A Stereoselective Synthesis of Nonracemic (+)-Desoxoprosophylline by a Tandem Wittig [2+3]-Cycloaddition Reaction

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Keywords: L-Ascorbic acid / (+)-Desoxoprosophylline / Lactones / Alkaloids / Domino reactions

L-Ascorbic acid serves as chiral starting material for the synthesis of (+)-desoxoprosophylline. The synthetic pathway includes the formation of an *O*-protected 5-azido-2,3-dideoxysugar which is subjected to a tandem Wittig [2+3]-cycloaddition reaction, leading to the heterocyclic core unit of (+)-prosophylline. Stereoselective hydrogenation and chain elongation yields the desired alkaloid.

2,3,6-Substituted chiral piperidine alkaloids such as (+)-prosopine (**1**), (+)-prosopinine (**2**), (±)-prosophylline (**3**), and micropine (**4**) can be isolated from various *Prosopis* species[1] or, in the case of micropine from *Microcos philippinensis*.[2] These compounds have recently been targets of increasing interest for total synthesis. Some 6-alkyl-3-hydroxy-2-(hydroxymethyl)piperidines have been synthesized in racemic form,[3] but during the last few years a growing number of enantioselective syntheses of *Prosopis*[4] and *Microcos* alkaloids[5] and their derivatives have been published.

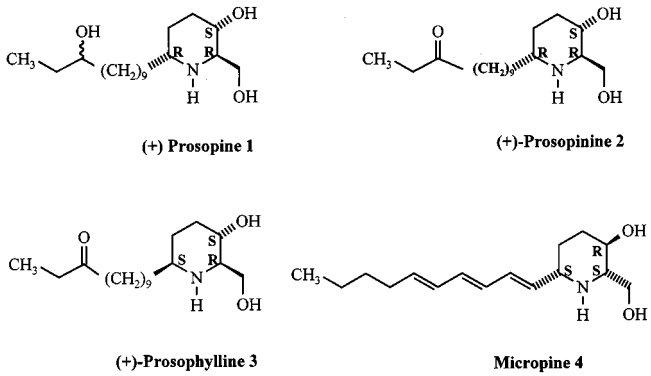
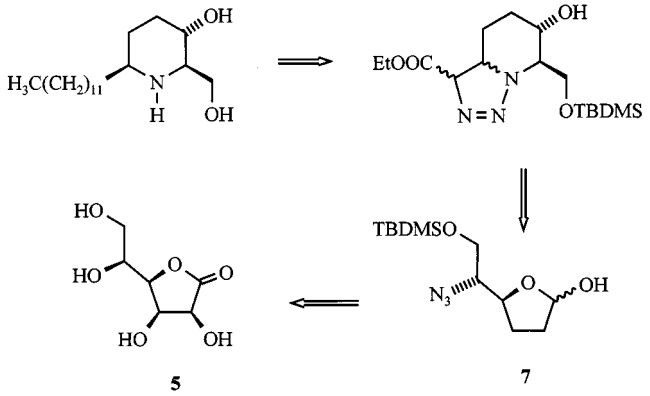


Figure 1

These compounds display some significant pharmacological activities, e.g. local anaesthetic, antibiotic, and hypotensive activities have been described for prosopine.[6] Furthermore, extracts from *Prosopis juliflora* used in indigenous medicine show activity against gonorrhea.[7]

In our continuing studies of chiral, nonracemic piperidine derivatives,[8] we now report a chiral-pool synthesis of (+)-desoxoprosophylline starting from L-gulonolactone **5**, which is a cheap chiral starting material that can be obtained by the catalytic hydrogenation of L-ascorbic acid.[9] Furthermore, its enantiomer, namely D-gulonolactone **6** is also commercially available at a reasonable price. This ensures that our reaction sequence for the (+)-enantiomer of desoxprosophylline and its derivatives also offers the possibility of synthesizing their optical antipodes.

The general strategy of the synthesis is outlined in Scheme 1. The heterocyclic ring system should be accessible by a tandem Wittig [2+3]-cycloaddition, a reaction sequence previously used by us in the synthesis of chiral, nonracemic piperidine derivatives.[8] The introduction of the side chain should be accomplished by standard procedures published by Cook, Beholz, and Stille.[3d,3e]



Scheme 1. Retrosythetic analysis

A key intermediate in our reaction sequence is the 5-azidolactole **7** that should be obtainable by diastereoselective synthesis from L-gulonolactone **5**. To this end, L-gulonolactone **5** is protected as its 5,6-isopropylidene derivative **8** according to a procedure described by Vekemans and Chittenden.[10] In the literature two pathways for deoxygenation of **8** are described.[10][11] Since neither method is suitable for scaling up, we developed an alternative method for the large-scale synthesis of **9**. Compound **8** should be treated according to the Corey–Winter reductive elimination procedure.[12] Unfortunately, the reaction of **8** with thiocarbonyldiimidazole (TCDI) failed to give a cyclic thionocarbonate. Instead, decomposition of starting material and TCDI occurred and an untractable mixture was isolated.

