

Orthogonally protected glycerols and 2-aminodiols: useful building blocks in heterocyclic chemistry

Anthony Ollivier,^{a,b} Marlène Goubert,^{a,b} Ahmatjan Tursun,^{a,b} Isabelle Canet,^{a,b*} and
Marie-Eve Sinibaldi^{a,b*}

^a Clermont Université, Université Blaise Pascal, Laboratoire SEESIB, BP 10448, F-63000
Clermont-Ferrand, France

^b CNRS, UMR 6504, SEESIB, F-63177 Aubière, France

E-mail: m-eve.sinibaldi-troin@univ-bpclermont.fr, isabelle.canet@univ-bpclermont.fr

DOI: <http://dx.doi.org/10.3998/ark.5550190.0011.910>

Abstract

The efficient synthesis of orthogonally protected glycerols, 2-aminopropane-1,3-diols and 2-aminobutane-1,4-diols that can constitute useful tools in heterocyclic chemistry, is reported. These interesting tri-functionalized small synthons were easily prepared from serine or aspartic acid. In addition, these substrates can be readily transformed into their iodide derivatives in very good yields.

Keywords: Amino acids, amino-alcohols, alcohols, amines, halohydrins

Introduction

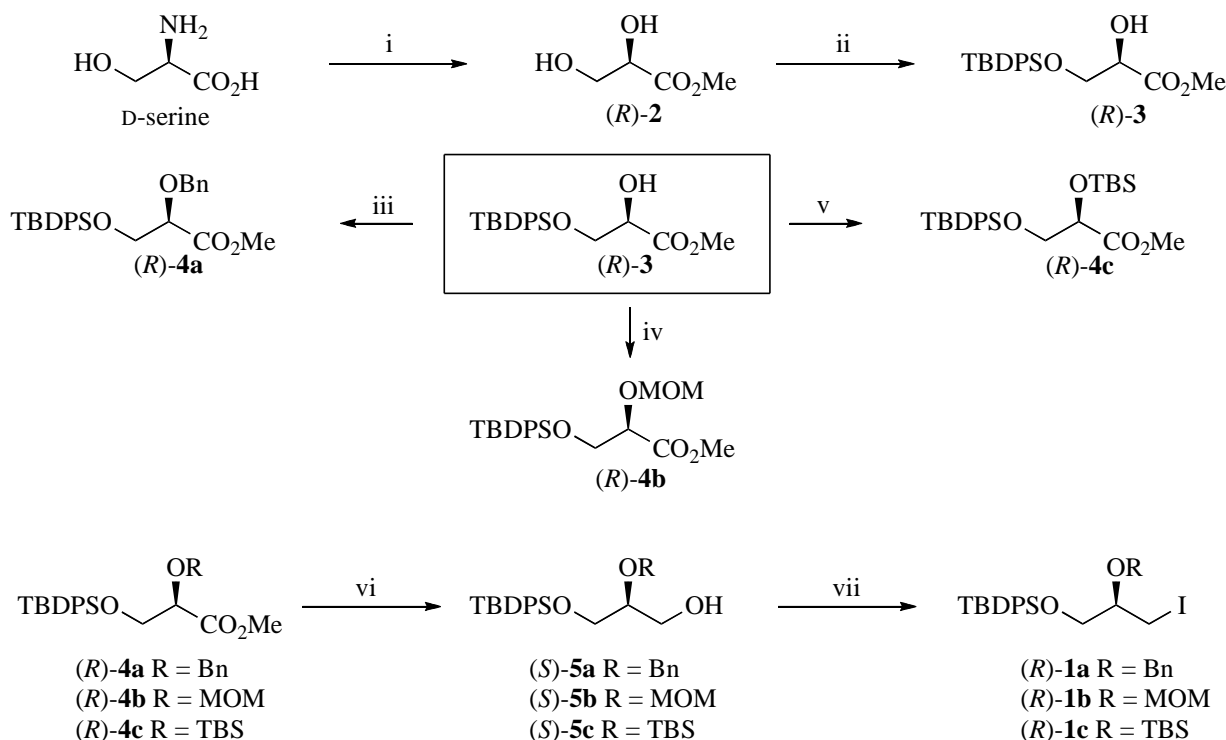
Polyfunctionalized small molecules such as glycerols and β -amino-alcohols are important and versatile units extensively used in the preparation of complex structures like macrolides,¹ morpholines,² hydroxyamidines³ and antibiotics. Moreover, 1,2-diols can serve as precursors for the preparation of *vic*-halohydrins, useful molecules for synthetic transformations having importance, for example, in the synthesis of halogenated marine products.⁴

Owing to their structures, these building blocks need at first to be protected with groups cleavable independently of the others. Lastly, synthesis of natural compounds required an enantioselective access to these substrates and that can be efficiently investigated starting from readily available natural amino acids.

In connection with our ongoing effort to synthesize spiroketals or analogues, based upon an iterative alkylation of acetone *N,N*-dimethylhydrazone with β - and γ -hydroxyiodides,⁵ we were induced to develop approaches^{5c,d} to several orthogonally protected iodopropanediols, aminopropanols and aminobutanols starting from D-serine or from L-aspartic acid. We describe herein the synthesis and the characterization of orthogonally protected glycerols and 2-aminodiols, together with their efficient conversions into iodides.

Results and Discussion

The synthesis of selectively protected (*R*)-iododiol **1a,b,c** was accomplished from D-serine in five steps in a range of 20-47% overall yield (Scheme 1). The first step was a transformation of D-serine into its corresponding alcohol^{6a,b} followed by esterification of the carboxylic acid to give (*R*)-**2** in 83% yield.^{6c} In the next step, diol **2** was selectively protected as its pivotal silyl ether **3**⁷ in 83% yield using tert-butyldiphenylsilyl chloride in the presence of imidazole at low temperature.



Scheme 1. Reagents and conditions : (i) NaNO₂, H₂SO₄, H₂O, 5 days, then HC(OMe)₃, H₂SO₄, MeOH, Δ, 30 min, 83%; (ii) TBDPSCl, imidazole, CH₂Cl₂, -40 °C, 1.5h, 83%; (iii) BnBr, Ag₂O, Et₂O, 20 °C, 82%; (iv) MOMCl, (*i*-Pr)₂EtN, CH₂Cl₂, 20 °C, 97%; (v) TBSCl, DMAP, imidazole, CH₂Cl₂, -10 °C then 20 °C, 48 h, 82%; (vi) LiBH₄, THF, 0 °C, (*S*)-**5a** (88%), (*S*)-**5b** (88%), (*S*)-**5c** (47%); (vii) I₂, imidazole, PPh₃, Et₂O/CH₃CN, -10 °C to 20 °C, **1a** (95%), **1b** (73%), **1c** (74%).

We then converted alcohol **3** into orthogonally protected derivatives **4a,b,c** in good yields using benzyl bromide/silver oxide for **4a**, methoxymethyl chloride/diisopropylethylamine for **4b**⁸ and *tert*-butyldimethylsilyl chloride/dimethylaminopyridine/imidazole for **4c**. In the case of **4b**, the yield was increased by modifying our previously reported procedure⁸ (see Experimental part). Reduction of methyl esters **4a,b** was cleanly achieved with lithium borohydride in tetrahydrofuran at 0 °C producing the glycerols **5a**⁹ and **5b** in 88% yields; alternatively, **4c** was converted in a moderate yield of 47% into **5c**, certainly due to the instability of the *tert*-

butyldimethylsilyl group in this series. In a last step, alcohols **5a,b,c** were treated with iodine/imidazole in the presence of triphenylphosphine in a mixture of diethyl ether/acetonitrile (3/1). Best results were obtained using the following ratio of reactants: 2.4 equiv iodine, 2.2 equiv imidazole, 2.0 equiv triphenylphosphine (see Experimental part), leading almost quantitatively (TLC monitoring) to iodides **1a,b,c** (Scheme 1). Compounds **1b,c** were found to be slightly unstable during the purification procedure, lowering isolated yields. Moreover, if not used at once, these iodides must be kept at 0 °C under an inert atmosphere and because of their instability, usually require a filtration before their use in further synthetic transformations.

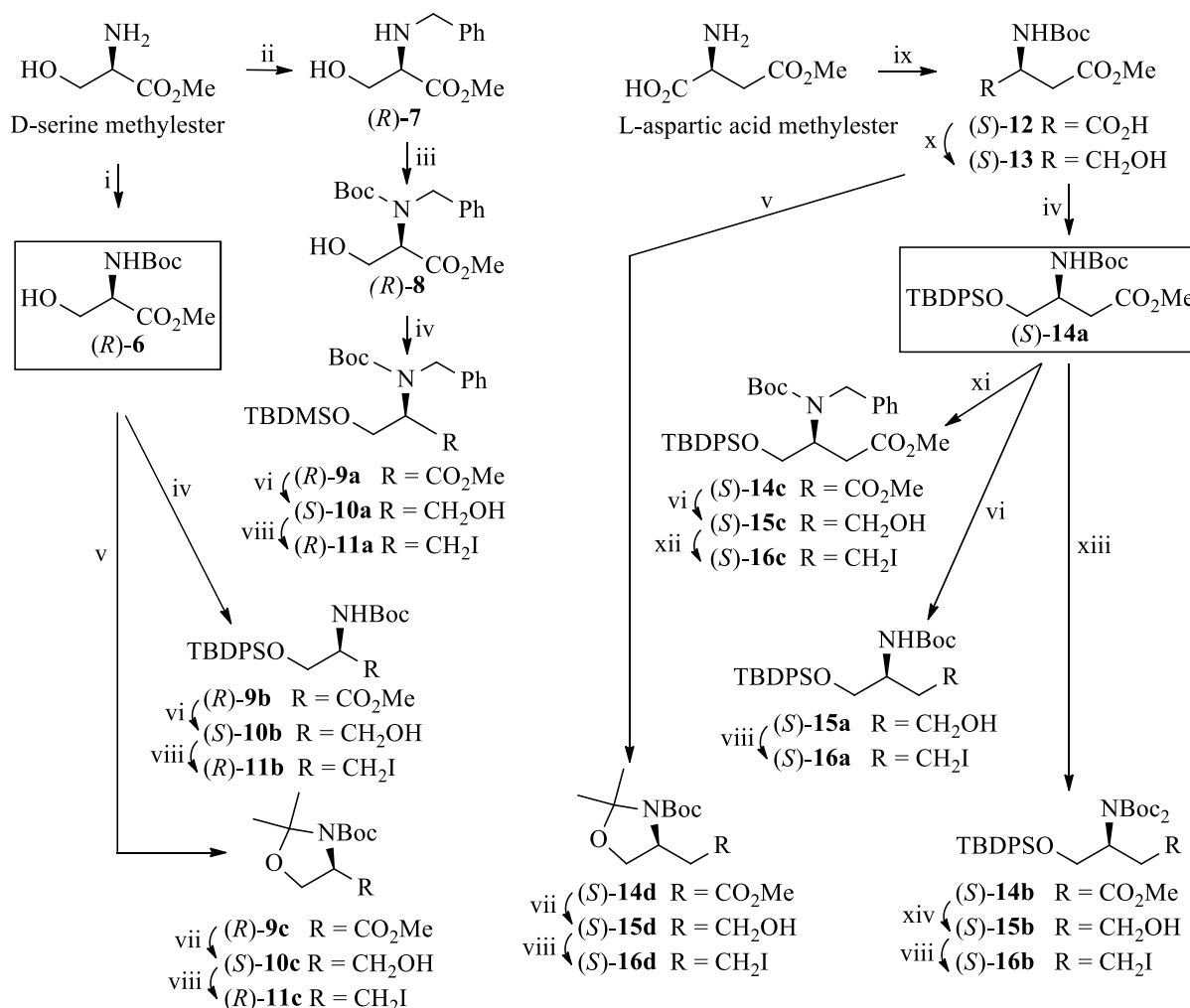
Protected 2-aminopropane-1,3-diols **10a,b,c** and 2-aminobutane-1,4-diols **15a,b,c,d** were obtained by a general pathway starting from inexpensive commercial D-serine methyl ester and L-aspartic acid methyl ester, respectively (Scheme 2). In these series, we targeted different protecting groups for the amino function. We chose an oxazolidine moiety (compounds **10c** and **15d**) in order to allow the simultaneous regeneration of β -aminoalcohols during the cleavage process. We also utilised the classical *tert*-butoxycarbonyl protecting group (synthons **10b** and **15a**). Finally, we tested *N*-diprotection, in which a carbamate was substituted with a benzyl group (compounds **10a** and **15c**) or a second *tert*-butoxycarbonyl moiety (compound **15b**) with the aim of acquiring, after selective deprotection, either a primary or a secondary amine. To protect the primary alcohol function of all these compounds, we introduced a silyl ether group (*tert*-butyldiphenylsilyl or *tert*-butyldimethylsilyl) selectively cleavable later with fluoride ion and stable in the deprotection conditions used for all others groups present in the molecules.

