Convenient Procedures for the Synthesis of *N*-BOC-D-Serinal Acetonide from L-Serine

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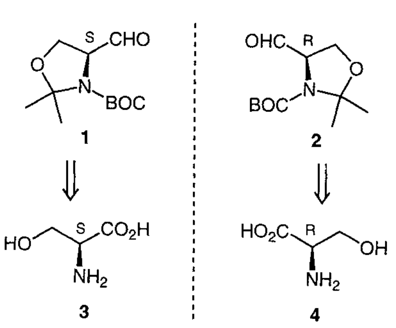
Two straightforward synthetic routes for the preparation of enantiomerically pure *N*-BOC-D-serinal acetonide (enantiomer of Garner's aldehyde) starting from naturally occurring L-serine are described.

Optically active *N*-protected α-amino aldehydes are important and versatile compounds which are widely used in asymmetric synthesis.[1] In particular, L-serinal (**1**; or Garner's aldehyde)[2] is a well-known chiral starting material for the stereocontrolled organic synthesis of a large variety of natural products such as amino acids, amino sugars or other derivatives. Apart from its ability to exert stereocontrol during asymmetric reactions, the special interest in this *N*-protected α-amino aldehyde stems from its ready and large scale availability[3] from the natural amino acid L-serine (**3**).

Several reports on the reactions of L-serinal (**1**) where the carbonyl group was used to form a new stereogenic centre have been published,[4] but there are not many examples[5] concerning the use of D-serinal (**2**), and in all cases **2** was obtained starting from D-serine (**4**) by a similar procedure to that described by Garner and Park for its enantiomer **1** (Scheme 1).



Scheme 1

In this context, and as a part of our research project on the asymmetric synthesis of α-amino acids,[6] we have exploited the behaviour of L-serinal (**1**) as a chiral building block to synthesize bis(α-amino acids) using a methodology that involves the asymmetric hydrogenation[7] of (*E*)- and (*Z*)-(*R*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-4-[2′-(benzamido)-2′-(methoxycarbonyl)ethenyl]-1,3-oxazolidines, both of which are readily available from L-serinal (**1**).

Encouraged by the excellent behaviour of L-serinal (**1**) in our asymmetric synthesis, and given the requirement of D-serinal (**2**) to obtain the opposite configuration of the reaction products, we have developed a new, straightforward synthetic route for the preparation of D-serinal (**2**) using naturally occurring L-serine (**3**) as the source of chirality. The advantage of this approach is that the precursor D-serine (**4**) is not a natural product and, although it is commercially available, it is three times more expensive than L-serine (**3**).

