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An efficient method for the stereoselective synthesis of *cis*-3-substituted prolines: conformationally constrained α-amino acids

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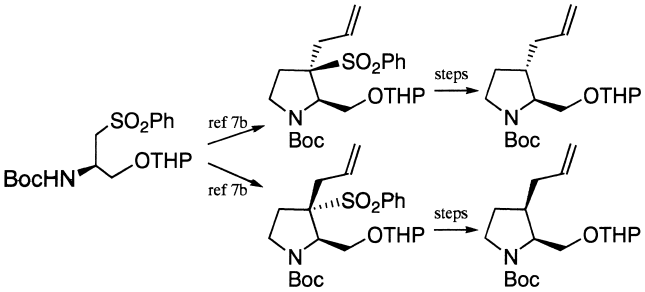
Abstract—An efficient synthesis of enantiomerically pure *cis*-3-substituted prolines is reported. Key steps involve the stereoselective organocuprate addition to the (*E*)-α,β-unsaturated ester **1**, obtained from the Garner's aldehyde, and expedient oxidation–cyclization sequences.

1. Introduction

Conformationally constrained α-amino acids have gained significant attention in recent years. This may be due to the observations that incorporation of such amino acids into peptides induces the conformational change and thus may serve as useful means for obtaining information on receptor recognition.[1] It also provides peptide mimetics that can be used as new drugs.[2] This type of amino acids *per se* exhibits interesting biological activities.[3] For designing such amino acids, construction of a proline analogue with a functional group at a specific position of the pyrrolidine framework has become a major strategy. Among these chimeric amino acids, the most intensively investigated one is the 3-substituted prolines in terms of conformational studies,[4] biological activities[5] and synthetic methodologies.[6a–z] Although some of the methods described so far are very efficient and can provide optically pure final products, it is still worthwhile developing a simple approach that can lead to a variety of chimeric amino acids. In the previous papers, we have described an unprecedented method for the asymmetric synthesis of 2,3-disubstituted pyrrolidine derivatives via the 'dianion [N–C–C]+bis-electrophile [C–C]' annelation protocol (Scheme 1).[7] However, compared with its excellent efficacity for the synthesis of enantio- and diastereomerically pure 2,3-*trans*-disubstituted pyrrolidines, this method has turned out to be somewhat less satisfactory for the *cis*-isomers in terms of diastereoselectivity. Indeed, the preparation of *cis*-3-substituted prolines is a challenging task due to their propensity of epimerizing to thermodynamically more stable *trans*-isomers.



Scheme 1.

2. Results and discussion

As part of our continuing pursuit for an easy access to optically pure chimeric α-amino acids, we have established an efficient method which gives only the desired *cis*-products starting from chiral oxazolidine α,β-unsaturated ester (**1**) which is easily available from the Garner's aldehyde.[8] (Scheme 2)

It has been reported that the 1,4-addition of dialkylcuprate to the chiral oxazolidine α,β-unsaturated ester (**1**) in the presence of trimethylsilyl chloride provides the *syn*-diastereomer with excellent diastereoselectivity.[9,10] In fact, the 1,4-addition of lithium dimethylcuprate to **1** provided the single *syn*-**2a** in 94% yield. The same addition reaction with the divinylmagnesium cuprate also gave the single *syn*-**2b** in 91% yield. However, in the case of the

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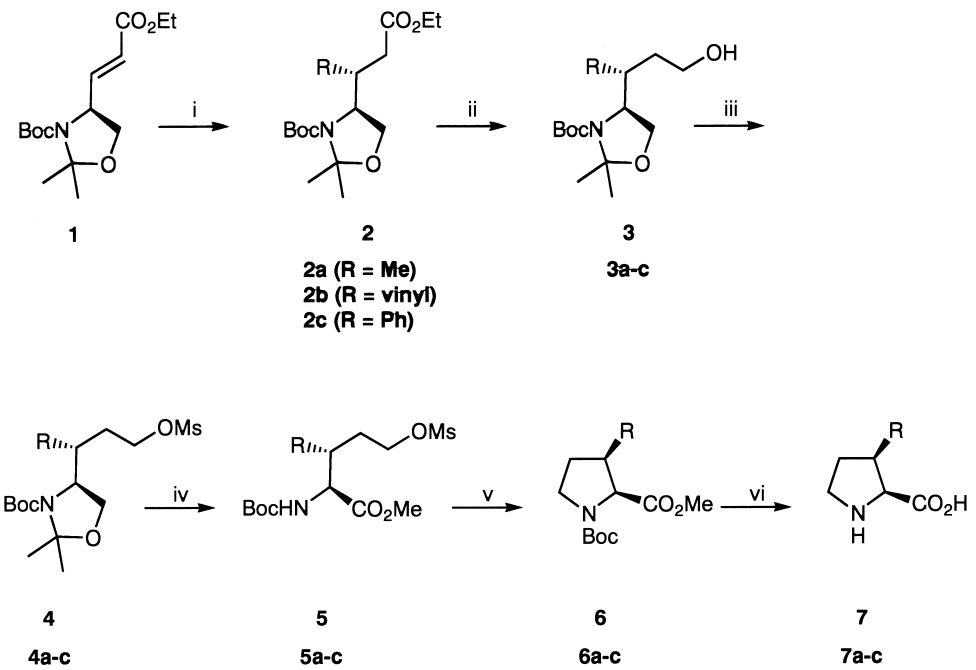
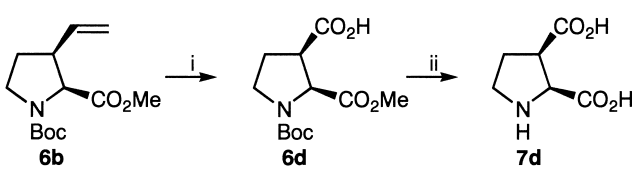


Scheme 2. *Reagents and conditions*: (i) for **2a**: MeLi, CuI, Me_3SiCl, THF, −78°C→rt, 94%; for **2b**: CH_2=CHMgBr, CuI, Me_3SiCl, THF, −78°C→rt, 91%; for **2c**: PhMgBr, CuCN, Me_3SiCl, THF, −25°C→rt, 3 h, 64%. (ii) $LiAlH_4$, THF, rt, 98% **3a**, 98% **3b**, 97% **3c**. (iii) MsCl, Et_3N, CH_2Cl_2, 0°C, 87% **4a**, 94% **4b**, 96% **4c**. (iv) (a) Jones oxidation, 0°C, 4 h; (b) CH_2N_2, Et_2O, 58% **5a**, 70% **5b**, 76% **5c**. (v) NaH, DMF, −25°C, 78% **6a**, 92% **6b**, 76% **6c**. (vi) 6N HCl, AcOH, reflux, 4 h, 98% **7a**, 90% **7b**, 98% **7c**.

preparation of adduct **2c**, we encountered some difficulties. In our hands, application of the same reaction conditions described in the literature ended up with the recovery of the starting material.[10c,d] Fortunately, the condition described by Hruby[10e] provided the desired *syn*-**2c** as a single diastereomer in 64% yield. Reduction of compounds **2** with $LiAlH_4$ to **3** followed by treatment with mesylchloride afforded oxazolidine mesylate **4** in excellent yields. Direct Jones oxidation of **4** and subsequent treatment with diazomethane provides the methyl esters **5**. The yields were 58, 70 and 76% for **5a**–**5c**, respectively. Ester **5b** was subjected to cyclization by treatment with NaH in DMF at 0°C to afford *cis*-3-vinyl proline derivative **6b** in 90% yield with 10% epimerization at C-2 position. Lowering the reaction temperature to −25°C could simply surmount this undesired epimerization. In this manner, *cis*-3-substituted proline derivatives **6a**, **6b**, **6c** were obtained in 78, 92 and 76% yield, respectively, as a single diastereomer judging from ^1H and ^{13}C NMR analyses. Potentiality of compound **6b** as a starting material for other *cis*-3-substituted proline derivatives was demonstrated in the synthesis of *cis*-3-carboxyproline **7d** (Scheme 3).

Thus, conventional ozonolysis followed by Jones oxidation gave **6d** in 50% yield. After the removal of the protecting groups by treatment with 6N HCl, *cis*-3-substituted prolines **7** were obtained by purification with ion exchange column chromatography. In order to confirm the stereochemical integrity of the 2,3-disubstituted pyrrolidines obtained according to the present method, the absolute stereochemistry of **6c**, deduced from that of the starting material, was determined by single-crystal X-ray analysis. The Fig. 1 irrefutably shows the *cis*-configurational relationship between the two functional groups at C-2 and C-3 positions. Torsion angle values indicate that the pyrrolidine ring exhibits an envelope conformation with carbon atom at C-4



Scheme 3. *Reagents and conditions*: (i) (a) O_3, CH_2Cl_2; PPh_3; (b) Jones oxidation, 0°C, 4 h, 50%. (ii) 6N HCl, AcOH, reflux, 4 h, 98%.

