well represented in the medicinal chemistry literature.^{8,13-20} A less explored enantioselective method is the cyclisation of 4,5-epoxyenolates. The reaction

when the appropriate 4,5-epoxycarbonyl derivative is treated with base. Hindered bases including lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LHMDS) have been reported in the case of ester cyclisations.^{29,30}

A number of variations on the intramolecular cyclisation using epoxides have been developed. The requisite 4,5-epoxyenolates are most commonly prepared as intermediates when malonates are treated with epichlorohydrin in the presence of bases such as ethoxide and even triethylamine.^{25,31,32} The reaction sequence can also be initiated with the addition of a nucleophile to 4,5-epoxy-2,3-dehydrovalerates.³³

Throughout the 1990s, the group of Ebata used the Baeyer-Villiger reaction on **1** and derivatives to prepare γ -butyrolactones which can be converted into 4,5-epoxyesters (Scheme 1).³⁴⁻³⁶ We demonstrate here that epoxide (**S**)-**8a** and derivatives are suitable cyclopropanation substrates and can be used in the synthesis of bioactive cyclopropanes.

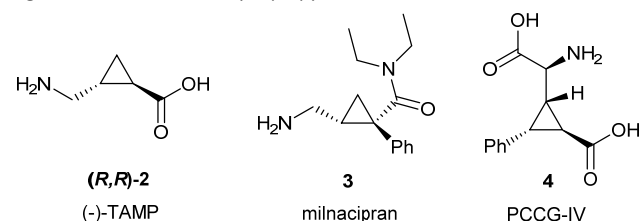
Results and Discussion

Starting with **1**, both enantiomers of epoxyvalerate **8** were synthesised as shown in Scheme 1. Hydrogenation of **1** and Baeyer-Villiger oxidation afforded hydroxymethylbutyrolactone **6** in 91% overall yield for the two steps. Ebata reported that only 40% yield of butyrolactone (**S**)-**6** was obtained if *m*-CPBA was used as oxidant,³⁷ however, when catalysed by *p*-toluenesulfonic acid (TsOH) the reaction afforded an excellent yield of (**S**)-**6** in 16 hours. Mesylation generated (**S**)-**7**, and then reaction with 1.05 equivalents of sodium ethoxide in ethanol gave ethyl 4,5-epoxyvalerate (**S**)-**8a** in 58% yield for the 2-steps. Due to the slight volatility of ethyl epoxyvalerate (**S**)-**8a** and later products, the bulkier cyclohexyl epoxyvalerate (**S**)-**8b** was also synthesised from (**S**)-**7** using the lithium salt of cyclohexanol. The enantiomer (**R**)-**8b** was prepared by the cyclisation of epoxide (**S**)-**8a** to furnish the lactone (**R**)-**6** which was treated as per its enantiomer to give (**R**)-**8b**.

The results of the base-promoted cyclisation reactions for ester (**S**)-**8a**, (**S**)-**8b** and (**R**)-**8b** using LHMDS are shown in Table 1. The best yields were obtained at higher temperatures, while at lower temperatures competing dimerisations dominated giving complex mixtures (entries 2, 9, 10 and 13).

Scheme 1. Synthesis of enantiomers of **8a** and **8b**.

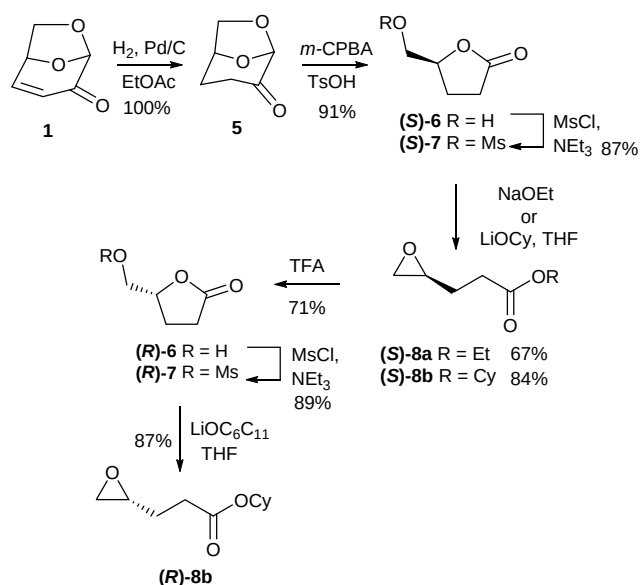
Figure 1. Some CNS active cyclopropyl amino acid derivatives.



affords 2-(hydroxymethyl)cyclopropyl esters²¹⁻²⁵ or ketones²⁶⁻²⁸

^a School of Science and Technology, University of New England, Armidale, NSW, Australia, 2351

Electronic Supplementary Information (ESI) available: ¹H and ¹³C NMR spectra for all new compounds. See DOI: 10.1039/x0xx00000x

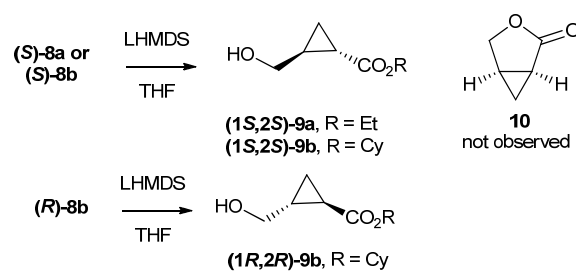


The reaction at 50 °C afforded 65% of the *trans*-cyclopropane **9a** as determined by ¹H NMR with 1,3-diphenylbutadiene as internal standard (entry 13). Only a single diastereomer was isolated from the reactions and no other stereoisomers were visible in the crude NMR or were isolated. To exclude the possibility of lactone formation from the *cis*-cyclopropyl isomer, (±)-3-oxabicyclo[3.1.0]hexan-2-one (**10**) was prepared via the Simmons-Smith cyclopropanation of but-2-ene-1,4-diol followed by oxidation with TEMPO/TCC. There was no evidence of **10** in any GCMS chromatograms obtained from crude reactions in Table 1.

With adequate quantities of cyclopropane in hand, the conversion to the GABA_c receptor partial agonist (1S,2S)-**2** was examined (Scheme 2). Although less active, (1S,2S)-**2** was directly accessible from **1** without epimerisation and so its synthesis was used to establish the methodology. Taking alcohol (1S,2S)-**9b** through to (1S,2S)-**2** was achieved by mesylation to (1S,2S)-**11**, substitution with azide to furnish (1S,2S)-**12** and finally hydrogenation under acidic conditions to give the amino acid in 82% yield for the three steps. Attempted crystallisation of (1S,2S)-**2** by vapour diffusion from methanol/diethyl ether gave methyl ester (1S,2S)-**13**.