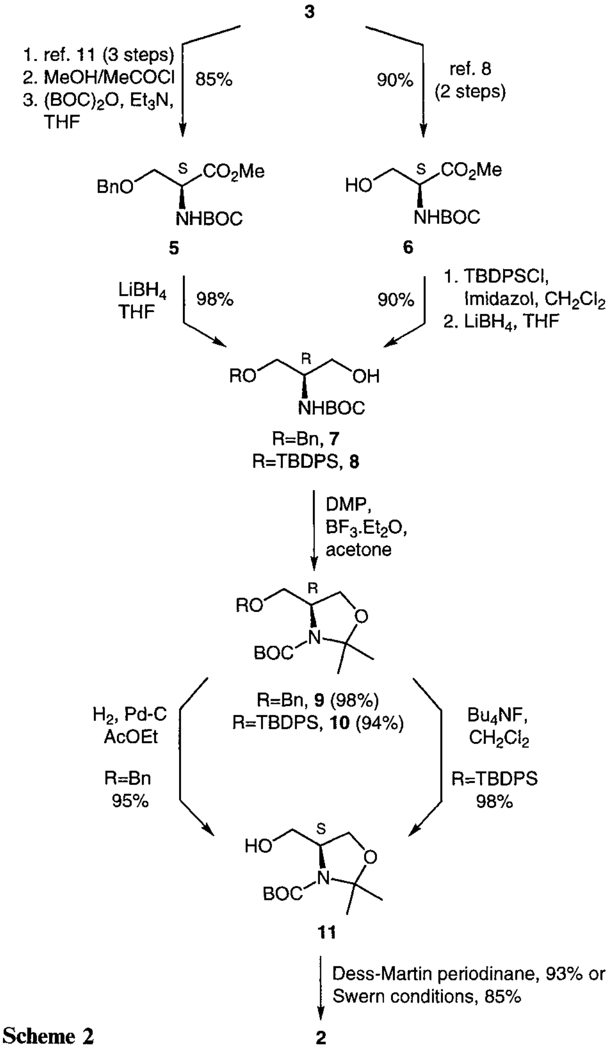
In this paper, we report two new, high-yielding syntheses of chemically and optically pure D-serinal (**2**) on a multigram scale in seven or nine steps and 73–75% overall yield from L-serine (**3**), taking into account that L-serinal (**1**) was initially prepared in four steps and 61% overall yield from L-serine (**3**).[3] Furthermore, several authors (McKillop et al.,[8] Meffre et al.[9] amongst others) have improved the overall yield of L-serinal (**1**) and, in a more recent publication, Williams et al.[10] have obtained L-serinal (**1**) in five steps and 63% overall yield, avoiding the reduction of *N*-BOC-L-serine acetonide methyl ester with DIBAL, which is often problematic.

The synthesis of D-serinal (**2**) started from L-serine (**3**), which was converted to *O*-benzyl-L-serine in 85% overall yield, according to the efficient three-step procedure described in the literature.[11] *O*-Benzyl-L-serine was then quantitatively esterified with diazomethane to afford *O*-benzyl-L-serine methyl ester. Alternatively, in order to avoid the use of diazomethane in the esterification step, this compound was also obtained in quantitative yield by reaction of *O*-benzyl-L-serine with methanol/acetyl chloride (Scheme **2**).

Furthermore, *tert*-butoxycarbonylation of the *O*-benzyl-L-serine methyl ester with di-*tert*-butyl dicarbonate in triethylamine, using THF as the solvent, quantitatively gave the *O*-benzyl-*N*-BOC-L-serine methyl ester (**5**), which could be efficiently reduced by the action of lithium borohydride in THF under an inert atmosphere to obtain the corresponding alcohol **7** in 98% yield after 12 hours, as described by Meffre et al.[9] (Scheme 2).

Formation of the oxazolidine ring was achieved under mild conditions by the use of the procedure developed by Moriwake et al.,[12] and later assayed by McKillop,[8] consisting of the transformation of the resulting alcohol **7** into *O*-benzyl-*N*-BOC-D-serinol acetonide (**9**) (98%) by the addition of 2,2-dimethoxypropane (DMP) in acetone at room temperature with $BF_3 \cdot OEt_2$ as a catalyst. D-Serinol (**9**) was easily debenzylated by hydrogenolysis using palladium/carbon as a catalyst in ethyl acetate at room temperature to give *N*-BOC-L-serinol acetonide **(11)**, which was oxidized with Dess–Martin periodinane[13] or under Swern conditions[14] to afford the required D-serinal **(2)** (Scheme 2).

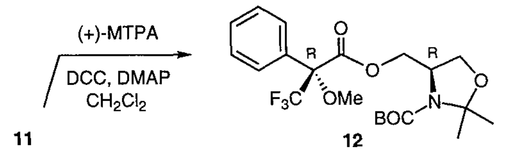
Swern oxidation gave a lower yield than Dess–Martin periodinane and, in the latter case, D-serinal **(2)** was obtained in nine steps with a 73% overall yield *without* epimerization of the stereogenic centre: the enantiomeric purity of D-serinal **(2)** was checked by means of ^{1}H NMR, using a europium(III) chelate as a chiral shift reagent.[15] On the other hand, the D-serinal **(2)**, obtained from Swern oxidation, had undergone racemization of 15% (Scheme 2).