Access to compounds **10** and **15** was performed through the reduction of their methyl esters **9** and **14**. This was carried out using lithium aluminium hydride in tetrahydrofuran for oxazolidines **9c** and **14d** and using either lithium borohydride in tetrahydrofuran or tetrahydrofuran/ethanol or diisobutylaluminium hydride in ether for all the others compounds **9a,b** and **14a,b,c**. The polyfunctionalized alcohols **10a,b,c** and **15a,b,d** thus obtained were then easily iodinated with iodine, triphenylphosphine, imidazole in toluene in the same ratio as that used for the transformation of **5** into **1**. For alcohol **15c**, activation through its mesylate derivative was required before iodination.

The method of preparation of esters **9** and **14** differed from the nature of the protecting groups of the amino function (Scheme 2).

Thus, (*R*)-**9a** was prepared in three steps and 56% overall yield from D-serine methylester. First, a reductive amination using benzaldehyde and sodium borohydride permitted the nearly quantitative formation of alcohol (*R*)-**7**¹⁰ which was treated with di-*tert*-butyl dicarbonate to give the carbamate (*R*)-**8**. The *O*-silylether (*R*)-**9a** was then isolated after reaction with *tert*-butyldimethylsilyl chloride/imidazole in anhydrous methylene chloride. Reduction with lithium borohydride furnished alcohol (*S*)-**10a** which was synthesized in four steps and 53% overall yield from D-serine methylester. Even the iodination seemed to proceed in good yield, as monitored by TLC, we were however unable to isolate **11a** because of the instability of the *tert*-butyldimethylsilyl group during the purification process.

Ester (*R*)-**6**¹¹ was efficiently prepared by protection of D-serine methyl ester as its carbamate and was then transformed either into the *tert*-butyldiphenylsilyl ether (*R*)-**9b**¹² in 98% yield or into the previously reported oxazolidine (*R*)-**9c**.¹³ Alcohols (*S*)-**10b**¹⁴ and (*S*)-**10c**¹³ were finally obtained in three steps and 73% and 59% overall yields respectively.



Scheme 2. Reagents and conditions : (i) Boc_2O , NEt_3 , THF, 0 °C then 20 °C (12h) and 50 °C (2h), 75% (ii) NEt_3 , PhCHO, MeOH, then NaBH_4 , MeOH, 99%; (iii) Boc_2O , Et_2O , 20 °C, 12 h, 71%; (iv) TBDPSCl or TBDMSCl , imidazole, CH_2Cl_2 , 0 °C, 10 min. then 20 °C, 12 h, (*R*)-**9a** (80%), (*R*)-**9b** (98%), (*S*)-**14a** (98%); (v) DMPE, *p*-TsOH, CH_2Cl_2 , 20 °C, (*R*)-**9c** (83%), (*S*)-**14d** (87%); (vi) LiBH_4 , 0 °C, 10 min. then 20 °C, 12 h, THF/EtOH (1/9) for (*S*)-**10a** (95%), THF for (*S*)-**10b** (99%), (*S*)-**15a** (98%) and (*S*)-**15c** (99%); (vii) LiAlH_4 , THF, 0 °C then 20 °C, 12 h, (*S*)-**10c** (95%), (*S*)-**15d** (quant.); (viii) I_2 , imidazole, PPh_3 , (*S*)-**11b** (toluene, 77%), (*S*)-**11c** (toluene, 74%), (*S*)-**16a** (toluene, 92%), (*S*)-**16b** ($\text{Et}_2\text{O}/\text{CH}_3\text{CN}$, 92%), (*S*)-**16d** (toluene, 82%); (ix) Boc_2O , Na_2CO_3 , dioxane/ H_2O , 20 °C, 12 h, 89%; (x) DCC, CH_2Cl_2 , *N*-hydroxysuccinimide, 20 °C, 12 h, then NaBH_4 , THF/EtOH (3/1), 0 °C, 15 min, 79%; (xi) NaH, BrCH_2Ph , Bu_4NI , DMF, 69%; (xii) MsCl , DMAP, NEt_3 , CH_2Cl_2 , 0 °C then NaI, acetone, 20 °C, 12 h, 71%; (xiii) Boc_2O , DMAP, CH_3CN , 20 °C, 12 h, 54%; (xiv) DIBAL-H, Et_2O , -78 °C, 45 min, 84%.

Iodination of (*S*)-**10b** and (*S*)-**10c** was efficiently achieved using our standard conditions affording the polyfunctionalized substrates (*R*)-**11b** and (*R*)-**11c**. These iodo-compounds can be kept several weeks at 0 °C under argon but needed, as for iodides **1a** and **1b**, a filtration on flash silica gel column before use (Scheme 2).

L-Aspartic acid methyl ester was classically transformed into its known carbamate (*S*)-**12**.^{15,16} The selective reduction of the carboxylic acid of (*S*)-**12** was then realized in two steps by activation with dicyclohexylcarbodiimide/*N*-hydroxysuccinimide followed by treatment with sodium borohydride, leading to (*S*)-**13**¹⁷ in 79% yield. Alcohol (*S*)-**13** was finally protected giving the pivotal *tert*-butyldiphenylsilyl ether (*S*)-**14a** in 98% yield using *tert*-butyldiphenylsilyl chloride/imidazole. This latter was further converted to the original esters **14b,c**. Indeed, introduction of a second *tert*-butoxycarbonyl group on **14a** was accomplished with di-*tert*-butyl dicarbonate/dimethylaminopyridine affording (*S*)-**14b** in 54% yield. Reaction of the carbamate (*S*)-**14a** with benzyl bromide in the presence of tetrabutylammonium iodide, furnished (*S*)-**14c** in 69% yield.

All these esters were submitted to a reduction process and led finally, from L-aspartic acid methyl ester, to (*S*)-**15a** (four steps, 68% overall yield), (*S*)-**15b** and (*S*)-**15c** (five steps, 31% and 47% overall yields, respectively).

Additionally, oxazolidine protection of (*S*)-**13** was accomplished, as reported,¹⁵ with *para*-toluenesulfonic acid/2,2-dimethoxypropane in methylene chloride giving (*S*)-**14d** in 87% yield, the reduction of which, using lithium aluminium hydride, afforded quantitatively alcohol (*S*)-**15d**¹⁸ (four steps and 61% overall yield from L-aspartic acid methylester).

In a last step, all the alcohols **15** were transformed into their iodide derivatives **16a**, **16b**, **16c** and **16d**¹⁹ in a range of 71-92% yields using our standard conditions for **16a,b,d** and through its mesylate for **16c** (Scheme 2).

Since compounds **5a**, **9c**, **10c**, **11c**, **14d**, **15d**, **16d** were not fully described with regard to their characterisation data, and as some preparative procedures were different to those previously published, we report them in this paper, together with complete sets of data.

Conclusions

In conclusion, D-serine or L-aspartic acid constitute inexpensive commercially available substrates for the rapid and efficient synthesis of enantiomerically pure orthogonally protected glycerols and 2-aminodiols, applying short synthetic pathways and convenient transformations. Furthermore, these small polyfunctionalized synthons were efficiently transformed into their iodide derivatives. These products constitute useful building blocks for the elaboration of more complex structures.

Experimental Section

General. Melting points were measured using a Reichert melting point apparatus and are uncorrected. Infra-Red spectra were recorded on a Perkin-Elmer 881 instrument. Nuclear magnetic resonance spectra were obtained using BRUKER AC 400 spectrometer (^1H , 400 MHz, ^{13}C , 100 MHz). Chemical shifts (δ values) are expressed in parts per million (ppm) with solvents as internal standards and coupling constants (J) are expressed in Hertz. Mass spectra were recorded with a Hewlett Packard 5989B instrument and high resolution mass spectra (HRMS) were performed with a Q-TOF micromass. Chromatography was performed using silica gel 60 (230-400 mesh) and thin layer chromatography (TLC) was performed on silica gel 60PF₂₅₄ plates. Compounds were identified using UV fluorescence ($\lambda = 254$ nm) and/or staining with a 5% phosphomolybdic acid solution in ethanol following by heating. Commercially reagents were used as received from the manufacturers except for tetrahydrofuran (distilled from potassium/benzophenone) and dichloromethane (dried over calcium hydride prior to use).

General procedure for the preparation of iodides

To a stirred solution of the appropriate alcohol (1.02 mmol) in a 3/2 mixture of diethyl ether/acetonitrile (15 mL) at 0 °C or in toluene (15 mL) at 20 °C were successively added imidazole (2.25 mmol), iodine (2.45 mmol) and triphenylphosphine (2.04 mmol). The stirring was maintained for 1 h at 0 °C and then for 24 h at 20 °C or directly at 20 °C for 24 h when toluene was used. The reaction was quenched by addition of a 10% aqueous sodium thiosulfate solution (6 mL) followed by saturated aqueous ammonium chloride solution (3 mL). The organic layer was extracted with ether, washed with a 10% aqueous sodium thiosulfate solution until the solution became colourless. Then it was washed with brine, dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography using as solvents a mixture of ethyl acetate/cyclohexane to afford the corresponding iodide.

General procedure for reduction of esters: method A with LiBH_4 in THF

To a stirred solution of the appropriate ester (1.04 mmol) in anhydrous tetrahydrofuran (20 mL), at 0 °C and under argon atmosphere, was dropwise added a 2.0 M lithium borohydride solution (1.56 mmol) in tetrahydrofuran. The resulting mixture was stirred for 12 h at 20 °C, quenched by addition of saturated aqueous ammonium chloride solution (1.0 mL). After extraction with ethyl acetate, the organic layer was washed with brine, dried (MgSO_4) and concentrated under reduced pressure. The residue was then purified by flash column chromatography (ethyl acetate/cyclohexane) to afford the corresponding alcohol.

General procedure for reduction of esters: method B with LiBH_4 in THF/EtOH

To a stirred solution of ester (1.56 mmol) in tetrahydrofuran/ethanol (v/v 1/9), at 0 °C and under argon atmosphere was dropwise added a 2.0 M lithium borohydride solution (0.78 mmol) in tetrahydrofuran. The resulting mixture was stirred for 12 h at 20 °C, and the reaction was stopped

by addition of a 0.5 M hydrochloric acid solution. After extraction with diethyl ether, the organic layer was washed with saturated aqueous sodium bicarbonate solution, followed by brine, dried (MgSO_4) and concentrated under reduced pressure. The residue was then purified by flash column chromatography (ethyl acetate/cyclohexane) to afford the corresponding alcohol.

General procedure for reduction of esters: method C with LiAlH_4 in THF

To a stirred solution of ester (1.94 mmol) in anhydrous tetrahydrofuran (5 mL), at 0 °C and under argon atmosphere, was dropwise added a 1.0 M lithium aluminium hydride solution in tetrahydrofuran (1.16 mmol). The resulting mixture was stirred for 12 h at 20 °C. The reaction was quenched at 0 °C by sequential addition of water, 15% sodium hydroxide solution and water. The resulting mixture was dried (MgSO_4), filtered and the solvent was concentrated under reduced pressure to afford the corresponding pure alcohol.