The enantiomer (1R,2R)-**2** was synthesised starting with epoxide (R)-**8b** which was treated with base to give cyclopropane (1R,2R)-**9b** in 40% yield. Conversion of cyclopropane (1R,2R)-**9b** through to (-)-TAMP (1R,2R)-**2** proceeded in 79% combined yield via mesylate (1R,2R)-**11** and then azide (1R,2R)-**12**. For ease of comparison, (1R,2R)-**2** was also converted to the methyl ester (1R,2R)-**13**. It was found that the magnitude of the optical rotations had excellent agreement for the products as well as the intermediates indicating that epimerisation did not occur at any stage of the synthesis.

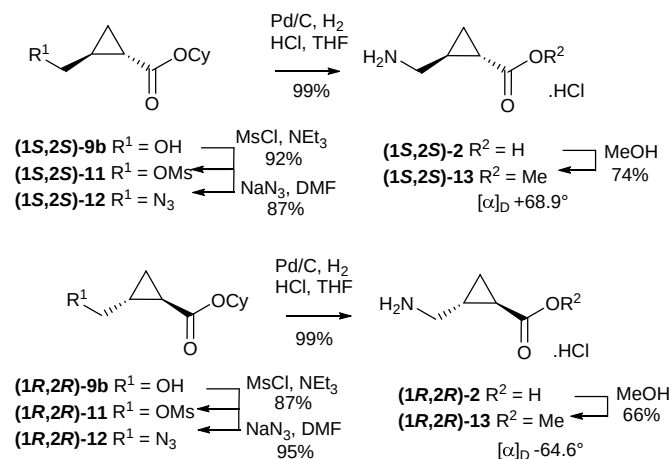
Table 1: Base-promoted cyclopropanation reactions of (S)-**8a** and **8b**.



Entry ^a	Solvent	Substrate	Temp. (°C)	Yield ^b
1	THF	(S)- 8a	25	50 (nd)
2	THF	(S)- 8a	-10	nd (36)
3	Et ₂ O	(S)- 8a	25	36 (nd)
4 ^c	THF	(S)- 8a	25	47 (nd)
5	THF	(S)- 8a	50	46 (nd)
6	THF	(S)- 8b	25	53 (nd) ^d
7	THF	(S)- 8b	25	58 (50)
8 ^e	THF	(S)- 8b	25	38 (nd)
9	THF	(S)- 8b	-78	0 (0)
10	THF	(S)- 8b	-78 to 25	18 (nd)
11 ^f	THF	(S)- 8b	-78	13(nd)
12 ^g	Toluene	(S)- 8b	80	30 (nd)
13	THF	(S)- 8b	50	65 (nd)
14	THF	(R)- 8b	25	(40)

^a Reactions were performed by the addition of 200 mg of epoxide to LHMDS (1.2 equiv) in THF (15 mL) unless otherwise indicated. ^b Conversion determined by ¹H NMR with 1,3-diphenylbutadiene or *p*-dimethoxybenzene as internal standard. ^c 1.2 equiv LHMDS was used. ^d 5 mL total solvent volume. ^e Inverse addition. ^f 10 mol% BF₃·Et₂O. ^g 1.0 equiv. of LHMDS was used in toluene (15 mL).

Scheme 2. Synthesis of both enantiomers of TAMP (**2**)



In order to expand the scope of the cyclopropanation to 1,1,2- and 1,2,3-trisubstituted cyclopropanes, we applied the methodology to substituted butyrolactones of type **15**, **20** and **28** (Scheme 3). These butyrolactones can be accessed from **1** or the 3-iododerivative **14** using Heck, Suzuki and palladium-mediated hydroarylation reactions followed by Baeyer-Villiger oxidation.⁴ Thus, conversion of **15** to mesylate **16** and then reaction with ethoxide afforded the epoxyvalerate **17** as a 1:1 mixture of diastereomers ready for cyclisation. Likewise, the epoxide **22** was prepared from the corresponding

butyrolactone **20** by mesylation to give **21** and then reaction with ethoxide in THF/ethanol. The diastereomer **27** was prepared as previously described⁴ using the Heck reaction of **1** with PhI followed by hydrogenation with Pd/C. Baeyer-Villiger oxidation afforded lactone **28** which was converted to epoxide **30** via mesylate **29**.

The reaction of phenyl-substituted epoxide **17** with LHMDS afforded the *trans*-isomer **18** and lactone **19**³⁸ formed from the *cis*-isomer in a 29:6 isolated yield ratio (5:1 by ¹H NMR). The stereochemistry of **18**⁸ was confirmed on the basis of crosspeaks in the NOESY spectrum between the phenyl and exocyclic hydroxymethylene resonances. Compound **19** has been used for the preparation of the CNS drug milnacipran **3**, however, the low yield obtained in the cyclisation and the reaction selectivity would make the current synthesis unfeasible.

The cyclisation of **22** under the optimised conditions afforded **23** in excellent yield with complete diastereoselectivity (Scheme 3). A small amount of the *O*-silylated derivative **24** (10%) and traces of dimerised compound **25** arising from an intermolecular transesterification were also isolated from the reaction mixture. The silylated adduct **24** was readily converted to **23** by stirring in ethanolic HCl confirming the structural assignment. Morpholinamide **26** is an advanced intermediate used in the synthesis of the metabotropic glutamate receptor

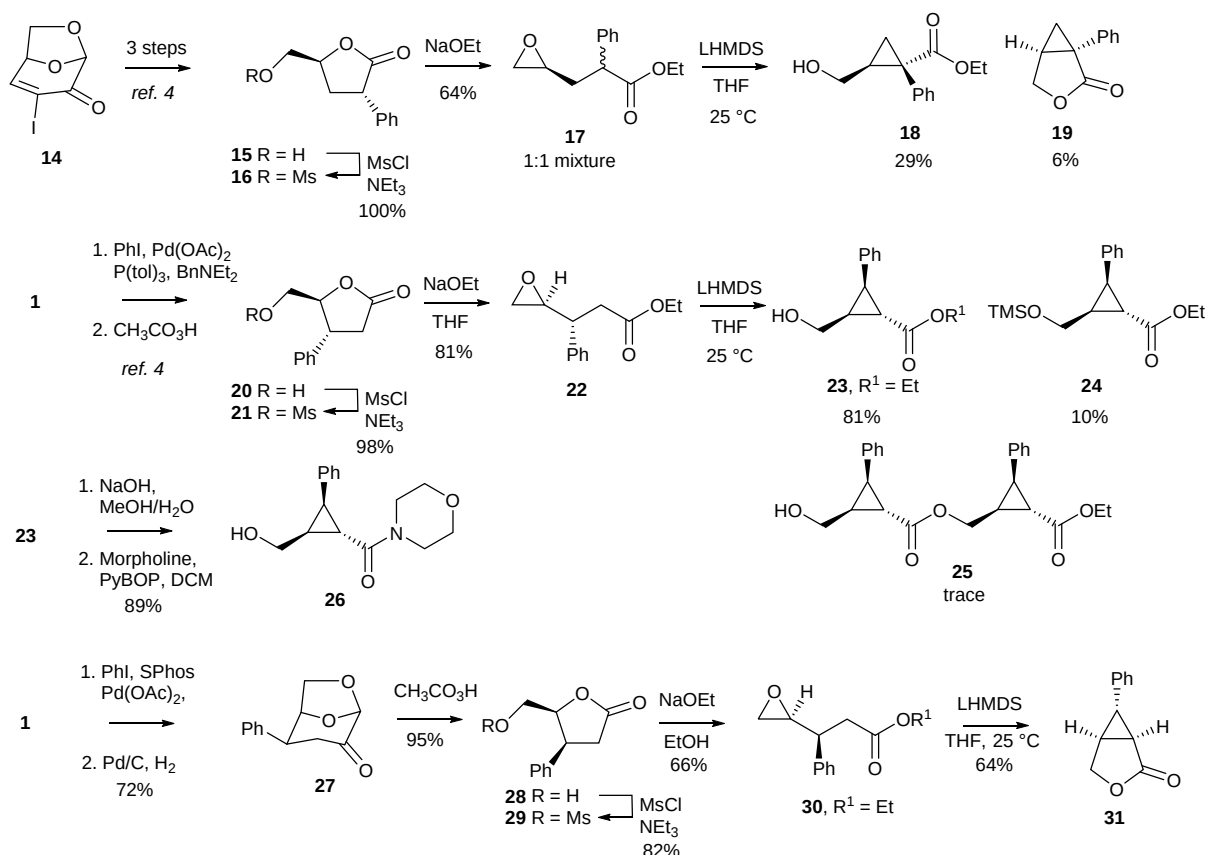
antagonist PCCG-4 (**4**)⁹ and was obtained from ester **23** by hydrolysis and PyBOP coupling with morpholine in 89% yield for the two-steps. The sequence **1** to **26** therefore represents a formal synthesis of **4**.