Scheme 2

In order to improve the synthetic method for D-serinal **(2)** by attempting to minimize the number of steps involved, the hydroxy group of *N*-BOC-L-serine methyl ester **6** (obtained by conversion of the carboxylic acid and amino groups of L-serine **3** into the methyl ester and *tert*-butoxycarbonylamino groups, respectively) was protected with *tert*-butyldiphenylsilyl chloride[16] and the methyl ester group was subsequently reduced to obtain compound **8**. Starting from compound **8**, the acetonide formation in compound **10** occurred without hydrolysis of the O–Si bond. This compound was desilylated by treatment with tetrabutylammonium fluoride to afford alcohol **11**. In this way, D-serinal **(2)** was obtained in 75% overall yield from L-serine **(3)**, using seven steps (Scheme 2).

The optical purity of compound **11** was determined by preparation of its Mosher esters.[17] Analysis of ^{1}H and ^{19}F NMR spectra of the ester **12** showed the presence of only one diastereomer. Anyway, in order to be sure that compound **11** is enantiomerically pure, we have determined that there is not cross-contamination by conversion of this compound to its Mosher ester derivative *epi*-**12** (Scheme 3).



Scheme 3

In conclusion, we have developed two straightforward synthetic routes, using simple reagents, to obtain the enantiomer of Garner's aldehyde, a valuable chiral building block in asymmetric synthesis. The advantage of these routes is that they start from L-serine instead of the non-naturally occurring and more expensive D-serine, which is used in other methods described to date. Applications of this aldehyde in several asymmetric reactions are currently under investigation.

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using a Bruker ARX-300 spectrometer. ^{1}H, ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and ^{19}F NMR in $CFCl_3$ as the external standard. Chemical shifts are reported in ppm on the δ scale. Melting points were determined using a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out using a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values (C $\pm$0.15%, H $\pm$0.08%, N $\pm$0.04%, F $\pm$0.05%).

(*S*)-*O*-Benzyl-*N*-BOC-serine Methyl Ester (5):

Acetyl chloride (5 mL) was added dropwise to MeOH (35 mL) cooled in ice. The solution was stirred for 5 min and *O*-benzyl-L-serine (5.01 g, 25.7 mmol) was added in one portion and the solution slowly heated to reflux. Heating under reflux was continued for 2 h. The mixture was cooled and the solvent removed by evaporation under reduced pressure to give crude *O*-benzyl-L-serine methyl ester hydrochloride as a white crystalline solid which was used without further purification; yield: 6.30 g (~100%).

O-Benzyl-L-serine methyl ester hydrochloride (5.59 g, 22.8 mmol) was suspended in THF (70 mL) and Et_3N (4.96 g, 49.1 mmol) was added. The resulting white suspension was cooled to 0 °C and a solution of $(BOC)_2O$ (5.09 g, 22.6 mmol) in THF (35 mL) was added dropwise over 20 min. The mixture was allowed to warm to r.t. and stirred for 6 h and then warmed to 50 °C for a further 2 h. The solvent was removed in vacuo and the white residue partitioned between $\mathrm{Et_2O}$ (70 mL) and $\mathrm{H_2O}$ (70 mL). The aqueous phase was extracted with $\mathrm{Et_2O}$ (2 × 55 mL) and the combined organic phases were washed with aq 3 % HCl (55 mL), aq 5 % $\mathrm{NaHCO_3}$ (55 mL), and brine (70 mL). Drying ($\mathrm{Na_2SO_4}$) and evaporation of the solvent afforded **5** as a colourless oil which was used without further purification; yield: 7.02 g (100 %); $[\alpha]_D$: +11.8 (*c* 1.94, $\mathrm{CHCl_3}$). The physicochemical properties were identical with those described in the literature: [Lit.[18] **(5)** $[\alpha]_D$: +13.9 (*c* 0.90, $\mathrm{CHCl_3}$)].