General procedure for preparation of oxazolidines

To a solution of aminoalcohol (3.47 mmol) in anhydrous dichloromethane (40 mL) at 20 °C, was added *para*-toluenesulfonic acid (60 mg, 3.12 mmol) followed by 2,2-dimethoxypropane (1.29 mL, 10.4 mmol). The mixture was stirred 48 h at 20 °C before neutralization by sodium carbonate. After filtration on a Celite[®] pad, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (ethyl acetate/cyclohexane, 3:7).

(2R)-2-(Benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-1-iodopropane (1a). Compound **1a** was prepared from alcohol (*S*)-**5a** in diethyl ether/acetonitrile following the general procedure for the preparation of iodides. Pale yellow oil (515 mg, 95%); R_f 0.89 (EtOAc/cyclohexane, 1/19); $[\alpha]_D^{25} = -9.24$ (c 0.99, CHCl_3); IR (neat) ν_{max} 2929, 2857, 2360, 2344, 1472, 1456, 1427, 1188, 1113; ^1H NMR (CDCl_3) δ 7.72-7.68 (m, 4H, H-Ar), 7.46-7.30 (m, 11H, H-Ar), 4.62 (d, 1H, $J = 12.5$ Hz, CH_2Ph), 4.55 (d, 1H, $J = 12.5$ Hz, CH_2Ph), 3.82 (dd, 1H, $J = 10.5, 5.0$ Hz, $\text{CH}_2\text{-O}$), 3.74 (dd, 1H, $J = 10.5, 5.5$ Hz, $\text{CH}_2\text{-O}$), 3.52-3.40 (m, 3H, $\text{CH}_2\text{-I}$ and CH-O), 1.09 (s, 9H, *t*-Bu); ^{13}C NMR (CDCl_3) δ 138.1 (C-Ar), 135.8 (C-Ar), 133.4 (C-Ar), 130.0 (C-Ar), 128.5 (C-Ar), 127.9 (C-Ar), 78.5 (CH-O), 72.1 (CH_2Ph), 65.1 ($\text{CH}_2\text{-O}$), 27.0 (*t*-Bu), 19.9 (C), 7.0 ($\text{CH}_2\text{-I}$); HRMS-ESI m/z calcd for $\text{C}_{26}\text{H}_{31}\text{O}_2\text{SiIna}$ $[\text{M} + \text{Na}]^+$: 553.1036, found : 553.1014.

(2R)-3-(*tert*-Butyldiphenylsilyloxy)-1-iodo-2-(methoxymethoxy)propane (1b). Compound **1b** was prepared from alcohol (*S*)-**5b** in diethyl ether/acetonitrile following the general procedure for the preparation of iodides. Pale yellow oil (360 mg, 73%); R_f 0.90 (EtOAc/cyclohexane, 1/1); $[\alpha]_D^{25} = -7.9$ (c 1.03, CHCl_3); IR (neat) ν_{max} 2954, 2931, 2858, 2360, 2343, 1473, 1428, 1112; ^1H NMR (CDCl_3) δ 7.70-7.65 (m, 4H, H-Ar), 7.44-7.37 (m, 6H, H-Ar), 4.66 (s, 2H, O- $\text{CH}_2\text{-O}$), 3.77 (dd, 1H, $J = 10.5, 5.0$ Hz, $\text{CH}_2\text{-O}$), 3.68 (dd, 1H, $J = 10.5, 5.0$ Hz, $\text{CH}_2\text{-O}$), 3.58 (quint, 1H, $J = 5.0$ Hz, CH-O), 3.47 (dd, 1H, $J = 10.5, 5.0$ Hz, $\text{CH}_2\text{-I}$), 3.39 (dd, 1H, $J = 10.5, 5.0$ Hz, $\text{CH}_2\text{-I}$), 3.25 (s, 3H, OCH_3), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR (CDCl_3) δ 135.7 (C-Ar), 133.2 (C-Ar), 129.8 (C-Ar), 127.8 (C-Ar), 96.0 (O- $\text{CH}_2\text{-O}$), 76.5 (CHO), 65.3 ($\text{CH}_2\text{-O}$), 55.9 (OCH_3), 26.8 (*t*-Bu), 19.2 (C), 7.4 ($\text{CH}_2\text{-I}$); HRMS-ESI m/z calcd for $\text{C}_{21}\text{H}_{30}\text{O}_4\text{SiNa}$ $[\text{M} + \text{Na}]^+$: 507.0828, found : 507.0836.

(2R)-2-(tert-Butyldimethylsilyloxy)-3-(tert-butyldiphenylsilyloxy)-1-iodopropane (1c). Compound **1c** was prepared from alcohol (*S*)-**5c** in diethyl ether/acetonitrile following the general procedure for the preparation of iodides. Pale yellow oil (415 mg, 74%); R_f 0.90 (EtOAc/cyclohexane, 1/9); IR (neat) ν_{\max} 2956, 2929, 2858, 2360, 2343, 1473, 1428, 1126, 1112, 1107; ^1H NMR (CDCl_3) δ 7.70-7.65 (m, 4H, H-Ar), 7.47-7.37 (m, 6H, H-Ar), 3.63 (m, 1H, CHO), 3.58-3.53 (m, 2H, $\text{CH}_2\text{-O}$), 3.47 (dd, 1H, $J = 10.0, 4.0$ Hz, $\text{CH}_2\text{-I}$), 3.36 (dd, 1H, $J = 10.0, 4.0$ Hz, $\text{CH}_2\text{-I}$), 1.06 (s, 9H, *t*-Bu), 0.85 (s, 9H, *t*Bu), 0.06 (s, 3H, CH_3), - 0.06 (s, 3H, CH_3); ^{13}C NMR (CDCl_3) δ 135.9 (C-Ar), 135.8 (C-Ar), 135.6 (C-Ar), 135.5 (C-Ar), 133.3 (C-Ar), 133.2 (C-Ar), 129.8 (C-Ar), 127.7 (C-Ar), 71.7 (CH-O), 66.8 ($\text{CH}_2\text{-O}$), 26.9 (*t*-Bu), 25.8 (*t*-Bu), 19.2 (C), 18.0 (C), 11.6 ($\text{CH}_2\text{-I}$), - 4.6 (CH_3), - 4.7 (CH_3); HRMS-ESI m/z calcd for $\text{C}_{25}\text{H}_{39}\text{O}_2\text{Si}_2\text{INa}$ [$\text{M} + \text{Na}$] $^+$: 577.1431, found : 577.1432.

Methyl (2R)-2-(benzyloxy)-3-(tert-butyldiphenylsilyloxy)propanoate (4a). To a stirred solution of (*R*)-**3** (2.80 g, 7.83 mmol) in anhydrous diethyl ether (35 mL), at 20 °C and under argon atmosphere, were added silver oxide (I) (2.72 g, 11.75 mmol) followed by benzyl bromide (2.33 mL, 19.58 mmol). The reaction mixture was stirred at 20 °C for further 3 days. After filtration on a Celite[®] pad, the filtrate was concentrated. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:19) to afford **4a** (2.88 g, 82%) as a colorless oil; R_f 0.82 (EtOAc/cyclohexane, 1/1); $[\alpha]_{\text{D}}^{25} = + 37.09$ (c 0.86, CHCl_3); IR (neat) ν_{\max} 2954, 2932, 2858, 1749, 1428; ^1H NMR (CDCl_3) δ 7.68-7.61 (m, 4H, H-Ar), 7.36-7.21 (m, 11H, H-Ar), 4.68 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.45 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.06 (t, 1H, $J = 5.0$ Hz, CH-O), 3.88 (dd, 1H, $J = 10.5, 5.5$ Hz, $\text{CH}_2\text{-O}$), 3.86 (dd, 1H, $J = 10.5, 5.5$ Hz, $\text{CH}_2\text{-O}$), 3.67 (s, 3H, OCH_3), 0.96 (s, 9H, *t*-Bu); ^{13}C NMR (CDCl_3) δ 171.4 (CO_2Me), 137.5 (C-Ar), 135.7 (C-Ar), 133.2 (C-Ar), 129.7 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 79.3 (CH-O), 72.5 (CH_2Ph), 64.8 ($\text{CH}_2\text{-O}$), 51.9 (OCH_3), 26.7 (*t*-Bu), 19.2 (C); HRMS-ESI m/z calcd for $\text{C}_{27}\text{H}_{32}\text{O}_4\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$: 471.1968, found: 471.1963.

Methyl (2R)-3-(tert-butyldiphenylsilyloxy)-2-(methoxymethoxy)propanoate (4b). Diisopropylethylamine (1.97 mL, 11.43 mmol) followed 15 min later by methoxymethane chloride (0.91 mL, 11.43 mmol) were added under argon atmosphere to a stirred solution of (*R*)-**3** (1.37 g, 3.81 mmol) in anhydrous dichloromethane (10 mL). The resulting mixture was kept at 20 °C for 12 h before additional diisopropylethylamine (0.68 mL, 3.81 mmol) and methoxymethane chloride (0.30 mL, 3.81 mmol) were added followed, one more time, 6 h later, by the addition of the same amounts of the two reagents. After 48 h, the reaction was quenched by water (2.5 mL). The layers were separated and the organic one was washed with water and dried (MgSO_4) before concentration to afford **4b** as a pale oil (1.484 g, 97%); R_f 0.51 (EtOAc/cyclohexane, 1/4); $[\alpha]_{\text{D}}^{25} = + 7.0$ (c 1.3, CHCl_3). For details of ^1H and ^{13}C NMR spectroscopic data, see our previously reported work described in reference 8.

Methyl (2R)-2-(tert-butyldimethylsilyloxy)-3-(tert-butyldiphenylsilyloxy)propanoate (4c). 4-Dimethylaminopyridine (0.034 g, 0.28 mmol) and imidazole (0.105 g, 1.54 mmol) were added consecutively at -10 °C under argon atmosphere to a stirred solution of (*R*)-**3** (0.500 g, 1.39 mmol) in anhydrous dichloromethane (10 mL). The mixture was stirred for 15 min before adding

tert-butyldimethylsilyl chloride (0.232 g, 1.54 mmol) and the stirring was pursued 48 h. The reaction was stopped by adjunction of water (4 mL) and the resulting solution was extracted with ethyl acetate. The organic layer was washed with brine and dried (MgSO₄). Solvent evaporation afforded after purification by flash chromatography (ether/pentane; 1:19) **4c** as an oil (0.540 g, 82%), *R_f* 0.74 (ether/pentane, 1/19); [α]_D²⁵ = + 0.80 (c 1.12, CHCl₃); IR (neat) ν_{\max} 2953, 2931, 2858, 1759, 1473, 1428, 1151, 1113; ¹H NMR (CDCl₃) δ 7.61-7.59 (m, 4H, H-Ar), 7.35-7.28 (m, 6H, H-Ar), 4.25 (t, 1H, *J* = 5.0 Hz, CH-O), 3.75 (bd, 2H, *J* = 5.0 Hz, CH₂-O), 3.65 (s, 3H, O-CH₃), 0.95 (s, 9H, *t*Bu), 0.82 (s, 9H, *t*-Bu), 0.00 (s, 3H, CH₃), -0.03 (s, 3H, CH₃); ¹³C NMR (CDCl₃) δ 172.5 (CO₂Me), 135.6 (C-Ar), 135.5 (C-Ar), 133.3 (C-Ar), 133.1 (C-Ar), 129.7 (C-Ar), 127.7 (C-Ar), 73.7 (CH-O), 66.5 (CH₂-O), 51.8 (O-CH₃), 26.6 (*t*-Bu), 25.7 (*t*-Bu), 19.2 (C), -5.2 (CH₃); HRMS-ESI *m/z* calcd for C₂₆H₄₀O₄Si₂Na [M + Na]⁺: 495.2363; found: 495.2351.

