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Improved preparation of β-hydroxy-α-amino acids: direct formation of sulfates by sulfuryl chloride

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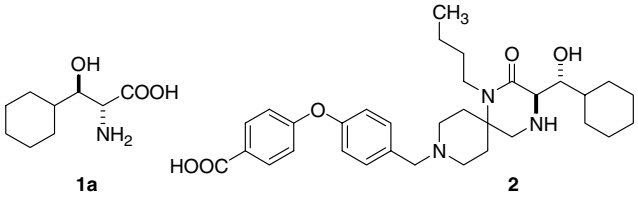
Abstract—Two β-(alkyl)-β-hydroxy-α-amino acids [alkyl = Bu^t, $BnO–(CH_2)_3–$] have been synthesized by a sequence based on Sharpless asymmetric dihydroxylation. The key sulfate intermediates were prepared from enantiomerically enriched diols by direct treatment with sulfuryl chloride. The scope and the appropriate conditions for sulfate formation have also been studied.

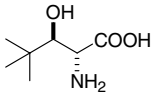
1. Introduction

Over the last decade, we have been involved in a project devoted to the asymmetric synthesis of non-proteinogenic amino acids.[1] β-Hydroxy-α-amino acids are an important subclass of this family, as they are constituents of many biologically active natural products and medicinally important compounds.[2] Several stereoselective syntheses of β-hydroxy-α-amino acids have already been reported to date.[3–7] The sequence developed by Sharpless et al.,[8] which is particularly suitable for *erythro* amino acids, includes the following steps: (a) enantioselective preparation of a dihydroxy ester by asymmetric dihydroxylation of an unsaturated ester, (b) reaction of a vicinal diol with thionyl chloride to give a cyclic sulfite; (c) ruthenium-catalyzed oxidation of the sulfite to sulfate with periodate and (d) ring opening with azide and reduction to amine. During the development of a large scale synthesis for (2*R*,3*R*)-2-amino-3-hydroxy-3-cyclohexyl-propanoic acid **1a**, a key component in the anti-inflammatory and CCR5 antagonist drug for HIV treatment ONO-4128 **2**, we found that the sequence developed by the Sharpless group was highly convenient and was thus scaled up.[9] Moreover, the sequence was improved upon when we discovered that the sulfate intermediate could be prepared directly by sulfuryl chloride treatment, instead of by the usual two step sequence of sulfite formation/ruthenium oxidation.[9] Compared to the Sharpless synthesis, this methodology is highly advantageous: it is shorter, features a simpler work-up and does not require the use of heavy metals.

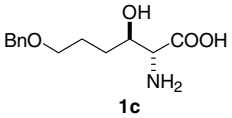


1a **2**

Somewhat surprisingly, the direct preparation of sulfates from diols using sulfuryl chloride has scarcely been used to date; the large majority of sulfates having been prepared by oxidation of the corresponding sulfites. Only a few examples of cyclic or electron-deficient diols have been reported to give good yields of sulfate when treated with sulfuryl chloride in methylene chloride[10] or ethyl acetate.[11] Encouraged by the excellent results obtained in the preparation of amino acid **1a**, we were intrigued about the scope of this reaction. Herein we report the direct preparation of sulfates from diols and the enantioselective synthesis of two protected β-hydroxy-α-amino acids **1b–c** by this methodology.



1b



1c

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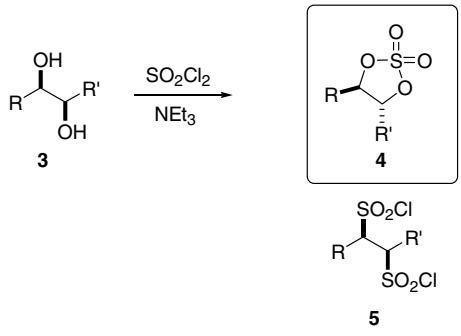
2. Results and discussion