The synthesis of the **9** was therefore carried out as outlined in Scheme 2. Deoxygenation of the α- and β-positions of **8** was accomplished by a 4-step procedure, which in-

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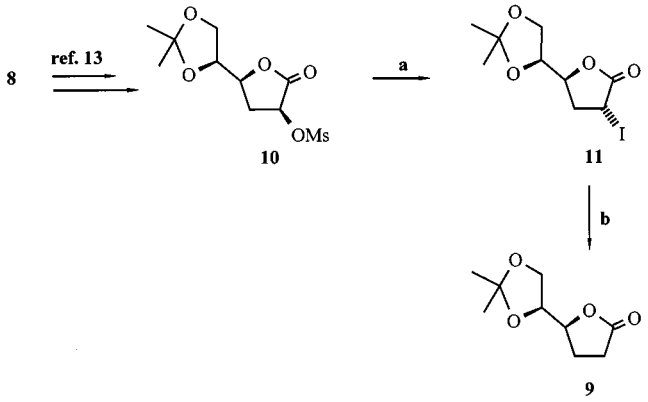
volved two steps already described by Vekemans and Chittenden leading to the α-mesylated lactone **10**.[13] Nucleophilic substitution of the α-mesyl group by iodine lead to the crystalline light-sensitive α-iodolactone **11**. In this reaction acetone was the solvent of choice because cleavage of the isopropylidene-protecting group occurred when the reaction was run in acetonitrile. The α-iodolactone could then be converted into lactone **9** by catalytic hydrogenation in the presence of a palladium catalyst and an excess of triethylamine. This reaction sequence turned out to be superior to the known methods on a large scale.

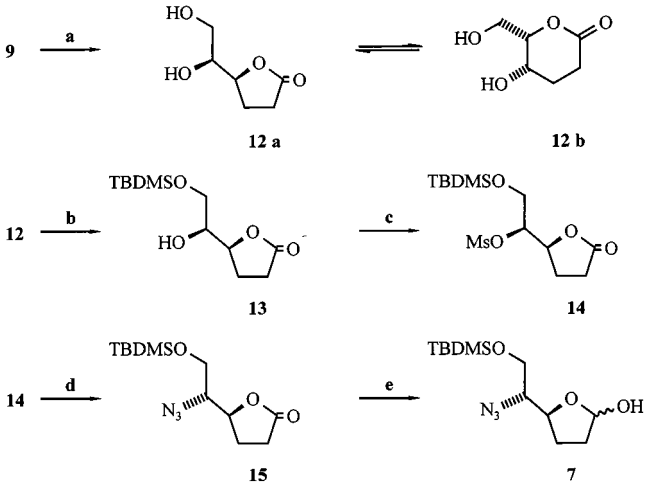


Scheme 2. a) NaI, acetone, reflux, 92%. – b) H_2, Et_3N, 10% Pd/C, 20–30 h, 82%.

The isopropylidene-protecting groups were then removed, giving the unprotected lactone **12**. NMR spectra of this molecule revealed the presence of an equilibrium mixture of γ- and δ- lactones **12a** and **12b**, but this did not cause serious problems because similar mixtures had been completely converted into the butanolide form by blocking the primary alcohol function with a sterically demanding protecting group.[14] For this transformation we chose the TBDMS group because of its stability towards bases and dilute acids, and its facile deprotection with ethanolic hydrogen chloride solution. Introduction of the silyl group with TBDMS chloride in DMF with an excess of imidazole proved troublesome at first because of the long reaction times and unacceptable yields. It therefore proved advantageous to carry out the reaction in the presence of a catalytic amount of DMAP.[15] It must be noted that an excess of base was needed and TBDMS chloride had to be added in separate portions in order to obtain the primary silyl ether **13** in quantitative yield.

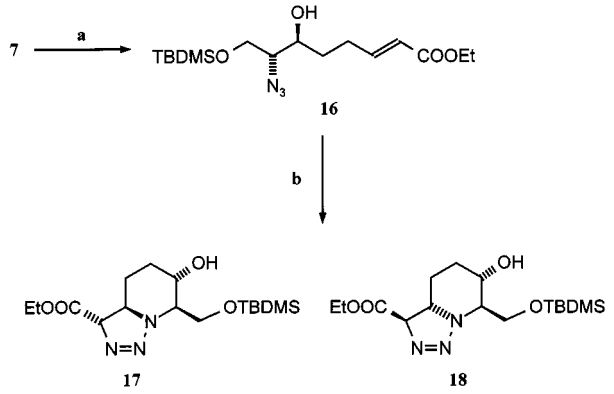
Mesylation of the secondary alcohol function, followed by introduction of azide by stereoselective nucleophilic substitution, gave rise to lactone **14** and the 5-azidolactone **15**, respectively. The lactole **7** could then be synthesized by reduction of **15** with DIBAlH in THF at −78°C.