(2S)-2-(Benzyloxy)-3-(tert-butyldiphenylsilyloxy)propanol (5a). Compound **5a** was obtained from reduction of (*R*)-**4a** using the general Method A of reduction. Oil (0.384 g, 88%); *R_f* 0.55 (EtOAc/cyclohexane, 1/4); [α]_D²⁵ = - 24.1 (c 1.7, CHCl₃) (lit⁹ [α]_D²⁵ = - 24.5 (c 1.1, CHCl₃); IR (neat) ν_{\max} 3445, 3069, 1472, 1427, 1113, 1106; ¹H NMR (CDCl₃) δ 7.70-7.68 (m, 4H, H-Ar), 7.45-7.29 (m, 11H, H-Ar), 4.65 (d, 1H, *J* = 11.5 Hz, CH₂Ph), 4.53 (d, 1H, *J* = 11.5 Hz, CH₂Ph), 3.84-3.62 (m, 5H, CH₂-O, CH-O, CH₂-OH), 2.09 (dd, 1H, *J* = 6.5, 5.5 Hz, OH), 1.08 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 138.3 (C-Ar), 135.6 (C-Ar), 133.2 (C-Ar), 129.8 (C-Ar), 128.5 (C-Ar), 127.8 (C-Ar), 79.6 (CH-O), 72.2 (CH₂), 63.6 (CH₂), 62.8 (CH₂), 26.9 (*t*-Bu), 19.2 (C); HRMS-ESI *m/z* calcd for C₂₆H₃₂O₃SiNa [M + Na]⁺: 443.2018, found: 443.2018.

(2S)-3-(tert-Butyldiphenylsilyloxy)-2-(methoxymethoxy)propanol (5b). Compound **5b** was obtained from reduction of (*R*)-**4b** using the general Method A of reduction. Oil (342 mg, 88%); *R_f* 0.33 (EtOAc/cyclohexane, 3/7); [α]_D²⁵ = - 36.11 (c 1.15, CHCl₃); IR (neat) ν_{\max} 3452, 3072, 3052, 1473, 1428, 1112, 1106; ¹H NMR (CDCl₃) δ 7.69-7.67 (m, 4H, H-Ar), 7.46-7.38 (m, 6H, H-Ar), 4.68 (s, 2H, O-CH₂-O), 3.83-3.66 (m, 5H, CH₂-OH, CH-O, CH₂-O), 3.37 (s, 3H, OCH₃), 2.67 (dd, 1H, *J* = 8.0, 5.0 Hz, OH), 1.07 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 135.6 (C-Ar), 133.2 (C-Ar), 129.8 (C-Ar), 127.8 (C-Ar), 96.7 (O-CH₂-O), 80.2 (CH-O), 63.8 (CH₂-O), 63.4 (CH₂-OH), 55.6 (O-CH₃), 26.8 (*t*-Bu), 19.2 (C); HRMS-ESI *m/z* calcd for C₂₁H₃₀O₄SiNa [M + Na]⁺: 397.1811, found: 397.1794.

(2S)-2-(tert-Butyldimethylsilyloxy)-3-(tert-butyldiphenylsilyloxy)propanol (5c). Compound **5c** was obtained from reduction of (*R*)-**4c** using the general Method A of reduction. Oil (0.217 g, 47%); *R_f* 0.62 (EtOAc/cyclohexane, 1/9); [α]_D²⁵ = - 15.86 (c 1.60, CHCl₃); IR (neat) ν_{\max} 3450, 3082, 3058, 1473, 1428, 1113, 1106; ¹H NMR (CDCl₃) δ 7.69-7.65 (m, 4H, H-Ar), 7.46-7.36 (m, 6H, H-Ar), 3.78 (m, 1H, CH-O), 3.74-3.68 (m, 2H, CH₂-O), 3.64 (m, 1H, CH₂-I), 3.59 (dd, 1H, *J* = 10.5, 5.0 Hz, CH₂-I), 1.05 (s, 9H, *t*-Bu), 0.84 (s, 9H, *t*-Bu), 0.01 (s, 3H, CH₃), -0.06 (s, 3H, CH₃); ¹³C NMR (CDCl₃) δ 135.6 (C-Ar), 133.3 (C-Ar), 133.2 (C-Ar), 129.8 (C-Ar), 127.8 (C-Ar), 72.5 (CH-O), 65.1 (CH₂-O), 64.7 (CH₂-OH), 26.8 (*t*-Bu), 25.7 (*t*-Bu), 19.1 (C), 18.0 (C), -5.0 (CH₃); HRMS-ESI *m/z* calcd for C₂₅H₄₀O₃Si₂Na [M + Na]⁺: 467.2414, found: 467.2433.

Methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-hydroxypropanoate (6). To a stirred solution of D-serine methyl ester hydrochloride (2.870 g, 18.40 mmol) in anhydrous tetrahydrofuran (60

mL) was added, at 0 °C under argon atmosphere, triethylamine (5.60 mL, 39.60 mmol) followed 15 min later by di-*tert*-butyl dicarbonate (4.02 g, 18.40 mmol) in anhydrous tetrahydrofuran (30 mL). The reaction mixture was stirred 12 h at 20 °C and then heated at 50 °C for 2 h. After concentration, the residue was dissolved by addition of diethyl ether (60 mL) and water (60 mL). The aqueous layer was extracted. The organic layer was successively washed by a 3% aqueous hydrochloric acid solution, a 5% aqueous sodium bicarbonate solution and then by brine before being dried (MgSO₄). The solvent was then evaporated under vacuo to give **6** as a pale yellow oil (3.02 g, 75%); *R_f* 0.58 (EtOAc/cyclohexane 7/3); $[\alpha]_{\text{D}}^{25} = +17.8$ (c 7.5, MeOH) (lit. for the (*S*)-isomer¹¹ $[\alpha]_{\text{D}}^{25} = -17.5$ (c 5.0, MeOH)); IR (neat) ν_{max} 3400, 1749, 1692; ¹H NMR (CDCl₃) δ 5.46 (bs, 1H, NH), 4.40 (bs, 1H, CH), 3.95 (m, 2H, CH₂-O), 3.79 (s, 3H, OMe), 2.32 (bs, 1H, OH), 1.45 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 171.4 (CO₂Me), 155.7 (CO₂*t*-Bu), 80.1 (C), 63.1 (CH₂O), 55.6 (CH), 52.5 (OCH₃), 28.2 (*t*-Bu).

Methyl (2*R*)-2-(benzylamino)-3-hydroxypropanoate (7). To a stirred suspension of D-serine methyl ester hydrochloride (3.90 g, 25.00 mmol) in methanol (25 mL) at 0 °C and under argon atmosphere, was added triethylamine (3.5 mL, 25.0 mmol) followed after 15 min by benzaldehyde (2.60 mL, 25.00 mmol). The reaction mixture was stirred 2 h at 20 °C then cold at 0 °C. Sodium borohydride was slowly and portion wise added (1.90 g, 50.00 mmol) followed 30 min. later by a 4M hydrochloric acid solution (50 mL) and diethyl ether (125 mL). The organic layer was extracted and washed with a 4M hydrochloric acid solution (50 mL). The aqueous layers were then combined, neutralized with solid sodium bicarbonate and extracted with diethyl ether. The organic layer thus obtained was dried (MgSO₄) and the solvent was evaporated under vacuo to give (*R*)-**7** (5.2 g, 99%) as a yellow oil. *R_f* 0.60 (EtOAc); $[\alpha]_{\text{D}}^{25} = +36.6$ (c 6.2, CHCl₃); IR (neat) ν_{max} 3325, 1737; ¹H NMR (CDCl₃) δ 7.42-7.25 (m, 5H, H-Ar), 3.87 (dd, *J* = 13.0, 4.5 Hz, 1H, CH₂Ph), 3.77 (dd, *J* = 11.0, 4.5 Hz, 1H, CH₂-OH), 3.74 (s, 3H, O-CH₃), 3.73 (m, 1H, CH₂Ph), 3.62 (dd, *J* = 11.0, 6.5 Hz, 1H, CH₂-OH), 3.44 (m, 1H, CH-N), 2.35 (bs, 2H, OH, NH); ¹³C NMR (CDCl₃) δ 173.4 (CO₂Me), 139.2 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 127.3 (C-Ar), 62.4 (CH₂-O), 61.8 (CH-N), 52.2 (CH₂Ph), 52.0 (OCH₃); HRMS-ESI *m/z* calcd for C₁₁H₁₆NO₃ [M + H]⁺: 210.1130, found: 210.1136.

Methyl (2*R*)-2-[benzyl(*tert*-butoxycarbonyl)amino]-3-hydroxypropanoate (8). To a stirred solution of (*R*)-**7** (4.00 g, 19.10 mmol) in anhydrous diethyl ether (6 mL) was added under argon di-*tert*-butyl dicarbonate (4.00 g, 18.10 mmol). The reaction mixture was stirred 12 h at 20 °C. The solution was then successively washed with a 0.1M hydrochloric acid solution, a saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 2:3) affording **8** as a pale yellow oil (4.00 g, 71%). *R_f* 0.70 (EtOAc/cyclohexane 2/3); $[\alpha]_{\text{D}}^{25} = +28.7$ (c 2.4, CHCl₃); ¹³C NMR (CDCl₃) δ 173.4 (CO₂Me), 155.3 (CO₂*t*-Bu), 137.9 (C-Ar), 137.5 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 127.7 (C-Ar), 127.5 (C-Ar), 81.3 (C), 61.8 (CH₂-O), 61.0 (CH-N), 52.2 (CH₂Ph), 52.0 (OCH₃), 28.2 (*t*-Bu).

Methyl (2*R*)-2-[benzyl(*tert*-butoxycarbonyl)amino]-3-(*tert*-butyldimethylsilyloxy)propaneate (9a).

To a stirred solution of (*R*)-**8** (4.00 g, 12.90 mmol) and imidazole (3.50 g, 51.60 mmol) in anhydrous dichloromethane (60 mL) was added dropwise under argon atmosphere a solution of *tert*-butyldimethylsilyl chloride (2.90 g, 19.40 mmol) in anhydrous dichloromethane (60 mL). The reaction was stirred for 3 h at 20 °C before being diluted with diethyl ether. The organic layer was washed with water and dried (MgSO₄). The solvent was evaporated and the residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:4) furnishing **9a** as a colourless oil (4.40 g, 80%) which appeared at room temperature in the NMR spectra as a mixture of two rotamers *a* and *b*; *R_f* 0.28 (EtOAc/cyclohexane 1/4); [α]_D²⁵ = + 32.2 (c 2.9, CHCl₃); ¹H NMR (CDCl₃) δ 7.35-7.15 (m, 5H, H-Ar, *a* and *b*), 4.95 (d, *J* = 15.0 Hz, 1H, CH₂Ph, *a*), 4.72 (d, *J* = 16.0 Hz, 1H, CH₂Ph, *b*), 4.50 (m, 1H, CH, *b*), 4.39 (d, *J* = 16.0 Hz, 1H, CH₂Ph, *b*), 4.28 (d, *J* = 15.0 Hz, 1H, CH₂Ph, *a*), 4.10-3.90 (m, 3H, CH₂-O, *a* and *b*, CH, *a*), 3.63 (s, 3H, O-CH₃, *b*), 3.59 (s, 3H, O-CH₃, *a*), 1.41 (s, 9H, *t*-Bu, *a*), 1.33 (s, 9H, *t*-Bu, *b*), 0.88 (s, 9H, *t*-Bu, *a*), 0.82 (s, 9H, *t*-Bu, *b*), 0.00 (s, 6H, CH₃, *a*), -0.02 (s, 3H, CH₃, *b*), -0.08 (s, 3H, CH₃, *b*); ¹³C NMR (CDCl₃) δ 170.4 (CO₂Me, *a* and *b*), 155.7 (CO₂*t*Bu, *b*), 155.1 (CO₂*t*Bu, *a*), 139.3 (C-Ar, *b*), 138.1 (C-Ar, *a*), 128.2 (C-Ar, *a* and *b*), 128.0 (C-Ar, *b*), 127.0 (C-Ar, *a*), 126.6 (C-Ar, *a* and *b*), 80.7 (C, *a*), 80.4 (C, *b*), 62.4 (CH₂-O, *a*), 62.0 (CH₂-O, *b*), 61.3 (CH-N, *a*), 61.0 (CH-N, *b*), 51.9 (CH₂Ph, *a*), 51.8 (O-CH₃, *b*), 51.7 (O-CH₃, *a*), 51.3 (CH₂Ph, *b*), 28.3 (*t*-Bu, *a*), 28.2 (*t*-Bu, *b*), 25.8 (*t*-Bu, *a* and *b*), 18.1 (C, *a* and *b*), -3.6 (CH₃, *a*), -5.6 (CH₃, *b*). HRMS-ESI *m/z* calcd for C₂₂H₃₇NO₅SiNa [M + Na]⁺: 446.2339, found: 446.2359.

