A Stereodivergent Route to Four Stereoisomeric 3′-Acetoxycyclopentenylglycine Derivatives

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Abstract: A short and efficient synthetic route to four stereoisomeric 3′-acetoxycyclopentenylglycine derivatives from L-serine has been developed. The method features a stereoselective conjugate addition and ring-closing metathesis as key steps.

Key words: amino acids, chiral pool, metathesis, Michael addition, stereoselective synthesis

Non-natural amino acids with highly lipophilic side chains have recently started to attract attention as components of enzyme inhibitors.[1,2] Of the various cycloalkyl glycines,[3] cyclopentylglycines (Cpg)[4] and cyclopentenylglycines[5] are important for several reasons, including their natural occurrence,[6] their use as competitive inhibitors[7] of isoleucine uptake in *E. coli*, and as starting materials in the design and synthesis of angiotensin II antagonists[8] and neuraminidase inhibitors,[9] to mention a few. It has further been observed[10] that appendage of functional groups at the 3′-position in cyclopentylglycines can increase the potency of enzyme inhibition, depending on the configuration of the chiral centres. Thus, synthesis and biological evaluation of stereoisomeric cyclopentylglycines of general structure **1** (Figure 1), for example, 3′-amino-,[11a] 3′-carboxy,[11b,c] 3′-hydroxymethyl-,[11d] 3′-hydroxylamino-[11e] and 3′-hydroxycyclopentylglycine,[11f] is a matter of considerable current interest. Moreover, 3′-substituted cyclopentenylglycine derivatives are also of synthetic and biological interest since they form the core structure of carbocyclic analogues of some important natural products such as polyoxins, nikkomycins[12] and furanomycin.[13] In a continuation of our efforts[14] on the asymmetric synthesis of non-natural α-amino acids of interest, herein, we describe the stereoselective synthesis of two epimeric 3′-acetoxycyclopentenylglycine derivatives, **2** and **3**, and their enantiomers, *ent*-**2** and *ent*-**3**, which are relevant to some of these applications.

We have recently reported[15] the synthesis of 2-azetidinylglycine derivative **6** via diastereoselective conjugate addition of benzylamine to the known[16] unsaturated ester **4** (Scheme 1). It appeared to us that an analogous stereoselective addition of a vinyl cuprate to the unsaturated ester **4** could be explored for the preparation of the title compounds.

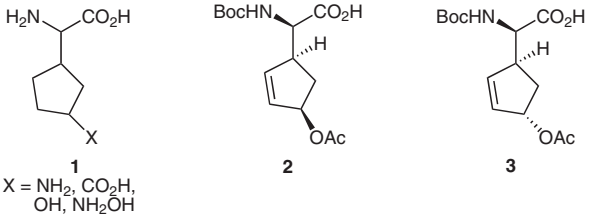
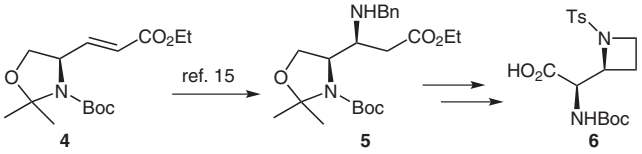


Figure 1 Some cyclopentenylglycine derivatives of importance



Scheme 1 Background of the present work

Addition of divinylmagnesium cuprate to compound **4** proceeded well under the previously reported conditions[17] to provide the corresponding *syn*-adduct **7** in very good yield as a single isolable stereoisomer (Scheme 2). Reduction of **7** with $LiAlH_4$ to the corresponding primary alcohol **8**, followed by its oxidation under conventional conditions, proceeded uneventfully to provide the desired aldehyde **9** in good overall yield. Addition of vinylmagnesium bromide to aldehyde **9** proceeded with little diastereocontrol, as expected, to provide a mixture (ca. 1:1) of the epimeric alcohols **10** and **11** (configuration not determined at this stage), which were cleanly separated by column chromatography. The faster running diastereomer **10** was then subjected to ring closing metathesis (RCM) with the Grubbs catalyst[18] benzylidene bistricyclohexylphosphinoruthenium (IV) dichloride (**12**). Pleasingly, the corresponding cyclopentenol derivative **13** was obtained as a viscous liquid in high yield. Similar treatment of diene **11** provided rapid access to the epimeric cyclopentenol **15** under comparable conditions. The RCM of dienol derivatives leading to the corresponding cylopentenols have occasionally been found to be problematic.[18] Successful RCM of dienols **10** and **11** is therefore of significance.

The corresponding acetate derivatives **14** and **16** were separately prepared from cyclopentenols **13** and **15**, respectively. One-pot deprotection and oxidation of the oxazolidine unit in each of the compounds **14** and **16** separately with Jones reagent[19] then led to the desired 3′-acetoxycyclopentenylglycine derivatives **2** and **3**, respectively.

