Alkylated and bicyclic sugar amino acids : synthesis and applications

Risseeuw, M.D.P.

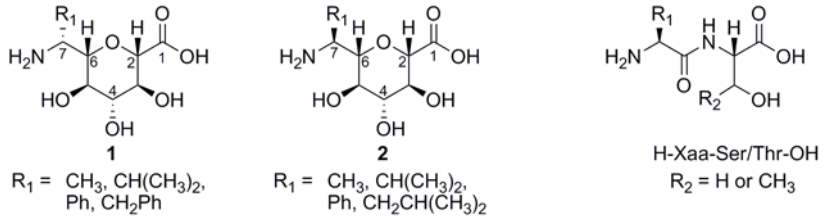
3 Synthesis of Alkylated Sugar Amino Acids

Conformationally Restricted L-Xaa-L-Ser/Thr Mimics

Introduction

As part of ongoing research on artificial peptide-like materials, the synthesis of glucopyranose-based sugar amino acids (SAAs) **1** (Figure 1) was recently reported.[1] In dipeptide isosteres **1**, the stereocentre at C2 has the *S*-configuration, thereby resembling the α-carbon in L-serine or L-threonine.[2] The α-substituted amine at the N-terminus (C7) in **1** resembles the side-chain at the α-carbon of amino acids other than glycine. By tuning the nature of the R^1 group, functionalities corresponding to specific amino acid side-chains can be incorporated into the SAAs.[3] This feature distinguishes compounds **1** from SAAs reported in the literature,[4] of which the large majority are α-unsubstituted amines.[5] As a whole, SAAs **1** can be viewed as conformationally constrained H-Xaa-Ser/Thr-OH mimics. The configuration of C7 corresponds to that of the α-carbons in D-amino acids, rather than the proteinogenic L-amino acids. In contrast to the stereochemical control over the C-terminal portion, which originates from selection of the carbohydrate template, controlling the configuration of the newly introduced stereocentre at C7 stems from asymmetric organic synthesis. This chapter concerns adaptation of the synthetic strategy applied to prepare SAAs **1** to provide C7-*S* configured SAA building blocks **2**.

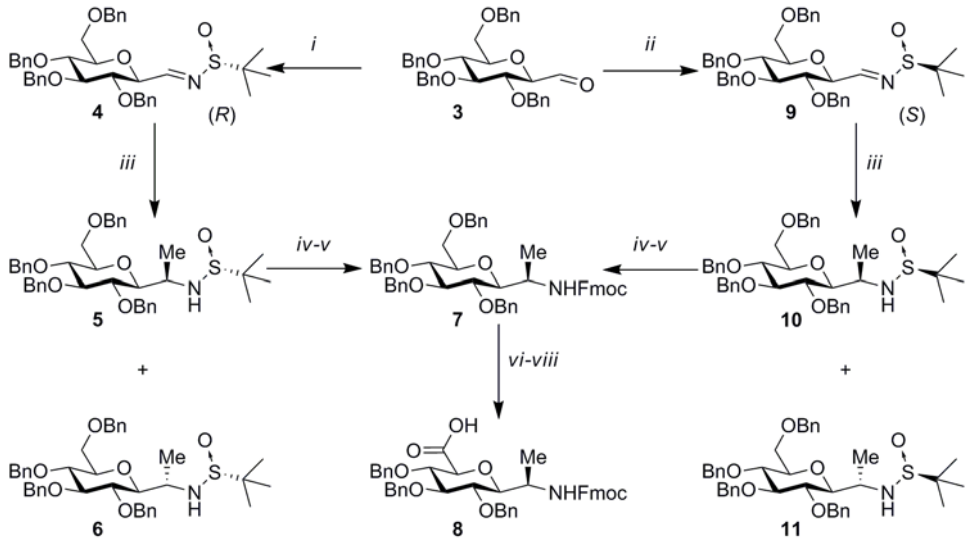
Figure 1. Pyranoid sugar amino acids as dipeptide isosteres.



Results and Discussion

Protected SAAs **1** were previously prepared using the stereoselective alkylation of *R*-*tert*-butanesulfinimide **4**, which was obtained by the condensation of formyl tetra-*O*-benzyl-β-D-*C*-glucopyranoside **3**[6] with *R*-*tert*-butanesulfinyl amide[7] (Scheme 1). Alkylation of compound **4**, subsequent acid-mediated hydrolysis of the *R*-*tert*-butanesulfonyl group and installment of the Fmoc protective group gave compound **7**, which could be transformed into carboxylate **8** by selective acidolysis of the primary benzyl ether, ester hydrolysis and oxidation. The alkylation of sulfinimide **4** proceeded in good diastereoselectivity. For instance, reaction of **4** with 3 equivalents of MeMgBr in methylene chloride at –78 °C gave *R*-methyl adduct **5** in 20-fold excess over the other diastereoisomer **6**. Similar results were obtained by using toluene as a solvent. Performing the alkylation in THF resulted in a drop in diastereoselectivity (**5**:**6** = 13:1).

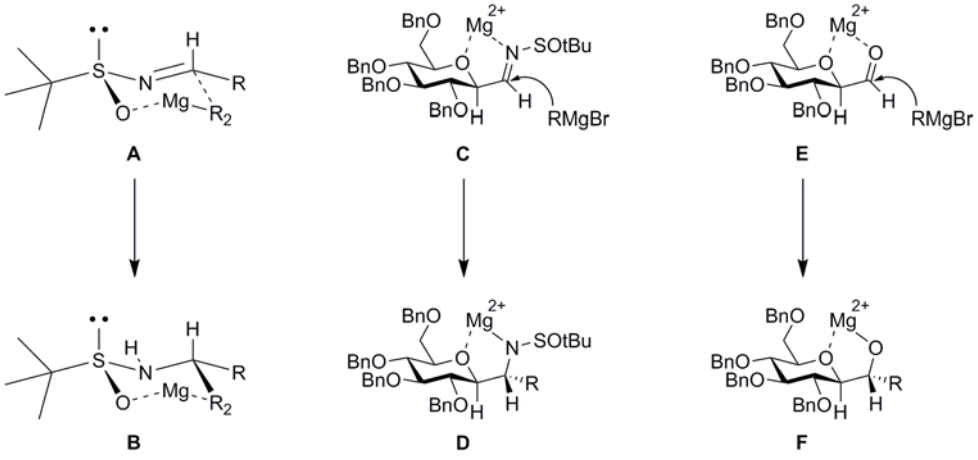
Scheme 1. Synthetic efforts towards methylated SAAs using *tert*-butylsulfinamides as chiral auxiliaries .



Reagents and conditions: [**i**] *R*-*tert*-butanesulfinamide, $Ti(OiPr)_4$, CH_2Cl_2, 70% [**ii**] *S*-*tert*-butanesulfinamide, $Ti(OiPr)_4$, CH_2Cl_2, 72% [**iii**] MeMgBr, CH_2Cl_2 , –78 °C [**iv**] HCl, MeOH, [**v**] FmocOSu, DIPEA, dioxane, CH_2Cl_2, (from **4**: 71%, from **9**: 75%, over three steps) [**vi**] $ZnCl_2$, HOAc, Ac_2O [**vii**] HCl, MeOH [**viii**] TEMPO, $PhI(OAc)_2$, CH_2Cl_2, H_2O (64%, two steps).

Either the *R*-*tert*-butanesulfinyl chiral auxiliary or the chiral carbohydrate template, or a combination of both may be responsible for the observed diastereoselectivity. Would the first be true, then *L*,*L*-dipeptide isostere SAAs **2** would be directly accessible by following the same synthetic scheme, but employing *S*-*tert*-butanesulfinimide as the chiral auxiliary. In order to investigate this possibility, *S*-*tert*-butanesulfinimide **9** the diastereoisomer of **4** with respect to the chirality at the sulfur atom. Treatment of *S*-*tert*-butanesulfinimide **9** with 3 equivalents of MeMgBr (CH_2Cl_2, –78 °C) gave a diastereoisomeric ratio for **10**:**11** of 13 : 1, as monitored by inverse gated ^{13}C NMR measurements[8] on the crude Grignard products (Scheme 1). The absolute stereochemistry of **10** was unambiguously established by acidic removal of the *S*-*tert*-butanesulfonyl group, giving, after Fmoc-protection, a compound that in all spectroscopical aspects was identical to the previously synthesized **7** ($R^1 = CH_3$).[1] From this it follows that the minor product **11** is the *S*-methyl diastereomer of **10** with respect to the newly formed stereocentre. Apparently, *re*-side addition is favored irrespective of the nature of the chiral auxiliary on the imine nitrogen. Changing the solvent system from CH_2Cl_2 to THF resulted in a slightly more favored *si*-side addition, and **10** and **11** were formed in equal amounts. This result is the best that was obtained in favor of the desired diastereoisomer **11** and it can be concluded that at least in this system chiral sulfinylimides are not useful intermediates in the construction of *L*,*L*-dipeptide isosteres.