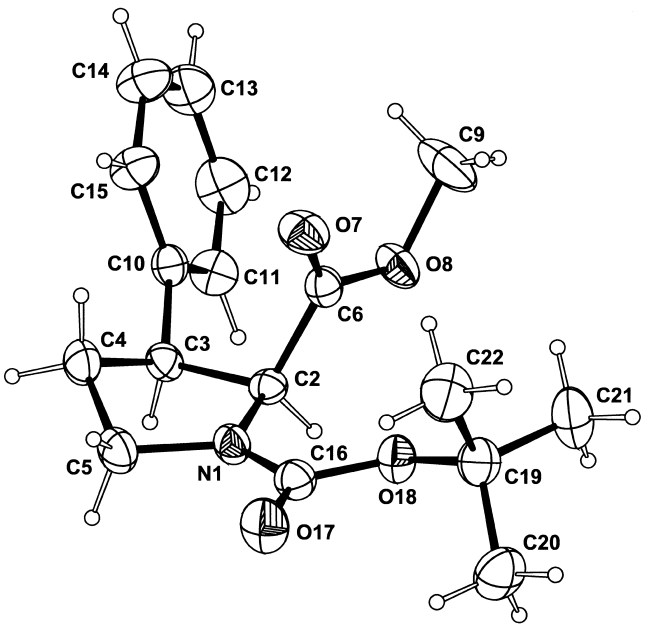
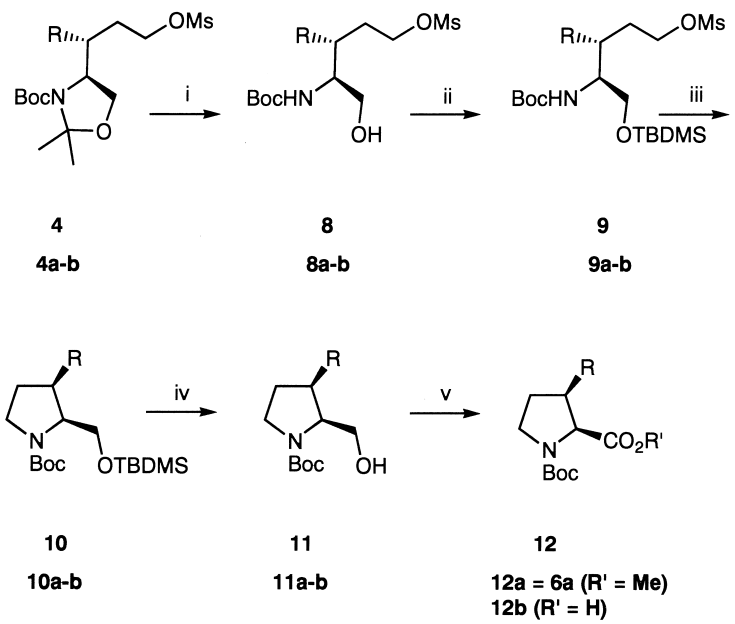


Figure 1. ORTEP drawing of **6c**. Displacement ellipsoids are shown at the 30% probability level.



Scheme 4. *Reagents and conditions*: (i) $CeCl_3{\cdot}7H_2O$, $(CO_2H)_2$, CH_3CN, rt, 2 h, 90% **8b**. (ii) TBDMSCl, imidazole, DMF, rt, 83% **9b**. (iii) NaH, DMF, 0°C, 83% for three steps **10a**, 90% **10b**. (iv) Bu_4NF, THF, rt, 15 h, 81% **11a**, 81% **11b**. (v) For **6a** (a) Jones oxidation, 0°C, 4 h; (b) CH_2N_2, Et_2O, 0°C, 58%; for **12b** Jones oxidation, 0°C, 1.5 h, 56%.

position deviating out of the mean plane by 0.571(3) Å. The dihedral angle between the pyrrolidine ring and the phenyl group is 61.5°.

Initially, we transformed **4** to α-amino alcohol **8**[11] that was then cyclized to the pyrrolidines **10**. Further deprotection-oxidation protocol also provided desired *cis*-3-substituted prolines **12** as illustrated in Scheme 4. Although the preparation of *cis*-3-vinyl proline **12b** by this route could be carried out with ease, the conversion of **4a** to **10a** required much precaution. The intermediates **8a** and **9a** were found to be so unstable that they had to be used immediately for the subsequent transformations. Since more convenient route was established as shown in Scheme 1, we did not pursue this route for the synthesis of *N*-Boc-*cis*-3-phenyl proline.

Diastereomeric excess (de) of each final product was assessed by ^{1}H NMR spectroscopy and was determined to be of 95–98%. This is further confirmed by the HPLC analysis (vide infra in Section 4). In compound **7d**, the presence of its *trans*-diastereomer was detected in ^{1}H NMR spectra in 3–5% by integration. These figures were further refined by HPLC analysis. In this case it is assumed that epimerization has taken place at C-2 or C-3 position. Enantiomeric excess (ee) of the final products, **7a** and **7b**, is assumed to be that of the starting material, D-serine, that is purchased as optically pure amino acid. It should be noted that only one diastereomer was obtained during the organocuprate addition to α,β-unsaturated ester **1**.

3. Conclusion

Starting from easily available α,β-unsaturated ester **1**, a straight-forward method has been developed for the synthesis of highly enantio- and diastereomerically pure *cis*-3-substituted prolines in six step sequences in 34–53% overall yields. Transformation of **6b** to other *cis*-3-substituted prolines continues in this laboratory.

4. Experimental

4.1. General

All reactions requiring anhydrous conditions or in an inert atmosphere were conducted under an atmosphere of Argon. Tetrahydrofuran, benzene were distilled from sodium-benzophenone and methylene chloride from P_2O_5 immediately prior to use. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum BX spectrometer. ^{1}H and ^{13}C NMR spectra were measured on Brucker AM-300 and AC-250 (300 and 250 MHz, respectively) spectrometers with tetramethylsilane as internal standard (δ, ppm). Flash chromatography was performed using Kieselgel 60 (230–400 mesh, E. Merck) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. Optical rotations were determined on a JASCO P-1010 polarimeter at room temperature. HPLC analyses were carried out on an Alliance (Waters 2690) onto an analytical column (Hypercarb Thermohypersil, 4.6×100 mm, 5 μ) with solvent mixtures of water (+TFA 0.1%) and acetonitrile (+TFA 0.1%). Eluted compounds were detected by absorbance at 213 nm (Waters 996 Photodiode Array Detector) and by mass (Waters Micromass ZQ). Mass spectra were run on a Kratos MS-80 spectrometer (CI), a Navigator of Thermo Quest spectrometer (ESI), an AEI MS-9 spectrometer (IE) and a MALDI TOF spectrometer (high resolution) respectively. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Elemental analyses were carried out by the microanalytical laboratory at the ICSN.

4.1.1. (2′*E*,4*S*)-4-(2′-Ethoxycarbonyl-vinyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (1). To a solution of Garner's aldehyde (11.1 g, 48.4 mmol) in benzene (300 mL) was added ethyl (triphenylphosphoranylidene) acetate (18.9 g, 53.2 mmol). After stirring at rt for 36 h, the reaction mixture was filtered through Celite, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (heptane/EtOAc=4:1) to give **1** (12.4 g, 85%) as two rotamers: mp 48–49°C; $[\alpha]_D$=+60 (*c* 1.9, $CHCl_3$), {lit. $[\alpha]_D$=+54.3 (*c* 3.66, $CHCl_3$) (Ref. 10a)); IR ($CHCl_3$) ν 3026, 2984, 2938, 2881, 1712, 1693, 1477, 1456, 1391, 1368, 1303 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, *J*=7.7, 15.2 Hz, 1H), 5.91 (br t, *J*=15.2 Hz, 1H), 4.56–4.37 (m, 1H), 4.25–4.15 (m, 2H), 4.08 (dd, *J*=6.4, 9.0 Hz, 1H), 3.79 (dd, *J*=2.6, 9.0 Hz, 1H), 1.64 (s, 1.5H), 1.60 (s, 1.5H), 1.53 (s, 1.5H), 1.49 (s, 1.5H), 1.42 (s, 9H), 1.28 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.1, 151.5, 145.8, 122.3, 94.2, 80.4, 67.3, 60.4, 58.0, 28.3, 27.3, 26.4, 24.6, 23.6, 14.2; MS (CI) *m/z* 300 $[M+H]^+$. Anal. calcd for $C_{15}H_{25}NO_5$: C 60.18; H 8.42; N 4.68. Found: C 60.05; H 8.64; N 4.88.