Our first objective was to identify the key parameters of the reaction. After some experimentation, it was observed that the main side-reactions responsible for most unsuccessful runs were sulfate ring opening by chloride anion, as well as the formation of bis(chlorosulfate) **5** (reaction with two molecules of sulfuryl chloride). 3-Cyclohexyl-2,3-dihydroxy propanoate **3a** was used as a benchmark compound (Scheme 1 and Table 1). The addition of sulfuryl chloride to a solution of diol and triethylamine in methylene chloride at −78 °C (entry 1) afforded a 1:1.7 mixture of the desired sulfate **4a** and bis(chlorosulfate) **5a**. When ethyl acetate was used as a solvent, the undesired **5a** was the main reaction product (entry 2). We reasoned that the intramolecular cyclization may require a higher temperature than the intermolecular reaction. Most gratifyingly, by increasing the temperature to 0 °C, a clean reaction took place yielding 88% of sulfate **4a** after work up and chromatography. As predicted, the ratio between **4a** and **5a** was very sensitive to dilution. Apart from temperature, solvent and concentration, it was found that the rate of sulfuryl chloride addition was also crucial to the success of the reaction. For instance, the rapid addition of sulfuryl chloride to **3a** (0.4 mL/min) led to a 0.7:1 mixture of sulfate **4a** and byproduct **5a**, whereas a slow addition (0.1 mL/min) gave exclusively the desired sulfate **4a**. This effect was also found for diol **3b**, whereby a rapid addition of reagent (0.48 mL/min) yielded a 3:1 mixture of sulfate **4b** and bis(chlorosulfate) **5b**. In contrast, the slow addition of this reagent (over 0.012 mL/min) led to a 13:1 mixture of **4b/5b**. Once the optimal reaction conditions for direct sulfate formation by SO_2Cl_2 were found, we decided to test the scope using different structural types of diols. Compounds **3a–c** were prepared in enantiomerically enriched forms by Sharpless dihydroxylation of known alkenes, whereas **3d–f** were commercially available. The diols were treated with sulfuryl chloride under the optimized conditions, the results of which are summarized in Table 1. Diol **3b**, selected as a representative of a tertiary alkyl dihydroxypropanoate, gave the corresponding sulfate in excellent yield. Diol **3c**, selected as a primary alkyl dihydroxypropanaoate also gave a good yield of sulfate **4c**. Both sulfates were converted (vide infra) into the corresponding β-hydroxy-α-amino acids. Diethyl tartrate **3d** also afforded the known sulfate **4d** in good yield (70% vs 69% described by Sharpless et al. for their two step procedure[8]). To determine if simple diaryl or dialkyl sulfates could be prepared using this method, we performed the reaction on butane-2,3-diol **3e** as a representative dialkyl substituted diol, on butane-1,2-diol **3f** as a terminal diol and 1,2-diphenyl-1,2-ethanediol **3g** as a diaryl substrate.[12] As shown in Table 1, only **3g** gave good yields for the sulfate. The low yields obtained with simple alkyl diols are probably due to opening of the sulfate ring during chromatographic purification.



Scheme 1.

As a synthetic application of this sulfate formation, we planned to transform compounds **4b** and **4c** into the corresponding Boc-protected β-hydroxy-α-amino esters **7b** and **7c**. Somewhat surprisingly, to the best of our knowledge, 3-*tert*-butyl-3-hydroxy serine **1b** had yet to be described in the literature. Ring opening with sodium azide afforded azido alcohol **6b** in good yield. Finally, hydrogenation and in situ protection with Boc_2O afforded the desired protected ester **7b** in excellent yield (Scheme 2).

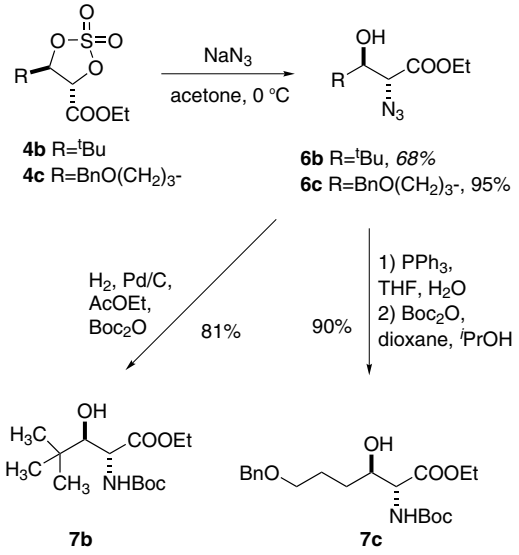
Hydroxy amino acid **1c** is a key intermediate in the syntheses of mycestericin D and F, two new lipids isolated from *Mycelia sterilia* with novel type of immunosuppressive activity.[13] It is also an unnatural amino acid used in the preparation of new sialyl Lewis X mimetics (SLe^x), potentially useful as anti-inflammatory agents[14] Moreover, using simple transformations **1c** has been transformed into 3-hydroxypipecolic acid, a precursor,