The diastereomer **30** likewise proceeded with good selectivity in the cyclisation reaction and afforded lactone **31** in moderate isolated yield. It was not possible to isolate the ester before lactonisation occurred, a consequence of the *syn*-substitution of the alcohol and ester in the product.

The product **23** formed from aryl substituted epoxide **22** had the ester group and hydroxymethyl group *anti* in the product while cyclisation of epimer **30** had the two groups *syn*. The ester and phenyl are *anti* in both products **23** and **31** indicating that the enolate-phenyl relationship was likely a controlling element.

To understand the interactions occurring in the transition states (TS) leading to the possible products, the *E*-enolates generated from **22** and **30** were modelled using Spartan '14 B3LYP/6311+G(d,p) and MP2/631G(d) in vacuum and the DFT TS structures found using each method are shown in Figure 1.^{39,40} These levels of theory were chosen as they are computationally affordable and reasonably reflect the relative energies in S_N2 transition states compared to the best CCSD(T) calculations.⁴¹ Based upon the work of Ireland, the *E*-enolates

Scheme 3. Preparation of trisubstituted cyclopropanes



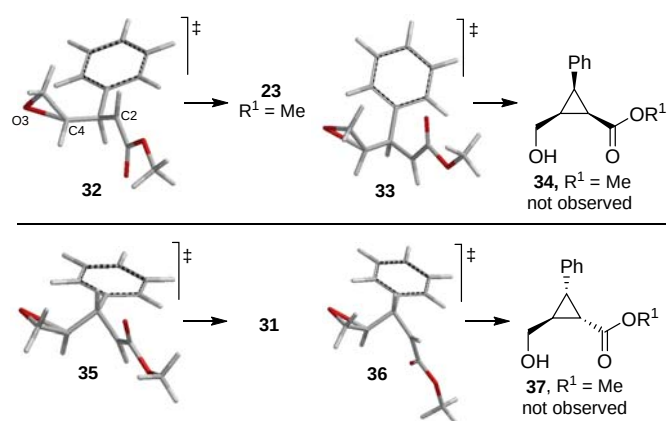


Figure 2. Model DFT/B3LYP 6311+G(d,p) transition states leading to methyl ester analogues of observed products **23** and **30**.

Table 2. Key bond distances and energies in **32**, **33**, **35** and **36** at B3LYP/6311+G(d,p) and MP2/631-G(d).

TS		Interatomic Distances		Rel. Energies (kcal.mol ⁻¹)
		C2-C4	C4-O3	
32	B3LYP	2.11	1.91	0.0
	MP2	1.99	1.90	0.0
33	B3LYP	2.09	1.95	+5.56
	MP2	1.97	1.93	+4.65
35	B3LYP	2.08	1.96	0.0
	MP2	1.97	1.94	0.0
36	B3LYP	2.11	1.93	+2.03
	MP2	1.99	1.93	+0.60

were expected when the esters were enolised with LHMDs in THF.⁴² The geometry of the enolate was not expected to greatly affect the reaction outcome as monomeric transition states with a coordinated epoxide and enolate were not possible. We have not probed the effects of enolate geometry using calculations on the reaction outcome.

The transition states **32**, **33**, **35** and **36** exhibited single imaginary frequencies and upon energy minimisation led to the observed products or reactants. In both cases, the observed product was correctly predicted by the calculated energies using either level of theory. Using the B3LYP model, transition state **33** leading to the all *cis*-cyclopropane **34** was 5.56 kcal.mol⁻¹ less stable than the alternate **32** which led to the observed cyclopropane **23**. TS **35** leading to the observed cyclopropane **31** following lactonisation was 1.65 kcal.mol⁻¹ lower in energy than the alternate **36**. The MP2 transition states differed by 1.1 kcal.mol⁻¹ and these structures demonstrated a shorter C2-C4 bond and therefore later TS. During the cyclisation, the ester enolate in **32** and **35** was on the opposite face to the large phenyl substituent due to larger steric interactions of the ester and phenyl compared to the ester and epoxide. These results suggest that calculations could be used to predict the outcomes of cyclisations of this type.

We attributed the increased yield of cyclised products from **22** and **30** relative to the unsubstituted epoxide **8** to a Thorpe-Ingold effect and the closing of the C2-C3-C4 bond angle due to the β -phenyl group.^{43,44} The energy-minimised geometries of the methyl ester analogues of the starting enolates had bond

angles supporting a Thorpe-Ingold-type rate acceleration in the cyclisation. Unsubstituted enolate derived from **8** (R = Me) had a calculated C2-C3-C4 bond angle of 112.5° while the enolate derived from methyl ester analogue of **22** had a calculated bond angle of 107.7° and the enolate obtained from **30** had a calculated bond angle of 109.5° (see electronic SI).

Conclusions

The procedures described in this report yielded both enantiomers of the GABA_c receptor antagonist TAMP with (+)-TAMP synthesised in 8 steps from **1** in 35% overall yield, and (-)-TAMP in 10 steps in 15% overall yield. We have also shown that the products of palladium-catalysed cross coupling reactions on **1** are suitable substrates for conversion through to cyclopropyl esters via intramolecular ring-closure reactions. The 3-substituted epoxy valerate **22** underwent cyclisation to the corresponding 1,2,3-trisubstituted cyclopropane in excellent yield leading to a formal synthesis of **4** and this reaction bodes well for the synthesis of other 1,2,3-trisubstituted cyclopropanes and potentially 1,2,3-tetrasubstituted cyclopropanes.