4.1.2. (1′*R*,4*S*)-4-(2′-Ethoxycarbonyl-1′-methyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (2a). To a stirred suspension of CuI (20.5 g, 108 mmol) in THF (250 mL) at 0°C was added methyl lithium in Et_2O (1.6 M, 134 mL, 215 mmol). This mixture was cooled to −78°C for 15 min and TMSCl (13.7 mL, 108 mmol) and **1** (5.36 g, 18 mmol) in THF (100 mL) were added dropwise respectively. The temperature was allowed to reach rt gradually. The reaction was quenched with a NH_4OH/NH_4Cl (1/9) pH 8 buffer solution and the mixture was extracted with Et_2O. The ether extracts were washed with brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (10/1) afforded compound **2a** (5.32 g, 94%) as two rotamers: $[\alpha]_D$=+18 (*c* 2.0, $CHCl_3$), (lit. $[\alpha]_D$=+19.8 (*c* 2.18, $CHCl_3$) (Ref. 10a)); IR ($CHCl_3$) ν 3027, 2983, 2937, 2881, 1727, 1688, 1477, 1456, 1392, 1367, 1257, 1174 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.14 (q, *J*=7.2 Hz, 2H), 3.96–3.77 (m, 3H), 2.56–2.46 (m, 2H), 2.20–1.96 (m, 1H), 1.63–1.37 (m, 15H), 1.26 (t, *J*=7.2 Hz, 3H), 0.95 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.2, 152.5, 94.3, 94.0, 80.0, 64.2, 61.2, 60.3, 37.1, 36.5, 33.0, 32.6, 28.4, 26.9, 26.3, 24.0, 22.7, 16.7, 16.5, 14.3; MS (ESI) *m/z* 316 $[M+H]^+$, 338 $[M+Na]^+$. Anal. calcd for $C_{16}H_{29}NO_5$: C 60.93; H 9.27; N 4.44. Found: C 60.84; H 9.51; N 4.31.

4.1.3. (1′*S*,4*S*)-4-(1′-Ethoxycarbonylmethyl-allyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (2b). To a stirred suspension of CuI (19.1 g, 100 mmol) in THF (200 mL) at −5°C was added vinyl magnesium bromide in THF (1 M, 200 mL, 200 mmol). After being stirred at −5°C for 15 min, the mixture was cooled to −78°C for 15 min and TMSCl (12.8 mL, 100 mmol) and **1** (5.0 g, 16.7 mmol) in THF (60 mL) were added dropwise. The temperature was allowed to reach rt gradually. The reaction was quenched with a NH_4OH/NH_4Cl (1/9) pH 8 buffer solution and extracted with Et_2O. The ether extracts were washed with brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (15/1) afforded compound **2b** (4.96 g, 91%) as two rotamers: $[\alpha]_D$=+10 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) ν 3025, 3016, 2982, 2938, 1727, 1690, 1477, 1455, 1392, 1367, 1258 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77–5.56 (m, 1H), 5.15–5.01 (m, 2H), 4.07 (q, *J*=7.2 Hz, 2H), 4.03–3.96 (m, 0.5H), 3.93–3.82 (m, 1.5H), 3.82–3.74 (m, 1H), 3.17–3.03 (m, 1H), 2.48 (dd, *J*=3.8, 15.3 Hz, 1H), 2.35–2.20 (m, 1H), 1.58 (s, 1.5H), 1.54 (s, 1.5H), 1.45 (s, 9H), 1.42 (s, 6H), 1.19 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 152.9, 152.5, 137.6, 117.3, 117.0, 94.5, 94.0, 80.2, 64.7, 64.4, 60.4, 59.8, 43.0, 42.8, 35.2, 34.2, 28.4, 27.0, 26.3, 24.2, 22.7, 14.3; MS (ESI) *m/z* 328 $[M+H]^+$, 350 $[M+Na]^+$, 366 $[M+K]^+$, 677 $[2M+Na]^+$, 693 $[2M+K]^+$. Anal. calcd for $C_{17}H_{29}NO_5$: C 62.36; H 8.93; N 4.28. Found: C 62.38; H 9.09; N 4.21.

4.1.4. (1′*S*,4*S*)-4-(2′-Ethoxycarbonyl-1′-phenyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (2c). To a solution of **1** (1.01 g, 3.39 mmol) in THF (10 mL) at −25°C was added CuCN (30 mg, 0.34 mmol). This mixture was stirred for 10 min before TMSCl (0.04 mL, 0.34 mmol) was added. After stirring for 25 min, phenyl magnesium bromide in Et_2O (3 M, 1.24 mL, 3.72 mmol) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 3 h. The reaction was quenched with NH_4Cl and extracted with Et_2O. The ether extracts were washed with brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (25/1) afforded compound **2c** (823 mg, 64%) as two rotamers: $[\alpha]_D$=-31 (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) ν 3023, 3019, 3016, 2982, 2937, 1727, 1691, 1392, 1376, 1367, 1257, 1169, 1107, 1089, 1061, 1031, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.15 (m, 5H), 4.21–4.12 (m, 0.5H), 4.00 (q, *J*=7.3 Hz, 2H), 4.05–3.85 (m, 2.5H), 3.81–3.66 (m, 1H), 2.85–2.81 (m, 2H), 1.67 (s, 1.5H), 1.57 (s, 9H), 1.53 (s, 1.5H), 1.49 (s, 1.5H), 1.44 (s, 1.5H), 1.14–1.03 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 152.8, 152.2, 140.4, 128.7, 128.2, 127.9, 126.9, 94.4, 94.3, 80.4, 64.1, 63.7, 61.9, 61.7, 60.3, 43.0, 33.8, 32.5, 28.5, 26.7, 26.2, 23.9, 22.5, 14.1; MS (ESI) *m/z* 400 $[M+Na]^+$, 416 $[M+K]^+$, 777 $[2M+Na]^+$. Anal. calcd for $C_{21}H_{31}NO_5$: C 66.82; H 8.28; N 3.71. Found: C 66.56; H 8.47; N 3.53.

4.1.5. (1′*R*,4*S*)-4-(3′-Hydroxy-1′-methyl-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (3a). To a solution of **2a** (5.32 g, 16.9 mmol) in THF (170 mL) at 0°C was added $LiAlH_4$ (730 mg, 18.6 mmol). After stirring at rt for 1.5 h, the mixture was cooled to 0°C and water (0.73 mL), 15% NaOH aqueous solution (0.73 mL) and water (2.19 mL) were added sequentially. The mixture was stirred for 30 min and filtered through Celite/Na_2SO_4. The filtrate was evaporated in vacuo and purified by chromatography on silica gel (heptane/EtOAc=2/1) to give 4.54 g (98%) of **3a** as two rotamers: $[\alpha]_D$=+52 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) ν 3467, 3012, 2979, 2881, 1686, 1477, 1456, 1393, 1378, 1367, 1254, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94–3.58 (m, 5H), 2.17–2.10 (m, 2H), 1.82–1.71 (m, 1H), 1.59 (br s, 3H), 1.44 (s, 12H), 1.40–1.27 (br s, 1H), 0.91 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.0, 152.8, 93.9, 93.7, 80.0, 79.6, 64.7, 61.7, 60.7, 34.5, 32.3, 28.3, 26.7, 26.3, 24.3, 22.8, 16.3; MS (CI) *m/z* 274 $[M+H]^+$. Anal. calcd for $C_{14}H_{27}NO_4$: C 61.51; H 9.96; N 5.12. Found: C 61.85; H 10.18; N 5.08.