Methyl (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-(*tert*-butyldiphenylsilyloxy)propanoate (9b).

To a stirred solution of (*R*)-**6** (0.800 g, 3.65 mmol) in anhydrous dichloromethane (10 mL) at 0 °C and under argon atmosphere was added *tert*-butyldiphenylsilyl chloride (1.90 mL, 7.30 mmol) followed slowly by a solution of imidazole (486 mg, 7.30 mmol) in anhydrous dichloromethane (2 mL). The reaction mixture was then stirred at 20 °C for 12 h and quenched with water (10 mL). The organic layer was washed twice with water. After drying (MgSO₄), the solvent was evaporated in vacuo and the residue was purified by flash column chromatography (diethyl ether/pentane, 1:9) furnishing **9b** as a yellow oil (1.64 g, 98%). *R_f* 0.48 (EtOAc/cyclohexane 3/7); [α]_D²⁵ = - 15.5 (c 4.5, CHCl₃) (for (*S*)-**9b** lit^{12a} [α]_D²⁵ = + 14.2 (c 1.0, CHCl₃) and lit^{12b} [α]_D²⁵ = + 14.3 (c 1.0, CHCl₃); IR (neat) ν_{\max} 3447, 1750, 1719; ¹H NMR (CDCl₃) δ 7.61 (m, 4H, H-Ar), 7.40 (m, 6H, H-Ar), 5.42 (d, *J* = 9.0 Hz, 1H, NH), 4.40 (dt, *J* = 9.0, 3.0 Hz, 1H, CH), 4.07 (dd, *J* = 10.0, 3.0 Hz, 1H, CH₂-O), 3.89 (dd, *J* = 10.0, 3.0 Hz, 1H, CH₂-O), 3.74 (s, 3H, OCH₃), 1.47 (s, 9H, *t*-Bu), 1.03 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 171.2 (CO₂Me), 155.3 (CO₂*t*Bu), 135.5 (C-Ar), 135.4 (C-Ar), 132.9 (C-Ar), 132.7 (C-Ar), 129.8 (C-Ar), 127.7 (C-Ar), 79.9 (C), 64.6 (CH₂-O), 55.5 (CH), 52.2 (OCH₃), 28.3 (*t*-Bu), 26.7 (*t*-Bu), 19.2 (C); MS (ESI) *m/z* 481 ([M + Na + 1]⁺, 30), 480 ([M + Na]⁺, 100), 424 (10).

Methyl [(4*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]carboxylate (9c).

Compound **9c** was prepared from (*R*)-**6** following the general procedure of preparation of oxazolidinones and appeared in the NMR spectra at room temperature, as a mixture of two rotamers *a* and *b*. Pale yellow oil (0.746 g, 83%); *R_f* 0.67 (EtOAc/cyclohexane 2/3); [α]_D²⁵ = +

53.6 (c 2.02, CHCl₃) (lit.^{13b} $[\alpha]_D^{20} = +49.8$ (c 1.04, CHCl₃)); IR (neat) ν_{\max} 1758, 1708; ¹H NMR (CDCl₃) δ 4.48 (dd, $J = 7.0, 2.5$ Hz, 1H, CH, *a*), 4.37 (dd, $J = 7.0, 3.0$ Hz, 1H, CH, *b*), 4.15 (dd, $J = 9.0, 7.0$ Hz, 1H, CH₂-O, *a*), 4.12 (dd, $J = 9.0, 7.0$ Hz, 1H, CH₂-O, *b*), 4.05 (dd, $J = 9.0, 2.5$ Hz, 1H, CH₂-O, *a*), 4.02 (dd, $J = 9.0, 3.0$ Hz, 1H, CH₂-O, *b*), 3.75 (s, 3H, O-CH₃, *a* and *b*), 1.67 (s, 3H, CH₃, *b*), 1.63 (s, 3H, CH₃, *a*), 1.53 (s, 3H, CH₃, *b*), 1.49 (s, 9H, *t*-Bu *a*), 1.42 (s, 3H, CH₃, *a*), 1.41 (s, 9H, *t*-Bu, *b*); ¹³C NMR (CDCl₃) δ 171.5 (CO₂Me, *b*), 171.0 (CO₂Me, *a*), 151.9 (CO₂*t*Bu, *a*), 151.0 (CO₂*t*Bu, *b*), 94.8 (C, *b*), 94.2 (C, *a*), 80.6 (C, *a*), 80.0 (C, *b*), 66.0 (CH₂-O, *b*), 65.8 (CH₂-O, *a*), 59.1 (CH, *b*), 59.0 (CH, *a*), 52.1 (O-CH₃, *a*), 52.0 (O-CH₃, *b*), 28.1 (*t*-Bu, *a*), 28.0 (*t*-Bu, *b*), 25.8 (CH₃, *b*), 25.0 (CH₃, *b*), 24.7 (CH₃, *a*), 24.2 (CH₃, *a*).

***tert*-Butyl *N*-benzyl-*N*-[(1*S*)-1-[(*tert*-butyldimethylsilyloxy)methyl]-2-hydroxyethyl]carbamate (10a).** Compound **10a** was obtained from reduction of (*R*)-**9a** using the general Method B of reduction. Colourless oil (0.588 g, 95%); R_f 0.49 (EtOAc/cyclohexane 3/7); $[\alpha]_D^{25} = +6.3$ (c 4.4, CHCl₃); ¹H NMR (CDCl₃) δ 7.35-7.15 (m, 5H, H-Ar), 4.70 (m, 1H, CH₂Ph), 4.30 (m, 1H, CH₂Ph), 4.00-3.60 (m, 5H, CH₂-OH, CH₂-O, CH), 1.80 (bs, 1H, OH), 1.41 (s, 9H, *t*Bu), 0.85 (s, 9H, CH₃), 0.00 (s, 6H, CH₃); ¹³C NMR (CDCl₃) δ 156.6 (CO₂*t*Bu), 139.2 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 127.1 (C-Ar), 80.5 (C), 63.3 (CH₂-O), 62.0 (CH-N), 61.9 (CH₂-OH), 52.4 (CH₂Ph), 28.3 (*t*Bu), 25.7 (CH₃), 18.1 (CH₃), -5.6 (CH₃).

***tert*-Butyl *N*-[(1*S*)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-2-hydroxyethyl]carbamate (10b).** Compound **10b** was obtained from reduction of (*R*)-**9b** using the general Method A of reduction. White solid (0.442 g, 99%); mp 77-78 °C (EtOAc); R_f 0.60 (EtOAc/cyclohexane 2/3); $[\alpha]_D^{25} = -4.7$ (c 3.7, CHCl₃) (lit.¹⁴ $[\alpha]_D^{25} = -4.1$ (c 1.12, CHCl₃)); ¹H NMR (CDCl₃) δ 7.65 (m, 4H, H-Ar), 7.41 (M, 6H, H-Ar), 5.09 (d, $J = 5.0$ Hz, 1H, NH), 3.84-3.65 (m, 5H, CH, CH₂-O, CH₂-OH), 2.53 (bs, 1H, OH), 1.44 (s, 9H, *t*-Bu), 1.07 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 156.1 (CO₂*t*Bu), 135.5 (C-Ar), 132.8 (C-Ar), 129.9 (C-Ar), 127.8 (C-Ar), 79.6 (C), 64.1 (CH₂-O), 63.6 (CH₂-OH), 53.0 (CH-N), 28.3 (CH₃), 26.8 (CH₃), 19.2 (C).

***tert*-Butyl [(4*S*)-2,2-dimethyl-4-(hydroxymethyl)-1,3-oxazolidin-3-yl]carboxylate (10c).** Compound **10c** was obtained from reduction of (*R*)-**9c** using the general Method C of reduction and was detected at room temperature as a mixture of two rotamers *a* and *b*. Colourless oil (0.420 g, 95%); R_f 0.30 (EtOAc/cyclohexane 2/3); $[\alpha]_D^{25} = +24.5$ (c 2.3, CHCl₃) (lit.^{13b} $[\alpha]_D^{20} = +23.6$ (c 1.44, CHCl₃) and lit.^{13a} $[\alpha]_D^{20} = +17.9$ (c 2.13, CHCl₃)); IR (neat) ν 3427, 1697; ¹H NMR (CDCl₃) δ 4.02-3.88 (m, 3H, CH, CH₂-O), 3.77-3.54 (m, 3H, CH₂-OH, OH), 1.53 (s, 3H, CH₃, *a*), 1.50 (s, 3H, CH₃, *b*), 1.44 (s, 12H, CH₃ and *t*-Bu *a* and *b*); ¹³C NMR (CDCl₃) δ 153.9 (CO₂*t*Bu, *a* and *b*), 93.9 (C, *a* and *b*), 81.0 (C, *a* and *b*), 65.2 (CH₂-O, *b*), 64.7 (CH₂-O, *a*), 64.7 (CH₂-O, *b*), 62.7 (CH₂-O, *a*), 59.3 (CH, *b*), 58.3 (CH, *a*), 28.3 (*t*-Bu, *a* and *b*), 27.1 (CH₃, *b*), 26.6 (CH₃, *a*), 24.4 (CH₃, *b*), 22.9 (CH₃, *a*).

***tert*-Butyl *N*-[(1*R*)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-2-iodoethyl]carbamate (11b).** Compound **11b** was prepared from alcohol (*S*)-**10b** in toluene following the general procedure for the preparation of iodides. Yellow oil (0.424 g, 77%); R_f 0.71 (EtOAc/cyclohexane 1/4); $[\alpha]_D^{25} = +8.79$ (c 7.3, CHCl₃); IR (neat) ν_{\max} 3431, 1717; ¹H NMR (CDCl₃) δ 7.66 (d, $J = 7.0$ Hz, 4H, H-Ar), 7.45 (t, $J = 8.0$ Hz, 2H, H-Ar), 7.40 (t, $J = 8.0$ Hz, 4H, H-Ar), 4.81 (d, $J = 8.0$ Hz,

1H, NH), 3.84 (dd, $J = 10.0, 3.0$ Hz, 1H, CH₂-O), 3.70 (m, 1H, CH), 3.62 (dd, $J = 10.0, 5.5$ Hz, 1H, CH₂-O), 3.49 (dd, $J = 15.5, 7.0$ Hz, 1H, CH₂-I), 3.43 (dd, $J = 15.5, 9.0$ Hz, 1H, CH₂-I), 1.45 (s, 9H, *t*-Bu), 1.08 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 154.9 (CO₂*t*-Bu), 135.6 (C-Ar), 132.9 (C-Ar), 132.8 (C-Ar), 129.9 (C-Ar), 127.8 (C-Ar), 79.8 (C), 64.5 (CH₂-O), 51.8 (CH), 28.3 (*t*-Bu), 26.8 (*t*-Bu), 19.3 (C), 8.7 (CH₂-I); HRMS-ESI m/z calcd for C₂₄H₃₄INO₃SiNa [M + Na]⁺: 562.1250, found: 562.1241.