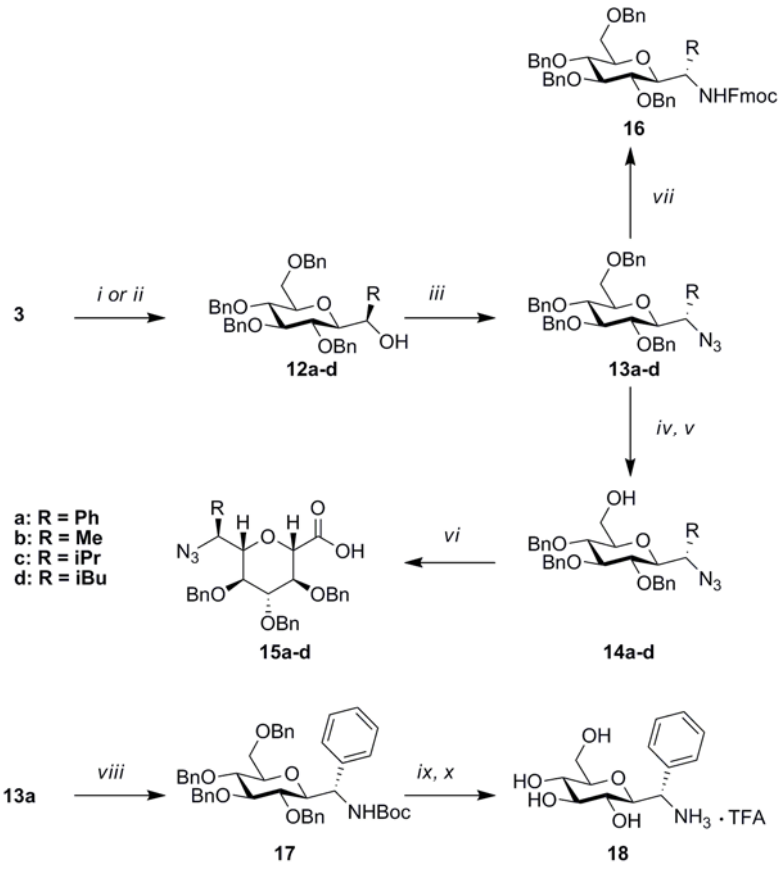
Figure 2. Transition states for Grignard reactions (**A**→**B**: sulfinimines in general, **C**→**D**: glycosyl sulfinimide through intramolecular chelation, **E**→**F**: glycosyl aldehyde through intramolecular chelation).



Currently there is no satisfactory model that explains the different product ratios that were observed, but it seems likely that the chelation model proposed by Ellman and co-workers in their explanation[7f] of chirality transfer (**A** to **B**, Fig. 2) is counterbalanced by

competing chelation of magnesium ions to hetero-atoms on the carbohydrate template. This chelation (for instance **C**, leading to **D**) may occur irrespective of the configuration on the sulfur atom. Whether this reasoning is valid or not, it does present an obvious strategy towards the desired *L*,*L*-dipeptide isosteres. When one assumes that a formyl-*C*-glycoside chelates just as the sulfinimines do with the magnesium ion and that addition occurs with the same *re*-selectivity (**E** to **F**), then the target compounds are within reach by introduction of a nitrogen substituent by replacement of the resulting alcohol function with concomitant reversal of configuration. This reasoning proved to be valid, as is outlined in Scheme 2.

Scheme 2. Synthetic efforts towards alkylated SAAs using intramolecular chelation.



Reagents and conditions: [**i**] PhMgBr, THF, −78 °C (66%) [**ii**] RMgBr or RMgCl, THF, 0 °C (**a** 66%; **b** 51%; **c** 36%; **d** 48%) [**iii**] HN_3, DEAD, PPh_3, toluene (**a** 78%; **b** 83%; **c** 48%; **d** 92%) [**iv**] $ZnCl_2$, HOAc, Ac_2O [**v**] NaOMe, MeOH (**a** 73%; **b** 78%; **c** 68%; **d** 81%, two steps) [**vi**] TEMPO, $PhI(OAc)_2$, CH_2Cl_2, H_2O (**a** 89%; **b** 91%; **c** 76%; **d** 92%) [**vii**] first Me_3P, THF, H_2O, then FmocCl, CH_2Cl_2–dioxane, DIPEA (73%) [**viii**] H_2, Lindlars catalyst, Boc_2O, MeOH (85%) [**ix**] Pd/C, H_2, MeOH [**x**] TFA (97%, two steps).

Grignard addition of 3 equivalents of either PhMgBr, MeMgBr, iPrMgCl or iBuMgBr to aldehyde **3** proceeded in good diastereoselectivity to give **12a–d**, respectively, as the single isolated diastereomers in moderate to good yields (Scheme 2). The absolute configuration of the newly formed stereocentre in alcohol **12b** could be assigned as *R* since its analytical data were in excellent agreement with published values.[9] The crystals obtained from recrystallization of compound **12d** proved to be suitable for an X-ray structural determination to show the anticipated (*R*)-configuration at the newly created stereocentre.[10]

Mitsunobu displacement of the secondary alcohols **12a–d** with azide (HN_3, PPh_3, DEAD, toluene)[11] gave, with inversion of configuration, azides **13a–d**. Of these, phenylglycine analogue **13a** was transformed by a three step sequence (reduction of the azide with concomitant Boc protection yielding derivative **17** followed by hydrogenolytic cleavage of the benzylethers and TFA treatment) into known glucosylamine derivative **18**.[12] All analytical data on **18** are in agreement with those reported in the literature for the same compound thereby validating the assignment of the newly formed stereocentre in azide **13a**. The structural integrity of the compounds was further established by transformation of azide **13b** into the corresponding Fmoc-protected amide **16** (first Staudinger reduction, then treatment with 9-fluorenylmethoxycarbonyl chloride and DIPEA), which gave a compound with the same mass but with otherwise distinct spectroscopical properties from *R*-configured *C*-glycoside **7**. Selective acidolysis of the primary benzyl ethers, deacetylations and subsequent oxidation of the resulting primary hydroxyls gave, the *L*,*L*-dipeptide isosters **15a–d**.

Conclusion

In conclusion, a straightforward and flexible route towards glucopyranose derived *L*,*L* Xaa–Ser(Thr) dipeptide isosteres was developed. The application of the SAA derivatives described in this chapter within peptidic structures with potential biological properties is described in chapter 7.

Experimental section

All reactions described were performed under an argon atmosphere and at ambient temperature unless stated otherwise. Dichloromethane was distilled from P_2O_5 and THF was distilled from $LiAlH_4$ prior to use. Grignard reagents were purchased from Sigma-Aldrich in 1.0-3.0 M stock solutions in THF or diethyl ether. All other reagents were purchased from Sigma-Aldrich or Acros and were used as received. Reactions were monitored by TLC analysis using TLC aluminum sheets (Merck, Silica gel 60, F_{254}) with detection by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in H_2SO_4 (10 %) followed by charring. Column chromatography was performed on 60Å silica gel (40-63 µm). High resolution spectra were recorded

with a Finnigan LTQ Orbitrap Mass spectrometer. ^{1}H- and ^{13}C-APT-NMR spectra were recorded with a Bruker DMX-400 (400/100 MHz) spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as an internal standard (^{1}H NMR) or $CDCl_3$ (^{13}C NMR). Coupling constants are given in Hz. All presented ^{13}C-APT spectra are proton decoupled. Optical rotations were measured with a Propol automatic polarimeter (λ= 589 nm) and IR (ATR-IR) spectra were recorded with a Shimadzu FTIR-8300 spectrometer. Melting points are given uncorrected and were determined on a Stuart Scientific SMP3 melting point apparatus. Throughout this chapter the atoms in all compounds are numbered according to Figure 1.