4.1.6. (1′*S*,4*S*)-4-[1′-(2″-Hydroxy-ethyl)-allyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (3b). To a solution of **2b** (1.34 g, 4.1 mmol) in THF (20 mL) at 0°C was added $LiAlH_4$ (192 mg, 4.9 mmol). After stirring at rt for 2 h, the mixture was cooled to 0°C and water (0.25 mL), 15% NaOH aqueous solution (0.25 mL) and water (0.75 mL) were added sequentially. The mixture was stirred for 30 min and filtered through Celite/Na_2SO_4. The filtrate was evaporated in vacuo and purified by column chromatography on silica gel (heptane/EtOAc=2/1) to give **3b** (1.14 g, 98%) as two rotamers: $[\alpha]_D$=+23 (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) ν 3629, 3482, 3024, 3009, 2981, 2938, 2882, 1685, 1477, 1455, 1392, 1367, 1254, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77–5.57 (m, 1H), 5.14–5.02 (m, 2H), 4.01–3.75 (m, 3H), 3.73–3.64 (m, 1H), 3.61–3.52 (m, 1H), 2.64–2.52 (m, 1H), 2.18 (br s, 1H), 1.81–1.68 (m, 1H), 1.61–1.44 (m, 1H), 1.61 (s, 1.5H), 1.57 (s, 1.5H), 1.50 (s, 1.5H), 1.47 (s, 9H), 1.44 (s, 1.5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.8, 152.2, 139.0, 117.2, 116.7, 94.0, 93.6, 80.0, 79.7, 65.3, 60.6, 44.5, 44.3, 33.0, 32.6, 28.3, 26.9, 26.3, 24.4, 22.8; MS (EI) *m/z* 285 $[M]^+$, 230, 212. Anal. calcd for $C_{15}H_{27}NO_4$: C 63.13; H 9.54; N 4.91. Found: C 63.32; H 9.88; N 4.83.

4.1.7. (1′*S*,4*S*)-4-(3′-Hydroxy-1′-phenyl-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (3c). To a solution of **2c** (630 mg, 1.67 mmol) in THF (10 mL) at 0°C was added $LiAlH_4$ (85 mg, 2.17 mmol). After stirring at rt for 30 min, the temperature was cooled to 0°C and water (0.09 mL), 15% NaOH aqueous solution (0.09 mL) and water (0.27 mL) were added sequentially. The mixture was stirred for 30 min and filtered through Celite/Na_2SO_4. The filtrate was evaporated in vacuo and purified by column chromatography on silica gel (heptane/EtOAc=4/1) to give 548 mg (97%) of **3c** as two rotamers: $[\alpha]_D$=−15 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν 3627, 3480, 3025, 3015, 2982, 2938, 2885, 1688, 1494, 1477, 1454, 1392, 1368, 1248, 1171 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.18 (m, 5H), 4.12–4.05 (m, 1H), 3.99 (d, *J*=8.8 Hz, 1H), 3.82–3.73 (m, 1H), 3.68–3.58 (m, 1H), 3.53–3.39 (m, 2H), 2.34 (br s, 1H), 2.14–2.03 (m, 2H), 1.73–1.42 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.8, 152.7, 140.8, 128.7, 126.8, 94.7, 94.2, 80.2, 64.5, 64.3, 62.3, 61.3, 43.6, 31.3, 30.1, 28.5, 26.8, 26.3, 24.3, 22.7; MS (ESI) *m/z* 336 $[M+H]^+$, 358 $[M+Na]^+$, 374 $[M+K]^+$. HRMS Calcd for $C_{19}H_{29}NO_4Na$ (M+Na): 358.19943. Found: 358.19954.

4.1.8. (1′*R*,4*S*)-4-(3′-Methanesulfonyloxy-1′-methyl-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (4a). To a solution of **3a** (107 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at 0°C were added Et_3N (0.07 mL, 0.51 mmol) and MsCl (0.04 mL, 0.47 mmol). After stirring at rt for 1 h, the reaction was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with 1N HCl, water, saturated aqueous $NaHCO_3$ solution, brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (4/1) afforded compound **4a** (120 mg, 87%) as two rotamers: $[\alpha]_D$=+39 (*c* 4.5, $CHCl_3$); IR ($CHCl_3$) ν 3022, 3016, 2981, 2936, 2881, 1685, 1476, 1456, 1392, 1366, 1255, 1211, 1174 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.39–4.18 (m, 2H), 3.97–3.74 (m, 3H), 3.01 (s, 3H), 2.25–1.92 (m, 2H), 1.64–1.45 (m, 16H), 0.94 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.0, 152.4, 94.0, 93.8, 80.1, 79.8, 68.6, 68.3, 64.2, 61.3, 37.3, 31.7, 30.8, 30.5, 28.5, 26.7, 26.1, 24.0, 22.5, 15.9; MS (EI) *m/z* 351 $[M]^+$, 278. Anal. calcd for $C_{15}H_{29}NO_6S$: C 51.26; H 8.32; N 3.99; S 9.12. Found: C 51.17; H 8.41; N 4.01; S 8.89.

4.1.9. (1′*S*,4*S*)-4-[1′-(2″-Methanesulfonyloxy-ethyl)allyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (4b). To a solution of **3b** (1.13 g, 3.97 mmol) in CH_2Cl_2 (23 mL) at 0°C were added Et_3N (0.72 mL, 5.15 mmol) and MsCl (0.37 mL, 4.76 mmol). After stirring at rt for 1 h, the mixture was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with 1N HCl, water, saturated aqueous $NaHCO_3$ solution, brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (3/1) afforded compound **4b** (1.35 g, 94%) as two rotamers: $[\alpha]_D$=+33 (*c* 3.14, $CHCl_3$); IR ($CHCl_3$) ν 3029, 3010, 2982, 2938, 2882, 1688, 1476, 1455, 1392, 1366, 1252, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72–5.54 (m, 1H), 5.22–5.09 (m, 2H), 4.29 (dt, *J*=6.2, 9.3 Hz, 1H), 4.14 (ddd, *J*=4.5, 7.1, 9.8 Hz, 1H), 4.02–3.78 (m, 3H), 2.99 (s, 3H), 2.73–2.60 (m, 1H), 2.06–1.92 (m, 1H), 1.75–1.54 (m, 1H), 1.63 (s, 1.5H), 1.57 (s, 1.5H), 1.48 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.9, 152.2, 137.5, 118.8, 118.2, 94.3, 93.8, 80.3, 80.1, 68.4, 68.2, 64.9, 60.4, 43.6, 43.5, 37.4, 29.2, 28.4, 27.0, 26.3, 24.3, 22.7; MS (EI) *m/z* 363 $[M]^+$, 308, 290, 264. Anal. calcd for $C_{16}H_{29}NO_6S$: C 52.87; H 8.04; N 3.85; S 8.82. Found: C 52.72; H 8.18; N 3.82; S 8.71.

4.1.10. (1′*S*,4*S*)-4-(3′-Methanesulfonyloxy-1′-phenylpropyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (4c). To a solution of **3c** (91 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) at 0°C were added Et_3N (0.05 mL, 0.35 mmol) and MsCl (0.02 mL, 0.33 mmol). After stirring at rt for 1 h, the reaction was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with 1N HCl, water, saturated aqueous $NaHCO_3$ solution, brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (6/1) afforded compound **4c** (108 mg, 96%) as two rotamers: $[\alpha]_D$=−5 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν 3029, 3024, 3018, 2983, 1691, 1454, 1392, 1376, 1367, 1264, 1247, 1173 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.42–7.14 (m, 5H), 4.29–4.16 (m, 1H), 4.15–3.93 (m, 3H), 3.84–3.73 (m, 1H), 3.53–3.42 (m, 1H), 2.82 (s, 3H), 2.36–2.20 (m, 2H), 1.71–1.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 152.3, 139.4, 129.0, 128.7, 128.6, 128.2, 127.1, 94.6, 94.1, 80.3, 68.7, 68.4, 64.0, 63.7, 62.1, 61.9, 43.1, 37.1, 28.4, 27.6, 26.7, 26.5, 26.1, 24.0, 22.4; MS (ESI) *m/z* 436 $[M+Na]^+$, 452 $[M+K]^+$. Anal. calcd for $C_{20}H_{31}NO_6S$: C 58.09; H 7.56; N 3.39; S 7.75. Found: C 58.27; H 7.51; N 3.31; S 7.49.

4.1.11. (2*S*,3*R*)-2-*tert*-Butoxycarbonylamino-5-methanesulfonyloxy-3-methylpentanoic acid methyl ester (5a). Jones reagent (2.67 M, 1.48 mL, 3.95 mmol) was added to a solution of **4a** (336 mg, 0.96 mmol) in acetone (10 mL) at 0°C. After stirring at 0°C for 4 h, the reaction was quenched by addition of propan-2-ol. The mixture was stirred for 30 min and neutralized with saturated aqueous $NaHCO_3$ to pH 4–5 and extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was

dissolved in Et_2O and CH_2N_2 in Et_2O was added to the solution. The mixture was evaporated in vacuo and purified by column chromatography on silica gel (heptane/EtOAc=6/1) to afford compound **5a** (190 mg, 58%): $[\alpha]_D$=+20 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) ν 3437, 3022, 2980, 1739, 1711, 1502, 1457, 1438, 1357, 1226, 1173 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.14 (br d, *J*=9.3 Hz, 1H), 4.48–4.27 (m, 3H), 3.76 (s, 3H), 3.07 (s, 3H), 2.36–2.24 (m, 1H), 1.93–1.79 (m, 1H), 1.71–1.57 (m, 1H), 1.44 (s, 9H), 0.87 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.4, 155.9, 80.1, 68.0, 56.1, 52.5, 37.3, 32.6, 32.4, 28.3, 14.4; MS (ESI) *m/z* 340 $[M+H]^+$, 362 $[M+Na]^+$, 378 $[M+K]^+$. HRMS Calcd for $C_{13}H_{25}NO_7SNa$ (M+Na) 362.12494. Found: 362.12404.