***tert*-Butyl [(4*R*)-2,2-dimethyl-4-(iodomethyl)-1,3-oxazolidin-3-yl]carboxylate (11c).**

Compound **11c** was prepared from alcohol (*S*)-**10c** in toluene following the general procedure for the preparation of iodides and appeared in the NMR spectra at ambient temperature as a mixture of two rotamers *a* and *b*. Colourless liquid (0.257 mg, 74%); R_f 0.46 (EtOAc/cyclohexane 1/9); $[\alpha]_D^{25} = -5.5$ (c 1.86, CHCl₃); IR (neat) ν_{\max} 1698; ¹H NMR (CDCl₃) δ 4.18 (m, 1H, CH, *a*), 4.08 (m, 1H, CH, *b*), 3.99 (m, 2H, CH₂-O, *a* and *b*), 3.50 (dd, $J = 9.5, 2.5$ Hz, 1H, CH₂-I, *b*), 3.36 (bd, $J = 9.0$ Hz, 1H, CH₂-I, *a*), 3.14 (t, $J = 9.0$ Hz, 1H, CH₂-I, *a*), 3.12 (t, $J = 9.5$ Hz, 1H, CH₂-I, *b*), 1.61 (s, 3H, CH₃, *b*), 1.56 (s, 3H, CH₃, *a*), 1.47 (s, 9H, *t*-Bu, *a*), 1.46 (s, 9H, *t*-Bu, *b*), 1.46 (s, 3H, CH₃, *a*), 1.43 (s, 3H, CH₃, *b*); ¹³C NMR (CDCl₃) δ 152.0 (CO₂*t*Bu, *a*), 151.3 (CO₂*t*Bu, *b*), 94.8 (C, *b*), 94.3 (C, *a*), 80.6 (C, *a*), 80.3 (C, *b*), 67.2 (CH₂-O, *a* and *b*), 59.0 (CH, *b*), 58.9 (CH, *a*), 28.4 (*t*-Bu, *b*), 28.3 (*t*-Bu, *a*), 27.8 (CH₃, *a*), 27.1 (CH₃, *b*), 24.3 (CH₃, *a*), 23.0 (CH₃, *b*), 6.8 (CH₂-I, *b*), 6.7 (CH₂-I, *a*); HRMS-ESI m/z calcd for C₁₁H₂₀INO₃Na [M + Na]⁺: 364.0386, found: 364.0385.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-methoxy-4-oxobutanoic acid (12). To a stirred solution of L-aspartic acid methyl ester hydrochloride (1.00 g, 5.4 mmol) in dioxane (20 mL) was added at 0 °C a 0.5M aqueous sodium carbonate solution (22 mL) followed by di-*tert*-butyl dicarbonate (1.30 g, 6.0 mmol). The reaction mixture was stirred 12 h at 20 °C before being concentrated. The resulting solution was acidified at 0 °C (pH = 3.0) by adjunction of citric acid and extracted with ethyl acetate (3x20 mL). The combined organic layers were washed by water and dried (MgSO₄). The solvent was evaporated under vacuo to give a residue which was purified by flash column chromatography (ethanol/dichloromethane, 1/5) leading to (*S*)-**12** as a pale yellow oil (1.19 g, 89%). R_f 0.64 (EtOH/CH₂Cl₂ 1/5); $[\alpha]_D^{25} = +23.5$ (c 0.26, CHCl₃); IR (neat) ν 3300, 1750-1680; ¹H NMR (CDCl₃) δ 9.88 (bs, 1H, CO₂H), 5.61 (d, $J = 8.0$ Hz, 1H, NH), 4.58 (dt, $J = 8.0, 4.0$ Hz, 1H, CH), 3.68 (s, 3H, O-CH₃), 2.99 (dd, $J = 17.0, 4.0$ Hz, 1H, CH₂), 2.83 (dd, $J = 17.0, 4.5$ Hz, 1H, CH₂), 1.42 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 175.4 (CO₂H), 171.6 (CO₂Me), 155.6 (CO₂*t*Bu), 80.4 (C), 52.0 (O-CH₃), 49.8 (CH), 36.4 (CH₂), 28.2 (*t*-Bu); HRMS-ESI m/z calcd for C₁₀H₁₇NO₆Na [M + Na]⁺: 270.0954, found: 270.0963.

Methyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-hydroxybutanoate (13). To a stirred solution of (*S*)-**12** (1.500 g, 6.4 mmol) and *N*-hydroxysuccinimide (0.838 g, 7.7 mmol) in anhydrous dichloromethane (20 mL), was added, at 20 °C and under argon atmosphere, *N,N'*-dicyclohexylcarbodiimide (1.504 g, 7.7 mmol). The reaction mixture was stirred for 12 h at 20 °C and anhydrous MgSO₄ (1.0 g) was added. After 15 min, the solution was filtrated and the solvent was evaporated. The residue was dissolved by a 3/1 (v/v) mixture of tetrahydrofuran/ethanol (30 mL) and the resulting solution was placed at 0 °C. Sodium

borohydride (0.229 g, 6.4 mmol) was portionwise added and the stirring was pursued at this temperature 30 min after complete addition. The reaction mixture was diluted by ethyl acetate and filtered. The organic layer was dried (MgSO₄). The solvent was evaporated under vacuo and the residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 3:2) giving (*S*)-**13** as a colourless oil (1.179 g, 79%). *R*_f 0.60 (EtOAc/cyclohexane, 4/1); [α]_D²⁵ = + 4.0 (c 0.75, CHCl₃) (lit.¹⁷ [α]_D²⁵ = + 6.3 (c 0.5, CHCl₃)); IR (neat) ν 3360, 1733, 1691; ¹H NMR (CDCl₃) δ 5.21 (bs, 1H, NH), 3.98 (m, 1H, CH), 3.71 (t, *J* = 5.5 Hz, 2H, CH₂-OH), 3.70 (s, 3H, O-CH₃), 2.64 (d, *J* = 6.0 Hz, 2H, CH₂), 2.48 (bs, 1H, OH), 1.44 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 172.2 (CO₂Me), 155.7 (CO₂*t*-Bu), 79.6 (C), 63.8 (CH₂-O), 51.6 (O-CH₃), 49.2 (CH), 35.7 (CH₂), 28.2 (*t*-Bu); HRMS-ESI *m/z* calcd for C₁₀H₁₉NO₅Na [M + Na]⁺: 256.1161, found:256.1169.

Methyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-(*tert*-butyldiphenylsilyloxy)butanoate (14a).

To a stirred solution of (*S*)-**13** (1.43 g, 6.1 mmol) in anhydrous dichloromethane (50 mL) at 0 °C and under argon atmosphere was added imidazole (0.63 g, 9.2 mmol) followed 15 min later by *tert*-butyldiphenylsilyl chloride (90 mL, 7.3 mmol). The reaction mixture was slowly allowed to reach 20 °C (3 h) and stirring was continued for 1 h before dilution by diethyl ether. The organic layer was washed with water (30 mL), brine (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was purified by column chromatography (diethyl ether/pentane, 1:4) to give **14a** as a colourless oil (2.82 g, 98%). *R*_f 0.60 (EtOAc/cyclohexane 3/7); [α]_D²⁵ = - 7.9 (c 2.1, CHCl₃); IR (neat) ν_{\max} 3434, 1745, 1720; ¹H NMR (CDCl₃) δ 7.64 (d, *J* = 8.0 Hz, 4H, H-Ar), 7.45-7.37 (m, 6H, H-Ar), 5.09 (d, *J* = 7.5 Hz, 1H, NH), 4.12 (m, 1H, CH), 3.72 (m, 2H, CH₂-O), 3.64 (s, 3H, O-CH₃), 2.66 (m, 2H, CH₂), 1.44 (s, 9H, *t*-Bu), 1.07 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 171.8 (CO₂Me), 155.1 (CO₂*t*-Bu), 135.5 (C-Ar), 133.1 (C-Ar), 133.0 (C-Ar), 129.8 (C-Ar), 127.7 (C-Ar), 79.3 (C), 64.9 (CH₂-O), 51.6 (O-CH₃), 48.8 (CH), 35.9 (CH₂), 28.3 (*t*-Bu), 26.8 (*t*-Bu), 19.2 (C); MS (CI⁺) *m/z* 472 ([M + H]⁺, 20), 427 (20), 372 (100), 294 (11); HRMS-ESI *m/z* calcd for C₂₆H₃₇NO₅SiNa [M + Na]⁺: 494.2339, found:494.2342.

Methyl (3*S*)-3-[(bis(*tert*-butoxycarbonyl)amino)-4-(*tert*-butyldiphenylsilyl)oxy]-butanoate (14b).

To a stirred solution of (*S*)-**14a** (0.598 g, 1.31 mmol) in anhydrous acetonitrile (5 mL) were successively added, at 20 °C, 4-dimethylaminopyridine (0.032 g, 0.26 mmol) and di-*tert*-butyl dicarbonate (0.314 g, 1.44 mmol). After 12 h, additionnal di-*tert*-butyl dicarbonate (0.314 g, 1.44 mmol) was added to the mixture and the reaction was continued for another 12 h. The solvent was then evaporated under reduced pressure and the crude residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:9) to give **14b** as an oil (409 mg, 54%). *R*_f 0.44 (EtOAc/cyclohexane 1/9); [α]_D²⁵ = - 7.18 (c = 1.38, CHCl₃); IR (neat) ν_{\max} 2980, 2932, 2859, 1744, 1703; ¹H NMR (CDCl₃) δ 7.69-7.65 (m, 4H, H-Ar), 7.43-7.35 (m, 6H, H-Ar), 4.91 (quint, *J* = 8.0 Hz, 1H, CH), 3.94 (dd, *J* = 9.5, 8.0 Hz, 1H, CH₂-O), 3.73 (dd, *J* = 9.5, 7.0 Hz, 1H, CH₂-O), 3.64 (s, 3H, O-CH₃), 2.84 (dd, *J* = 15.5, 8.5 Hz, 1H, CH₂), 2.64 (dd, *J* = 16.0, 6.0 Hz, 1H, CH₂), 1.48 (s, 18H, *t*-Bu), 1.04 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 171.5 (CO₂Me), 152.9 (CO₂*t*Bu), 135.5 (C-Ar), 133.3 (C-Ar), 129.6 (C-Ar), 127.6 (C-Ar), 82.2 (C), 63.8 (CH₂-O), 55.1

(O-CH₃), 51.6 (CH), 35.1 (CH₂), 28.0 (*t*-Bu), 26.6 (*t*-Bu), 19.1 (C); HRMS-ESI *m/z* calcd for C₃₁H₄₅NO₇SiNa [M + Na]⁺: 594.2863, found: 594.2844.

Methyl (3S)-3-[benzyl(*tert*-butoxycarbonyl)amino]-4-(*tert*-butyldiphenylsilyloxy)butanoate (14c). A stirred solution of (*S*)-**14a** (1.00 g, 2.10 mmol) in anhydrous dimethylformamide (10 mL) at 0 °C and under argon atmosphere, was treated with benzyl bromide (377 µL, 3.15 mmol) and tetrabutylammonium iodide (1.16 g, 3.15 mmol) followed by a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.168 g, 4.20 mmol) in anhydrous dimethylformamide (2 mL) which was dropwise transferred via a cannula. The reaction was allowed to stir at 0 °C for 1 h before being stopped by adding saturated aqueous ammonium chloride solution (10 mL) and extracted twice with diethyl ether (20 mL). The organic layer was washed with brine, dried (MgSO₄), concentrated under reduced pressure and purified by column chromatography (ethyl acetate/cyclohexane, 1:9) to give **14c** as a pale yellow oil (0.815 g, 69%). Compound **14c** appeared in the NMR spectra at room temperature as a mixture of two rotamers *a* and *b*. *R_f* 0.51 (EtOAc/cyclohexane 1/4); [α]_D²⁵ = -20.5 (c = 2.42, CHCl₃); IR (neat) ν_{max} 1740, 1695; ¹H NMR (CDCl₃) δ 7.81-7.28 (m, 15H, H-Ar), 4.72 (m, 1H, CH₂Ph), 4.49 (m, 2H, CH₂Ph, CH, *a*), 4.29 (m, 1H, CH, *b*), 3.86 (m, 1H, CH₂-O), 3.74 (m, 1H, CH₂-O), 3.60 (s, 3H, O-CH₃), 2.76 (m, 2H, CH₂), 1.50 (s, 9H, *t*Bu, *a*), 1.46 (s, 9H, *t*-Bu, *b*), 1.14 (s, 9H, *t*-Bu, *b*), 1.10 (s, 9H, *t*Bu, *a*); ¹³C NMR (CDCl₃) δ 171.9 (CO₂Me, *a* and *b*), 155.6 (CO₂*t*-Bu, *a*), 155.1 (CO₂*t*-Bu, *b*), 138.8 (C-Ar, *a*), 135.4 (C-Ar, *a* and *b*), 133.0 (C-Ar, *a* and *b*), 132.9 (C-Ar, *a* and *b*), 129.7 (C-Ar, *a*), 129.6 (C-Ar, *a* and *b*), 129.3 (C-Ar, *b*), 128.3 (C-Ar, *a*), 127.6 (C-Ar, *a* and *b*), 80.2 (C, *a*), 79.8 (C, *b*), 64.6 (CH₂-O, *a*), 64.2 (CH₂-O, *b*), 56.1 (CH, *a* and *b*), 51.5 (O-CH₃), 50.5 (CH₂-Ph, *a* and *b*), 35.6 (CH₂, *a*), 34.8 (CH₂, *b*), 28.2 (*t*-Bu, *a* and *b*), 26.7 (*t*-Bu, *a* and *b*), 19.0 (C); MS (ESI) *m/z* 584 ([M + Na]⁺, 62), 462 (100), 310 (30), 141 (27); HRMS-ESI *m/z* calcd for C₃₃H₄₃NO₅SiNa [M + Na]⁺: 584.2808, found: 584.2794.