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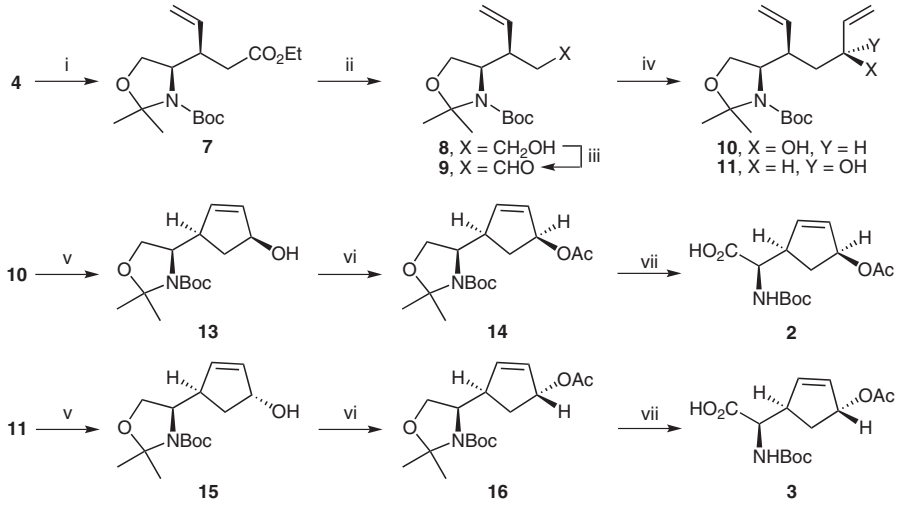


Scheme 2 *Reagents and conditions*: (i) vinylmagnesium bromide, CuI, TMSCl, THF, –78 °C to r.t., 2 h, 89%; (ii) $LiAlH_4$, 0 °C, Et_2O, 1.5 h, 87%; (iii) TPAP, NMO, CH_2Cl_2, r.t., 2 h, 84%; (iv) vinylmagnesium bromide, Et_2O, –78 °C to r.t., 89%; (v) Grubbs catalyst **12** (5 mol%), CH_2Cl_2, r.t., 2 h, 79% for **13**, 86% for **15**; (vi) Ac_2O, DMAP, CH_2Cl_2, r.t., 0.5 h, 86% for **14**, 88% for **16**; (vii) Jones reagent, acetone, 0 °C, 5 h, 59% for **2**, 56% for **3**.

Whereas the gross structures of the series of compounds **13**–**16**, **2** and **3** were easily secured, the stereochemistry at the new stereocentre (C*OH or C*OAc) in these compounds was correlated from chemical shift values based on precedence.[20,13] Thus, in compounds **15**, **16** and **3**, the methylene protons of the cyclopentene ring consistently appeared at around δ = 2.05 and 1.85 ppm, showing a chemical shift difference of only 0.2 ppm, which is characteristic for *trans*-3,5-disubstituted cyclopentenes. Whereas, in the *cis*-series (**13**, **14** and **2**), the same set of protons showed a chemical shift difference of around 0.9 ppm. Moreover, NOESY studies on compound **2** revealed correlations between protons at δ = 2.55 and 3.36, 2.55 and 5.63 ppm, and between the geminal protons at δ = 2.55 and 1.69 ppm, as shown in Figure 2.

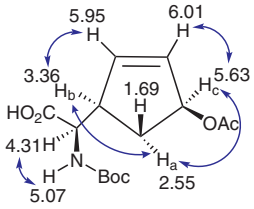
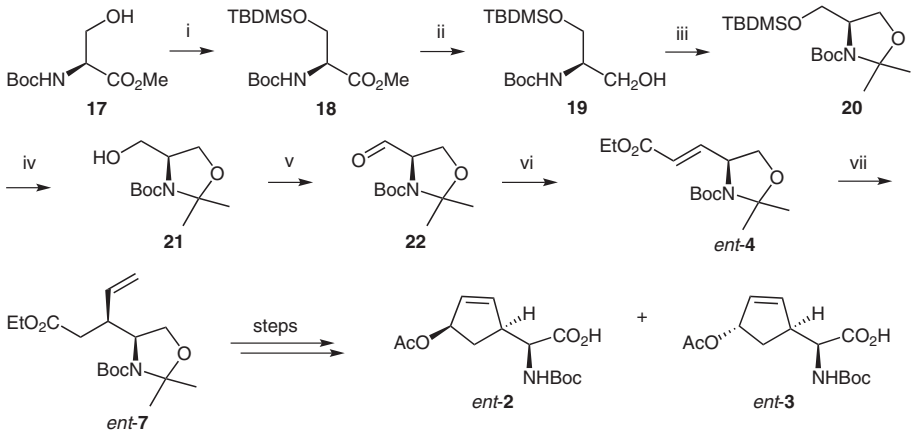


Figure 2 NOESY correlations of compound **2**

Since the prepared cyclopentenylglycine derivatives **2** and **3** have *R*-configuration at the α-amino centre, we became interested in extending this study to prepare cyclopentenylglycine derivatives having the natural *S*-configuration at the α-amino centre.

Although the use of D-serine instead of L-serine as starting material would deliver the desired configuration, we opted to use L-serine because of its lower price and ready availability. Thus, the enantiomeric unsaturated ester *ent*-**4** was prepared from L-Boc-Ser-OMe (**17**) in a six-step sequence (Scheme 3) involving OTBS formation, reduction of the ester functionality in the resulting **18** to the alcohol



Scheme 3 *Reagents and conditions*: (i) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 6 h, 96%; (ii) $LiAlH_4$, THF, 0 °C, 2 h, 61%; (iii) 2,2-dimethoxypropane, *p*-TsOH (cat.), toluene, reflux, 1.5 h, 95%; (iv) TBAF, THF, 0 °C to r.t., 3 h, 90%; (v) oxalyl chloride, DMSO, NMM, CH_2Cl_2, –78 °C to 0 °C, 1.5 h, 80%; (vi) $(OEt)_2POCH_2CO_2Et$, K_2CO_3, TBAI, H_2O, r.t., 24 h, 86%; (vii) vinylmagnesium bromide, CuI, TMSCl, THF, –78 °C to r.t., 1 h, 82%.