(*R*)-*O*-Benzyl-*N*-BOC-serinol (7):

To a solution of the crude ester **5** (4.22 g, 13.6 mmol) in THF (20 mL) was added a 2.0 M solution of $\mathrm{LiBH_4}$ in THF (7 mL) at 0 °C. The reaction mixture was stirred for 12 h at r.t. and then treated at 0 °C with sat. $\mathrm{NH_4Cl}$. Extraction with EtOAc (50 mL) and the usual workup procedure gave **7** as a white solid which was used without further purification; yield: 3.75 g (98 %); mp 60–61 °C; $[\alpha]_D$: +9.8 (*c* 4.00, $\mathrm{CHCl_3}$). The physicochemical properties were identical with those described in the literature: [Lit.[19] **(7)** $[\alpha]_D$: +12.1 (*c* 1.00, $\mathrm{CHCl_3}$)]. The enantiomer of compound **7** was synthesized by Toogood: [Lit.[20] (*ent*-**7**) $[\alpha]_D$: −8.5 (*c* 1.00, $\mathrm{CH_2Cl_2}$)].

***tert*-Butyl (*R*)-4-Benzyloxymethyl-2,2-dimethyloxazolidine-3-carboxylate (9):**

Alcohol **7** (4.75 g, 16.9 mmol) was dissolved in a mixture of acetone (60 mL) and 2,2-dimethoxypropane (19 mL) and $\mathrm{BF_3{\cdot}OEt_2}$ (0.1 mL) was added. The resulting solution was stirred at r.t. for 2 h, after which time TLC showed no remaining starting material (EtOAc–hexane, 1:4, v/v). The solvent was removed in vacuo, the residual oil taken up in $\mathrm{CH_2Cl_2}$ (60 mL) and the resulting solution washed with a mixture of aqueous saturated $\mathrm{NaHCO_3}$ and $\mathrm{H_2O}$ (1:1 v/v, 30 mL) and brine (30 mL). The organic layer was dried ($\mathrm{Na_2SO_4}$) and the solvent was evaporated in vacuo to give compound **9** as a yellow oil, which was used without further purification; yield: 5.30 g (98 %); $[\alpha]_D$: +30.3 (*c* 4.20, $\mathrm{CHCl_3}$).

^{1}H NMR ($\mathrm{CDCl_3}$)[21]: δ = 1.41–1.60 (m, 15 H, 5CH$_3$), 3.35 ('t', 1 H, *J* = 8.7 Hz, PhCH$_2$OC*H*$_2$), 3.42 ('t', 1 H, *J* = 9.0 Hz, PhCH$_2$OC*H*$_2$), 3.57 (brd, 1 H, *J* = 7.5 Hz, PhCH$_2$OC*H*$_2$), 3.70 (brd, 1 H, *J* = 8.4 Hz, PhCH$_2$OC*H*$_2$), 3.90–4.19 (m, 3 H, CH$_2$O + CHN), 4.49 (d, 1 H, *J* = 11.7 Hz, PhCH$_2$O), 4.57 (d, 1 H, *J* = 11.7 Hz, PhCH$_2$O), 7.20–7.40 (m, 5 H, arom).

^{13}C NMR ($\mathrm{CDCl_3}$)[21]: δ = 23.0, 24.3 (CH$_3$), 26.7, 27.5 (CH$_3$), 28.4 [C(*C*H$_3$)$_3$], 56.4, 56.5 (CHN), 65.4, 65.7 (CH$_2$O), 69.2, 69.5 (PhCH$_2$OCH$_2$O), 73.2, 73.4 (Ph*C*H$_2$O), 79.7, 80.2 [*C*(CH$_3$)$_3$], 93.3, 93.7 [*C*(CH$_3$)$_2$], 127.6, 127.7, 128.4, 138.0, 138.2 (Ph), 151.6, 152.2 [N*C*O$_2$C(CH$_3$)$_3$].