Experimental

(S)-5-(Hydroxymethyl)dihydrofuran-2(3H)-one ((S)-6).⁴⁵ To a stirred solution of 2,3-dihydrolevoglucosenone **5** (4.0 g, 31.2 mmol) in DCM (50 mL) cooled using a water bath was added 70% *m*-chloroperbenzoic acid (11.5 g, 47 mmol) then TsOH (800 mg, 5.0 mmol). The mixture was stirred for 16 hours and then the volatiles were removed under reduced pressure. To the residue was added 1M HCl (20 mL) and the resulting solution stirred overnight. The mixture was filtered, the precipitate washed with water and the filtrate concentrated under reduced pressure. Purification of the residue by flash chromatography (ethyl acetate) to remove residual *m*-chloroperbenzoic acid afforded the title compound (3.07 g, 85%); [α]_D +50.0 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.66-4.60 (m, 1H), 3.90 (dd, *J* = 12.5, 2.5 Hz, 1H), 3.64 (dd, *J* = 12.5, 4.5 Hz, 1H), 2.66-2.49 (m, 2H), 2.44 br s, 1H), 2.30-2.22 (m, 1H), 2.18-2.10 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.8, 80.9, 64.0, 28.7, 23.2; MS (EI) *m/z* 116.1 ([M]⁺, 0.5), 86 (12), 85 (100), 57 (10).

(S)-5-(Methanesulfonyloxymethyl)dihydrofuran-2(3H)-one ((S)-7).⁴⁶ To a solution of **(S)-6** (5.08 g, 43.7 mmol) in DCM (50 mL) cooled using a water bath was added triethylamine (9.2 mL, 66 mmol) then methanesulfonyl chloride (4.7 mL, 61 mmol). The mixture was stirred for 3 hours then quenched with a saturated solution of NH₄Cl and the DCM removed under reduced pressure. The aqueous layer was extracted twice with ethyl acetate then the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate) to give **(S)-7** as a yellow syrup (7.38 g, 87%); [α]_D²⁵ +33.3 (c 1.5, DCM); FT-IR (neat) 2940, 1769, 1164 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ

4.88-4.71 (m, 1H), 4.43 (dd, J = 11.5, 3.0 Hz, 1H), 4.29 (dd, J = 11.5, 4.9 Hz, 1H), 3.07 (s, 3H), 2.67-2.52 (m, 2H), 2.47-2.32 (m, 1H), 2.23-2.06 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.0, 76.6, 69.7, 37.7, 27.9, 23.4; MS (EI) m/z 195.1 $[\text{M} + \text{H}]^+$ 217.1 $[\text{M} + \text{Na}]^+$.

(S)-Ethyl 3-(oxiran-2-yl)propanoate ((S)-8a).^{47,48} To a suspension of mesylate **(S)-7** (1.80 g, 9.3 mmol) in dry EtOH (20 mL) was added solid sodium ethoxide (0.70 g, 10.2 mmol) and the mixture was stirred for 3 hours. The mixture was quenched with saturated NH_4Cl and extracted three times with DCM. The combined organic extracts were dried (MgSO_4) and the DCM distilled. The residue was filtered through a bed of silica eluting with 1:2 ethyl acetate/hexanes and the filtrate concentrated to give a colourless oil (0.88 g, 67%); $[\alpha]_{\text{D}}^{22}$ -14.8 (c 1.35, CHCl_3); FT-IR (neat) 2982, 1730, 1179 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.14 (q, J = 7.0 Hz, 2H), 3.03-2.93 (m, 1H), 2.76 (dd, J = 4.4, 4.4 Hz, 1H), 2.50 (dd, J = 4.4, 2.8 Hz, 1H), 2.45 (dd, J = 7.5, 7.5 Hz, 2H), 2.02-1.89 (m, 1H), 1.84-1.72 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.7, 60.3, 51.0, 46.9, 30.3, 27.5, 14.0; MS (ESI) m/z 145.1 $[\text{M} + \text{H}]^+$.

(S)-Cyclohexyl 3-(oxiran-2-yl)propanoate ((S)-8b). To cyclohexanol (1.25 g, 12.5 mmol) in dry THF (15 mL) cooled to -60°C was slowly added a solution of MeLi in THF/cumene (0.83 M, 12.8 mL). The mixture was stirred for 10 minutes and then a solution of **(S)-7** (1.73 g, 8.91 mmol) in dry THF (15 mL) was added and the mixture was allowed to come to room temperature over the course of an hour. The reaction was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The organic layer was dried (MgSO_4) and concentrated and the residue purified by column chromatography (1:9 ethyl acetate/hexanes) to give **(S)-8b** as a colourless oil (1.51 g, 84%); $[\alpha]_{\text{D}}^{33}$ -11.8 (c 1.52, EtOH); FT-IR (neat) 2934, 2858, 1727, 1176 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.77-4.58 (m, 1H), 2.95-2.81 (m, 1H), 2.66 (dd, J = 4.5, 4.5 Hz, 1H), 2.41 (dd, J = 5.0, 2.7 Hz, 1H), 2.35 (dd, J = 7.4, 7.4 Hz, 2H), 2.01-1.53 (m, 6H), 1.52-1.08 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.0, 72.5, 51.0, 46.8, 31.4, 30.6, 27.6, 25.2, 23.5; MS (ESI) m/z 221.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3\text{Na}$ 221.1154; Found 221.1152.

(R)-5-(Hydroxymethyl)dihydrofuran-2(3H)-one ((R)-6).⁴⁹ Trifluoroacetic acid (5 mL) was cooled to -10°C and epoxide **(S)-5a** (1.25 g, 8.67 mmol) was added. The mixture was stirred at -10°C for 20 minutes then the mixture was diluted with toluene and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate) to give **(R)-6** as a colourless oil that was spectroscopically identical to **(S)-6** (715 mg, 71%); $[\alpha]_{\text{D}}^{21}$ -50.5 (c 1.5, CHCl_3).

(R)-5-(Methanesulfonyloxymethyl)dihydrofuran-2(3H)-one ((R)-7). Methylhydroxy lactone **(R)-6** (510 mg, 4.39 mmol) was treated as per the procedure for **(S)-7** to give **(R)-7** which was spectroscopically identical to **(S)-7** (762 mg, 89%); $[\alpha]_{\text{D}}^{23}$ -30.0 (c 1.1, DCM).