19, simultaneous O,N-protection of the latter leading to the oxazolidine derivative **20**, unmasking of the OTBS protection, and subsequent oxidation of the resulting primary alcohol **21** leading to the (*S*)-Garner's aldehyde[21] **22**, and subsequent olefination with triethyl phosphonoacetate, providing *ent*-**4**. The latter compound was obtained pure from a 19:1 crude mixture and showed spectroscopic and optical properties similar to those reported.[22] The enantiomeric purity of compounds **4** and *ent*-**4** were also determined by HPLC using a Chiralpak AD-H column [hexane–ethyl acetate, 95:5; flow rate 1 mL/min] and was found to be 98 and 96%, respectively. Conjugate addition of vinyl cuprate to *ent*-**4** then led to the desired product *ent*-**7** in a manner similar to that used for **7**. From the conjugate addition product *ent*-**7**, the enantiomeric cyclopentenylglycine derivatives *ent*-**2** and *ent*-**3** were then prepared by following the same steps detailed in Scheme 1. Moreover, these compounds also displayed spectral and optical properties that were in close agreement with those observed for their enantiomers, thus indicating homogeneity.

In conclusion, we have developed a convenient route to four stereoisomeric 3′-acetoxycyclopentenylglycine derivatives from a common source by using a standard set of reactions. The compounds prepared may find applications as modified α-amino acids in the design and synthesis of peptides, building blocks in organic synthesis, and as substrates for use in biology. The methodology developed is short and efficient and should complement those existing in the literature. The approach may also find use in the preparation of similar cyclopentenylglycine derivatives of interest.

Optical rotations were recorded in spectroscopic grade $CHCl_3$ with a Rudolph Autopol IV polarimeter, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded with a Perkin–Elmer Spectrum-1 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance-400 spectrometer purchased through a DST-FIST grant. Data for rotamers are presented within parentheses wherever appropriate. Chemical shifts are recorded relative to residual solvent peak. Mass spectra were recorded with a JEOL-JMS 600 instrument (I. I. C. B., Kolkata or IACS, Kolkata). Chiral HPLC studies were performed with an Agilent 1100 instrument as a paid service from Chembiotek, Kolkata. Petroleum ether (PE) refers to the fraction boiling in the range 60–80 °C. Silica gel (60–120 mesh) for column chromatography was purchased from Spectrochem, India.

(*R*)-*tert*-Butyl 4-[(*R*)-1-Ethoxy-1-oxopent-4-en-3-yl]-2,2-dimethyloxazolidine-3-carboxylate (7)

Vinylmagnesium bromide (6 mL, 6.0 mmol) was added dropwise to a stirred suspension of CuI (572 mg, 3.0 mmol) in anhydrous THF (6 mL) at –5 °C under argon. After 15 min, the reaction mixture was cooled to –78 °C and trimethylsilyl chloride (380 μL, 3 mmol) followed by a solution of unsaturated ester **4** (150 mg, 0.5 mmol) in anhydrous THF (6 mL) were sequentially added dropwise over 15 min. The reaction mixture was allowed to come to r.t. and then slowly quenched with sat. aq NH_4Cl (3 mL), extracted with EtOAc (2 × 25 mL) and the organic layer was washed successively with sat. aq NH_4Cl (20 mL), H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo to leave a crude product that was purified by column chromatography over silica gel (EtOAc–PE, 1:19) to provide the product **7**.

Colourless liquid; yield: 147 mg (89%); $[\alpha]_D^{25}$ –9.6 (*c* 0.48, $CHCl_3$).

IR ($CHCl_3$): 2981, 1739, 1699, 1642, 1479, 1456, 1386, 1367, 1258, 1176 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71–5.68 (m, 1 H), 5.13–5.09 (m, 2 H), 4.14–4.08 (m, 2.5 H), 3.92 (d, *J* = 6.4 Hz, 1.5 H), 3.81 (d, *J* = 8.0 Hz, 1 H), 3.17–3.06 (m, 1 H), 2.52 (dd, *J* = 3.6, 14.8 Hz, 1 H), 2.35–2.26 (m, 1 H), 1.63–1.56 (s, 3 H), 1.49–1.47 (m, 12 H), 1.23 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 152.9 (152.3), 137.5, 117.3 (117.0), 94.4 (93.3), 80.1, 64.6 (64.4), 60.3 (59.7), 42.9 (42.7), 35.1 (34.1), 28.4, 26.9 (26.2), 24.0 (22.6), 14.2.

Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.57; H, 9.06; N, 4.20.

MS (TOF, ES+): *m*/*z* (%) = 350 (100) [M + Na].

Compound *ent*-7

Prepared as described above from *ent*-**4**.

Colourless liquid; yield: 135 mg (82%); $[\alpha]_D^{25}$ +8.9 (*c* 0.47, $CHCl_3$) [Lit.[17b] +10 (*c* 2.2, $CHCl_3$)].

(*R*)-*tert*-Butyl 4-[(*R*)-1-Hydroxypent-4-en-3-yl)-2,2-dimethyloxazolidine-3-carboxylate (8)

A solution of **7** (300 mg, 0.92 mmol) in anhydrous Et_2O (5 mL) was added dropwise over 20 min to a suspension of $LiAlH_4$ (52 mg, 1.38 mmol) in anhydrous Et_2O (8 mL) at 0 °C under nitrogen. The reaction mixture was allowed to come to r.t. and stirred for 1.5 h, then cooled to 0 °C and slowly quenched with aq. NaOH (2.5 M, 2 mL). The organic layer was separated and the thick aqueous layer was triturated with Et_2O (20 mL). The combined organic extract was washed successively with H_2O (2 × 25 mL) and brine (25 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo to leave a crude product that was purified by column chromatography over silica gel (EtOAc–PE, 1:3) to provide the product **8**.