Table 1. Direct formation of sulfates **4a–g** from diols **3a–g** by treatment with sulfuryl chloride (Scheme 1)

Entry	Diol	*R*	*R′*	mol SO_2Cl_2	Conditions[a]	Product	Yield %[b]
1	**3a**	Cyclohexyl	COOEt	5	NEt_3 (5 mol), CH_2Cl_2, −78 °C	**4a+5a (1:1.7)**	—
2	**3a**	Cyclohexyl	COOEt	5	NEt_3 (5 mol), AcOEt, −78 °C	**5a**	80
3	**3a**	Cyclohexyl	COOEt	5	NEt_3 (12 mol), CH_2Cl_2, 0 °C	**4a**	15
4	**3a**	Cyclohexyl	COOEt	5	NEt_3 (12 mol), AcOEt, 0 °C	**4a**	88
5	**3b**	*tert*-Butyl	COOEt	5	NEt_3 (12 mol), AcOEt, 0 °C	**4b**	83
6	**3c**	BnO–$(CH_2)_3$–	COOEt	5	NEt_3 (12 mol), AcOEt, 0 °C	**4c**	60
7	**3d**	COOEt	COOEt	5	NEt_3 (12 mol), AcOEt, 0 °C	**4d**	70
8	**3e**	Methyl	Methyl	5	NEt_3 (12 mol), AcOEt, 0 °C	Mixture	—
9	**3f**	Ethyl	H	5	NEt_3 (12 mol), AcOEt, 0 °C	**4f**	18
10	**3g**	Phenyl	Phenyl	5	NEt_3 (12 mol), AcOEt, 0 °C	**4g**	68[c]

[a] Concentration of the substrate: 0.025 M.
[b] Isolated yield. Flash chromatography purification (SiO_2).
[c] Yield determined by ^1H NMR.

for instance, of swainsonine, which has shown potent and specific α-D-mannosidase inhibitory activity.[15] Following a sequence similar to that used for **7b**, but reducing the azide with triphenylphosphine to prevent hydrogenolysis of the benzyloxy group, a protected form of amino acid **7c** was prepared in excellent overall yield (Scheme 2).



Scheme 2.

3. Conclusion

In conclusion, we have found that under the appropriate conditions of solvent, temperature, dilution and addition rate, the simple addition of sulfuryl chloride is a very convenient way to prepare sulfates from diols. Since 3-alkyl-2,3-dihydroxy propanoates are amongst the best substrates for this reaction, the optimized reaction conditions have been used in the preparation of two important β-hydroxy-α-amino acids, in what constitutes an improved version of the known Sharpless synthetic sequence.

4. Experimental

4.1. General

Optical rotations were measured at room temperature on a Perkin–Elmer 241MC polarimeter (concentration in g/100 mL). Infrared spectra were recorded on a Nicolet 510FT-IR instrument using NaCl film or KBr pellet techniques. NMR spectra were acquired on a 400 MHz instrument. ^{1}H NMR were obtained at 400 MHz (s = singlet, d = doublet, t = triplet, dt = double triplet, m = multiplet and br = broad) ^{13}C NMR were obtained at 100 MHz. ^{1}H chemical shifts are quoted relative to TMS and ^{13}C shifts relative to solvent signals. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. High-resolution mass spectra (CI) were measured by the Servicio de Espectrometría de Masas de la Universidad de Santiago de Compostela. Chromatographic separations were carried out using SiO_2 or NEt_3-pretreated (2.5% v/v) SiO_2 (70–230 mesh) and eluting with hexane/ethyl acetate mixtures of increasing polarity. Ethyl 6-benzyloxy-2-hexenoate was prepared from 4-benzyloxy-1-butanol by the standard sequence of Swern oxidation[16] and Wadsworth–Emmons olefination.[17] Compound **3a** was prepared according to Ref. 9.

4.2. Sharpless asymmetric dihydroxylation. General procedure

The ligand $(DHQD)_2PHAL$ (7.8 mg, 0.01 mmol), $K_2Fe(CN)_6$ (990 mg, 3 mmol), K_2CO_3 (415 mg, 3 mmol), $K_2OsO_4{\cdot}2H_2O$ (1.5 mg, 0.004 mmol) and $CH_3SO_2NH_2$ (95 mg, 1 mmol) were dissolved in a 1:1 mixture of water and *tert*-butyl alcohol (5 mL of each, 10 mL total) at room temperature. The vigorously stirred mixture was cooled to 0 °C and the olefin (1 mmol) added in one portion. After complete consumption of the starting material the reaction was quenched at 0 °C by the addition of sodium sulfite (1.5 g) and then warmed to room temperature and stirred for 60 min. The reaction mixture was then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were washed with 2 M KOH (10 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography gave the pure diol.