Compound 9: Aldehyde **3** (1.10 g, 2.0 mmol) and *S-tert*-butane sulfinamide (276 mg, 2.20 mmol) were taken up in 15 mL dry CH_2Cl_2 and placed under an argon atmosphere. To this solution, $Ti(OiPr)_4$ (1.3 mL, 4.4 mmol) was added and the mixture was stirred for 4 h at room temperature. Concentration *in vacuo* followed by silica gel chromatography of the residue (0 → 20% EtOAc in light petroleum) yielded sulfinimine **9** (945 mg, 1.44 mmol 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 (s, 9 H, *t*Bu), 3.52-3.58 (m, 1 H, H2), 3.65-3.78 (m, 3 H, H1, H3, H5), 3.79-3.84 (m, 1 H, H4), 4.14-4.19 (m, 1H, H6), 4.50-4.90 (m, 8 H, 4×$\underline{CH_2}$Ph), 7.13-7.30 (m, 20 H, 4×CH_2Ph), 8.17 (d, 1 H, J = 4 Hz, -CH=N-); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.08 (CMe_3), 56.77 (CMe_3), 68.42 (C^1), 77.24 ($\underline{CH_2}$Ph), 74.44 ($\underline{CH_2}$Ph), 74.72 ($\underline{CH_2}$Ph), 75.34 ($\underline{CH_2}$Ph), 77.74 (C^3), 78.86 (C^6), 79.29 (C^5 + C^2), 86.57 (C^4), 127.19, 127.26, 127.32, 127.39, 127.43, 127.49, 127.54, 127.64, 127.90, 127.98, 128.07, 128.10, 128.14, 128.17, 128.22, 128.30, 137.29, 137.67, 137.85, 137.98, 164.51 (-CH=N-); IR neat (cm^{-1}): 695.8, 734.6, 910.0, 1069.7, 1270.6, 1453.8, 1591.9, 1724.1, 2869.8, 3031.1, 3064.4, 3290.5; $[\alpha]_D^{20}$ + 45.6 (c 1.0, $CHCl_3$); HRMS: calcd. for $C_{39}H_{46}O_6NS$ ([M+H]) 656.30404, found 656.30450.

Compound 7: Imine **9** (660 mg, 1.0 mmol) was coevaporated twice with toluene (10 mL) and dissolved in freshly distilled CH_2Cl_2 60 mL and placed under an argon atmosphere. After cooling of the solution to - 78°C MeMgBr (1.0 mL, 3.0 M in Et_2O) was added dropwise. After stirring for 80 minutes at -78 °C the reaction was quenched by the addition of sat. aq. NH_4Cl and the temperature was allowed to rise to RT. The reaction mixture was extracted twice with diethyl ether and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, water, dried (Na_2SO_4), and concentrated *in vacuo*. The crude sulfonamide was taken up in 100 mL methanol and 1.25 mL HCl in 1,4-dioxane (4.0 M) was added. The methanolic mixture was stirred for half an hour and concentrated and coevaporated with methanol (2 × 20 mL). The crude hydrochloride was dissolved in 100 mL of CH_2Cl_2 and 1,4-dioxane (1:1 v/v) and DIPEA (3.0 mmol, 530 µL) and FmocOSu (1.5 mmol, 508 mg)were added. Stirring was continued for 2.5 hr after which the reaction mixture was diluted with CH_2Cl_2 and water (100 mL each). The organic phase was separated and washed with 10% aq. citric acid, satd. aq. $NaHCO_3$, and water (100 mL each). The organic layer was dried on Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (10% → 20% EtOAc in light petroleum v/v) yielding 592 mg (0.75 mmol, 75 %) of the title compound as a pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (d, 1 H, *J* = 6.8 Hz, H8), 3.20 (d, 1 H, *J* = 9.6 Hz, H6), 3.40-3.48 (m, 2 H, H2 and H5), 3.61 (t, 1 H, *J* = 9.4 Hz), 3.69-3.74 (m, 3 H, H1 and H4), 4.21 (t, 1 H, *J* = 6.8 Hz, CHFmoc), 4.28-4.33 (m, 1 H, H7), 4.44 (d, 2 H, *J* = 7.2 Hz, CH_2 Fmoc), 4.55 (dd, 2 H, *J* = 4.0Hz, *J* = 12 Hz $\underline{CH_2}$Ph), 4.62 (t, 2 H, *J*= 10 Hz, $\underline{CH_2}$Ph), 4.82 (dd, 2 H *J* = 10.8, *J* = 8.8, $\underline{CH_2}$Ph), 4.94 (s, 2H, $\underline{CH_2}$Ph), 5.25 (d, 1 H, J = 10 Hz, NH), 7.15-7.39 (m, 24 H, ArBn and ArFmoc), 7.59, (dd, 2 H, *J* = 3.2 Hz, *J* = 7.6 Hz, ArFmoc), 7.72 (d, 2 H, J = 7.6 Hz, ArFmoc); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.05, 45.35, 47.28, 66.36, 68.91, 73.20, 74.92, 75.40, 78.13, 78.44, 78.64, 80.69, 87.02, 119.86, 124.93, 126.97, 127.46, 127.55, 127.61, 127.69, 127.81, 128.32, 128.36, 128.50, 137.87, 137.97, 138.47, 141.20, 143.83, 143.90, 155.84; IR neat (cm^{-1}): 621.0, 698.2, 729.0, 906.5, 995.2, 1026.1, 1211.2, 1450.4, 1500.5, 1716.5, 2341.4; $[\alpha]_D^{20}$ + 16.2 (c 1.0, $CHCl_3$); HRMS: calcd. for $C_{51}H_{55}O_7N_2$ ([M+NH_4]) 807.40038, found 807.40118.

Compound 12a. Aldehyde **3** (2.31g, 4.18 mmol) was coevaporated thrice with toluene (25 mL) dissolved in 40 mL freshly distilled THF and placed under an argon atmosphere. The solution was cooled to -78°C and 12.6 mL phenylmagnesium bromide (1.0 M in THF 3.0 eq.) was added over 30 minutes. The reaction was stirred for another 3 hours and poured into 100 mL of NH_4Cl (sat. aq.) and diluted with 100 mL diethyl ether. The organic layer was washed with water (2× 100 mL) and saturated aqueous NaCl (100 mL). The organic fractions were dried on Na_2SO_4 and concentrated *in vacuo*. Chromatography of the residue on silica gel (0 → 20 % EtOAc in light petroleum) yielded the title compound (1.74 g, 2.76 mmol, 66%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.37 (m, 1 H, H2), 3.51 (d, 1 H, *J* = 9.6 Hz, H6), 3.63-3.68 (m, 3H, H3, H1), 3.75 (t, 1 H, *J* = 8.8 Hz, H4), 3.83 (t, 1 H, *J* = 9.2 Hz, H5), 4.44-4.98 (m, 8 H, 4×CH_2Ph), 4.92 (s, 1 H, H7), 7.17-7.45 (m, 25 H, 4×CH_2Ph, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 68.84 (C^1), 71.15 (C^7), 73.27 ($\underline{CH_2}$Ph), 74.99 ($\underline{CH_2}$Ph), 75.22 ($\underline{CH_2}$Ph), 75.51 ($\underline{CH_2}$Ph), 78.14 (C^3), 78.46 (C^5), 78.46 (C^2), 81.39 (C^6), 87.08 (C^4), 126.37, 127.23, 127.63, 127.75, 127.83, 127.88, 127.93, 128.08, 128.33, 128.38, 128.42, 128.48, 138.05, 138.10, 142.03; IR neat (cm^{-1}): 694.3, 1002.9, 1068.5, 1311.5, 1496.7, 1701.1, 2866.0; $[\alpha]_D^{20}$ + 7.0 (c 1.0, $CHCl_3$); HRMS: calcd. for $C_{41}H_{46}O_6N$ ([M+NH_4]) 648.33196, found 648.33215.