Viscous colourless liquid; yield: 260 mg (87%); $[\alpha]_D^{25}$ –35 (*c* 0.49, $CHCl_3$).

IR ($CHCl_3$): 3437, 2979, 1699, 1479, 1456, 1392, 1367, 1256, 1175 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68–5.65 (m, 1 H), 5.18–5.06 (m, 2 H), 3.94–3.82 (m, 3 H), 3.72–3.55 (m, 2 H), 2.61–2.59 (m, 1 H), 2.18 (s, 1 H), 1.70–1.47 (m, 17 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9 (152.2), 139.1 (138.3), 117.4 (116.9), 94.2 (93.6), 80.1 (79.8), 65.3, 61.1 (60.7), 44.6 (44.4), 32.9 (32.6), 28.3, 26.9 (26.3), 24.4 (22.8).

Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.29; H, 9.76; N, 4.79.

MS (TOF, ES+): *m*/*z* (%) = 308 (100) [M + Na].

Compound *ent*-8

Prepared as described above from *ent*-**7**.

Colourless viscous liquid; yield: 246 mg (94%); $[\alpha]_D^{25}$ +34.0 (*c* 0.5, $CHCl_3$).

(*R*)-*tert*-Butyl 2,2-Dimethyl-4-[(*R*)-1-oxopent-4-en-3-yl]oxazolidine-3-carboxylate (9) and *ent*-9

TPAP (20 mg, 0.07 mmol, 10 mol%) and NMO (175 mg, 1.44 mmol) were added in single portions to a stirred suspension of alcohol **8** (200 mg, 0.72 mmol) and molecular sieves (4 Å, 250 mg) in anhydrous CH_2Cl_2 (20 mL). The reaction mixture was stirred for 2 h and then diluted with anhydrous Et_2O (30 mL), filtered through Celite and the filtrate was concentrated in vacuo to leave a crude

product that was purified by column chromatography over silica gel (EtOAc–PE, 1:9) to provide the product **9**.

Colourless liquid; yield: 167 mg (84%); $[\alpha]_D^{25}$ –12.6 (*c* 1.03, $CHCl_3$).

IR ($CHCl_3$): 2980, 1728, 1697, 1388, 1367, 1258, 1175 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 5.80–5.60 (m, 1 H), 5.14 (m, 2 H), 3.95–3.91 (m, 2 H), 3.80 (d, *J* = 8.4 Hz, 1 H), 3.40–3.20 (m, 1 H), 2.60 (d, *J* = 14 Hz, 1 H), 2.55–2.40 (m, 1 H), 1.58–1.47 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9 (201.4), 153.1, 137.3, 117.5, 94.6 (94.1), 80.5, 64.4 (59.7), 42.9 (42.6), 40.14, 29.7 (29.3), 28.4, 26.8 (26.2), 24.0 (22.5).

MS (TOF, ES+): *m*/*z* (%) = 284 (100) [M + H].

Compound *ent*-9
Prepared as described above from *ent*-**8**.

Colourless liquid; yield: 171 mg (86%); $[\alpha]_D^{25}$ +11.2 (*c* 0.28, $CHCl_3$).

(*R*)-*tert*-Butyl 4-[(3*R*,5*S*)-5-Hydroxyhepta-1,6-dien-3-yl]-2,2-dimethyloxazolidine-3-carboxylate (10), (*R*)-*tert*-Butyl 4-[(3*R*,5*R*)-5-Hydroxyhepta-1,6-dien-3-yl]-2,2-dimethyloxazolidine-3-carboxylate (11), *ent*-10 and *ent*-11
Vinylmagnesium bromide (1 M in THF, 2 mL, 2 mmol) was added dropwise to a stirred solution of aldehyde **9** (200 mg, 0.70 mmol) in anhydrous Et_2O (12 mL) at –78 °C over 20 min. The reaction mixture was stirred for 1 h at –78 °C, 2 h at –40 °C and then allowed to come to r.t. and stirring was continued for 3 h. The reaction was then cooled to –5 °C and slowly quenched with aq NaOH (1 N, 4 mL). The organic layer was separated and the thick aqueous layer was triturated with EtOAc (25 mL). The combined organic extract was washed successively with HCl (1 N, 10 mL), H_2O (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a crude product that was purified by column chromatography over silica gel (EtOAc–PE, 1:9) to provided, sequentially, the product **10** (101 mg, 46%) and **11** (96 mg, 43%) as colourless viscous liquids in a combined yield of 89%. Compounds *ent*-**10** and *ent*-**11** were prepared similarly.

Compound 10
$[\alpha]_D^{25}$ –30.7 (*c* 0.35, $CHCl_3$).

IR ($CHCl_3$): 3468, 3078, 2980, 2933, 2343, 1698, 1686, 1643, 1479, 1456, 1392, 1367, 1256, 1175 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.92–5.86 (m, 1 H), 5.84–5.69 (m, 1 H), 5.23 (d, *J* = 17.1 Hz, 1 H), 5.16–5.07 (m, 3 H), 4.13 (br s, 1 H), 3.94–3.89 (m, 2 H), 3.83 (br s, 2 H), 2.80 (br s, 1 H), 1.69–1.62 (merged singlets, 8 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 141.5 (141.4), 139.1 (138.4), 117.7 (117.1), 114.2 (113.9), 94.2 (93.7), 80.1 (77.4), 70.5, 65.4 (65.3), 60.6, 44.2 (43.6), 38.4 (37.1), 29.7 (28.4), 26.9 (26.3), 24.4 (22.8).

Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.69; H, 9.56; N, 4.39.