4.2.1. Ethyl (2*S*,3*R*)-2,3-dihydroxy-4,4-dimethyl-propanoate 3b. Starting from 3-*tert*-butyl-acrylic acid ethyl ester (1 g, 6.4 mmol) and following the general procedure, 827 mg of **3b** (68%) were obtained as a white solid. $[\alpha]_D = -7.3$ (*c* 0.98, $CHCl_3$). IR (film): ν_{max} 3489, 2957, 1734, 1210, 1115 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.33 (d, 1H, $J = 2$ Hz, C*H*), 4.28 (q, 2H, $J = 7$ Hz, CH_2), 3.55 (br, 1H, C*H*), 3.13 (s, 1H, O*H*), 2.28 (s, 1H, O*H*), 1.32 (t, 3H, $J = 7$ Hz, CH_3), 1.01 (s, 9H, ((CH_3)$_3$)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.9 (CO), 78.7 (CH), 70.2 (CH), 62.4 (CH_2), 35.4 (C), 26.4 (CH_3), 14.3 (CH_3) ppm. MS (CI-NH_3) *m*/*z*: 155.1 [(M−35)$^+$, 100%], 87.1 [(M−103)$^+$, 35%], 191.3 [(M+1)$^+$, 8%]. HRMS (ESI): calcd for $C_9H_{18}NaO_4$ 213.1097, found 213.1094.

4.2.2. Ethyl (2*S*,3*R*)-6-benzyloxy-2-3-dihydroxy-hexanoate 3c. Following the general procedure starting from ethyl 6-benzyloxy-2-hexenoate (390 mg, 1.57 mmol) 354 mg of **3c** (80% yield) were obtained. $[\alpha]_D = +8.5$ (*c* 1.00, $CHCl_3$). IR (film): ν_{max} 3457, 2936, 2860, 1736, 1098 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.26 (m, 5H, C*H*), 4.52 (s, 2H, CH_2), 4.28 (q, 2H, $J = 7$ Hz, CH_2), 4.06 (br, 1H, C*H*), 3.92 (br, 1H, C*H*), 3.53 (m, 2H, CH_2), 3.05 (br, 1H, O*H*), 2.63 (br, 1H, O*H*), 1.75 (m, 4H, CH_2), 1.30 (t, 3H, $J = 7$ Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6 (CO), 138.3 (C), 128.6 (CH), 127.86 (CH), 127.82 (CH), 73.6 (CH_2), 73.2 (CH_2), 72.5 (CH), 70.3 (CH), 62.1 (CH_2), 31.3 (CH_2), 26.4 (CH_2), 14.3 (CH_3) ppm. MS (CI-CH_4) *m*/*z*: 91 [(M−191)$^+$, 100%]. HRMS (CI+): calcd for $C_{15}H_{22}O_5$ 282.1467, found 282.1460. HPLC Chiracel-OD. Heptane/*i*-PrOH 90:10, 1 mL/min, $\lambda = 210$ nm, t_R

(2*S*,3*R* isomer) = 12.1 min, t_R (2*R*,3*S* isomer) = 15.1 min showing an enantiomeric purity of 96.9% for (2*S*,3*R* isomer) and 96% for (2*R*,3*S* isomer).

4.3. Preparation of cyclic sulfates. General procedure

Diol **3x** (1 mmol) was dissolved in ethyl acetate (40 mL) under a nitrogen atmosphere. NEt_3 (1.6 mL, 12 mmol) was then added and the mixture cooled to 0 °C. Sulfuryl chloride (401 μL, 5 mmol) was added dropwise over a period of 10 min. The reaction mixture was stirred at this temperature for 15–20 min. Water was added (15 mL) and the layers separated and the organic one was washed twice with water and brine, dried and concentrated. Purification by flash chromatography afforded pure sulfate.