Compound 12b. In an oven-dried flask, 1.8 mL of a 3.0 M solution of methyl magnesiumbromide in diethylether, was placed under an argon atmosphere, diluted with 3.5 mL freshly distilled THF and cooled on ice to 0°C. Aldehyde **3** (0.98 g, 1.77 mmol) was coevaporated twice with toluene (20 mL), taken up in 5 mL freshly distilled THF and added dropwise to the precooled Grignard reagent. The reaction was stirred for 3 hrs at 0°C, diluted with 20 mL of ether after which 30 mL of sat. aq. NH_4Cl was added. The organic layer was separated and the aqueous layer was extracted once with 20 mL of ether. The organic layers were combined and extracted with sat. aq NaCl, was dried on Na_2SO_4 and concentrated *in vacuo*. Chromatography of the residue on silica gel (10 → 25% EtOAc in light petroleum, shallow gradient) yielded 512 mg (0.90 mmol, 51%) of the *R*-alcohol **12b** as a colorless oil. Further elution allowed the isolation of the *S*-isomer (222mg, 0.39 mmol, 22%) whose physical data were in agreement with earlier published data.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.31 (d, 3 H, *J* = 6.5 Hz, H8), 3.11 (m, 1 H, H6), 3.61 (m, 1 H, H3), 3.67-3.75 (m, 4 H, H1, H4, H5), dq (1 H, *J* = 6.5 Hz, *J* = 1.0 Hz, H7), 4.50-4.95 (m, 8 H, 4×CH_2Ph), 7.13-7.34 (m, 20 H, ArBn); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.31 (C^8), 65.25 (C^7), 68.99 (C^6), 73.28 ($\underline{CH_2}$Ph), 74.90 ($\underline{CH_2}$Ph), 75.04 ($\underline{CH_2}$Ph), 75.38 ($\underline{CH_2}$Ph), 78.20 (C^3), 78.33 (C^5), 78.64 (C^2), 81.33 (C^6), 87.04 (C^4), 127.48, 127.54, 127.61, 127.65, 127.84, 127.87, 128.30, 128.36, 137.99, 138.03, 138.12, 138.55; IR neat (cm^{-1}): 694.3, 1045.3, 1242.1, 1361.7, 1454.7, 1735.8, 2866.0; $[\alpha]_D^{20}$ + 16.0 (c 1.0, $CHCl_3$); HRMS: calcd. for $C_{36}H_{44}O_6N$ ([M+NH_4]) 586.31631, found 586.31647.

Compound 12c. Aldehyde **3** (1.33 g, 2.40 mmol) was transformed into alcohol **12c** analogously to the synthesis of compound **12b** but by using 3.6 mL isopropylmagnesium chloride (2.0 M in diethyl ether). Before addition of the aldehyde, the concentration of the Grignard reagent was adjusted to ~1 M by the addition of 3.6 mL THF. Workup and chromatography on silica (10 → 25% EtOAc in light petroleum) yielded 516 mg (0.87 mmol, 36%) of the title compound as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3 H, *J* = 6.4 Hz, Me), 1.05 (d, 3 H, *J* = 6.8 Hz, Me), 1.88 (m, 1H, $CH(Me)_2$), 3.37 (d, 2 H, *J* = 8.4, H6, H7), 3.44 (m, 1H, H2), 3.59 (t, 1 H, *J* = 9.6 Hz, H3), 3.66-3.80 (m, 4 H, H1, H4, H5), 4.44-4.92 (m, 8 H, 4 × CH_2Ph), 7.09-7.33 (m, 20 H, 4 × $CH_2\underline{Ph}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.18 (Me), 19.56 (Me), 31.48 (C^8), 69.16 (C^1), 73.32 ($\underline{CH_2}$Ph), 74.42 (C^7), 74.92 ($\underline{CH_2}$Ph), 75.07 ($\underline{CH_2}$Ph), 75.48 ($\underline{CH_2}$Ph), 78.19 (C^3), 78.28 (C^1 and C^5), 78.73 (C^2), 87.20 (C^4), 127.52, 127.59, 127.61, 127.66, 127.84, 128.03, 128.16, 128.36, 138.13, 138.31, 138.62; IR neat (cm^{-1}): 694.3, 1049.2, 1091.6, 1454.2, 1496.7, 1732.0, 2032.8, 21.60.1, 2869.9, 2923.9, 3031.9; $[\alpha]_D^{20}$ + 15.2 (c 1.0, $CHCl_3$); HRMS: calcd. for $C_{36}H_{48}O_6N$ ([M+NH_4]) 614.34761, found 614.34784.

Compound 12d. Aldehyde **3** (1.22 g, 2.20 mmol) was transformed into alcohol **12c** analogously to the synthesis of compound **12b** but by using 3.3 mL isobutylmagnesium bromide (2.0 M in diethyl ether). Before addition of the aldehyde, the concentration of the Grignard reagent was adjusted to ~1 M by the addition of 3.3 mL THF. Workup and chromatography on silica (10 → 25% EtOAc in light petroleum) yielded 645 mg (1.06 mmol, 48%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.91 (d, 3 H, *J* = 6.4 Hz, Me), 0.93 (d, 3 H, *J* = 6.8 Hz, Me), 1.23-1.30 (m, 1 H, H8^a), 1.62-1.70 (m, 1 H, H8^b), 1.74-1.84 (m, 1 H, H9), 3.13 (d, 1 H, *J* = 8.0 Hz, H1), 3.45 (dd, 1 H, *J* =9.4, 2.4Hz, H2), 3.59 (t, 1 H, *J* = 8.8 Hz, H3), 3.66-3.77 (m, 4 H, H1, H4, H5), 3.90 (dd, 1 H, *J* = 9.0, 3.8 Hz, H7), 4.51-4.60, 4.73-4.76, 4.82-4.96 (m, 8 H, 4 × CH_2Ph), 7.11-7.42 (m, 20 H, 4 × CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.95 (Me), 23.38 (Me), 24.59 (C^9), 43.39 (C^8), 67.12 (C^7), 69.19 (C^1), 73.32 (CH_2Ph), 74.98 (CH_2Ph), 75.23 (CH_2Ph), 75.46 (CH_2Ph), 78.33 (C^3, C^5), 78.82 (C^2), 80.74 (C^6), 87.15 (C^4), 127.59, 127.62, 127.72, 127.79, 127.91, 128.04, 128.33, 128.38, 128.45, 138.12, 138.20, 138.65, IR neat (cm^{-1}): 698.2, 736.8, 952.8, 1049.2, 1207.4, 1365.5, 1978.8 2954.7; $[\alpha]_D^{20}$ + 24.0 (c 1.0, $CHCl_3$); mp: 102°C (from ethanol); HRMS: calcd. for $C_{39}H_{50}O_6N$ ([M+NH_4]) 628.36326, found 628.36346.

Compound 13a. Hydrazoic acid solution (**CAUTION: HN_3 is volatile, highly toxic and explosive!)**: Sodium azide (4.0 g, 61.5 mmol) was dissolved in 10 mL water. Toluene (50 mL) was added and the resulting biphasic system was cooled on ice to 0°C. Under vigorous stirring, 8 mL concentrated sulfuric acid was added dropwise. After 30 minutes of stirring, the organic layer was separated and stored on anhydrous Na_2SO_4.
Alcohol **12a** (568 mg, 0.90 mmol) was coevaporated twice with toluene (20 mL) and taken up in 10 mL toluene. DEAD, (0.85 mL, ~40% in toluene, ~1.85 mmol) and triphenylphosphine (475 mg, 1.81 mmol) were added. Finally 4.0 mL of the hydrazoic acid solution was added. The reaction was stirred for 1hr at room temperature during which the color shifted from bright yellow to cloudy white. The reaction mixture was concentrated *in vacuo*. Column chromatography (0 → 10 % EtOAc in light petroleum) allowed isolation of the product (442 mg, 0.70 mmol, 78%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.22 (t, 1 H, *J* = 9.2 Hz, H5), 3.51 (m, 1 H, H2), 3.65 (t, 1 H, *J* = 9.6 Hz, H3), 3.75 (t, 1 H, *J* = 8.8 Hz), 3.84 (m, 2 H, H1), 3.88, (dd, 1 H, *J* = 10 Hz, *J* = 2.8 Hz), 4.30-4.34, 4.55-4.65, 4.76-4.82, 4.90-4.93 (m, 8H, 4×CH_2Ph), 4.68 (d, 1 H, *J* = 2.8 Hz, H7), 7.06-7.48, (m, 25 H, 4×Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 64.27 (C^7), 68.80 (C^1), 71.31 (CH_2Ph), 74.18 (CH_2Ph), 74.86 (CH_2Ph), 75.33 (CH_2Ph), 78.03 (C^3), 78.51 (C^5), 78.96 (C^2), 80.88 (C^6), 87.20 (C^4), 127.21, 127.23, 127.33, 127.43, 127.51, 127.59, 127.64, 127.74, 127.82, 128.21, 128.29, 128.29, 128.33, 128.40, 128.52.; IR neat (cm^{-1}): 536.1, 696.1, 730.7, 908.7, 1094.9, 1361.0, 1454.0, 1497.0, 20.97.7, 2865.9, 3030.8; $[\alpha]_D^{20}$ + 28.2 (c 2.0, $CHCl_3$); HRMS: calcd. for $C_{41}H_{45}O_5N_4$ ([M+NH_4]) 673.33845, found 673.33887.