(R)-Cyclohexyl 3-(oxiran-2-yl)propanoate ((R)-8b). To cyclohexanol (870 mg, 8.65 mmol) in dry THF (10 mL) cooled to -60°C was added a solution of *n*-butyl lithium in THF (1.6 M, 4.73 mL, 7.57 mmol) and the mixture stirred for 10 minutes. To this was added **(R)-7** (1.05 g, 5.41 mmol) dissolved in THF (5 mL) and the mixture was allowed to come to room temperature over the course of 1.5 hours. The mixture was quenched with a saturated solution of NH_4Cl and extracted twice with ethyl acetate. The combined organic extracts were dried (MgSO_4), concentrated under reduced pressure and the residue purified by column chromatography (1:9 ethyl acetate/hexanes) to give **(R)-8b** as a colourless oil that was spectroscopically identical to **(S)-8b** (936 mg, 87%); $[\alpha]_{\text{D}}^{22}$ +11.4 (c 1.32, EtOH).

(1S,2S)-Ethyl 2-(hydroxymethyl)cyclopropanecarboxylate ((1S,2S)-9a).¹³ A solution of LHMDS in toluene (1 M, 1.82 mL) was added to THF (3.2 mL) and the mixture cooled to -5°C . To this was slowly added a solution **(S)-8a** (0.220 g, 1.53 mmol) in THF (5 mL) over the course of 10 minutes. The mixture was quenched with 10% w/v NaH_2PO_4 (10 mL) and extracted with DCM (3 x 20 mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure using a 20°C water bath and the residue purified by column chromatography (1:1 ethyl acetate/hexanes) to give **(1S,2S)-9a** as a colourless oil (85 mg, 39%); $[\alpha]_{\text{D}}^{30}$ +57.5 (c 0.8, DCM); FT-IR (neat) 3424, 2981, 1721, 1177 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.11 (q, J = 7.0 Hz, 2H), 3.61 (dd, J = 11.3, 6.0 Hz, 1H), 3.47 (dd, J = 11.3, 6.8 Hz, 1H), 1.78-1.65 (m, 1H), 1.62 (br. s, 1H), 1.55 (app. td, J = 8.6, 4.3 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.22-1.14 (m, 1H), 0.84 (ddd, J = 8.3, 6.2, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.7, 64.6, 60.6, 24.2, 18.3, 14.2, 12.6; MS (EI) m/z 144.1 $[\text{M}]^+$, trace), 101.1 (36), 99.1 (73), 98.1 (43), 88.1 (64), 73.1 (100), 70.1 (39), 55.1 (98), 43.1 (27).

(1S,2S)-Cyclohexyl 2-(hydroxymethyl)cyclopropane carboxylate ((1S,2S)-9b). Cyclohexyl ester **(1S,2S)-8b** (248 mg, 1.25 mmol) was treated as per the method for **(1S,2S)-9a** except that the reaction was performed at room temperature and the column eluent was 2:3 ethyl acetate/hexanes to give **(1S,2S)-9b** as a colourless oil (123 mg, 50%); $[\alpha]_{\text{D}}^{32}$ +51.5 (c 2.00, EtOH); FT-IR (neat) 3420, 2934, 2858, 1719, 1175 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.77-4.57 (m, 1H), 3.54 (dd, J = 11.5, 6.2 Hz, 1H), 3.43 (dd, J = 11.5, 6.4 Hz, 1H), 2.48 (br. s., 1H), 1.86-1.58 (m, 5H), 1.54-1.43 (m, 2H), 1.43-1.09 (m, 6H), 0.80 (ddd, J = 8.4, 6.2, 4.4 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3, 72.7, 64.3, 31.5, 25.3, 24.0, 23.6, 18.6, 12.6; MS (ESI) 221.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3\text{Na}$ 221.1154; Found 221.1178.

(1R,2R)-Cyclohexyl 2-(hydroxymethyl)cyclopropane carboxylate ((1R,2R)-9b). **(R)-8b** (936 mg, 4.72 mmol) was treated as per the method for **(1S,2S)-9b** to give **(1R,2R)-9b** as a colourless oil that was spectroscopically identical to **(1S,2S)-9b** (376 mg, 40%); $[\alpha]_{\text{D}}^{26}$ -47.6 (c 1.26, EtOH).

(1S,2S)-Cyclohexyl 2-(methanesulfonyloxymethyl)cyclopropanecarboxylate ((1S,2S)-11). To a solution of **(1S,2S)-9b** (683 mg, 3.44 mmol) in DCM (10 mL) was added triethylamine

(720 μL , 5.17 mmol) then methanesulfonyl chloride (380 μL , 4.82 mmol). The resulting mixture was stirred for 2 hours then quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The organic phase was dried (MgSO_4) then concentrated under reduced pressure and the residue purified by column chromatography (3:7 ethyl acetate/hexanes) to give **(1S,2S)-11** as a colourless syrup that crystallised on standing (829 mg, 87%); mp 62–64 °C; $[\alpha]_{\text{D}}^{24} +47.3$ (c 1.1, EtOH); FT-IR (neat) 2944, 2861, 1710, 1161 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.85–4.61 (m, 1H), 4.15 (dd, $J = 11.1$, 6.8 Hz, 1H), 4.07 (dd, $J = 11.1$, 7.2 Hz, 1H), 3.01 (s, 3H), 1.90–1.60 (m, 6H), 1.58–1.15 (m, 7H), 0.93 (ddd, $J = 8.5$, 5.8, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.9, 73.2, 71.5, 38.0, 31.5, 25.3, 23.7, 20.1, 19.4, 13.0; MS (ESI) m/z 277.1 $[\text{M} + \text{H}]^+$ 299.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_5\text{NaS}$ 299.0929; Found 299.0923.

(1R,2R)-Cyclohexyl 2-(methanesulfonyloxymethyl)cyclopropanecarboxylate ((1R,2R)-11). **(1R,2R)-9b** (487 mg, 2.46 mmol) was treated as per the method for **(1S,2S)-11** to give **(1R,2R)-11** as a colourless oil that crystallised upon standing and was spectroscopically identical to **(1S,2S)-11** (623 mg 92%); $[\alpha]_{\text{D}}^{30} -44.2$ (c 0.63, EtOH).

(1S,2S)-Cyclohexyl 2-(azidomethyl)cyclopropanecarboxylate ((1S,2S)-12). To a solution of **(1S,2S)-11** (555 mg, 2.01 mmol) in DMF (10 mL) was added NaN_3 (650 mg, 10.0 mmol) and the mixture stirred at 60 °C overnight. The mixture was diluted with ethyl acetate and washed with three portions of saturated NH_4Cl . The organic layer was dried (MgSO_4) and concentrated to give **(1S,2S)-12** as a colourless oil which was used without further purification (425 mg, 95%); $[\alpha]_{\text{D}}^{29} +40.8$ (c 0.49, EtOH); FT-IR (neat) 2935, 2858, 2086, 1717, 1202, 1177 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.83–4.61 (m, 1H), 3.19 (app. d, $J = 6.6$ Hz, 2H), 1.89–1.61 (m, 5H), 1.59–1.14 (m, 8H), 0.85 (ddd, $J = 8.5$, 6.0, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.4, 72.9, 53.2, 31.5, 25.3, 23.6, 20.4, 18.9, 13.0; MS (ESI) m/z 246.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{18}\text{N}_3\text{O}_2$ 224.1399; Found 224.1439.