MS (TOF, ES+): *m*/*z* (%) = 334 (100) [M + Na].

Compound 11
$[\alpha]_D^{25}$ –29.0 (*c* 0.35, $CHCl_3$).

IR ($CHCl_3$): 3435, 3079, 2980, 2935, 2343, 1698, 1642, 1478, 1456, 1392, 1367, 1256, 1175, 1093 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.84–5.73 (m, 2 H), 5.22 (d, *J* = 17.1 Hz, 1 H), 5.15–5.05 (m, 3 H), 4.13 (br s, 1 H), 3.94–3.91 (m, 2 H), 3.89–3.83 (m, 2 H), 2.56 (s, 1 H), 1.77–1.70 (m, 2 H), 1.63 (merged singlets, 6 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 139.8, 138.9, 116.9 (116.4), 115.5 (115.1), 93.7 (93.2), 79.6 (79.3), 71.7 (71.5), 64.7 (64.5), 60.2, 43.7, 36.7 (36.0), 27.9, 26.5 (25.8), 23.9 (22.2).

Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.75; H, 9.50; N, 4.44.

MS (TOF, ES+): *m*/*z* (%) = 334 (100) [M + Na].

Compound *ent*-10
Prepared as described above from *ent*-**9**.

Colourless viscous liquid; yield: 95 mg (43%); $[a]_D^{25}$ +28.00 (*c* 0.10, $CHCl_3$).

Compound *ent*-11
Prepared as described above from *ent*-**9**.

Colourless viscous liquid; yield: 88 mg (40%); $[\alpha]_D^{25}$ +27.8 (*c* 0.66, $CHCl_3$).

(*R*)-*tert*-Butyl 4-[(1*R*,4*S*)-4-Hydroxycyclopent-2-enyl]-2,2-dimethyloxazolidine-3-carboxylate (13), (*R*)-*tert*-Butyl 4-[(1*R*,4*R*)-4-Hydroxycyclopent-2-enyl]-2,2-dimethyloxazolidine-3-carboxylate (15), *ent*-13 and *ent*-15
Catalyst **12** (9 mg, 0.01 mmol, 5 mol%) was added to a stirred solution of diene **10** (68 mg, 0.22 mmol) in anhydrous and degassed CH_2Cl_2 (20 mL) under argon, and the homogeneous mixture was stirred at r.t. for 2 h. The reaction mixture was then concentrated in vacuo to leave a crude product that, on chromatography over silica gel (EtOAc–PE, 1:5), provided the product **13**. Cyclopentene derivatives **15**, *ent*-**13** and *ent*-**15** were prepared in a similar way.

Compound 13
Colourless liquid; yield: 49 mg (79%); $[\alpha]_D^{25}$ –12.3 (*c* 0.52, $CHCl_3$).

IR ($CHCl_3$): 3413, 2979, 2935, 2876, 1697, 1456, 1391, 1366, 1255, 1173, 1091 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.93–5.85 (m, 1 H), 5.87–5.82 (m, 1 H), 4.80 (br s, 1 H), 4.03–3.89 (m, 3 H), 3.83–3.80 (m, 1 H), 3.09 (br s, 1 H), 2.39 (td, *J* = 8.1, 13.2 Hz, 1 H), 1.62–1.58 (m, 7 H), 1.48 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 134.6 (134.3), 133.7, 93.2 (92.8), 79.3 (78.9), 76.7, 64.8 (64.5), 59.6 (59.1), 46.7, 35.5 (35.1), 27.4, 26.2 (25.7), 23.3 (21.9).

MS (TOF, ES+): *m*/*z* (%) = 306 (100) [M + Na].

Compound 15
Prepared as described above from **11**.

Colourless viscous liquid; yield: 53 mg (86%); $[\alpha]_D^{25}$ +36.4 (*c* 0.24, $CHCl_3$).

IR ($CHCl_3$): 3429, 2979, 2932, 1695, 1388, 1366, 1255, 1173 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.93–5.87 (m, 2 H), 4.90 (br s, 1 H), 3.95–3.80 (m, 2 H), 3.62 (d, *J* = 8.4 Hz, 1 H), 3.46–3.40 (m, 1 H), 2.06–2.02 (m, 1 H), 1.82 (ddd, *J* = 2.5, 8, 13.5 Hz, 1 H), 1.62 (s, 3 H), 1.49–1.45 (m, 13 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8 (152.1), 136.9, 134.7 (134.2), 94.3 (93.8), 80.2 (79.9), 65.7 (65.2), 60.4 (60.2), 48.1 (47.8), 36.3 (36.2), 28.3, 27.4 (26.7), 22.9 (22.6).

MS (TOF, ES+): *m*/*z* (%) = 306 (100) [M + Na].

Compound *ent*-13
Prepared as described above from *ent*-**10**.

Colourless viscous liquid; yield: 46 mg (75%); $[\alpha]_D^{25}$ +11.7 (*c* 0.67, $CHCl_3$).

Compound *ent*-15

Prepared as described above from *ent*-**11**.

Colourless viscous liquid; yield: 56 mg (90%); $[\alpha]_D^{25}$ –37.5 (*c* 0.3, $CHCl_3$).