Compound 13b. Alcohol **12b** (723 mg, 1.27 mmol) was transformed into its corresponding azide according to the procedure described for compound **13a**. Column chromatography (0 → 15 % EtOAc in light petroleum) yielded the title compound (603 mg, 1.06 mmol, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.16 (d, 3 H, *J* = 7.0 Hz, Me), 3.41 (t, 1 H, *J* = 8.5 Hz, H5), 3.45-3.47 (m, 1 H, H2) 3.50 (dd, 1 H, *J* = 9.5 Hz, *J* = 1.3 Hz, H6), 3.57 (m, 1 H, H7), 3.67 (t, 1 H, *J* = 9 Hz, H3), 3.71-3.79 (m, 3 H, H1, H4), 4.53-4.97 (m, 8 H, 4 × CH_2Ph), 7.20-7.33 (m, 20 H, 4 × CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.36 (Me), 56.21 (C^7), 68.84 (C^1), 73.49 (CH_2Ph), 74.57 (CH_2Ph), 74.98 (CH_2Ph), 75.54 (CH_2Ph), 77.94 (C^5), 78.25 (C^3), 79.15 (C^2), 80.81 (C^6), 87.42 (C^4), 127.45, 127.49, 127.60, 127.64, 127.74, 127.88, 127.95, 128.06, 128.29, 128.39, 128.43, 128.49, 137.68, 138.03, 138.35, IR neat (cm^{-1}): 694.3, 732.9, 1002.9, 1091.6, 1454.2, 1542.9, 2102.3, 2858.3, 3031.9; $[\alpha]_D^{20}$ + 6.0 (c 1.0, $CHCl_3$) HRMS: calcd for $C_{36}H_{43}O_5N_4$ ([M+NH_4]) 611.32280, found 611.32281.

Compound 13c. Alcohol **12c** (943 mg, 1.58 mmol) was transformed into its corresponding azide according to the procedure described for compound **13a** except with 72 hour stirring after the addition of the hydrazoic

acid solution. Column chromatography (0 → 10 % EtOAc in light petroleum) yielded the title compound (473 mg, 0.76 mmol, 48%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.96 (d, 3 H, *J* = 6.8 Hz, Me), 1.02 (d, 3 H, *J* = 6.8 Hz, Me), 1.93 (m, 1 H, $CHMe_2$), 3.34 (dd, 1 H, *J* = 8.4 Hz, *J* = 2.0 Hz, H7), 3.46 (m, 1 H, H2), 3.59-3.68 (m, 2 H, H3, H6), 3.69-3.75 (m, 4 H, H1, H4, H5), 4.54-4.94 (m, 8 H, 4 × $\underline{CH_2}$Ph), 7.18-7.34 (m, 20 H, 4 × $CH_2\underline{Ph}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.32 (Me), 20.65 (Me), 29.84 (C^8), 69.33 (C^1), 71.34 (C^7), 73.47 (CH_2Ph), 74.59 (CH_2Ph), 74.96 (CH_2Ph), 75.57 (CH_2Ph), 78.37 (C^3), 78.67 (C^5), 78.97 (C^6), 79.16 (C^2), 87.54 (C^4), 127.43, 127.46, 127.49, 127.56, 127.75, 127.90, 128.32, 128.34, 128.40, 138.08, 138.12, 138.42; IR neat (cm^{-1}): 694.3, 910.3, 1026.1, 1064.6, 1261.4, 1357.8, 1454.2, 1496.7, 2094.6, 1869.9; $[\alpha]_D^{20}$ -19.4 (c 1.0, $CHCl_3$); HRMS: calcd for $C_{38}H_{47}O_5N_4$ ([M+NH_4]) 639.35410 found 639.35443.

Compound 13d. Alcohol **12d** (1.62 g, 2.65 mmol) was transformed into its corresponding azide according to the procedure described for compound **13a**. Column chromatography (0 → 10 % EtOAc in light petroleum) yielded the title compound (1.55 g, 2.44 mmol, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3 H, *J* = 6.4 Hz, Me), 0.95 (d, 3 H, *J* = 6.1 Hz, Me), 1.21-1.28 (m, 1 H, H8^a), 1.75-1.88 (m, 2 H, H8^b, H9), 3.45-3.49 (m, 1 H, H2), 3.51-3.62 (m, 3 H, H2), 3.63-3.69 (t, 1 H, *J* = 9.4 Hz, H3), 3.71-3.79 (m, 3 H, H4, H1) 4.55-4.66, 4.80-4.97 (m, 8H, 4 × CH_2Ph), 7.19-7.36 (m, 20 H, 4 × $CH_2\underline{Ph}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.25 (Me), 23.55 (Me), 25.07 (C^9), 36.62 (C^8), 60.01 (C^7), 68.99 (C^1), 74.49 ($\underline{CH_2}$Ph), 74.79 ($\underline{CH_2}$Ph), 74.99 ($\underline{CH_2}$Ph), 75.50 ($\underline{CH_2}$Ph), 78.30 (C^3), 78.36 (C^5), 79.24 (C^2), 81.54 (C^6), 87.42 (C^4), 127.49, 127.60, 127.77, 127.83, 127.91, 128.30, 128.40, 128.41, 128.45, 137.75, 138.03, 138.37, 138.41; IR neat (cm^{-1}): 694.3, 732.9, 1026.1, 1095.5, 1454.2, 1496.7, 2102.3, 2866.0; $[\alpha]_D^{20}$ – 2.2 (c 1.0, $CHCl_3$); HRMS: calcd for $C_{39}H_{49}O_5N_4$ ([M+NH_4]) 653.36975 found 653.37006.

Compound 14a. Azide **13a** (1.22 g, 1.86 mmol) was taken up in 30 mL Ac_2O/AcOH (2:1 v/v). $ZnCl_2$ (5.0 g, 37.2 mmol, 20 eq.) was added and the reaction is stirred for 5 hr at room temperature. The color of the reaction slowly turned dark green during this time. The reaction mixture was poured into 30 mL water and diluted with 50 mL diethylether. The ether layer was washed with water (2× 50 mL), sat aq Na_2CO_3 (2× 50 mL), dried on Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in 50 mL methanol and the pH was adjusted to ± 10 by the addition of sodium methoxide (30% w/w solution in methanol) and stirred overnight at room temperature. The pH was adjusted to 7 by the addition of amberlyte IR120H resin, the solution was filtered and concentrated *in vacuo*. Residual benzyl alcohol was removed by twofold coevaporation with water 20 mL. The residue was coevaporated once with toluene and purified by silica gel chromatography (0 → 20% EtOAc in light petroleum) to yield the title compound (770 mg, 1.36 mmol, 73 %) as a colorless viscous oil which solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.06 (s, 1 H, OH), (3.21 (t, 1 H, *J* = 9.6 Hz, H5), 3.43-3.46 (m, 2 H, H2, H3), 3.73 (d, 1 H, *J* = 11.4 Hz, H1^a), 3.77 (t, 1 H, *J* = 8.4 Hz, H4), 3.90 (dd, 1 H, *J* = 10.2 Hz, *J* = 2.4 Hz, H6), 4.35-4.37 and 4.62-4.63 (m, 2 H, CH_2Ph), 4.71 (d, 1 H, *J* = 2.4 Hz, H7), 4.77-4.92 (m, 4 H, 2×$\underline{CH_2}$Ph), 7.16-7.38 (m, 20 H, 3×$CH_2\underline{Ph}$, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 62.01 (C^1), 64.45 (C^7), 74.18 ($\underline{CH_2}$Ph), 75.00 ($\underline{CH_2}$Ph), 75.40 ($\underline{CH_2}$Ph), 78.05 (C^3), 78.35 (C^5), 79.35 (C^2), 80.88 (C^6), 87.08 (C^4), 127.23, 127.45, 127.62, 127.68, 127.76, 127.82, 127.86, 128.36, 128.39, 128.42, 128.53, 128.66, 129.06, 134.75, 137.65, 137.92, 137.98; IR neat (cm^{-1}): 694.3, 740.6, 1014.5, 1068.5, 1357.8, 1454.2, 2094.6; $[\alpha]_D^{20}$ + 2.0 (c 1.0, $CHCl_3$); HRMS: calcd for $C_{34}H_{39}O_5N_4$ ([M+NH_4]) 583.29150 found 583.29181.