(*R*)-*O*-*tert*-Butyldiphenylsilyl-*N*-BOC-serinol (8):

(*S*)-*N*-BOC-serine methyl ester **6** was prepared in 90 % yield, according to the procedure described by McKillop et al.[8] starting from L-serine **(3)**, in two steps: quantitative esterification with methanol/acetyl chloride and *tert*-butoxycarbonylation with $\mathrm{(BOC)_2O}$. Alcohol **6** (3.80 g, 17.4 mmol) was dissolved in $\mathrm{CH_2Cl_2}$ (50 mL) and *t*-butyldiphenylsilyl chloride (10.00 g, 36.4 mmol) was added. The mixture was cooled to 0 °C and imidazole (2.48 g, 36.4 mmol) was added portionwise over 5 min. The cooling bath was removed and the mixture stirred for 12 h at r.t. The mixture was poured into $\mathrm{H_2O}$ (50 mL). The layers were separated and the organic layer was washed with $\mathrm{H_2O}$ (2 × 30 mL, dried ($\mathrm{Na_2SO_4}$), filtered, and concentrated to give a colourless oil. This oil was dissolved in THF (50 mL) and to the resulting solution was added a 2.0 M solution of $\mathrm{LiBH_4}$ in THF (13 mL, 26.0 mmol) at 0 °C. The reaction mixture was stirred for 12 h at r.t. and then treated at 0 °C with saturated $\mathrm{NH_4Cl}$. Extraction with EtOAc (2 × 5 mL) and the usual workup procedure gave a syrup which was chromatographed (flash chromatography) (EtOAc–hexane, 1:4, v/v) to give alcohol **8** as a white solid; overall yield from compound **6**: 4.80 g (90 %), mp 72–73 °C; $[\alpha]_D$: +4.1 (*c* 2.83, $\mathrm{CHCl_3}$).

^{1}H NMR ($\mathrm{CDCl_3}$): δ = 1.07 [s, 9 H, SiC(CH$_3$)$_3$], 1.44 [s, 9 H, OC(CH$_3$)$_3$], 2.41 (brs, 1 H, OH), 3.65–3.85 (m, 5 H, 2CH$_2$O, CHN), 5.09 (brs, 1 H, NH), 7.35–7.45 (m, 6 H, arom), 7.60–7.70 (m, 4 H, arom).

^{13}C NMR ($\mathrm{CDCl_3}$): δ = 19.2 [Si*C*(CH$_3$)$_3$], 26.9 [SiC(*C*H$_3$)$_3$], 28.4 [OC(*C*H$_3$)$_3$], 52.9 (CHN), 63.8, 64.2 (2 CH$_2$O), 79.6 [O*C*(CH$_3$)$_3$], 127.9, 130.0, 132.8, 135.5 (Ph), 156.1 [N*C*O$_2$C(CH$_3$)$_3$].

***tert*-Butyl (*R*)-4-*tert*-Butyldiphenylsilyl-2,2-dimethyloxazolidine-3-carboxylate (10):**

Alcohol **8** (3.80 g, 8.86 mmol) was dissolved in a mixture of acetone (35 mL) and 2,2-dimethoxypropane (10 mL) and $\mathrm{BF_3 \cdot OEt_2}$ (0.1 mL) was added. The resulting solution was stirred at r.t. for 2 h, after which time TLC showed no remaining starting material and clean formation of a single product (EtOAc–hexane, 1:4 v/v). The solvent was removed in vacuo, the residual oil taken up in $\mathrm{CH_2Cl_2}$ (35 mL) and the resulting solution washed with a mixture of saturated $\mathrm{NaHCO_3}$, $\mathrm{H_2O}$ (1:1 v/v, 20 mL) and brine (20 mL), and then dried ($\mathrm{Na_2SO_4}$). The solvent was evaporated in vacuo to give compound **10** as a white solid; yield: 3.92 g (94 %); mp 104–105 °C; $[\alpha]_D$: +21.8 (*c* 3.03, $\mathrm{CHCl_3}$).