(*R*)-*tert*-Butyl 4-[(1*R*,4*S*)-4-Acetoxycyclopent-2-enyl]-2,2-dimethyloxazolidine-3-carboxylate (14), (*R*)-*tert*-Butyl 4-[(1*R*,4*R*)-4-Acetoxycyclopent-2-enyl]-2,2-dimethyloxazolidine-3-carboxylate (16), *ent*-14 and *ent*-16

Ac_2O (0.1 mL, excess) and DMAP (5 mg) were added to a stirred solution of alcohol **13** (60 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (3 mL). The reaction mixture was stirred for 10 h at r.t. and then poured into ice-cooled H_2O (10 mL) while stirring for 30 min. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extract was washed with H_2O (2 × 10 mL), brine (10 mL), then dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuo to leave a crude product that, on column chromatography over silica gel (EtOAc–PE, 1:9), provided the product **14**. The acetate derivatives **16**, *ent*-**14** and *ent*-**16** were prepared similarly.

Compound 14

Colourless liquid; yield: 56 mg (86%); $[\alpha]_D^{25}$ –37.8 (*c* 1.08, $CHCl_3$).

IR ($CHCl_3$): 2979, 2935, 2877, 1736, 1697, 1387, 1377, 1366, 1243, 1085 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.90–5.86 (m, 2 H), 5.64 (br s, 1 H), 4.04–3.77 (m, 3 H), 3.28–3.12 (m, 1 H), 2.42 (dt, *J* = 8.4, 13.2 Hz, 1 H), 2.04 (s, 3 H), 1.68–1.47 (m, 16 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.9, 151.1, 137.2 (136.9), 129.6, 93.2 (92.7), 79.3 (78.9), 78.4 (78.2), 64.4 (63.5), 58.8 (58.6), 46.8 (46.1), 31.4 (30.9), 27.4, 26.3 (25.8), 23.2 (21.9), 20.2.

Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.88; H, 8.47; N, 4.21.

MS (TOF, ES+): *m*/*z* (%) = 348 (100) [M + Na].

Compound 16

Prepared as described above from **15**.

Colourless viscous liquid; yield: 61 mg (88%); $[\alpha]_D^{25}$ +72.0 (*c* 0.44, $CHCl_3$).

IR ($CHCl_3$): 2979, 2935, 2876, 1736, 1697, 1387, 1376, 1365, 1243, 1090 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.01 (d, *J* = 5.2 Hz, 1 H), 5.91–5.89 (m, 1 H), 5.71 (br s, 1 H), 3.97–3.80 (m, 2 H), 3.63 (d, *J* = 9.2 Hz, 1 H), 3.45–3.36 (m, 1 H), 2.08–2.02 (merged singlets, 4 H), 1.93 (ddd, *J* = 1.6, 7.6, 14.4 Hz, 1 H), 1.63 (1.57) (s, 3 H), 1.49–1.47 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 152.8 (152.1), 139.9, 130.1, 94.3 (93.8), 80.3, 79.9, 65.8 (65.2), 60.0, 48.3 (47.9), 33.1 (32.9), 28.4 (29.7), 27.4 (26.8), 24.3 (22.9), 21.3.

Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.93; H, 8.49; N, 4.37.

MS (TOF, ES+): *m*/*z* (%) = 348 (100) [M + Na].

Compound *ent*-14

Prepared as described above from *ent*-**13**.

Colourless viscous liquid; yield: 62 mg (90%); $[\alpha]_D^{25}$ +39.5 (*c* 0.42, $CHCl_3$).

Compound *ent*-16

Prepared as described above from *ent*-**15**.

Colourless viscous liquid; yield: 63 mg (91%); $[\alpha]_D^{25}$ –76.5 (*c* 0.81, $CHCl_3$).

(*R*)-2-[(1*R*,4*S*)-4-Acetoxycyclopent-2-enyl]-2-(*tert*-butoxycarbonylamino)acetic Acid (2), (*R*)-2-[(1*R*,4*R*)-4-Acetoxycyclopent-2-enyl]-2-(*tert*-butoxycarbonylamino)acetic Acid (3), *ent*-2 and *ent*-3

Jones reagent (2.67 M, 100 μL, 0.18 mmol) was added to a solution of oxazolidine derivative **14** (40 mg, 0.12 mmol) in acetone (2.5 mL) at 0 °C. The reaction mixture was stirred for 5 h and then quenched by adding 2-propanol (200 μL). The reaction mixture was stirred for 15 min, then neutralized with sat. aq $NaHCO_3$ to pH 4–5 and extracted with EtOAc (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL), brine (15 mL), dried over Na_2SO_4, then filtered and the filtrate was concentrated in vacuo to leave a crude product that, on column chromatography over silica gel (EtOAc–PE, 4:1), provided product **2**. Carboxylic acids **3**, *ent*-**2** and *ent*-**3** were prepared similarly.

Compound 2

Colourless liquid; yield: 23 mg (59%); $[\alpha]_D^{25}$ +15.7 (*c* 0.27, MeOH).

IR ($CHCl_3$): 3436, 2927, 2854, 1715, 1514, 1393, 1368, 1245, 1164, 1023 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.01 (d, *J* = 4.8 Hz, 1 H), 5.95 (d, *J* = 5.2 Hz, 1 H), 5.63 (d, *J* = 6 Hz, 1 H), 5.07 (d, *J* = 6.8 Hz, 1 H), 4.32–4.30 (m, 1 H), 3.37–3.35 (m, 1 H), 2.55 (dt, *J* = 14.4, 6.8 Hz, 1 H), 2.07 (s, 3 H), 1.69 (d, *J* = 14.4 Hz, 1 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 169.9, 155.2, 134.1, 132.3, 79.4, 77.7, 55.1, 44.7, 32.0, 27.3, 20.2.

HRMS (TOF, ES+): *m*/*z* [M^+ + Na] calcd for $C_{14}H_{21}NO_6Na$: 322.1267; found: 322.1264.

Compound 3

Prepared as described above from **16**.