Compound 14b. Azide **13b** (660 mg, 1.11 mmol) was debenzylated at the primary position using the procedure described for compound **14a**. Column chromatography (0 → 20 % EtOAc in light petroleum) yielded the title compound (332 mg, 0.66 mmol, 78 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.10 (d, 3 H, *J* = 7.2 Hz, Me), 2.30 (s, 1 H, OH), 3.44-3.40 (m, 2 H, H2, H3), 3.49-3.56 (m, 3 H, H5, H6, H7), 3.64 (dd, 1 H, *J* = 11.6 Hz, *J* = 4.4, H1^a), 3.73 (t, 1 H, *J* = 9.2 Hz, H4), 3.85 (d, 1 H, *J* = 10.8 Hz, H1^b), 4.57-4.67, 4.81-4.95 (m, 6 H,

3×$\underline{CH_2}$Ph), 7.22-7.32, (m, 15 H, 3×$CH_2\underline{Ph}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.03 (Me), 56.18 (C^7), 61.77 (C^1), 74.30 ($\underline{CH_2}$Ph), 74.78 ($\underline{CH_2}$Ph), 75.29 ($\underline{CH_2}$Ph), 77.62 (C^3), 77.98 (C^5), 79.15 (C^2), 80.74 (C^6), 87.02 (C^4), 127.39, 127.44, 127.64, 127.69, 127.74, 127.82, 127.99, 128.23, 128.27, 137.45, 137.69, 138.10; IR neat (cm^{-1}): 694.3, 910.3, 1060.8, 1149.5, 1234.4, 1357.8, 1454.2, 2103.3; $[\alpha]_D^{20}$ + 2.8 (c 1.0, $CHCl_3$); HRMS: calcd for $C_{29}H_{37}O_5N_4$ ([M+NH_4]) 521.27585 found 521.27588.

Compound 14c. Azide **13c** (156 mg, 0.25 mmol) was debenzylated at the primary position using the procedure described for compound **14a**. Column chromatography (0 → 20 % EtOAc in light petroleum) yielded the title compound (89 mg, 0.17 mmol, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.95 (d, 3 H, *J* = 6.6 Hz, Me), 1.00 (d, 3 H, *J* = 6.6 Hz, Me), 1.89 (m, 1 H, $CHMe_2$), 3.34 (d, 1 H, *J* = 8.4 Hz, H7), 3.37 (m, 1 H, H2), 3.63 (m, 1 H, H3), 3.70 (dd, 1 H, J = 11.4 Hz, *J* = 3.6 Hz, H1^a), 3.75-3.78 (m, 3 H, H4,H5,H6), 3.86 (dd, 1 H, *J* = 12 Hz, *J* = 1.8 Hz, H1^b), 3.67-3.71, 4.84-4.88, 4.93-4.97 (m, 6 H, 3 × $\underline{CH_2}$Ph), 7.21-7.33 (m, 15 H, 3 × $CH_2\underline{Ph}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.48 (Me), 20.61 (Me), 29.60 ($CHMe_2$), 61.87 (C^1), 71.68 (C^7), 74.59 (CH_2Ph), 75.04 (CH_2Ph), 75.58 (CH_2Ph), 77.76 (C^3), 78.35 (C^5), 79.03 (C^2), 79.23 (C^6), 87.23 (C^4), 127.31, 127.54, 127.62, 127.87, 127.91, 128.32, 128.40, 128.45, 137.38, 137.94, 138.22; IR neat (cm^{-1}): 695.2, 750.6, 1027.8, 1087.4, 1261.5, 1362.5, 1454.0, 1497.8, 1733.6, 2097.5, 2873.3. $[\alpha]_D^{20}$ - 47.6 (c 1.0, $CHCl_3$); HRMS: calcd for $C_{31}H_{41}O_5N_4$ ([M+NH_4]) 549.30715 found 549.30731.

Compound 14d. Azide **13d** (1.02 g, 1.61 mmol) was debenzylated at the primary position using the procedure described for compound **14a**. Column chromatography (0 → 20 % EtOAc in light petroleum) yielded the title compound (712 mg, 1.30 mmol, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85 (d, 3 H, *J* = 6.4 Hz, Me), 0.94 (d, 3 H, *J* = 6.4 Hz, Me), 1.21 (m, 1 H, H8^a), 1.78 (m, 2H, H8^b, H9), 2.14 (s, 1 H, OH), 3.40 (m, 1 H, H2), 3.48-3.57 (m 3 H, H3, H5, H7), 3.62-3.78 (m, 2 H, H1^a, H6), 3.75 (t, 1 H, H4), 3.86 (d, 1 H, *J* = 10.7 Hz, H1^b), 4.92-4.68, 4.82-4.97 (m, 6 H, 3×$\underline{CH_2}$Ph), 7.12-7.31 (m, 15 H, 3×$\underline{CH_2}$Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.07 (Me), 23.34 (Me), 24.91 (C^9), 36.12, (C^8), 59.93 (C^7), 61.92 (C^1), 74.62 (CH_2Ph), 74.89 (CH_2Ph), 75.35 (CH_2Ph), 78.05 (C^3), 78.20 (C^5), 79.34 (C^2), 81.64 (C^6), 87.10 (C^4), 127.26, 127.49, 127.58, 127.73, 127.80, 128.28, 128.31, 137.54, 137.69, 138.17; IR neat (cm^{-1}): 698.2, 729.0, 1064.6, 1353.9, 1662.5, 2106.1; $[\alpha]_D^{20}$ - 5.6 (c 1.0, $CHCl_3$); HRMS: calcd for $C_{32}H_{42}O_5N_4$ ([M+NH_4]) 563.32280 found 563.32300.

Compound 15a. Azido alcohol **14a** (634 mg, 1.12 mmol) was taken up in 5 mL CH_2Cl_2 and 2.5 mL water. The biphasic mixture was stirred vigorously and iodobenzene diacetate (BAIB, 0.91 g, 2.80 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 35 mg, 0.224 mmol) were added. Stirring was continued for 1 hour after which the reaction was quenched with 20 mL sat. aq. $Na_2S_2O_4$ and diluted with 30 mL CH_2Cl_2. The organic layer was separated and the aqueous phase was acidified with 1M HCl to pH 2 and extracted twice with CH_2Cl_2. The combined organic layers were dried on Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (0→15 % MeOH in CH_2Cl_2) to yield the title compound (580 mg, 1.00 mmol, 89%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.16 (dd, 1 H, *J* = 9.2, *J* = 8.4 Hz, H5), 3.64 (dd, 1 H, *J* = 17.7 Hz, *J* = 8.8 Hz, H3), 3.68 (dd, 1 H, *J* = 16.8 Hz, *J* = 8.8 Hz, H4), 3.83 (dd, 1 H, *J* = 10 Hz, *J* = 2.8, H6), 3.98 (d, 2 H, *J* = 8.8 Hz, H2), 3.25-2.28 and 4.54-4.80 (m, 7 H, 3×$\underline{CH_2}$Ph, H7), 7.10-7.35 (20 H, 3×$CH_2\underline{Ph}$, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 64.58 (C^7), 74.15 (CH_2Ph), 74.95 (CH_2Ph), 75.30 (CH_2Ph), 77.50 (C^2), 77.81 (C^5), 79.27 (C^3), 80.59 (C^6), 85.61 (C^4), 127.38, 127.59, 127.80, 127.84, 128.03, 128.10, 128.43, 128.44, 128.49, 128.70, 128.88, 129.42, 134.30, 137.18, 137.73, 137.79, 173.06 (C^1); IR neat (cm^{-1}): 694.3, 1026.1, 1087.8, 1249.8, 1357.8, 1454.2, 1496.7, 1724.2, 1978.8, 2098.4; $[\alpha]_D^{20}$ – 0.2 (c 1.0, $CHCl_3$); HRMS: calcd for $C_{34}H_{37}O_6N_4$ ([M+NH_4]) 597.27076 found 597.27100.