^{1}H NMR ($\mathrm{CDCl_3}$)[21]: δ = 1.04 [s, 9 H, SiC(CH$_3$)$_3$], 1.31 [s, 6 H, C(CH$_3$)$_2$], 1.46–1.52 [m, 9 H, OC(CH$_3$)$_3$], 3.50 ('t', 1 H, *J* = 9.3 Hz, CH$_2$O), 3.62 ('t', 1 H, *J* = 9.0 Hz, CH$_2$O), 3.76 (dd, 1 H, *J* = 9.3 Hz, *J* = 3.9 Hz, CH$_2$O), 3.83 (dd, 1 H, *J* = 9.3 Hz, *J* = 3.6 Hz, CH$_2$O), 3.90–4.05 (m, 2 H, CH$_2$O, CHN), 4.12 (d, 1 H, *J* = 8.1 Hz, CH$_2$O), 4.22 (d, 1 H, *J* = 7.8 Hz, CH$_2$O), 7.36–7.47 (m, 6 H, arom), 7.63–7.70 (m, 4 H, arom).

^{13}C NMR ($\mathrm{CDCl_3}$)[21]: δ = 19.2 [Si*C*(CH$_3$)$_3$], 23.1, 24.6, 26.7, 26.8, 27.3, 28.3, 28.4, 30.9 (8 CH$_3$), 58.2, 58.4 (CHN), 62.4, 62.9, 64.9, 65.2 (2 CH$_2$O), 79.6, 80.0 [O*C*(CH$_3$)$_3$], 93.4, 93.9 [*C*(CH$_3$)$_2$], 127.7, 129.6, 129.7, 133.3, 133.4, 135.4, 135.5 (Ph), 151.8, 152.2 [N*C*O$_2$C(CH$_3$)$_3$].

***tert*-Butyl (*S*)-4-Hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylate (11):**

Starting from compound **9**: Palladium on carbon (1:10 catalyst/substrate by weight) was added to a solution of benzyl ether **9** (4.02 g, 12.5 mmol) in EtOAc (30 mL). The suspension was stirred at r.t. until TLC (EtOAc–hexane, 1:4 v/v) showed no remaining starting material (usually 24 h). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give compound **11** as a colourless oil which was used without further purification; yield: 2.74 g (95 %); $[\alpha]_D$: +21.8 (*c* 3.85, $\mathrm{CHCl_3}$). The physicochemical properties were identical with those described in the literature: [Lit.[2] **(11)** $[\alpha]_D$: +23.6 (*c* 1.44, $\mathrm{CHCl_3}$) and Lit.[10] **(11)** $[\alpha]_D$: +17.9 (*c* 2.13, $\mathrm{CHCl_3}$)].

Starting from compound **10**: To a solution of compound **10** (4.10 g, 8.74 mmol) in THF (30 mL) was added, at r.t. a solution of tetrabutylammonium fluoride trihydrate (3.31 g, 10.5 mmol) in THF (20 mL). The mixture was stirred for 2 h at r.t. after which time TLC showed no remaining starting material. The solvent was removed in vacuo to give 7.32 g of a pale brown oil. Flash chromatography on silica gel eluting with EtOAc–hexane (1:4, v/v) gave pure alcohol **11** as a colourless oil; yield: 1.97 g (98 %); $[\alpha]_D$: +22.1 (*c* 1.50, $\mathrm{CHCl_3}$).