4.1.12. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-3-(2′-methanesulfonyloxyethyl)pent-4-enoic acid methyl ester (5b). Jones reagent (2.67 M, 1.82 mL, 4.86 mmol) was added to a solution of **4b** (588 mg, 1.62 mmol) in acetone (16 mL) at 0°C. After stirring at 0°C for 4 h, the reaction was quenched by addition of propan-2-ol. The mixture was stirred for 30 min and neutralized with saturated aqueous $NaHCO_3$ to pH 4–5 and extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was dissolved in Et_2O and CH_2N_2 in Et_2O was added to the solution. The mixture was evaporated in vacuo and purified by flash column chromatography on silica gel (heptane/EtOAc=6/1) to afford compound **5b** (393 mg, 70%): $[\alpha]_D$=+48 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν 3434, 3021, 2983, 2956, 1743, 1712, 1501, 1364, 1226, 1213, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (ddd, *J*=9.1, 10.3, 17.0 Hz, 1H), 5.23–5.12 (m, 2H), 5.06 (br d, *J*=8.8 Hz, 1H), 4.46 (dd, *J*=3.7, 8.8 Hz, 1H), 4.37–4.26 (m, 1H), 4.26–4.17 (m, 1H), 3.75 (s, 3H), 3.02 (s, 3H), 2.88–2.76 (m, 1H), 2.06–1.94 (m, 1H), 1.86–1.73 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.6, 155.7, 134.7, 119.6, 80.1, 67.7, 56.4, 52.3, 42.8, 37.2, 30.1, 28.2; MS (EI) *m/z* 352 $[M+H]^+$, 351 $[M]^+$, 278. HRMS Calcd for $C_{14}H_{25}NO_7SNa$ (M+Na): 374.12494. Found: 374.12581.

4.1.13. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-5-methanesulfonyloxy-3-phenyl-pentanoic acid methyl ester (5c). Jones reagent (2.67 M, 1.33 mL, 3.55 mmol) was added to a solution of **4c** (490 mg, 1.18 mmol) in acetone (12 mL) at 0°C. After stirring at 0°C for 4 h, the reaction was quenched by addition of propan-2-ol. The mixture was stirred for 30 min and neutralized with saturated aqueous $NaHCO_3$ to pH 4–5 and extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was dissolved in Et_2O and CH_2N_2 in Et_2O was added to the solution. The mixture was evaporated in vacuo and purified by flash column chromatography on silica gel (heptane/EtOAc=4/1) to afford compound **5c** (360 mg, 76%): $[\alpha]_D$=+49 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) ν 3432, 3029, 3020, 3016, 2982, 2954, 1743, 1711, 1496, 1455, 1437, 1393, 1367, 1174, 990, 971, 933, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (m, 3H), 7.15–7.10 (m, 2H), 4.92 (br d, *J*=9.2 Hz, 1H), 4.67 (dd, *J*=4.1, 9.2 Hz, 1H), 4.31–4.22 (m, 1H), 4.11–4.02 (m, 1H), 3.68 (s, 3H), 3.49–3.38 (m, 1H), 2.89 (s, 3H), 2.35–2.12 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 155.6, 137.3, 129.7, 128.1, 127.8, 80.0, 67.8, 57.0, 52.1, 43.9, 36.9, 30.9, 28.1; MS (EI) *m/z* 402 $[M+H]^+$, 346. Anal. calcd for $C_{18}H_{27}NO_7S$: C 53.85; H 6.78; N 3.49; S 7.99. Found: C 53.81; H 7.09; N 3.81; S 7.51.

4.1.14. (2*S*,3*R*)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (6a) from 5a. To a suspension of NaH (55–65% in mineral oil, 45 mg, 1.11 mmol, washed with pentane) in DMF (2 mL) at −25°C was added **5a** (190 mg, 0.56 mmol) in DMF (2 mL). After being stirred at −25°C for 1 h, the reaction mixture was quenched by addition of water and extracted with ether. The combined ether layers were washed with water and brine, dried, and evaporated. Column chromatography on silica gel (heptane/EtOAc=8/1) afforded compound **6a** (107 mg, 78%) as two rotamers: mp 46–47°C; $[\alpha]_D$=+12 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν 3025, 3022, 3020, 3019, 3018, 3016, 3014, 2975, 1741, 1687, 1404, 1367, 1170, 1150, 1119 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.27 (d, *J*=8.8 Hz, 0.4H), 4.20 (d, *J*=8.8 Hz, 0.6H), 3.75–3.58 (m, 4H), 3.38–3.23 (m, 1H), 2.60–2.37 (m, 1H), 2.00–1.87 (m, 1H), 1.84–1.60 (m, 1H), 1.45 (s, 3.6H), 1.41 (s, 5.4H), 0.99 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.4, 154.4, 153.8, 79.8, 63.4, 62.9, 51.6, 51.5, 46.2, 45.8, 37.1, 36.3, 32.0, 31.2, 28.4, 28.3, 14.8; MS (EI) *m/z* 244 $[M+H]^+$, 243 $[M]^+$, 184, 142. Anal. calcd for $C_{12}H_{21}NO_4$: C 59.24; H 8.70; N 5.76. Found: C 59.33; H 8.76; N 5.52.

4.1.15. (2*S*,3*S*)-3-Vinyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (6b). To a suspension of NaH (55–65% in mineral oil, 172 mg, 4.29 mmol, washed with pentane) in DMF (10 mL) at −25°C was added **5b** (753 mg, 2.14 mmol) in DMF (10 mL). After being stirred at −25°C for 1 h, the reaction mixture was quenched by addition of water and extracted with ether. The combined ether layers were washed with water and brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc=15/1) afforded compound **6b** (563 mg, 92%) as two rotamers: $[\alpha]_D$=+34 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν 3024, 3022, 3019, 2980, 2953, 1743, 1685, 1401, 1367, 1169, 1129 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74–5.59 (m, 1H), 5.20–5.10 (m, 2H), 4.37 (d, *J*=8.1 Hz, 0.4H), 4.29 (d, *J*=8.8 Hz, 0.6H), 3.77–3.64 (m, 4H), 3.43–3.30 (m, 1H), 3.13–2.98 (m, 1H), 2.14–1.91 (m, 2H), 1.46 (s, 3,6H), 1.40 (s, 5.4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 153.7, 134.6, 117.5, 80.1, 63.0, 62.5, 51.5, 46.3, 46.0, 45.7, 45.4, 29.3, 28.5, 28.3; MS (EI) *m/z* 256 $[M+H]^+$, 255$[M]^+$, 196, 154. Anal. calcd for $C_{13}H_{21}NO_4$: C 61.16; H 8.29; N 5.49. Found: C 61.11; H 8.33; N 5.43.

4.1.16. (2*S*,3*S*)-3-Phenyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (6c). To a suspension of NaH (55–65% in mineral oil, 54 mg, 1.36 mmol, washed with pentane) in DMF (2 mL) at −25°C was added **5c** (273 mg, 0.68 mmol) in DMF (2 mL). After being stirred at −25°C for 50 min, the reaction mixture was quenched by addition of water and extracted with ether. The combined ether layers were washed with water and brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc=8/1) afforded compound **6c** (158 mg, 76%) as two rotamers: mp 90.4°C; $[\alpha]_D$=+91 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν 3026, 3021, 3017, 3011, 2981, 1741, 1688, 1477, 1455, 1436, 1402, 1367, 1179, 1133, 997, 908 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.18 (m,

5H), 4.55 (d, J=8.8 Hz, 0.4H), 4.46 (d, J=8.5 Hz, 0.6H), 3.96–3.80 (m, 1H), 3.75–3.56 (m, 1H), 3.53–3.39 (m, 1H), 3.27 (s, 1.8H), 3.24 (s, 1.2H), 2.69–2.46 (m, 1H), 2.16–2.04 (m, 1H), 1.48 (s, 3.5H), 1.40 (s, 5.5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.8, 153.8, 136.9, 136.8, 128.5, 128.4, 128.0, 127.9, 127.6, 127.5, 80.2, 80.1, 64.4, 64.0, 51.4, 51.3, 48.1, 47.2, 46.3, 45.9, 28.5, 28.4, 27.6; MS (ESI) m/z 306 $[M+H]^+$, 328 $[M+Na]^+$, 344 $[M+K]^+$. Anal. calcd for $C_{17}H_{23}NO_4$: C 66.86; H 7.59; N 4.59. Found: C 66.68; H 7.57; N 4.39.