Colourless viscous liquid; yield: 21 mg (56%); $[\alpha]_D^{25}$ +19.6 (*c* 0.41, MeOH).

IR ($CHCl_3$): 3437, 2918, 2850, 1711, 1499, 1393, 1368, 1247, 1164, 1022 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.04 (br s, 1 H), 5.93 (br s, 1 H), 5.71 (br s, 1 H), 4.80 (d, *J* = 8.4 Hz, 1 H), 4.42–4.39 (m, 1 H), 3.54 (br s, 1 H), 2.19–2.17 (m, 1 H), 2.07–2.03 (merged singlet, 4 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 171.0, 156.0, 135.3, 133.4, 80.6, 79.4, 55.0, 46.8, 33.5, 29.7, 21.1.

HRMS (TOF, ES+): *m*/*z* [M^+ + Na] calcd for $C_{14}H_{21}NO_6Na$: 322.1267; found: 322.1253.

Compound *ent*-2

Prepared as described above from *ent*-**14**.

Colourless viscous liquid; yield: 20 mg (55%); $[\alpha]_D^{25}$ –14.82 (*c* 0.35, MeOH).

Compound *ent*-3

Prepared as described above from *ent*-**16**.

Colourless viscous liquid; yield: 21 mg (57%); $[\alpha]_D^{25}$ –20.62 (*c* 0.11, MeOH).

(*S*)-Methyl 2-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)propanoate (18)

A solution of TBDMSCl (0.9 g, 6 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C to a stirred solution of (*S*)-methyl L-Boc-Ser-OH (1.1 g, 5 mmol) and imidazole (0.410 g, 6 mmol) in CH_2Cl_2 (10 mL). The resulting solution was allowed to come to r.t. and stirred overnight. The reaction mixture was poured into aq HCl (1 N, 50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The com-

bined organic layer was washed with aq HCl (1 N, 50 mL), H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), then filtered and the filtrate was concentrated in vacuo to leave a crude oily liquid that was purified by chromatography over silica gel (EtOAc–PE, 1:19) to provide the product.

Colourless liquid; yield: 1.60 g (96%); $[\alpha]_D^{25}$ +18.1 (*c* 0.90, $CHCl_3$).

IR (neat): 3452, 2956, 2859, 1721, 1503 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.32 (d, *J* = 8.4 Hz, 1 H), 4.33 (td, *J* = 6, 2.8 Hz, 1 H), 4.02 (dd, *J* = 10, 2.4 Hz, 1 H), 3.79 (dd, *J* = 10, 2.8 Hz, 1 H), 3.72 (s, 3 H), 1.44 (s, 9 H), 0.84 (s, 9 H), 0.01 (s, 3 H), –0.01 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.2, 155.4, 79.8, 63.7, 55.6, 52.2, 28.3, 25.7, 18.1, –5.6, –5.7.

Anal. Calcd for $C_{15}H_{31}NO_5Si$: C, 54.02; H, 9.37; N, 4.20. Found: C, 54.12; H, 9.31; N, 4.25.

MS (TOF, ES+): *m*/*z* (%) = 334 (100) [M + H].

(*R*)-*tert*-Butyl 1-(*tert*-Butyldimethylsilyloxy)-3-hydroxypropan-2-ylcarbamate (19)

A solution of **18** (1.66 g, 5 mmol) in THF (12 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (285 mg, 7.5 mmol) in THF (12 mL) at 0 °C, and the resulting solution was stirred at the same temperature for 1.5 h under nitrogen. The reaction was quenched by dropwise addition of aq KOH (1 N, 2 mL) until a white precipitate appeared. The reaction mixture was extracted with EtOAc (2 × 50 mL) and the combined organic layer was washed with H_2O (2 × 50 mL), brine (50 mL), dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a crude viscous mass that was purified by chromatography over silica gel (EtOAc–PE, 2:8) to provide the product.

Colourless liquid; yield: 930 mg (61%); $[\alpha]_D^{25}$ +14.4 (*c* 1.52, $CHCl_3$).

IR (neat): 3450, 2956, 2932, 1695, 1504 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.02 (br s, 1 H), 3.77–3.71 (m, 3 H), 3.63–3.59 (m, 2 H), 2.74 (br s, 1 H), 1.38 (s, 9 H), 0.82 (s, 9 H), 0.2 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.0, 79.5, 63.7, 52.6, 28.4, 25.8, 18.2, –3.6, –5.6.

Anal. Calcd for $C_{14}H_{31}NO_4Si$: C, 55.04; H, 10.23; N, 4.59. Found: C, 55.14; H, 10.18; N, 4.66.

MS (TOF, ES+): *m*/*z* (%) = 306 (100) [M + H].

(*R*)-*tert*-Butyl 4-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyloxazolidine-3-carboxylate (20)

p-TsOH (~5 mg) was added to a solution of **19** (1.52 g, 5 mmol) and 2,2-dimethoxy propane (2.1 mL, 17 mmol) in toluene (25 mL) and the resulting solution was heated to reflux under nitrogen for 1.5 h. The reaction was then allowed to cool to r.t., concentrated in vacuo and the residual crude mass was purified by chromatography over silica gel (EtOAc–PE, 1:9) to provide the product.

Colourless liquid; yield: 1.64 g (95%); $[\alpha]_D^{25}$ +26.2 (*c* 1.77, $CHCl_3$).

IR (neat): 2957, 2932, 1704, 1473, 1389 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.97 (t, *J* = 8 Hz, 1 H), 3.86–3.82 (m, 1.5 H), 3.76–3.64 (m, 1.5 H), 3.44–3.32 (m, 1 H), 1.42 (s, 9 H), 0.83 (s, 9 H), 0.00 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.2 (151.8), (93.8) 93.3, 79.6 (80.0), 65.0 (64.8), 62.1 (61.3), 58.4 (58.5), 28.5 (28.4), 26.7 (27.3), 25.8, 23.1 (24.5), 18.2.