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

N-BOC-L-serinol acetonide **(11)** was oxidized with Dess–Martin periodinane (method A) or under Swern conditions (method B):

Method A: Dess–Martin periodinane (3.90 g, 9.23 mmol) was added to a solution of alcohol **11** (1.25 g, 5.43 mmol) in $\mathrm{CH_2Cl_2}$ (50 mL) and the mixture was stirred at r.t. for 2 h. $\mathrm{Et_2O}$ (100 mL) was added, the mixture was poured into sat. aq $\mathrm{NaHCO_3}$ solution, and an excess of aqueous 5 % $\mathrm{Na_2S_2O_3}$ added. The organic layer was washed with sat. aq $\mathrm{NaHCO_3}$ (50 mL) and brine (50 mL), dried ($\mathrm{Na_2SO_4}$), and the solvent evaporated in vacuo to give 1.15 g (93 %) of compound **2**, the enantiomer of Garner's aldehyde. After distillation, the enantiomeric purity was determined by ^{1}H NMR, using a chiral shift reagent and comparing its optical activity with that given in the literature; $[\alpha]_D$: +106.7 (*c* 1.08, $\mathrm{CHCl_3}$) [Lit.[2] **(2)** $[\alpha]_D$: +105.0].

^{1}H NMR ($\mathrm{CDCl_3}$)[21]: δ = 1.43–1.66 (m, 15 H, 5CH$_3$), 4.05–4.14 (m, 2 H, CH$_2$O), 4.17–4.23 (m, 1 H, CHN), 4.30–4.40 (m, 1 H, CHN), 9.54 (d, 1 H, $J = 2.4$ Hz, CHO), 9.60 (d, 1 H, $J = 1.2$ Hz, CHO).

^{13}C NMR ($CDCl_3$)[21]: δ = 23.8, 24.7, 25.8, 26.7, 28.3 (5 CH_3), 63.5, 63.9 (CH_2O), 64.7, 64.8 (CHN), 81.1, 81.4 [$C(CH_3)_3$], 94.4, 95.1 [$C(CH_3)_2$], 151.3, 152.6 [$NCO_2C(CH_3)_3$], 199.5 (CHO).

Method B: To a solution of oxalyl chloride (2.6 mL, 29.2 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added DMSO (3.4 mL, 47.9 mmol) dropwise via a syringe. The resulting solution was stirred for 5 min at −78 °C and a solution of alcohol **11** (5.53 g, 23.9 mmol) in CH_2Cl_2 (50 mL) was then added via a cannula. The mixture was stirred for 15 min at −78 °C and Et_3N (13.5 mL, 95.9 mmol) was added. The solution was allowed to warm to r.t. and the reaction was quenched by addition of aq sat. $NaHCO_3$ (100 mL) and then diluted with Et_2O (100 mL). The layers were separated and the organic phase was washed with 1 M $NaHSO_4$ (2 × 100 mL), sat. aqueous $NaHCO_3$ (100 mL), and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give crude aldehyde **2**, which was distilled; yield: 4.66 g (85 %); $[\alpha]_D$: + 89.0 (*c* 1.40, $CHCl_3$).

Preparation of (+)-(*R*)-MTPA and (−)-(*S*)-MTPA Esters of 11: To a solution of alcohol **11** (62.9 mg, 0.27 mmol), DCC (60.5 mg, 0.29 mmol), and DMAP (32.2 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of (+)-(*R*)-MTPA (71.8 mg, 0.31 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at r.t. for 4.5 h, after which time TLC (EtOAc–hexane, 2:3, v/v) showed the clean formation of product **12** from the starting material. The resulting white suspension was filtered to remove the *N,N'*-dicyclohexylurea. The filtrate was concentrated in vacuo to give a white slurry, to which Et_2O was added. The resulting suspension was filtered to remove the *N*-acyl-*N'*-cyclohexylurea and then concentrated to give 0.12 g of crude product as a waxy solid. Flash chromatography on silica gel (EtOAc–hexane, 1:1, v/v) yielded 0.11 g (91 %) of the ester; $[\alpha]_D$: +40.7 (*c* 1.73, $CHCl_3$) [Lit.[2] *ent*-**12** $[\alpha]_D$: −48.0 (*c* 1.87, $CHCl_3$)].