4.1.17. (2*S*,3*R*)-3-Methyl-pyrrolidine-2-carboxylic acid (7a). A solution of **6a** (19 mg, 78 μmol) in HCl (6N, 1.3 mL) and acetic acid (0.3 mL) was refluxed for 4 h. The volatile was evaporated. The residue was dissolved in EtOH. The solution was treated dropwise with propylene oxide under heating and evaporated to dryness. The residue was dissolved in water and passed through a column of Dowex 50WX8-200 ion-exchange resin (H^+ form). The column was washed thoroughly with water and the amino acid was eluted with 2 M NH_4OH to give **7a** (10 mg, 98%): mp 226–227°C, (lit. mp 225°C (Ref. 6k)); $[\alpha]_D$=−28 (c 0.4, 0.1 M HCl), {lit. $[\alpha]_D$=−30.5 (c 0.19, 0.1 M HCl) (Ref. 6k)); 99% de (HPLC, water, flow rate 0.8 mL/min, major diastereomer 3.0 min, minor diastereomer 4.0 min); IR (hydrochloride, nujol) ν 3379, 1723 cm^{-1}; ^{1}H NMR (250 MHz, D_2O) δ 4.11 (d, J=7.7 Hz, 1H), 3.55 (dt, J=7.4, 11.9 Hz, 1H), 3.36 (ddd, J=6.1, 8.4, 11.8 Hz, 1H), 2.79–2.71 (m, 1H), 2.29–2.14 (m, 1H), 1.86–1.75 (m, 1H), 1.03 (d, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 173.3, 66.0, 44.9, 35.2, 32.2, 14.8; MS (ESI) m/z 130 $[M+H]^+$, 152 $[M+Na]^+$, 168 $[M+K]^+$. HRMS Calcd for $C_6H_{11}NO_2Na$ (M+Na) 152.06875. Found: 152.06878.

4.1.18. (2*S*,3*S*)- 3-Vinyl-pyrrolidine-2-carboxylic acid (7b). A solution of **6b** (48 mg, 0.19 μmol) in HCl (6N, 1.3 mL) and acetic acid (0.3 mL) was refluxed for 4 h. The volatile was evaporated. The residue was dissolved in EtOH. The solution was treated dropwise with propylene oxide under heating and evaporated to dryness. The residue was dissolved in water and passed through a column of Dowex 50WX8-200 ion-exchange resin (H^+ form). The column was washed thoroughly with water and the amino acid was eluted with 2 M NH_4OH to give **7b** (24 mg, 90%): mp 201–212°C (decomp.); $[\alpha]_D$=−18 (c 0.45, H_2O); 95% de (HPLC, water, flow rate 0.8 mL/min, major diastereomer 5.9 min, minor diastereomer 8.4 min); IR (nujol) ν 3390, 1611 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 5.84–5.70 (m, 1H), 5.34–5.22 (m, 2H), 4.42 (d, J=8.1 Hz, 1H), 3.70–3.33 (m, 3H), 2.38–2.25 (m, 1H), 2.14–2.01 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 170.4, 133.1, 118.7, 63.8, 44.7, 43.9, 29.0; MS (ESI) m/z 142 $[M+H]^+$, 164 $[M+Na]^+$, 180 $[M+K]^+$. HRMS Calcd for $C_7H_{11}NO_2Na$ (M+Na) 164.06875. Found: 164.06887.

4.1.19. (2*S*,3*S*)-3-Phenyl-pyrrolidine-2-carboxylic acid (7c). A Solution of **6c** (18 mg, 59 μmol) in HCl (6N, 1.3 mL) and acetic acid (0.3 mL) was refluxed for 4 h. The volatile was evaporated. The residue was dissolved in EtOH. The solution was treated dropwise with propylene oxide under heating and evaporated to dryness. The residue was dissolved in water and passed through a column of Dowex 50WX8-200 ion-exchange resin (H^+ form). The column was washed thoroughly with water and the amino acid was eluted with 2 M NH_4OH to give **7c** (10 mg, 98%): mp 216–224°C (decomp.), (lit. mp 214–220°C (Ref. 6f)); $[\alpha]_D$=+82 (c 0.5, 6 M HCl), (lit. $[\alpha]_D$=+63.7 (c 4.5, 6 M HCl) (Ref. 6f)); 96% de (HPLC, water/acetonitrile=92:8, flow rate 0.6 mL/min, major diastereomer 22.6 min, minor diastereomer 21.3 min); IR (hydrochloride, nujol) ν 3413, 1723 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.43–7.25 (m, 5H), 4.31 (d, J=9.2 Hz, 1H), 3.88 (q, J=8.1 Hz;1H), 3.74 (ddd, J=4.4, 7.6, 12.0 Hz, 1H), 3.48–3.27 (m, 1H), 2.53–2.39 (m, 1H), 2;37–2.23 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ 170.9, 137.1, 129.5, 128.8, 128.7, 64.5, 46.7, 46.2, 30.2; MS (ESI) m/z 192 $[M+H]^+$, 214 $[M+Na]^+$, 230 $[M+K]^+$. HRMS Calcd for $C_{11}H_{13}NO_2Na$ (M+Na) 214.08440. Found: 214.08365.

4.1.20. (2*S*,3*R*)-Pyrrolidine-1,2,3-tricarboxylic acid 1-*tert*-butyl ester 2-methyl ester (6d). Ozone was introduced to a solution of **6b** (50 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) at −78°C. Ozonization was continued until the reaction was complete (until the mixture turned blue). PPh_3 (103 mg, 0.39 mmol) was added, the mixture was stirred overnight at rt and evaporated in vacuo. Jones reagent (2.67 M, 0.22 mL, 0.59 mmol) was added to a solution of the above obtained residue in acetone (2 mL) at 0°C. After stirring at 0°C for 4 h, the reaction was quenched by addition of propan-2-ol. The mixture was stirred for 30 min and neutralized with saturated aqueous $NaHCO_3$ to pH 4–5 and extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was purified by preparative TLC on silica gel (heptane/EtOAc=2/1) to afford compound **6d** (27 mg, 50%) as two rotamers: $[\alpha]_D$=+4 (c 1.1, $CHCl_3$); IR ($CHCl_3$) ν 3505, 3028, 2982, 2955, 1748, 1694, 1477, 1454, 1436, 1397, 1369 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 4.63 (d, J=8.1 Hz, 0.4H), 4.53 (d, J=8.1 Hz, 0.6H), 3.79–3.65 (m, 4H), 3.50–3.25 (m, 2H), 2.48–2.26 (m, 1H), 2.24–2.07 (m, 1H), 1.46 (s, 3.6H), 1.42 (s, 5.4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 171.1, 154.2, 153.6, 80.7, 80.6, 60.7, 60.3, 52.3, 52.1, 47.2, 46.3, 45.7, 45.4, 28.4, 28.2, 27.2, 26.4; MS (ESI) m/z 274 $[M+H]^+$, 296 $[M+Na]^+$, 312 $[M+K]^+$. HRMS Calcd for $C_{12}H_{19}NO_6Na$ (M+Na): 296.11101. Found: 296.11103.