Methyl [(4S)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]ethanoate (14d). Compound **14d** was prepared from (*S*)-**13** following the general procedure for preparation of oxazolidines and appeared in the NMR spectra at ambient temperature as a mixture of two rotamers *a* and *b*. Colourless oil (0.826 g, 87%). *R_f* 0.64 (EtOAc/cyclohexane, 1:1); [α]_D²⁵ = +28.2 (c 0.54, CHCl₃) (lit.¹⁵ [α]_D²⁵ = +27.9 (c 1.0, CHCl₃)); IR (neat): ν_{max} 1740, 1700; ¹H NMR (CDCl₃) δ 4.26 (m, 1H, CH, *a*), 4.15 (m, 1H, CH, *b*), 4.00 (m, 2H, CH₂-O, *a* and *b*), 3.82 (d, *J* = 9.0 Hz, 1H, CH₂-O, *a*), 3.82 (d, *J* = 9.0 Hz, 1H, CH₂-O, *b*), 3.67 (s, 3H, O-CH₃, *b*), 3.64 (s, 3H, O-CH₃, *a*), 2.91 (bd, *J* = 15.5 Hz, 1H, CH₂, *a*), 2.74 (bd, *J* = 15.5 Hz, 1H, CH₂, *b*), 2.52 (dd, *J* = 15.5, 11.0 Hz, 1H, CH₂, *b*), 2.47 (dd, *J* = 15.5, 11.0 Hz, 1H, CH₂, *a*), 1.56 (s, 3H, CH₃, *b*), 1.52 (s, 3H, CH₃, *a*), 1.46 (s, 18H, CH₃ and *t*-Bu *a* and *b*), 1.45 (s, 6H, CH₃, *a* and *b*); ¹³C NMR (CDCl₃) δ 171.7 (CO₂Me, *a* and *b*), 151.9 (CO₂*t*-Bu, *a*), 151.3 (CO₂*t*-Bu, *b*), 93.8 (C, *b*), 93.3 (C, *a*), 80.4 (C, *a*), 80.0 (C, *b*), 67.5 (CH₂-O, *b*), 67.3 (CH₂-O, *a*), 54.2 (CH, *a*), 53.9 (CH, *b*), 51.6 (O-CH₃, *a* and *b*), 37.7 (CH₂, *b*), 36.9 (CH₂, *a*), 28.4 (*t*-Bu, *a* and *b*), 27.6 (CH₃, *a*), 26.7 (CH₃, *b*), 24.4 (CH₃, *a*), 23.1 (CH₃, *b*).

***tert*-Butyl N-[(1S)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-hydroxypropyl]carbamate (15a).** Compound **15a** was prepared from (*S*)-**14a** following the general method A of reduction.

Colourless oil (0.452 g, 98%). R_f 0.58 (EtOAc/cyclohexane, 1:1); $[\alpha]_D^{25} = -6.7$ (c 2.0, CHCl₃); IR (neat) ν_{\max} 3440, 1695; ¹H NMR (CDCl₃) δ 7.63 (d, $J = 7.0$ Hz, 4H, H-Ar), 7.45 (t, $J = 7.0$ Hz, 2H, H-Ar), 7.40 (t, $J = 7.0$ Hz, 4H, H-Ar), 4.83 (d, $J = 9.0$ Hz, 1H, NH), 3.87 (m, 1H, CH), 3.80 (dd, $J = 10.5, 3.5$ Hz, 1H, CH₂-O), 3.66 (m, 2H, CH₂-OH), 3.62 (dd, $J = 10.5, 3.5$ Hz, 1H, CH₂-O), 3.42 (bs, 1H, OH), 1.72 (m, 1H, CH₂), 1.63 (m, 1H, CH₂), 1.46 (s, 9H, *t*-Bu), 1.08 (s, 9H, *t*Bu); ¹³C NMR (CDCl₃) δ 157.0 (CO₂*t*-Bu), 135.5 (C-Ar), 133.1 (C-Ar), 133.0 (C-Ar), 129.8 (C-Ar), 127.8 (C-Ar), 79.7 (C), 66.3 (CH₂-O), 58.7 (CH₂-OH), 48.6 (CH), 35.3 (CH₂), 28.3 (*t*-Bu), 26.8 (*t*-Bu), 19.3 (C); HRMS-ESI m/z calcd for C₂₅H₃₇NO₄SiNa [M + Na]⁺: 466.2390, found: 466.2369.

***tert*-Butyl *N*-[(1*S*)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-hydroxypropyl]bis-carbamate (15b).** To a stirred solution of (*S*)-**14b** (0.401 g, 0.70 mmol) in anhydrous ether (5 mL), at -78 °C and under argon atmosphere, was added a 1.0 M solution of diisobutylaluminium hydride in hexane (770 μ L, 0.77 mmol). After 45 min the reaction was quenched by adjunction of saturated aqueous potassium and aqueous sodium tartaric acid salts solution (5 mL). The aqueous portion was extracted with diethyl ether. The combined organic layers were washed by brine before drying (MgSO₄). The solvent was then evaporated under reduced pressure and the crude residue was purified by column chromatography (ethyl acetate/cyclohexane, 2:8) to give 0.375 g of di-*tert*-butyl [1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-oxopropyl]imidodicarbonate which was dissolved in absolute methanol (4 mL) at 0 °C. Then, sodium borohydride (0.053 g, 1.40 mmol) was added. Stirring was continued for an additional 30 min. The reaction was quenched by saturated aqueous ammonium chloride solution (4 mL) and the reaction mixture was diluted with ether (5 mL). The organic layer was separated, washed with brine and dried (MgSO₄). The solvent was concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/cyclohexane, 1:4) to give **15b** as a colourless oil (0.320 g, 84%). R_f 0.44 (EtOAc/cyclohexane, 1:4); $[\alpha]_D^{25} = +15.34$ (c 0.91, CHCl₃); IR (neat): ν_{\max} 3501, 1738, 1699; ¹H NMR (CDCl₃) δ 7.68-7.64 (m, 4H, H-Ar), 7.44-7.35 (m, 6H, H-Ar), 4.43 (m, 1H, CH), 4.13 (dd, $J = 10.0, 8.5$ Hz, 1H, CH₂-O), 3.66-3.58 (m, 3H, CH₂, CH₂-O), 2.94 (bs, 1H, OH), 1.85 (m, 1H, CH₂), 1.68 (m, 1H, CH₂), 1.49 (s, 18H, *t*-Bu), 1.04 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 154.1 (CO₂*t*Bu), 135.5 (C-Ar), 133.4 (C-Ar), 129.6 (C-Ar), 127.6 (C-Ar), 82.5 (C), 64.8 (CH₂-O), 59.0 (CH₂-OH), 56.8 (CH), 31.6 (CH₂), 28.0 (*t*-Bu), 26.7 (*t*-Bu), 19.2 (C); HRMS-ESI m/z calcd for C₃₀H₄₅NO₆SiNa [M + Na]⁺: 566.2914, found: 566.2894.

***tert*-Butyl *N*-benzyl-*N*-[(1*S*)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-hydroxypropyl]carbamate (15c).** Compound **15c** was prepared from (*S*)-**14c** using the general method A of reduction. Colourless oil (0.550 mg, 99%). R_f 0.49 (EtOAc/cyclohexane, 3/7); $[\alpha]_D^{25} = +2.4$ (c 1.0, CHCl₃); IR (neat) ν_{\max} 3437, 1684; ¹H NMR (CDCl₃) δ 7.60-7.21 (m, 15H, H-Ar), 4.48 (d, $J = 16.0$ Hz, 1H, CH₂-Ph), 4.43 (m, 1H, CH), 4.34 (d, $J = 16.0$ Hz, 1H, CH₂-Ph), 3.74 (m, 2H, CH₂-O), 3.45 (m, 2H, CH₂-OH), 3.22 (bs, 1H, OH), 1.60-1.35 (m, 2H, CH₂), 1.42 (s, 9H, *t*-Bu), 1.39 (s, 9H, *t*-Bu), 1.03 (s, 9H, *t*-Bu); ¹³C NMR (CDCl₃) δ 157.3 (CO₂*t*-Bu), 139.5 (C-Ar), 135.5 (C-Ar), 133.1 (C-Ar), 133.0 (C-Ar), 129.7 (C-Ar), 128.2 (C-Ar), 127.7 (C-Ar), 126.9 (C-Ar), 126.7 (C-Ar), 80.3 (C), 64.7 (CH₂-O), 58.6 (CH₂-OH), 54.1 (CH), 47.3 (CH₂-Ph), 32.0 (CH₂), 28.2 (*t*-Bu), 26.8 (*t*-Bu),

19.1 (C); MS (ESI) m/z 556 ($[M + Na]^+$, 100), 434 (100); HRMS-ESI m/z calcd for $C_{32}H_{43}NO_4SiNa$ $[M + Na]^+$: 556.2859, found: 556.2861.

***tert*-Butyl [(4*S*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-oxazolidin-3-yl]carboxylate (15d).**

Compound **15d** was prepared from (*S*)-**14d** using the general method C of reduction. White needles (0.473 g, quant.); *mp* 75 °C (pentane); R_f 0.46 (EtOAc/cyclohexane, 7/3); $[\alpha]_D^{25} = -12.2$ (c 1.06, $CHCl_3$) (lit.^{18b} $[\alpha]_D^{25} = -12.3$ (c 1.53, $CHCl_3$)); IR (KBr) ν_{max} 3260, 1690; 1H NMR ($CDCl_3$) δ 4.20 (m, 1H, CH), 3.99 (m, 2H, H-4, CH_2 -OH), 3.68 (d, $J = 9.0$ Hz, 1H, CH_2 -O), 3.63 (bs, 1H, OH), 3.53 (bt, $J = 10.5$ Hz, 1H, CH_2 -OH), 1.81 (m, 1H, CH_2), 1.71 (ddt, $J = 13.5, 10.5, 3.0$ Hz, 1H, CH_2), 1.53 (s, 3H, CH_3), 1.48 (s, 12H, CH_3 and *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 153.8 (CO_2t -Bu), 93.6 (C), 80.9 (C), 68.2 (CH_2 -O), 58.6 (CH_2 -OH), 54.0 (CH), 37.7 (CH_2), 28.3 (*t*-Bu), 27.7 (CH_3), 24.3 (CH_3).