(1R,2R)-Cyclohexyl 2-(azidomethyl)cyclopropanecarboxylate ((1R,2R)-12). **(1R,2R)-11** (581 mg, 2.10 mmol) was treated as per the method for **(1S,2S)-12** to give **(1R,2R)-12** as a colourless oil that was spectroscopically identical to **(1S,2S)-12** (408 mg, 87%); $[\alpha]_{\text{D}}^{26} -37.6$ (c 2.74, EtOH).

(1S,2S)-Methyl 2-aminomethylcyclopropanecarboxylate hydrochloride ((1S,2S)-13).⁵⁰ To a solution of **(1S,2S)-12** (414 mg, 1.90 mmol) in 2:1 THF/2M HCl (9 mL) was added 5% Pd/C (40 mg) and the mixture stirred overnight under an atmosphere of H_2 . The mixture was filtered through Celite and concentrated under reduced pressure then the residue was suspended in 2M HCl (5 mL) and stirred at 50 °C overnight. Removal of the volatiles under reduced pressure gave crude 2-aminomethylcyclopropanecarboxylate hydrochloride **(1S,2S)-2** (278 mg, 99%) which was recrystallised by vapour diffusion from methanol/ether to give **(1S,2S)-13** as translucent crystals (208 mg, 74%); mp 188–192 °C; $[\alpha]_{\text{D}}^{24} +68.9$ (c 1.03, H_2O); ^1H NMR

(300 MHz, D_2O) δ 3.70 (s, 3H), 3.04 (dd, $J = 13.4$, 7.0 Hz, 1H), 2.95 (dd, $J = 13.4$, 7.9 Hz, 1H), 1.82 (ddd, $J = 8.7$, 4.7 Hz, 1H), 1.78–1.66 (m, 1H), 1.32 (ddd, $J = 9.8$, 4.7 Hz, 1H), 1.09 (ddd, $J = 8.7$, 6.4, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 176.5, 53.2, 42.8, 19.7, 19.5, 14.2; MS (ESI) m/z 116.0 $[\text{M}]^+$.

(1R,2R)-Methyl 2-aminomethylcyclopropanecarboxylate hydrochloride ((1R,2R)-13).⁵⁰ **(1R,2R)-12** (344 mg, 1.54 mmol) was treated as per the method for **(1S,2S)-13** to give **(1R,2R)-13** as translucent crystals that were spectroscopically identical to **(1S,2S)-13** (168 mg, 66%); $[\alpha]_{\text{D}}^{26} -64.6$ (c 0.43, EtOH).

(3S,5S)-5-(Methanesulfonyloxymethyl)-3-phenyldihydrofuran-2(3H)-one (16). To a solution of **15** (414 mg, 2.16 mmol) in DCM (5 mL) cooled in a water bath was added triethylamine (0.45 mL, 3.2 mmol) then methanesulfonyl chloride (0.23 mL, 3.0 mmol). The mixture was stirred for 1.5 hours then quenched with saturated aqueous NH_4Cl and extracted twice with ethyl acetate. The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure and the residue purified by column chromatography (3:2 EtOAc/hexanes) to give **16** as a yellow syrup that crystallised upon standing (591 mg, 100%); mp 102–104 °C; $[\alpha]_{\text{D}}^{23} +50.8$ (c 1.26, DCM); FT-IR (neat) 3032, 2978, 1736, 1344, 1180, 1141 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.56–7.09 (m, 5H), 4.95–4.81 (m, 1H), 4.47 (dd, $J = 11.5$, 3.0 Hz, 1H), 4.36 (dd, $J = 11.5$, 4.5 Hz, 1H), 3.99 (dd, $J = 9.8$, 8.1 Hz, 1H), 3.09 (s, 3H), 2.67 (ddd, $J = 13.5$, 9.8, 4.9 Hz, 1H), 2.55 (ddd, $J = 13.4$, 8.2, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.4, 136.6, 129.1, 127.9, 127.6, 74.8, 70.0, 45.2, 37.7, 32.5; MS (ESI) m/z 271.1 $[\text{M} + \text{H}]^+$ 293.0 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5\text{NaS}$ 293.0460; Found 293.0468.

(1S,2S)-Ethyl 2-(hydroxymethyl)-1-phenylcyclopropane carboxylate (18).⁸ To a stirred solution of **16** (455 mg, 1.68 mmol) in ethanol/THF (2:1, 15 mL) was added sodium ethoxide (475 mg, 2.02 mmol). After 1 hour the reaction was neutralised with saturated NH_4Cl and extracted twice with DCM. The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure and the residue purified by column chromatography (1:9 ethyl acetate/hexanes) to give **17** as a 1:1 mixture of diastereomers (253 mg, 64%). A solution of LHMDS in toluene (1.0 M, 712 μL) was added to THF (5 mL) and a portion of **17** (112 mg, 0.508 mmol) in THF (5 mL) added over the course of 10 minutes. The mixture was stirred for a further 20 minutes then quenched with 10% w/v NaH_2PO_4 and extracted twice with DCM. The combined organic extracts were dried (MgSO_4) and concentrated and the residue purified by column chromatography (2:3 ethyl acetate/hexanes) to give **18** (33 mg, 29%) and **19** (5 mg, 6%); **18**: $[\alpha]_{\text{D}}^{16} +12.5$ (c 0.24, DCM); ^1H NMR (300 MHz, CDCl_3) δ 7.57–7.01 (m, 5H), 4.25–3.93 (m, 2H), 3.39 (dd, $J = 11.7$, 5.8 Hz, 1H), 3.18 (dd, $J = 11.7$, 7.9 Hz, 1H), 2.18 (dddd, $J = 9.2$, 7.9, 6.6, 5.8 Hz, 1H), 1.70 (dd, $J = 9.2$, 4.5 Hz, 1H), 1.47 (br. s., 1H), 1.27 (dd, $J = 6.6$, 4.5 Hz, 1H), 1.16 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) 173.8, 135.5, 131.0, 128.2, 127.4, 62.4, 61.1, 33.8, 29.5, 18.1, 14.1; MS (ESI) m/z 221.1 $[\text{M} + \text{H}]^+$ 243.1 $[\text{M} + \text{Na}]^+$. **(1R,5S)-1-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one (19)**³⁸: FT-IR (neat) 3060, 2973, 2907, 1758, 1602 cm^{-1} ; ^1H

NMR (300 MHz, CDCl_3) δ 7.80–6.86 (m, 5H), 4.47 (dd, $J = 9.2, 4.7$ Hz, 1H), 4.29 (d, $J = 9.2$ Hz, 1H), 2.55 (ddd, $J = 7.9, 4.8, 4.7$ Hz, 1H), 1.65 (dd, $J = 7.9, 4.8$ Hz, 1H), 1.36 (dd, $J = 4.8, 4.8$ Hz, 1H); ^{13}C NMR δ 175.9, 134.1, 128.6, 128.3, 127.7, 68.0, 31.7, 25.1, 20.2; MS (ESI) m/z 175.0 $[\text{M} + \text{H}]^+$ 197.0 $[\text{M} + \text{Na}]^+$.