4.3.1. (4*S*,5*R*)-4-Ethoxycarbonyl-5-*tert*-butyl-1,2,3-dioxathiolane-2,2-dioxide 4b. Starting from: **3b** (211 mg, 1.35 mmol) and following the general procedure, 310 mg of **4b** (88% yield) was obtained as a colourless oil. $[\alpha]_D = +65.2$ (*c* 0.885, $CHCl_3$). IR (film): ν_{max} 2973, 1745, 1397, 1303, 1209 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.91 (d, 1H, $J = 6$ Hz, C*H*), 4.81 (d, 1H, $J = 6$ Hz, C*H*), 4.35 (m, 2H, CH_2), 1.35 (t, 3H, $J = 7$ Hz, CH_3), 1.06 (s, 9H, ($(CH_3)_3$)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1 (CO), 90.5 (CH), 76.3 (CH), 63.5 (CH_2), 34.2 (C), 24.7 (CH_3), 14.1 (CH_3) ppm. MS (CI-CH_4) *m*/*z*: 253.2 [$(M+1)^+$, 4%], 155.1 [$(M-96)^+$, 100%]. HRMS (ESI): calcd for $C_9H_{16}NaO_6S$ 275.056, found 275.055.

4.3.2. (4*S*,5*R*)-4-Ethoxycarbonyl-5-(3-benzyloxy)propyl-1,2,3-dioxathiolane-2,2-dioxide 4c. Starting from **3c** (50 mg, 0.17 mmol) and following the general procedure, 34 mg of **4c** (60% yield) was obtained. $[\alpha]_D = +17.2$ (*c* 1.35, $CHCl_3$). IR (film): ν_{max} 2934, 2861, 1769, 1744, 1397, 1210 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.29 (m, 5H, C*H*), 5.02 (ddd, 1H, $J = 8$, 6 and 4 Hz, C*H*), 4.87 (d, 1H, $J = 8$ Hz, C*H*), 4.50 (s, 2H, CH_2), 4.32 (dq, 2H, $J = 7$ and 1 Hz, CH_2), 3.54 (m, 2H, CH_2), 2.10 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 1.33 (t, 3H, $J = 7$ Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9 (CO), 138.2 (C), 128.6 (CH), 127.9 (CH), 127.8 (CH), 81.2 (CH), 80.0 (CH), 73.2 (CH_2), 68.8 (CH_2), 63.4 (CH_2), 30.4 (CH_2), 25.2 (CH_2), 14.1 (CH_3) ppm.

4.3.3. Ethyl (2*R*,3*R*)-2-azido-3-hydroxy-4,4-dimethyl-pentanoate 6b. To a solution of **4b** (65 mg, 0.26 mmol) in a 5:1 mixture of acetone:water (2.1 mL), cooled to 0 °C, NaN_3 (34 mg, 0.52 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 48 h. After evaporation of the solvent, the crude was treated with Et_2O:20% H_2SO_4 (1:1, 2.7 mL) and stirred at room temperature overnight. Then, excess of $NaHCO_3$ was added to the reaction mixture and the aqueous layer extracted with Et_2O (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$, and evaporated to yield 38 mg of crude **6b** (68% yield), which was used in the next step without further purification. $[\alpha]_D = -52$ (*c* 0.88, $CHCl_3$). IR (film): ν_{max} 3514, 2960, 2106, 1737, 1180, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.28 (m, 2H, CH_2), 3.77 (d, 1H, $J = 6$ Hz, C*H*), 3.64 (d, 1H, $J = 6$ Hz, C*H*), 1.34 (t, 3H, $J = 7$ Hz, CH_3), 0.99 (s, 9H, ($(CH_3)_3$)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1 (CO), 79.5 (CH), 62.23 (CH), 62.18 (CH_2), 35.2 (C), 26.0 (CH_3), 14.2 (CH_3) ppm.

4.3.4. Ethyl (2*R*,3*R*)-2-azido-3-hydroxy-6-benzyloxy-hexanoate 6c. Starting from sulfate **4c** (150 mg, 0.435 mmol) and following the procedure described for **6b**, 127 mg of azido alcohol **6c** (95%) was obtained as a colourless oil. $[\alpha]_D$ +33.5 (*c* 0.830, $CHCl_3$). IR (film): ν_{max} 3416, 2925, 2108, 1738, 1454, 1196, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.21 (m, 5H, C*H*), 4.52 (s, 2H, CH_2), 4.28 (q, 2H, $J = 7$ Hz, CH_2), 3.98 (m, 1H, C*H*), 3.93 (d, 1H, $J = 6$ Hz, C*H*), 3.52 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.32 (t, 3H, $J = 7$ Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1 (CO), 137.9 (C), 128.6 (CH), 127.94 (CH), 127.93 (CH), 73.3 (CH_2), 72.0 (CH), 70.3 (CH_2), 66.3 (CH), 62.1 (CH_2), 30.8 (CH_2), 26.2 (CH_2), 14.3 (CH_3) ppm.