***tert*-Butyl *N*-[(1*S*)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-iodopropyl]carbamate (16a).**

Compound **16a** was obtained from (*S*)-**15a** following the general procedure for preparation of iodides using toluene as solvent. Pale yellow foam (520 mg, 92%); R_f 0.44 (EtOAc/cyclohexane 1/9); *mp* 57-58 °C (pentane); $[\alpha]_D^{25} = -16.9$ (c 2.46, $CHCl_3$); IR (KBr) ν_{max} 3440, 1707; 1H NMR ($CDCl_3$) δ 7.63 (m, 4H, H-Ar), 7.42 (m, 6H, H-Ar), 4.71 (d, $J = 8.5$ Hz, 1H, NH), 3.73 (m, 1H, CH), 3.69 (dd, $J = 10.0, 2.5$ Hz, 1H, CH_2 -O), 3.60 (bd, $J = 10.0$ Hz, 1H, CH_2 -O), 3.13 (m, 2H, CH_2 -I), 2.10 (q, $J = 6.5$ Hz, 2H, CH_2), 1.45 (s, 9H, *t*-Bu), 1.07 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 155.5 (CO_2t -Bu), 135.5 (C-Ar), 133.0 (C-Ar), 133.0 (C-Ar), 129.9 (C-Ar), 127.8 (C-Ar), 79.4 (C), 65.2 (CH_2 -O), 52.8 (CH), 36.7 (CH_2), 28.4 (*t*-Bu), 26.9 (*t*-Bu), 19.3 (C), 1.5 (CH_2 -I); MS (ESI) m/z 592 ($[M + K]^+$, 100), 576 ($[M + Na]^+$, 92), 454 ($M - Boc$, 26); HRMS-ESI m/z calcd for $C_{25}H_{36}INO_3SiNa$ $[M + Na]^+$: 576.1407, found: 576.1421.

Di-*tert*-butyl *N*-[(1*S*)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-iodopropyl]imidodicarbonate (16b).

Compound **16b** was obtained from (*S*)-**15b** following the general procedure for preparation of iodides in diethyl ether/acetonitrile. Colourless oil (613 mg, 92%). R_f 0.56 (EtOAc/cyclohexane, 1/19); $[\alpha]_D^{25} = -12.08$ (c 0.76, $CHCl_3$); IR (neat) ν_{max} 3069, 2979, 2931, 2859, 1739, 1701, 1428; 1H NMR ($CDCl_3$) δ 7.63 (m, 4H, H-Ar), 7.42 (m, 6H, H-Ar), 4.48 (m, 1H, CH), 3.94 (dd, $J = 10.0, 8.5$ Hz, 1H, CH_2 -O), 3.66 (dd, $J = 10.0, 6.5$ Hz, 1H, CH_2 -O), 3.21-3.08 (m, 2H, CH_2 -I), 2.33 (m, 1H, CH_2), 2.08 (m, 1H, CH_2), 1.48 (s, 9H, *t*-Bu), 1.04 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$) δ 153.1 (CO_2t -Bu), 135.5 (C-Ar), 133.4 (C-Ar), 129.7 (C-Ar), 129.6 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 82.3 (C), 64.1 (CH_2 -O), 59.4 (CH), 34.2 (CH_2), 28.0 (*t*-Bu), 26.7 (*t*-Bu), 19.2 (C), 1.7 (CH_2 -I); HRMS-ESI m/z calcd for $C_{30}H_{44}INO_5SiNa$ $[M + Na]^+$: 676.1931, found: 676.1905.

***tert*-Butyl *N*-benzyl-*N*-[(1*S*)-1-[(*tert*-butyldiphenylsilyloxy)methyl]-3-iodopropyl]carbamate (16c).**

A stirred solution of (*S*)-**15c** (0.885 g, 1.66 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C and under argon atmosphere was successively treated with triethylamine (348 μ L, 2.48 mmol), 4-dimethylaminopyridine (0.040 g, 0.33 mmol) and methanesulfonyl chloride (260 μ L, 3.32 mmol). After 20 min, the reaction mixture was diluted with diethyl ether. The organic layer was washed with water followed by brine and dried ($MgSO_4$). After filtration and concentration, the crude mesylate of **15c** thus obtained was diluted in acetone (25 mL). Sodium iodide (4.97 g,

33.2 mmol) was added and the reaction mixture was stirred at 20 °C for 12 h. The precipitate was dissolved by adjunction of water and the crude mixture was extracted with diethyl ether. The organic layer was washed twice with 10% aqueous sodium thiosulfate solution, water and brine. After drying (MgSO₄), the resulting solution was filtered and the solvent was evaporated under vacuo. The residue was purified by column chromatography (diethyl ether/pentane, 1:9) affording **16c** as a yellow oil (755 mg, 71%). Compound **16c** was detected in the NMR spectra at ambient temperature as a mixture of two rotamers *a* and *b*. *R_f* = 0.56 (EtOAc/cyclohexane, 1/19); [α]_D²⁵ = - 14.4 (c 1.13, CHCl₃); IR (neat) ν_{\max} 1694; ¹H NMR (CDCl₃) δ 7.60-7.21 (m, 15H, H-Ar *a* and *b*), 4.47 (m, 2H, CH₂-Ph, *a*), 4.41 (m, 2H, CH₂-Ph, *b*), 4.07 (m, 1H, CH, *a*), 3.90 (m, 1H, CH, *b*), 3.71 (m, 2H, CH₂-O, *b*), 3.60 (m, 2H, CH₂-O, *a*), 2.96 (m, 2H, CH₂-I, *a*), 2.82 (m, 2H, CH₂-I, *b*), 2.14 (m, 2H, CH₂, *b*), 2.03 (m, 2H, CH₂, *a*), 1.44 (s, 9H, *t*-Bu, *a*), 1.39 (s, 9H, *t*-Bu, *b*), 1.03 (s, 9H, *t*Bu, *a* and *b*); ¹³C NMR (CDCl₃) δ 156.0 (CO₂*t*Bu, *a*), 155.4 (CO₂*t*Bu, *b*), 139.4 (C-Ar, *b*), 139.0 (C-Ar, *a*), 135.4 (C-Ar, *a* and *b*), 133.0 (C-Ar, *a* and *b*), 129.6 (C-Ar, *a* and *b*), 128.3 (C-Ar, *a* and *b*), 127.6 (C-Ar, *a* and *b*), 127.0 (C-Ar), 80.1 (C, *a*), 79.7 (C, *b*), 64.5 (CH₂-O, *a*), 64.1 (CH₂-O, *b*), 59.3 (CH, *a* and *b*), 49.6 (CH₂-Ph, *a* and *b*), 34.4 (CH₂, *a*), 34.1 (CH₂, *b*), 28.3 (*t*-Bu, *a* and *b*), 26.7 (*t*-Bu, *a* and *b*), 19.0 (C, *a* and *b*), 2.4 (CH₂-I, *a* and *b*); HRMS-ESI *m/z* calcd for C₃₂H₄₂INO₃Si [M + Na]⁺: 666.1876, found: 666.1845.

***tert*-Butyl N-[(4*S*)-4-(2-iodoethyl)-2,2-dimethyl-1,3-oxazolidin-3-yl]carboxylate (16d).**

Compound **16d** was prepared in toluene following the general procedure for the preparation of iodides. Yellow foam (0.297 g, 82%); *mp* 45-47 °C (pentane); *R_f* 0.60 (EtOAc/cyclohexane, 3/7); [α]_D²⁵ = + 17.8 (c 0.1, CHCl₃) (for its (*R*)-enantiomer lit.¹⁹ [α]_D²⁵ = - 16.2 (c 2.6, CHCl₃)); IR (KBr) ν_{\max} 1698; ¹H NMR (C₆D₆, 70 °C) δ 3.69 (m, 1H, CH), 3.52 (ddt, *J* = 9.0, 6.0, 1.0 Hz, 1H, CH₂-O), 3.29 (dt, *J* = 9.0, 1.5 Hz, 1H, CH₂-O), 2.86 (td, *J* = 9.0, 5.5 Hz, 1H, CH₂-I), 2.74 (dt, *J* = 9.0, 8.0 Hz, 1H, CH₂-I), 2.15 (m, 1H, CH₂), 1.85 (dtd, *J* = 14.0, 8.0, 6.0 Hz, 1H, CH₂), 1.55 (s, 3H, CH₃), 1.43 (s, 3H, CH₃), 1.39 (s, 9H, *t*-Bu); ¹³C NMR (C₆D₆, 70 °C) δ 150.9 (CO₂*t*Bu), 94.0 (C), 79.7 (C), 66.7 (CH₂-O), 58.6 (CH), 38.2 (CH₂), 28.6 (*t*-Bu), 27.3 (CH₃), 24.0 (CH₃), 0.3 (CH₂-I); MS-ESI *m/z* 378 ([M+Na]⁺, 100), 338 (34), 33 (21).

References

1. (a) Troast, D. M.; Yuan, J.; Porco Jr., J. A. *Adv. Synth. Catal.* **2008**, 350, 1701. (b) Reymond, S.; Cossy, J. *Tetrahedron* **2007**, 63, 5918.
2. Dave, R.; Sasaki, N. A. *Tetrahedron: Asymmetry* **2006**, 17, 388.
3. Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T. ; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115.
4. Faulkner, D. J. *Nat. Prod. Prep.* **1984**, 25.
5. (a) For a pioneering work see Enders, D.; Gatzweiler, W.; Dederichs, E. *Tetrahedron* **1990**, 46, 4757. (b) Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, 37, 5649. (c) Tursun, A.; Canet, I.; Aboab, B.; Sinibaldi, M.-E. *Tetrahedron Lett.* **2005**, 46, 2291. (d) Tursun, A.; Aboab, B.; Martin, A.-S.; Sinibaldi, M.-E.; Canet, I. *Synlett* **2005**, 15, 2397.

6. (a) Hirth, G.; Walther, W. *Helv. Chim. Acta* **1985**, *68*, 1863. (b) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.-I.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121. (c) For spectroscopic data of (*S*)-**2** enantiomer see Eichelberger, U.; Mansourova, M.; Hennig, L.; Findeisen, M.; Giesa, S.; Müller, D.; Welzel, P. *Tetrahedron* **2001**, *57*, 9737.
7. (*2R*)-Alcohol **3** possessed spectral data consistent with those reported in the literature by Green, M. E.; Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 4117.
8. Goubert, M.; Toupet, L.; Sinibaldi, M.-E.; Canet, I.; *Tetrahedron* **2007**, *63*, 8255.
9. For the spectroscopic data of (*S*)-**5a** see Peters, U.; Bankova, W.; Welzel, P. *Tetrahedron* **1987**, *43*, 3803.
10. For its (*S*)-isomer see (a) Barco, A.; Benetti, S.; Spallutto, G. *J. Org. Chem.* **1992**, *57*, 6279. (b) Chalker, J. M.; Yang, A.; Deng, K.; Cohen, T. *Org. Lett.* **2007**, *9*, 3825.
11. For preparation and spectroscopic data for its (*S*)-isomer see: (a) McNulty, J.; Still, I. W. J. *Synth. Commun.* **1992**, *22*, 979. (b) Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem.* **2008**, *73*, 1661.
12. (a) Dave, R.; Sasaki, N. A. *Org. Lett.* **2004**, *6*, 15. (b) Dondoni, A.; Perrone, D.; Merino, P. J. *Org. Chem.* **1995**, *60*, 8074.
13. (a) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
14. For another method of preparation and spectroscopic data of (*S*)-**10b** see: Cong, X.; Hu, F.; Liu, K.-G.; Liao, Q.-J.; Yao, Z.-J. *J. Org. Chem.* **2005**, *70*, 4516.
15. Kadota, I.; Saya, S.; Yamamoto, Y. *Heterocycles* **1997**, *46*, 335.
16. For another method of preparation and partial spectroscopic data of (*S*)-**12** see Brinkmann, T.; Gilg, A.; Hamm, A.; Lüscher, H.; Morbach, G.; Uzar, H. C. *Tetrahedron: Asymmetry* **2000**, *11*, 3827.
17. Markidis, T.; Kokotos, G. *J. Org. Chem.* **2001**, *66*, 1919.
18. (a) For another method of preparation of (*S*)-**15d** see Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206. (b) Paintner, F. F.; Allmendinger, L.; Bauschke, G.; Klemann, P. *Org. Lett.* **2005**, *7*, 1423. (c) Ksander, G. M.; DeJesus, R.; Yuan, A.; Ghai, R. D.; Trapani, A.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 495.
19. Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Tetrahedron Lett.* **1999**, *40*, 5263.