Compound 15b. Azido alcohol **14b** (514 mg, 1.02 mmol) was oxidized to azido acid **15b** according to the protocol described for compound **15a**. Column chromatography (0 → 15 % MeOH in CH_2Cl_2) yielded the title compound (482 mg, 0.93 mmol, 91%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3 H, *J* = 6.8 Hz, Me), 3.46, (dd, 1 H, *J* = 9.6 Hz, *J* = 8.0 Hz, H5), 3.56 (dd, 1 H, *J* = 10 Hz, *J* = 2.0 Hz, H6), 3.63 (dq, 1 H, *J* = 6.8 Hz, *J* = 2.0 Hz, H7), 3.70-3.80 (m, 2 H, H3, H4), 3.98 (d, 1 H, *J* = 8.8 Hz, H2), 4.58-3.92 (m, 6 H, 3×$\underline{CH_2}$Ph), 7.23-7.36, (m, 15 H, 3×$CH_2\underline{Ph}$), ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.34 (Me), 56.19 (C^7), 74.45 ($\underline{CH_2}$Ph), 74.83 ($\underline{CH_2}$Ph), 75.45 ($\underline{CH_2}$Ph), 77.14 (C^5), 77.67 (C^2), 79.33 (C^3), 80.72 (C^6), 98.05 (C^4), 127.62, 127.69, 127.83, 127.97, 128.02, 128.29, 128.37, 128.43, 137.30, 137.87, 173.42 (C^1) IR neat (cm^{-1}): 462.1, 696.7, 752.7, 1026.3, 1083.8, 1214.0, 1361.4, 1497.7, 1740.6, 2109.6, $[\alpha]_D^{20}$ + 21.6 (c 1.0, $CHCl_3$), mp: 133°C (from hexane), HRMS: calcd for $C_{29}H_{35}O_6N_4$ ([M+NH_4]) 535.25511 found 535.25513.

Compound 15c. Azido alcohol **14c** (890 mg, 0.17 mmol) was oxidized to azido acid **15c** according to the protocol described for compound **15a**. Column chromatography (0→15 % MeOH in CH_2Cl_2) yielded the title compound (71 mg, 0.13 mmol, 76%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.95 (d, 3 H, 6.5 Hz, Me), 1.00 (d, 3 H, J = 6.5 Hz, Me), 1.90 (m, 1 H, $CHMe_2$), 3.35 (dd, 1 H, *J* = 8.0 Hz, *J* = 1.5 Hz, H7), 3.75-3.82 (m, 3 H, H4, H5, H6), 3.86 (t, 1 H, *J* = 8.5 Hz, H3), 4.01 (d, 1 H, *J* = 8.5 Hz, H2), 4.64-4.87 (m, 6 H, 3×CH_2Ph), 7.18-7.34 (m, 15 H, 3×$CH_2\underline{Ph}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.05 (Me), 20.55 (Me), 29.84 ($CHMe_2$), 71.19 (C^7), 74.24 ($\underline{CH_2}$Ph), 74.62 ($\underline{CH_2}$Ph), 75.14 ($\underline{CH_2}$Ph), 77.59 (C^2), 77.83 (C^5), 78.75 (C^6), 78.88 (C^3), 84.83 (C^4), 127.50, 127.68, 127.79, 127.94, 128.06, 128.26, 128.46, 129.75, 137.38, 137.77, 137.90, 172.48 (C^1); IR neat (cm^{-1}): 695.2, 959.7, 1027.8, 1088.1, 1149.3, 1251.3, 1363.3, 1454.1, 1497.9, 1683.9, 1737.6, 2098.4, 2361.3, 2914.1, 3031.5; $[\alpha]_D^{20}$ - 44.8 (c 0.5, $CHCl_3$); ESI-MS: calcd for $C_{31}H_{35}O_6N_3Na$ ([M+Na]) 568.24 found 568.60.

Compound 15d. Azido alcohol **14d** (791 mg, 1.45 mmol) was oxidized to azido acid **15d** according to the protocol described for compound **15a**. Column chromatography (0 → 15 % MeOH in CH_2Cl_2) yielded the title compound (742 mg, 1.33 mmol, 92%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86 (d, 3 H, *J* = 6.4 Hz, Me), 0.93 (d, 3 H, *J* = 6.4 Hz), 1.24 (m, 1 H, H8^a), 1.73-1.82 (m, 2 H, H8^b, $CH(Me)_2$), 3.57-3.63 (m, 2 H, H5, H7), 3.68 (dd, 1 H, *J* = 9.6 Hz, *J* = 1.6 Hz, H6), 3.77 (dd, 1 H, *J* = 16.4 Hz, *J* = 8.8 Hz, H4), 3.80 (dd, 1 H, *J* = 17.2 Hz, *J* = 8.8 Hz, H3), 3.99 (d, 1 H, *J* =8.8 Hz, H2), 4.58-4.93 (m, 6 H, 3×$\underline{CH_2}$Ph), 7.21-7.35 (m, 15 H, 3×$CH_2\underline{Ph}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.22 (Me), 23.40 (Me), 25.00 ($CHMe_2$), 36.80 (C^8), 60.12 (C^7), 74.68 ($\underline{CH_2}$Ph), 74.94 ($\underline{CH_2}$Ph), 75.40 ($\underline{CH_2}$Ph), 77.51 (C^2), 77.68 (C^5), 79.00 (C^3), 81.45 (C^6), 85.68 (C^4), 127.61, 127.80, 127.97, 128.03, 128.14, 128.43, 128.50, 137.19, 137.40, 137.89, 173.10 (C1); IR neat (cm^{-1}): 696.0, 748.9, 1056.7, 1127.7, 1361.7, 1453.8, 1674.0, 2117.1, 2907.9; $[\alpha]_D^{20}$ - 25.2 (c 1.0, $CHCl_3$); mp: 122°C (from hexane), HRMS: calcd for $C_{32}H_{41}O_6N_4$ ([M+NH_4]) 577.30206 found 577.30225.

Compound 16. Compound **13b** (422 mg, 0.71 mmol) was taken up in 8 mL THF and 2 mL water and cooled on ice. Me_3P (3.5 mL, 1 M in Toluene) was added and the reaction was stirred for 4 hr. The solvents were removed and the residue was coevaporated twice with toluene. The crude amine was taken up in 70 mL CH_2Cl_2/1,4 dioxane (1:1 v/v) and DIPEA (2.10 mmol, 370 µL) and FmocCl (1.05 mmol, 272 mg) were added. Stirring was continued for 2.5 hr after which the reaction mixture was diluted with CH_2Cl_2 and water (50 mL each). The organic phase was separated and washed with 10% aq. citric acid, sat. aq. $NaHCO_3$, and water (50 mL each). The organic layer was dried on Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (10% → 20% EtOAc in light petroleum v/v) yielding 411 mg (0.52 mmol, 73 %) of the title compound as an off-white wax. The compound exists as a 5:1 mixture of rotamers. Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.02 (d, 3 H, *J* = 6.8 Hz, Me), 3.35-3.45 (m, 3 H, H2, H5, H6), 3.60 (t, 1 H, *J* = 9.2 Hz, H3), 3.68-3.73 (m, 3 H, H1, H4), 4.17, (m, 1 H, H7), 4.22 (t, 1 H, *J* = 7.2 Hz, - $OCH_2\underline{CH}$Fmoc), 4.40 (d, 2 H, J = 7.2 Hz, -$O\underline{CH_2}$CHFmoc), 4.52-4.70 and 4.81-