^{1}H NMR ($CDCl_3$): δ = 1.42–1.57 [m, 15 H, $C(CH_3)_3$, $C(CH_3)_2$], 3.54 (s, 3 H, OCH_3), 3.75 ('t', 1 H, $J = 9.0$ Hz), 3.90 (dd, 1 H, $J = 9.3$ Hz, $J = 4.8$ Hz), 4.07–4.14 (m, 1 H), 4.20 (m, 1 H), 4.49 (d, 1 H, $J = 6.9$ Hz), 7.35–7.43 (m, 3 H, arom), 7.45–7.60 (m, 2 H, arom).

^{13}C NMR ($CDCl_3$)[21]: δ = 23.0, 24.2 (CH_3), 26.6, 27.4 (CH_3), 28.3 [$C(CH_3)_3$], 55.2, 55.3 (OCH_3), 55.4, 55.5 (CHN), 64.2, 64.6, 64.8, 65.2 (2 CH_2O), 80.5, 80.9 [$C(CH_3)_3$], 93.7, 94.2 [$C(CH_3)_2$], 121.3, 125.1, 127.2, 127.7, 128.5, 128.8, 129.7, 132.1, 134.8 (Ph, CCF_3), 151.4, 152.2 [$NCO_2C(CH_3)_3$], 166.2 (CO_2).

^{19}F NMR ($CDCl_3$): δ = −127.04.

An essentially identical procedure was performed with **11** and (−)-(*S*)-MTPA and resulted in the isolation of *epi*-**12**. $[\alpha]_D$: −8.0 (*c* 1.78, $CHCl_3$) [Lit.[2] (***epi*-12**) $[\alpha]_D$: −9.7 (*c* 1.06, $CHCl_3$)].

^{1}H NMR ($CDCl_3$)[21]: δ = 1.42–1.57 [m, 15 H, $C(CH_3)_3$, $C(CH_3)_2$], 3.53, 3.54 (2 s, 3 H, OCH_3), 3.79 (dd, 1 H, $J = 9.3$ Hz, $J = 4.5$ Hz), 3.86–3.95 (m, 1 H), 3.97–4.07 (m, 1 H), 4.14–4.24 (m, 1 H), 4.55 (d, 1 H, $J = 5.7$ Hz), 4.62 (d, 1 H, $J = 7.2$ Hz), 7.35–7.43 (m, 3 H, arom), 7.44–7.60 (m, 2 H, arom).

^{13}C NMR ($CDCl_3$)[21]: δ = 23.0, 24.5 (CH_3), 26.6, 27.3 (CH_3), 28.4 [$C(CH_3)_3$], 55.1, 55.2 (OCH_3), 55.4 (CHN), 64.1, 64.3, 64.8, 65.1 (2 CH_2O), 80.5, 80.9 [$C(CH_3)_3$], 93.8, 94.1 [$C(CH_3)_2$], 121.3, 125.1, 126.8, 127.2, 128.5, 128.8, 129.8, 132.0 (Ph, CCF_3), 151.4, 152.2 [$NCO_2C(CH_3)_3$], 166.1 (CO_2).

^{19}F NMR ($CDCl_3$)[21]: δ = −126.96, −127.11.

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9.63 ppm and 9.67 ppm corresponding to the splitting in the other conformer, by the action of Eu(tfc)$_3$.

(16) Another protective group (*tert*-butyldimethylsilyl) for the hydroxy substituent of L-serine (**3**) was tested. This group could not be used in the total synthesis of **2** since it caused several problems in the formation of the oxazolidine ring due to the action of an acid medium, which produced hydrolysis of the O–Si bond.

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