4.1.21. (2*S*,3*R*)-Pyrrolidine-2,3-dicarboxylic acid (7d). A solution of **6d** (21 mg, 77 μmol) in HCl (6N, 1.3 mL) and acetic acid (0.3 mL) was refluxed for 4 h. The volatile was evaporated. The residue was dissolved in EtOH. The solution was treated dropwise with propylene oxide under heating and evaporated to dryness. The residue was dissolved in water and passed through a column of Dowex 50WX8-200 ion-exchange resin (H^+ form). The column was washed thoroughly with water and the amino acid was eluted with 2 M NH_4OH to give **7d** (12 mg, 98%): mp>300°C; $[\alpha]_D$=−39 (c 0.5, H_2O), (lit. $[\alpha]_D$=−40.8 (c 0.1, H_2O) (Ref. 6n)); 97% de (HPLC, water, flow rate 0.6 mL/min, major diastereomer 3.8 min, minor diastereomer 7.3 min); IR (nujol) ν 3406, 1611 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 4.12 (d, J=6.6 Hz, 1H), 3.56 (ddd, J=8.1, 9.2, 11.8 Hz, 1H), 3.42 (ddd, J=3.7, 9.4, 11.8 Hz, 1H), 3.33–3.26 (m, 1H), 2.40 (ddt, J=7.7, 9.6, 13.6 Hz, 1H), 2.26–2.14 (m, 1H); ^{13}C NMR (62.5 MHz, D_2O) δ 180.1, 173.5, 65.5, 48.4, 44.7, 29.8; MS (ESI) m/z 160

$[M+H]^+$, 182 $[M+Na]^+$. HRMS Calcd for $C_6H_9NO_2Na$ (M+Na) 182.04293. Found: 182.04288.

4.1.22. (2*S*,3*R*)-2-*tert*-Butoxycarbonylamino-5-methanesulfonyloxy-3-methyl-1-pentanol (8a). To a solution of **4a** (505 mg, 1.14 mmol) in acetonitrile (10 mL) at 0°C were added $CeCl_3{\cdot}7H_2O$ (1.07 g, 2.88 mmol) and oxalic acid (6.4 mg, 0.07 mmol). After stirring at rt for 2 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution, filtered through Celite/Na_2SO_4 and evaporated. The crude product **8a** was used directly for the next reaction without purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.80 (br d, J=7.9 Hz, 1H), 4.38–4.18 (m, 2H), 3.68–3.55 (m, 3H), 2.98 (s, 3H), 2.75 (br s, 1H), 2.03–1.76 (m, 2H), 1.66–1.46 (m, 1H), 1.39 (s, 9H), 0.88 (d, J=6.7 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.6, 79.7, 68.4, 63.5, 55.1, 37.3, 33.0, 30.4, 28.4, 14.5; MS (EI) m/z 312 $[M]^+$, 280, 238.

4.1.23. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-5-methanesulfonyloxy-3-vinyl-1-pentanol (8b). To a solution of **4b** (120 mg, 0.33 mmol) in acetonitrile (2 mL) at 0°C were added $CeCl_3{-}7H_2O$ (246 mg, 0.66 mmol) and oxalic acid (1.5 mg, 0.01 mmol). After stirring at rt for 2 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution, filtered through Celite/Na_2SO_4 and evaporated. Flash chromatography on silica gel (heptane/EtOAc=1/1) afforded compound **8b** (95 mg, 90%) as two rotamers: $[\alpha]_D$=+23 (c 1.9, $CHCl_3$); IR ($CHCl_3$) ν 3488, 3025, 3008, 2982, 2936, 1706, 1500, 1466, 1393, 1340, 1234, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (dt, J=9.7, 16.7 Hz, 1H), 5.27–5.15 (m, 2H), 4.72 (br d, J=8.8 Hz, 1H), 4.36–4.28 (m, 1H), 4.24–4.15 (m, 1H), 3.73–3.60 (m, 3H), 3.01 (s, 3H), 2.64–2.48 (m, 1H), 2.44–2.20 (br s, 1H), 2.08–1.94 (m, 1H), 1.82–1.67 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.4, 136.4, 119.3, 79.9, 68.1, 63.9, 54.7, 41.5, 37.4, 30.7, 28.4; MS (ESI) m/z 324 $[M+H]^+$, 346 $[M+Na]^+$, 362 $[M+K]^+$. Anal. calcd for $C_{13}H_{25}NO_6S$: C 48.28; H 7.79; N 4.33; S 9.91. Found: C 48.31; H 7.91; N 4.23; S 9.89.

4.1.24. (2*S*,3*R*)- 2-*tert*-Butoxycarbonylamino-5-methanesulfonnyloxy-1-(*tert*-butyl-dimethyl-silanyloxy)-3-methylpentane (9a). To a solution of crude product **8a** (447 mg, 1.14 mmol) in DMF (15 mL) were added imidazole (247 mg, 3.6 mmol) and TBDMSCl (243 mg, 1.58 mmol). After stirring at rt for 2 h, the mixture was diluted with water, extracted with Et_2O. The ether extracts were washed with 1N HCl, water, saturated aqueous $NaHCO_3$ solution, brine, dried and evaporated. The crude product **9b** was used directly for the next reaction without purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.60 (br d, J=8.5 Hz, 1H), 4.36–4.20 (m, 2H), 3.68–3.52 (m, 3H), 2.97 (s, 3H), 2.10–1.76 (m, 2H), 1.66–1.48 (m, 1H), 1.41 (s, 9H), 0.91–0.83 (m, 12H), 0.02 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.0, 79.3, 68.4, 63.3, 54.2, 37.3, 33.1, 30.5, 28.4, 25.9, 18.2, 14.5, −5.4, −5.5.

4.1.25. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-5-methanesulfonyloxy-1-(*tert*-butyl-dimethyl-silanyloxy)-3-vinylpentane (9b). To a solution of **8b** (543 mg, 1.68 mmol) in DMF (10 mL) were added imidazole (289 mg, 4.20 mmol) and TBDMSCl (284 mg, 1.85 mmol). After stirring at rt for 5 h, the mixture was diluted with water, extracted with Et_2O. The ether extracts were washed with 1N HCl, water, saturated aqueous $NaHCO_3$ solution, brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (10/1) afforded compound **9b** (609 mg, 83%) as two rotamers: $[\alpha]_D$=+5 (c 2, $CHCl_3$); IR ($CHCl_3$) ν 3443, 3020, 2956, 2931, 2858, 1707, 1499, 1471, 1392, 1362, 1256, 1225, 1217, 1174, 1101 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.58 (dt, J=9.6, 17.1 Hz, 1H), 5.19–5.06 (m, 2H), 4.50 (br d, J=9.2 Hz, 1H), 4.30–4.11 (m, 2H), 3.71–3.46 (m, 3H), 2.96 (s, 3H), 2.59–2.47 (m, 1H), 2.00–1.85 (m, 1H), 1.80–1.65 (m, 1H), 1.40 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.8, 136.4, 118.8, 79.4, 68.3, 63.2, 54.1, 41.0, 37.3, 30.5, 28.4, 25.9, 18.2, −5.5; MS (EI) m/z 437 $[M]^+$.

4.1.26. (2*S*,3*R*)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (10a). To a suspension of NaH (55–65% in mineral oil, 230 mg, 5.75 mmol, washed with pentane) in DMF at 0°C (5 mL) was added **9a** (611 mg, 1.44 mmol) in DMF (5 mL). After being stirred at rt for 50 min, the reaction mixture was quenched by addition of water and extracted with ether. The combined ether layers were washed with brine, dried, and evaporated. Column chromatography on silica gel (heptane/EtOAc=30/1) afforded compound **10a** (395 mg, 83% for three steps) as two rotamers: $[\alpha]_D$=−29 (c 2.5, $CHCl_3$); IR ($CHCl_3$) ν 3006, 2957, 2882, 2858, 1681, 1472, 1456, 1407, 1366, 1256, 1175, 1133, 1122, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (dd, J=3.6, 10.7 Hz, 0.5H), 3.75 (dd, J=4.4, 10.3 Hz, 0.5H), 3.69–3.46 (m, 2H), 3.40–3.13 (m, 2H), 2.31–2.12 (m, 1H), 1.85–1.70 (m, 2H), 1.41 (s, 9H), 1.07 (d, J=6.6 Hz, 3H), 0.83 (s, 9H), −0.01– −0.05 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 79.0, 78.7, 61.6, 61.1, 61.0, 60.9, 46.4, 46.0, 36.5, 35.7, 32.5, 31.5, 28.7, 28.6, 25.9, 18.1, 14.3, 14.2, −5.3, −5.6; MS (ESI) m/z 330 $[M+H]^+$, 352 $[M+Na]^+$, 368 $[M+K]^+$, 681 $[2M+Na]^+$. Anal. calcd for $C_{17}H_{35}NO_3Si$: C 61.96; H 10.70; N 4.25. Found: C 61.48; H 11.04; N 4.34.