4.94 (m, 8 H, 4×$\underline{CH_2}$Ph), 5.22 (d, 1 H, *J* = 9.2 Hz), 7.19-7.40 (m, 24 H, 4×CH$_2\underline{Ph}$, ArFmoc), 7.59 (d, 2 H, J = 7.6 Hz, ArFmoc), 7.75 (d, 2 H, *J* = 7.6 Hz, ArFmoc); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.03 (Me), 46.38 (C^7), 47.27 (OCH$_2\underline{CH}$Fmoc), 66.49 (O$\underline{CH_2}$CHFmoc), 73.30 ($\underline{CH_2}$Ph), 74.42 ($\underline{CH_2}$Ph), 74.99 ($\underline{CH_2}$Ph), 75.48 ($\underline{CH_2}$Ph), 78.03 (C^5), 78.40 (C^3), 78.89 (C^2), 80.63 (C^6), 87.27 (C^4), 119.80, 119.89, 125.00, 125.04, 126.98, 127.40, 127.53, 127.59, 127.61, 127.74, 127.82, 127.85, 128.05, 128.20, 128.34, 128.39, 128.41, 128.43, 137.79, 138.03, 138.19, 138.39, 141.24, 143.94, 144.03, 155.53 (COFmoc), IR neat (cm-1): 694.1, 734.2, 911.7, 1037.8, 1093.5, 1256.9, 1452.1, 1553.9, 1680.3, 2846.4, 3031.7, 3302.8. $[\alpha]_D^{20}$ + 2.0 (c 1.0, $CHCl_3$), HRMS: calcd for $C_{51}H_{55}O_7N_2$ ([M+NH_4]) 807.40038, found 807.40137.

Compound 17. Compound **13a** (607 mg, 0.93 mmol) was taken up in 20 mL dry methanol. To this solution Lindlars Catalyst (Pd/$CaCO_3$/Pb, 120 mg, 20 % by wt.) and di-*tert*-butyl dicarbonate (250 mg, 1.15 mmol) were added. Hydrogen gas was bubbled through the reaction mixture until TLC indicated full conversion into a more polar product (6 hr). the reaction was filtered concentrated in vacuo and the residue was purified by silica gel column chromatography (10% → 35% EtOAc in light petroleum v/v) yielding 577 mg (0.79 mmol 85 %) of the title compound as an colorless syrup. The compound exists as a 3.5:1 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.34 (minor) and 1.40 (major) (s, 9 H, CMe_3), 3.06 (t, 1 H, *J* = 7.2 Hz, H5), 3.47-3.55 (m, 2 H, H2, H3), 3.73-3.83 (m, 4 H, H1, H4, H6), 4.33-4.96 (mm, 8 H, 4×$\underline{CH_2}$Ph), 4.96 (m, H7 minor rotamer) 5.11 (dd, *J* = 7.2 Hz, *J* = 2.4 Hz , H7 major rotamer), 5.57 (d, *J* = 6.8 Hz, NH minor rotamer), 5.71 (d, *J* = 7.2 Hz), 7.18-7.44 (m, 25 H, 4×CH$_2\underline{Ph}$, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.28 (CMe_3), 54.35 (C^7), 68.96 (C^1), 73.11 ($\underline{CH_2}$Ph), 73.97 ($\underline{CH_2}$Ph), 74.91 ($\underline{CH_2}$Ph), 75.29 ($\underline{CH_2}$Ph), 78.26 (C^3 and C^5), 78.75 (C^2), 79.21 (CMe_3), 80.73 (C^6), 87.33 (C^4), 126.97, 127.23, 127.29, 127.41, 127.48, 127.67, 127.74, 127.91, 128.09, 138.301, 128.33, 128.10, 137.881,138.066, 138.186, 138.23, 138.84, 154.73 (C=O); IR neat (cm^{-1}): 649.8, 733.3, 1094.9, 1158.1, 1364.7, 1454.0, 1489.8, 1713.8, 2865.9, 3444.2; $[\alpha]_D^{20}$ + 22.0 (c 1.0, $CHCl_3$); ESI-MS: [M+H] 730.6, [M -Boc+2H],630.4.

Compound 18. Compound **17** (577 mg, 0.79 mmol) was taken up in 20 mL methanol. To the solution 10 % Pd/C was added. Hydrogen gas was bubbled through for 4 hours after which the reaction was filtered and concentrated *in vacuo*. The residue was taken up in 10 mL trifluoroacetic acid and the solution was stirred for 30 minutes. Concentration of the acidic mixture yielded the product (207 mg, 0.77 mmol 97%) as an oil which solidified over time. ^{1}H NMR (400 MHz, D_2O) δ = 2.69 (t, 1 H, *J* = 9.6 Hz, H5), 2.93 (t, 1 H, *J* = 9.6 Hz, H3), 3.32-3.37 (m, 2H, H2, H4), 3.54 (dd, 1 H, *J* = 12.0 Hz, *J* = 7.6 Hz, H1^a), 3.70 (dd, 1 H, *J* = 9.6 Hz, *J* = 2.8 Hz, H6), 3.82 (d, 1 H, *J* = 11.6 Hz, H1^b), 4.62 (d, 1 H, *J* = 2.4 Hz, H7), 7.33-7.38 (m, 5 H, Ph); ^{13}C NMR (100 MHz, D_2O) δ = 54.93 (C^7), 61.55 (C^1), 69.64 (C^3), 69.99 (C^5), 77.03 (C^6), 77.18 (C^2), 79.87 (C^4), 128.75, 128.79, 129.51, 131.43; IR neat (cm^{-1}): 628.4, 699.0, 799.8, 987.9, 1185.5, 1318.3, 1463.8, 1656.4, 3042.2; $[\alpha]_D^{20}$ + 20.0 (c 1.0, H_2O) lit.[12] $[\alpha]_D^{20}$ + 20.8 (c 1.0, H_2O); ESI-MS: [M+H] 270.1, [M+Na] 292.0

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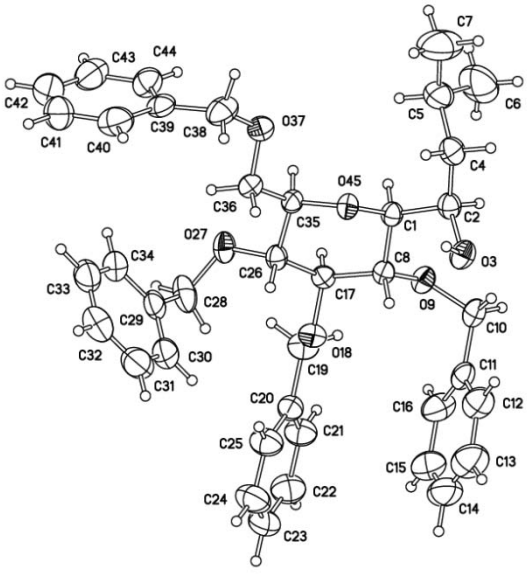

Empirical formula	**$C_{39}H_{46}O_6$**
Formula weight	**610.76**
T[K]	**293(2)**
λ[Å]	**0.71073**
Crystal system	**Orthorhombic**
Space group	**P $2_12_12_1$**
Unit cell dimensions	
a [Å]	**6.0520(2)**
b [Å]	**23.7560(5)**
c [Å]	**23.9440(5)**
V [$Å^3$]	**3442.5(2)**
Z	**4**
D_m [g/cm^3]	**1.178**
Absorption coefficient mm^{-1}	**0.078**
F(000)	**1312**
Crystal size [mm^3]	**0.6 x 0.3 x 0.15**
θ range	**3 → 27.5**
Reflections collected	**17437**
Independent reflections	**7673 [R_{int} = 0.0411]**
Data / restraints / parameters	**7673 / 0 / 566**
S	**1.025**
R [I>2σ(I)]	**R1 = 0.0465, wR2 = 0.0858**
R indices (all data)	**R1 = 0.0747, wR2 = 0.0965**
Absolute structure parameter	**-0.4(7)**

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