Anal. Calcd for $C_{17}H_{35}NO_4Si$: C, 59.09; H, 10.21; N, 4.05. Found: C, 59.23; H, 10.35; N, 4.21.

MS (TOF, ES+): *m*/*z* (%) = 346 (100) [M + H].

(*S*)-*tert*-Butyl 4-(Hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate (21)

A solution of TBAF (1.43 g, 5.5 mmol) in THF (7 mL) was added dropwise to a stirred solution of **20** (1.72 g, 5 mmol) in THF (24 mL) at 0 °C. The resulting solution was stirred at r.t. for 2 h, then concentrated in vacuo to leave a crude mass, which was extracted with EtOAc (2 × 50 mL). The organic extract was washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), then filtered and the filtrate was concentrated in vacuo to leave a crude mass that was purified by chromatography over silica gel (EtOAc–PE, 4:6) to provide the product.

Colourless liquid; yield: 1.04 g (90%); $[\alpha]_D^{25}$ +20.9 (*c* 0.73, $CHCl_3$) [Lit.[21b] +21.8 (*c* 3.85, $CHCl_3$)].

IR (neat): 3446, 1702, 1459, 1393, 1368 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 4.04–3.90 (m, 2 H), 3.67 (t, *J* = 8 Hz, 2 H), 3.52 (d, *J* = 6.8 Hz, 1 H), 2.71 (br s, 1 H), 1.46–1.36 (m, 15 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.4, 94.1, 81.2, 65.3, 59.5, 28.4, 27.1, 24.6.

MS (TOF, ES+): *m*/*z* (%) = 232 (100) [M + H].

(*R*)-*tert*-Butyl 4-Formyl-2,2-dimethyloxazolidine-3-carboxylate (22)

A solution of DMSO (2.1 mL, 28.5 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise to a stirred solution of oxalyl chloride (1.04 mL, 12 mmol) in CH_2Cl_2 (20 mL) at –78 °C. The reaction was stirred for 20 min at the same temperature, then a solution of alcohol **21** (2.31 g, 10 mmol) in CH_2Cl_2 (15 mL) was added dropwise to the above mixture and stirring was continued at –78 °C for 35 min. A solution of NMM (5.9 mL, 53.7 mmol) in CH_2Cl_2 (6 mL) was added to the reaction mixture, which was allowed to come to 0 °C and stirred vigorously for 5 min before being poured into cold aq HCl (1 N, 50 mL). The mixture was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layer was washed with H_2O (2 × 50 mL), brine (2 × 50 mL), dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a pale-yellow crude product that was purified by chromatography over silica gel (EtOAc–PE, 1:9) to provide the product.

Colourless liquid; yield: 1.84 g (80%); $[\alpha]_D^{25}$ +99.2 (*c* 1.01, $CHCl_3$) [Lit.[21] +105 (*c* 1.4, $CHCl_3$)].

IR (neat): 2981, 2933, 1741, 1709, 1479, 1459, 1393, 1380, 1368 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.55 (9.61) (s, 1 H), 4.36–4.19 (m, 1 H), 4.13–4.04 (m, 2 H), 1.52–1.50 (s, 9 H), 1.44 (s, 6 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 199.3 (199.4), 151.2 (152.5), 95.0 (94.3), 80.9 (81.2), 64.6 (64.7), 63.8 (63.3), 28.2 (28.1), 25.7 (26.6), 23.7 (24.6).

MS (TOF, ES+): *m*/*z* (%) = 230 (100) [M + H].

(*S*,*E*)-*tert*-Butyl 4-(3-Ethoxy-3-oxoprop-1-enyl)-2,2-dimethyloxazolidine-3-carboxylate (*ent*-4)

A mixture of aldehyde **22** (1.60 g, 7 mmol), TBAI (262 mg, 0.71 mmol), triethyl phosphonoacetate (2.86 mL, 14 mmol) and aq K_2CO_3 (3 M, 4.8 mL) was stirred vigorously at r.t. for 12 h, then extracted with hexane (2 × 50 mL) and the combined extract was washed with H_2O (2 × 50 mL) and brine (50 mL). The organic extract was then dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo to leave a pale-yellow crude product that was purified by chromatography over silica gel (EtOAc–PE, 1:19) to provide the product.

Colourless solid; yield: 1.80 g (86%); mp 46–48 °C; $[\alpha]_D^{25}$ +65.7 (*c* 0.4, $CHCl_3$) [Lit.[22] +66 (*c* 0.3, $CHCl_3$)].

IR (neat): 2987, 1718, 1702, 1662, 1379, 1367 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.85–6.80 (m, 1 H), 5.94 (5.89) (d, *J* = 16.0 Hz, 1 H), 5.56–4.41 (m, 1 H), 4.22–4.19 (m, 2 H), 4.09 (dd, *J* = 9.2, 6.8 Hz, 1 H), 3.80 (dd, *J* = 9.2, 2.4 Hz, 1 H), 1.64–1.42 (m, 15 H), 1.30 (app. t, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.0, 151.5 (152.0), 145.9 (145.7), 122.2, 94.4 (93.9), 80.1 (80.6), 67.3 (67.1), 67.3 (67.1), 57.9, 28.3, 26.4 (27.2), 23.5 (24.6), 14.2.

MS (TOF, ES+): *m/z* (%) = 300 (100) [M + H].

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