(4R,5S)-5-(Methanesulfonyloxymethyl)-4-phenyldihydrofuran-2(3H)-one (21). To a solution of **20** (1.91 g, 9.94 mmol) was added triethylamine (2.07 mL, 14.9 mmol) then methanesulfonyl chloride (0.92 mL, 11.9 mmol) and the mixture stirred for 3 hours. The reaction was quenched with saturated NaHCO_3 and extracted twice with ethyl acetate. The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure and the residue purified by column chromatography (1:1 ethyl acetate/hexanes) to give **21** as a pale yellow syrup (2.62 g, 98%); $[\alpha]_{\text{D}}^{22} +47.4$ (c 1.56, DCM); FT-IR (neat) 3030, 2938, 1781, 1603, 1350, 1171 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.30 (m, 2H), 7.29–7.23 (m, 1H), 7.22–7.16 (m, 2H), 4.61 (ddd, $J = 8.1, 4.3, 2.4$ Hz, 1H), 4.39 (dd, $J = 11.9, 2.4$ Hz, 1H), 4.26 (dd, $J = 11.9, 4.3$ Hz, 1H), 3.56 (ddd, $J = 9.8, 9.2, 8.1$ Hz, 1H), 3.01 (s, 3H), 2.97 (dd, $J = 18.0, 9.2$ Hz, 1H), 2.74 (dd, $J = 18.0, 9.8$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.4, 137.8, 129.5, 128.3, 127.1, 83.0, 67.7, 42.7, 37.8, 36.7; MS (ESI) m/z 271.1 $[\text{M} + \text{H}]^+$ 293.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5\text{NaS}$ 293.0460; Found 293.0446.

(R)-Ethyl 3-((S)-oxiran-2-yl)-3-phenylpropanoate (22). To a solution of **21** (2.60 g, 9.63 mmol) in 1:1 ethanol/THF (40 mL) was added sodium ethoxide (950 mg, 14.0 mmol) and the mixture stirred for 24 hours. The reaction was quenched with saturated NH_4Cl and extracted twice with DCM. The combined organic extracts were dried (MgSO_4) and concentrated and the residue purified by column chromatography (1:9 ethyl acetate/hexanes) to give **22** as a pale yellow oil (1.72 g, 81%); $[\alpha]_{\text{D}}^{13} -4.8$ (c 2.70, DCM); FT-IR (neat) 3063, 3030, 2981, 2927, 1729, 1602, 1251 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42–7.32 (m, 2H), 7.31–7.23 (m, 3H), 4.22–3.96 (m, 2H), 3.14 (ddd, $J = 7.2, 3.7, 2.4$ Hz, 1H), 3.01 (ddd, $J = 8.9, 7.2, 6.1$ Hz, 1H), 2.92 (dd, $J = 15.3, 6.1$ Hz, 1H), 2.79 (dd, $J = 15.3, 8.9$ Hz, 1H), 2.77 (dd, $J = 4.6, 3.7$ Hz, 1H), 2.61 (dd, $J = 4.6, 2.4$ Hz, 1H), 1.17 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.5, 139.8, 128.6, 127.7, 127.2, 60.4, 55.3, 46.9, 44.9, 37.6, 14.0; MS (ESI) m/z 221.1 $[\text{M} + \text{H}]^+$ 243.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{Na}$ 243.0997; Found 243.1003.

(1S,2S,3R)-Ethyl 2-(hydroxymethyl)-3-phenylcyclopropanecarboxylate (23). A solution of LHMDs in THF (1 M, 2.40 mL) was added to THF (17.6 mL) and a solution of **22** (441 mg, 2.0 mmol) in THF (10 mL) was then added rapidly. At the end of the addition the reaction was immediately quenched with Amberlite® IRP-69 ion exchange resin and filtered through Celite. The filtrate was concentrated and the residue purified by column chromatography (1:9 ethyl acetate/hexanes) to give **23** (356 mg, 81%) as well as its *O*-trimethylsilyl ether derivative **24** (61 mg, 10%) as colourless syrups; **23**: $[\alpha]_{\text{D}}^{17} -150$ (c 1.70, DCM); FT-IR (neat) 3423, 3027, 2981, 1720, 1602, 1176 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.26–

7.20 (m, 2H), 7.20–7.10 (m, 3H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.38 (dd, $J = 7.0, 7.0$ Hz, 1H), 3.35 (dd, $J = 7.0, 7.0$ Hz, 1H), 2.81 (dd, $J = 9.3, 5.3$ Hz, 1H), 2.04 (dd, $J = 5.3, 4.9$ Hz, 1H), 2.01 (dddd, $J = 9.3, 7.0, 7.0, 4.9$ Hz, 1H), 1.48 (br. s., 1H), 1.22 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.0, 135.4, 128.7, 128.5, 126.9, 60.85, 60.8, 30.4, 30.0, 23.5, 14.2; MS (ESI) m/z 221.1 $[\text{M} + \text{H}]^+$ 243.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{Na}$ 243.0997; Found 243.0988.

(1S,2S,3R)-Ethyl 2-(trimethylsilyloxymethyl)-3-phenylcyclopropanecarboxylate (24). $[\alpha]_{\text{D}}^{18} -92.2$ (c 0.51, DCM); FT-IR (neat) 3072, 3023, 2956, 2871, 1727, 1251, 1179 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 7.11–6.96 (m, 5H), 3.99 (q, $J = 7.1$ Hz, 2H), 3.31 (dd, $J = 7.0, 7.0$ Hz, 1H), 3.28 (dd, $J = 7.0, 7.0$ Hz, 1H), 2.98 (dd, $J = 9.5, 5.2$ Hz, 1H), 2.23 (dddd, $J = 9.5, 7.0, 7.0, 4.9$ Hz, 1H), 2.15 (dd, $J = 5.2, 4.9$ Hz, 1H), 0.98 (t, $J = 7.2$ Hz, 3H), -0.07 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2, 135.7, 129.0, 128.2, 126.7, 60.7, 60.5, 30.8, 30.0, 23.7, 14.2, -0.7; MS (ESI) m/z 293.1 $[\text{M} + \text{H}]^+$ 315.1 $[\text{M} + \text{Na}]^+$; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3\text{NaSi}$ 315.1392; Found 315.1403.