4.3.5. Ethyl (2*R*,3*R*)-2-*tert*-butoxycarbonylamino-3-hydroxy-4,4-dimethyl-pentanoate 7b. A solution of azide **6b** (56 mg, 0.26 mmol) and Boc_2O (68 mg, 0.31 mmol) in ethyl acetate (3 mL) was added to a suspension of 10% Pd/C (10 mg) in ethyl acetate (3 mL) under hydrogen. The mixture was stirred under a hydrogen atmosphere (balloon) until the starting material could not be detected by TLC (40 h). Then, the suspension was filtered through a pad of Celite and evaporated. Flash chromatography afforded 61 mg of **7b** (81% yield) as a colourless oil. $[\alpha]_D = -7.5$ (*c* 0.90, $CHCl_3$). IR (film): ν_{max} 3443, 2978, 1873, 1716, 1506, 1169, 1019 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.48 (br, 1H, N*H*), 4.43 (br, 1H, C*H*), 4.19 (m, 2H, CH_2), 3.46 (br, 1H, C*H*), 3.12 (br, 1H, O*H*), 1.44 (s, 9H, ($(CH_3)_3$)), 1.31 (t, 3H, $J = 7$ Hz, (CH_3)$_3$), 0.96 (s, 9H, ($(CH_3)_3$)) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.2 (CO), 155.5 (CO), 81.2 (CH), 80.4 (C), 61.7 (CH_2), 55.0 (CH), 35.3 (C), 28.4 (CH_3), 26.1 (CH_3), 14.3 (CH_3) ppm. MS (CI-CH_4) *m*/*z*: 104 [$(M+1)^+$, 100%]. HRMS (CI+): calcd for $C_{14}H_{28}NO_5$ 290.1967, found 290.1978. HPLC: Chiracel OD, Hexane/IPA, 98:2; 0.5 mL/min, $\lambda = 220$ nm; t_R (2*R*, 3*R* isomer) = 15.6 min, t_R (2*S*, 3*S* isomer) = 23.3 min. Enantiomeric excess: 90.5%.

4.3.6. Ethyl (2*R*,3*R*)-2-*tert*-butoxycarbonylamino-3-hydroxy-6-benzyloxy-hexanoate 7b. To a solution of **6c** (34 mg, 0.11 mmol) in THF (0.85 mL) and water (16 μL), PPh_3 (49 mg, 0.18 mmol, 1.7 equiv) was added and the reaction mixture heated at 45 °C. After 18 h, the solvent was removed and the crude dissolved in dioxane (0.3 mL) and ^iPrOH (0.13 mL). Boc_2O (25 mg, 0.121 mmol, 1.1 equiv) was added in one portion and the reaction mixture stirred for 72h at room temperature. Removal of the solvent and purification by column chromatography yielded 36 mg of **7c** (90% yield, two steps). $[\alpha]_D = -14.2$ (*c* 0.720, $CHCl_3$). IR (film): ν_{max} 3421, 2977, 2932, 2865, 1716, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.21 (m, 5H, C*H*), 5.44

(dbr, 1H, $J = 7$ Hz, NH), 4.50 (s, 2H, CH_2), 4.34 (br, 1H, CH), 4.22 (m, 2H, CH_2), 3.89 (m, 1H, CH), 3.51 (td, 2H, $J = 6$ and 1 Hz, CH_2), 3.41 (dbr, 1H, $J = 7$ Hz, OH), 1.78 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.45 (s, 9H, $(CH_3)_3$), 1.27 (t, 3H, $J = 7$ Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8 (CO), 156.1 (CO), 138.2 (C), 128.5 (CH), 127.81 (CH), 127.78 (CH), 80.3 (C), 73.1 (CH, CH_2), 70.3 (CH_2), 61.7 (CH_2), 58.7 (CH), 31.0 (CH_2), 28.5 (CH_3), 26.6 (CH_2), 14.4 (CH_3) ppm. MS (CI-CH_4) m/z: 282.2 $[(M-100)^+$, 100%], 382.7 $[(M+1)^+$, 73%]. HRMS (CI+): calcd for $C_{20}H_{32}NO_6$ 382.2230, found 382.2244.

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