4.1.27. (2*S*,3*S*)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-vinyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (10b). To a suspension of NaH (55–65% in mineral oil, 10 mg, 0.67 mmol, washed with pentane) in DMF at 0°C (2 mL) was added **9b** (73 mg, 0.17 mmol) in DMF (1mL). After being stirred at rt for 3 h, the reaction mixture was quenched by addition of water and extracted with ether. The combined ether layers were washed with brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc=30/1) afforded compound **10b** (52 mg, 90%) as two rotamers: $[\alpha]_D$=−11 (c 2.7, $CHCl_3$); IR ($CHCl_3$) ν 3007, 2979, 2956, 2930, 2884, 2858, 1682, 1471, 1404, 1367, 1256, 1175, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01–5.86 (m, 1H), 5.15–5.03 (m, 2H), 3.98 (dd, J=2.9, 10.7 Hz, 0.5H), 3.79 (dd, J=3.9, 10.5 Hz, 0.5H), 3.76–3.70 (m, 0.5H), 3.68–3.62 (m, 0.5H), 3.57 (d, J=10.7 Hz, 1H), 3.49–3.37 (m, 1H), 3.35–3.19 (m, 1H), 2.94–2.74 (m, 1H), 2.19–1.98 (m, 1H), 1.89–1.75 (m, 1H), 1.44 (s, 9H), 0.86 (s, 9H), 0.02 (s, 1.5H), 0.01 (s, 1.5H), −0.01 (s, 1.5H), −0.02 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 137.6, 137.4, 116.5, 116.3, 79.1, 78.9, 61.5, 62.0, 61.3, 46.7, 46.3, 46.0, 30.7, 29.6, 28.6, 25.9, 18.1, −5.5, −5.6; MS (EI) m/z 342 $[M+H]^+$, 341 $[M]^+$, 296, 268.

Anal. calcd for $C_{18}H_{35}NO_3Si$: C 63.30; H 10.33; N 4.10. Found: C 63.26; H 10.73; N 4.05.

4.1.28. (2*S*,3*R*)-2-Hydroxymethyl-3-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (11a). To a solution of **10a** (258 mg, 0.78 mmol) in THF (8 mL) was added tetrabutylammonium fluoride in THF (1 M, 1.58 mL, 1.58 mmol) at rt. After stirring for 15 h, the solvent was evaporated, and the residue was separated in EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The organic extracts were washed with brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (4/1) afforded compound **11a** (136 mg, 81%) as two rotamers: $[\alpha]_D=-18$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν 3363, 3008, 2975, 2933, 2883, 1664, 1476, 1456, 1409, 1368, 1170, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45–4.37 (m, 0.5H), 3.90–3.82 (m, 0.5H), 3.75–3.66 (m, 1H), 3.53–3.45 (m, 1H), 3.40–3.32 (m, 1H), 3.29–3.19 (m, 1H), 2.47 (br s, 1H), 2.32–2.17 (m, 1H), 1.89–1.79 (m, 1H), 1.62–1.48 (m, 1H), 1.47 (s, 9H), 1.03 (d, *J*=6.6 Hz, 1H), 0.95 (d, *J*=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 80.0, 63.9, 62.3, 46.3, 36.3, 35.5, 32.0, 31.4, 28.5, 14.1; MS (ESI) *m*/*z* 216 $[M+H]^+$, 238 $[M+Na]^+$, 254 $[M+K]^+$, 453 $[2M+Na]^+$. HRMS Calcd for $C_{11}H_{21}NO_3Na$ (M+Na) 238.14191. Found: 238.14139.

4.1.29. (2*S*,3*S*)-2-Hydroxymethyl-3-vinyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (11b). To a solution of **10b** (347 mg, 1.02 mmol) in THF (10 mL) was added tetrabutylammonium fluoride in THF (1 M, 1.53 mL, 1.53 mmol) at rt. After stirring for 15 h, the solvent was evaporated, and the residue was separated in EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The organic extracts were washed with brine, dried and evaporated. Column chromatography on silica gel eluting with heptane/EtOAc (10/1) afforded compound **11b** (224 mg, 81%) as two rotamers: $[\alpha]_D=-14$ (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) ν 3384, 3084, 3022, 3009, 2981, 2933, 2887, 1668, 1476, 1455, 1405, 1368, 1223, 1169 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.85–5.71 (m, 1H), 5.23–5.08 (m, 2H), 4.24–4.16 (m, 0.5H), 4.08–3.96 (m, 0.5H), 3.79–3.67 (m, 1H), 3.61–3.42 (m, 2H), 3.42–3.31 (m, 1H), 2.97–2.83 (m, 1H), 2.50 (br s, 1H), 2.06–1.82 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.7, 136.3, 135.5, 116.8, 80.1, 79.9, 64.1, 64.0, 62.2, 61.6, 46.1, 45.9, 45.1, 29.6, 29.4, 28.4; MS (EI) *m*/*z* 228 $[M+H]^+$, 227$[M]^+$, 172, 154, 140. Anal. calcd for $C_{12}H_{21}NO_3$: C 63.41; H 9.31; N 6.16. Found: C 63.56; H 9.38; N 6.01.

4.1.30. (2*S*,3*R*)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (6a) from 11a. Jones reagent (2.67 M, 0.44 mL, 1.17 mmol) was added to a solution of **11a** (84 mg, 0.39 mmol) in acetone (5 mL) at 0°C. After stirring at 0°C for 4 h, the reaction was quenched by addition of propan-2-ol. The mixture was stirred for 30 min and neutralized with saturated aqueous $NaHCO_3$ to pH 4–5 and extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was dissolved in Et_2O and CH_2N_2 in Et_2O was added to the solution. The mixture was evaporated in vacuo and purified by column chromatography on silica gel (heptane/EtOAc=8/1) to afford compound **6a** (56 mg, 58%).

4.1.31. (2*S*,3*S*)-3-Vinyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (12b). Jones reagent (2.67 M, 1.78 mL, 4.75 mmol) was added to a solution of **11b** (360 mg, 1.58 mmol) in acetone (25 mL) at 0°C. After stirring at 0°C for 1.5 h, the reaction was quenched by addition of propan-2-ol and stirred for 30 min. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was purified by flash chromatography on silica gel (heptane/EtOAc=5/1) to afford compound **12b** (212 mg, 56%) as two rotamers: $[\alpha]_D=+34$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) ν 3691, 3505, 3026, 2981, 2932, 2888, 1720, 1690, 1477, 1455, 1401, 1368, 1227, 1170, 1150, 1131, 927, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.13 (br s, 1H), 5.85–5.68 (m, 1H), 5.23–5.11 (m, 2H), 4.38 (d, *J*=8.4 Hz, 0.4H), 4.28 (d, *J*=8.4 Hz, 0.6H), 3.77–3.62 (m, 1H), 3.44–3.31 (m, 1H), 3.17–3.01 (m, 1H), 2.10–1.92 (m, 2H), 1.46 (s, 3.4H), 1.42 (s, 5.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 176.2, 154.7, 154.0, 134.5, 134.4, 117.8, 117.7, 80.6, 80.4, 63.0, 62.5, 46.1, 45.8, 46.3, 45.3, 29.3, 28.6, 28.5, 28.3; MS (ESI) *m*/*z* 242 $[M+H]^+$, 264 $[M+Na]^+$, 280 $[M+K]^+$. Anal. calcd for $C_{12}H_{19}NO_4$: C 59.73; H 8.09; N 5.80. Found: C 59.73; H 7.94; N 5.59.

4.2. Crystallographic data

Colorless crystal of 0.18×0.42×0.57 mm, crystallized from a mixture dichlorometane/heptane. $C_{17}H_{23}NO_4$. Orthorhombic system, space group $P2_12_12_1$, Z=4 (four molecules in the unit cell), M_w=305.36; a=6.085(6), b=11.853(7), c=23.500(20) Å, V=1695 $Å^3$, d_c=1.196 g cm^{-3}, $F(000)$=1600, λ (Mo Kα)=0.71073 Å, μ=0.086 mm^{-1}. Data were measured with a Nonius Kappa-CCD area-detector diffractometer, using graphite monochromated Mo Kα radiation, in phi scans, up to θ=31.2°. Thus, 4089 data were collected leading to 2248 unique reflections, of which 1759 were considered as observed having $I\geq 2$sigma (I). The structure was refined by full-matrix least-squares, based upon unique F^2 with program SHELXL93. The hydrogen atoms, located in difference Fourier maps, were fitted at theoretical positions and treated as riding, and assigned an isotropic displacement parameter equivalent to 1.2 that one of the bonded atom. Thus, refinement of 203 parameters converged to $R1(F)$=0.0380 for the 1759 observed reflections and $wR2(F^2)$=0.0854 for all the 2248 data with a goodness-of-fit S factor of 1.042. The residual electron density was found between −0.10 and 0.11 e $Å^{-3}$. In the crystal packing, only van der Waals contacts are observed. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 187565. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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