((1S,2S,3R)-2-(Hydroxymethyl)-3-phenylcyclopropyl(morpholino)methanone (26). To a solution of **23** (67 mg, 0.30 mmol) in 1:1 THF/ H_2O (2 mL) and NaOH added (25 mg, 0.61 mmol) and the mixture heated for 20 minutes. A solution of HCl (1 M, 3 mL) was added and then the mixture concentrated under reduced pressure to give the crude carboxylic acid and NaCl. The residue was taken up in warm DCM (2 mL) and insoluble material removed by filtration. To the solution of the carboxylic acid were added morpholine (35 μL , 0.37 mmol), then PyBOP (190 mg, 0.37 mmol) and DIPEA (140 μL , 0.84 mmol) and the reaction mixture immediately applied to a column of silica and eluted with 3:17 methanol/ethyl acetate. Concentration of the appropriate fractions gave **26** as a colourless syrup (71 mg, 89%); ^1H NMR (500 MHz, CDCl_3) δ 7.44–7.04 (m, 5H), 3.64 (br. s., 8H), 3.52 (dd, $J = 11.6, 7.0$ Hz, 1H), 3.30 (dd, $J = 11.6, 7.3$ Hz, 1H), 2.81 (dd, $J = 9.6, 4.6$ Hz, 1H), 2.64 (br. s., 1H), 2.18 (dd, $J = 4.6, 4.6$ Hz, 1H), 2.02 (dddd, $J = 9.5, 7.3, 7.0, 4.6$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) 170.5, 136.2, 128.6, 128.5, 126.8, 66.7 (2C), 60.8, 29.8, 29.3, 22.2.

(4S,5S)-5-(Hydroxymethyl)-4-phenyldihydrofuran-2(3H)-one (28). To a stirred solution of **27** (442 mg, 2.16 mmol) dissolved in DCM (3 mL) was added 32% peracetic acid (600 μL , 2.78 mmol) and the mixture stirred overnight. The reaction was quenched with 10% Pd/C (15 mg) and stirred for 20 minutes or until the evolution of O_2 had ceased and a negative test for peroxides was obtained (starch/iodide). The mixture was then filtered through Celite, concentrated under reduced pressure and taken up in 1:1 THF/1M HCl (12 mL) and stirred for 3 hours. The volatiles were removed under reduced pressure and the residue purified by flash chromatography (1:1–7:3 ethyl acetate/hexanes) to give **28** as a crystalline solid (395 mg, 95%); mp 97–99 $^\circ\text{C}$ (tol.); $[\alpha]_{\text{D}}^{27} +172$ (c 1.01, CHCl_3); FT-IR (neat) 3413, 3070, 3039, 2947, 1754, 1603 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.42–7.34 (m, 2H), 7.34–7.28 (m, 1H), 7.28–7.21 (m, 2H), 4.80 (ddd, $J = 7.6, 5.5, 3.7$ Hz, 1H), 3.91 (ddd, $J = 9.2, 8.2, 7.6$ Hz, 1H),

3.53 (ddd, $J = 12.5, 5.3, 3.7$ Hz, 1H), 3.41 (br. ddd, $J = 12.5, 5.3, 5.3$ Hz, 1H), 3.02 (dd, $J = 17.4, 8.2$ Hz, 1H), 2.89 (dd, $J = 17.4, 9.2$ Hz, 1H), 1.86 (br. dd, $J = 5.3, 5.3$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.5, 136.4, 128.9, 127.9, 127.6, 83.2, 62.2, 43.1, 34.5; MS (ESI) m/z 193.1 $[\text{M} + \text{H}]^+$ 215.1 $[\text{M} + \text{Na}]^+$. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{Na}$ 215.0684; Found 215.0675.

(4S, 5S)-5-(Methanesulfonyloxymethyl)-4-phenyldihydrofuran-2(3H)-one (29). Alcohol **28** (245 mg, 1.28 mmol) was treated as per the method for **21** to give **29** as a colourless crystalline solid (281 mg, 82%); mp 137–139 °C (tol.); $[\alpha]_{\text{D}}^{19} +152$ (c 1.14, DCM); FT-IR (neat) 3032, 3015, 2961, 1766, 1763, 1600 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.50–7.31 (m, 3H), 7.25–7.14 (m, 2H), 4.99 (ddd, $J = 7.2, 6.4, 3.1$ Hz, 1H), 4.09 (dd, $J = 11.6, 3.1$ Hz, 1H), 3.95 (br. ddd, $J = 8.9, 7.2, 6.4$ Hz, 1H), 3.91 (dd, $J = 11.6, 6.4$ Hz, 1H), 3.00 (dd, $J = 17.7, 8.9$ Hz, 1H), 2.93 (s, 3H), 2.92 (dd, $J = 17.7, 6.4$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.3, 135.7, 129.4, 128.5, 127.5, 79.7, 68.5, 42.6, 37.5, 34.6; MS (ESI) m/z 271.1 $[\text{M} + \text{H}]^+$ 293.0 $[\text{M} + \text{Na}]^+$. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5\text{NaS}$ 293.0460; Found 293.0455.

(R)-Ethyl 3-((S)-oxiran-2-yl)-3-phenylpropanoate (30). Mesylate **29** (250 mg, 0.93 mmol) was treated as per the method for **22** to give **30** as a colourless oil (136 mg, 66%); $[\alpha]_{\text{D}}^{17} +11.0$ (c 1.36, DCM); FT-IR (neat) 3067, 3032, 2981, 2923, 1731, 1602 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.31 (m, 2H), 7.30–7.20 (m, 3H), 4.18–4.03 (m, 2H), 3.32 (ddd, $J = 7.6, 7.6, 5.6$ Hz, 1H), 3.21 (ddd, $J = 5.6, 4.0, 2.4$ Hz, 1H), 2.78 (dd, $J = 4.9, 4.0$ Hz, 1H), 2.79 (dd, $J = 15.6, 7.6$ Hz, 1H), 2.68 (dd, $J = 15.6, 7.6$ Hz, 1H), 2.54 (dd, $J = 4.9, 2.4$ Hz, 1H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.5, 139.5, 128.5, 127.9, 127.2, 60.5, 54.6, 45.9, 43.1, 36.9, 14.0; MS (ESI) m/z 243.0 $[\text{M} + \text{Na}]^+$. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{Na}$ 243.0997; Found 243.0996.

(1R,5S,6S)-6-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one (31).⁵¹ Epoxide **30** (123 mg, 0.56 mmol) was treated as per the method for **23** to give **30** as a crystalline solid (65 mg, 64%); mp 122–123 °C; $[\alpha]_{\text{D}}^{17} +130$ (c 0.50, CHCl_3); FT-IR (neat) 3068, 2963, 2905, 1737, 1602 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.27–7.21 (m, 2H), 7.20–7.14 (m, 1H), 7.02–6.97 (m, 2H), 4.39 (dd, $J = 9.5, 4.6$ Hz, 1H), 4.34 (br. d, $J = 9.5$ Hz, 1H), 2.48–2.44 (m, 1H), 2.2–2.23 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.9, 137.2, 128.7, 127.1, 125.9, 69.7, 29.3, 27.4, 26.1; MS (ESI) m/z 197.1 $[\text{M} + \text{Na}]^+$.

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