The next task was to carry out the tandem Wittig [2+3]-cycloaddition reaction (Scheme 4). This was achieved by treating **7** with (ethoxycarbonylmethylene)triphenylphosphorane in dry toluene. To our surprise, the Wittig reaction led to complete conversion after 80 minutes. In contrast a reaction time of 4 days was required for the cycloaddition step. The α,β-unsaturated azido ester **16** could be isolated



Scheme 3. a) concd. HCl, *i*PrOH, 48 h, 96%; b) excess TBDMSCl, Et_3N, DMAP, DMF, 12 min, 99%; c) MsCl, Et_3N, CH_2Cl_2, 20 min, 79%; d) NaN_3, DMPU, 70°C, 24 h, 65%; e) DIBAlH, THF, −78°C, 4–6 h, 69%

and completely characterized. A *trans* configuration was assigned to the double bond. At −20°C this compound can be stored for weeks without undergoing a remarkable conversion into the triazolines.

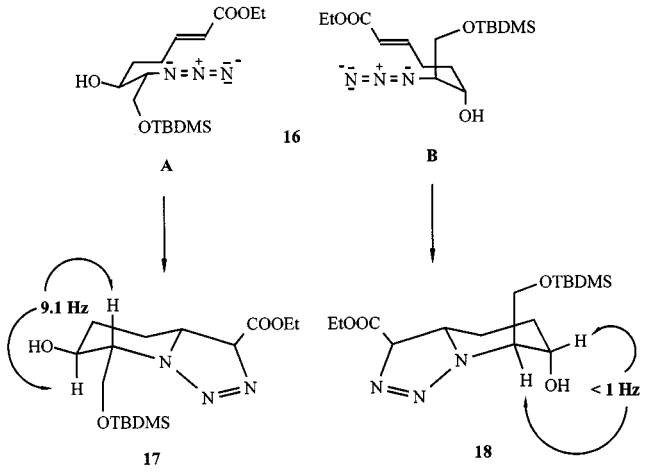


Scheme 4. a) $Ph_3PCHCOOEt$, toluene, room temp., 1 d; b) toluene, room temp, 4 d, 98%

When **16** was left at ambient temperature, two diastereomeric triazolines **17** and **18** resulted. Assignment of the stereochemistry was achieved by ^{1}H-NMR spectroscopy and by assuming that the triazoline ring is orientated in an equatorial position. The remaining substituents are then either both axially or both equatorially disposed. The observed ^{1}H-NMR coupling constants $^3J_{2',3}$ of 9.1 Hz for the major product **17** revealed that in fact, only equatorially orientated substituents are present, whereas in the minor product **18** this coupling constant was smaller than 1 Hz which indicates that both substituents, namely the hydroxy and the CH_2OTBDMS group, occupy axially orientated positions.

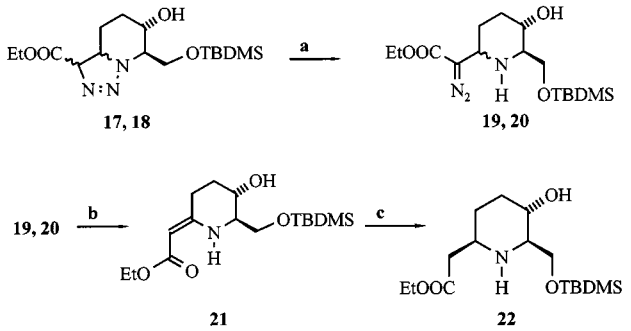
The cycloaddition shows moderate diastereoselectivity. The major product **17** is formed with a *d.e.* of 34% (determined by HPLC). Change of solvent did not cause substantial improvements of diastereoselectivity. We suspect that conformational constraints caused by the OTBDMS group

must prevent the double bond of the α,β-unsaturated ester moiety from attaining the proper alignment with the 1,3-dipolar azide functionality, so the activation barriers for both chair-like conformers **A** and **B** (Scheme 5) are rather high. In fact, when the $CH_2OTBDMS$ group is replaced by a methyl group, quantitative conversion into the triazolines could be observed within 48 h, and the α,β-unsaturated azido ester could not be isolated.[8b]



Scheme 5. Stereochemical outcome of the cycloaddition reaction

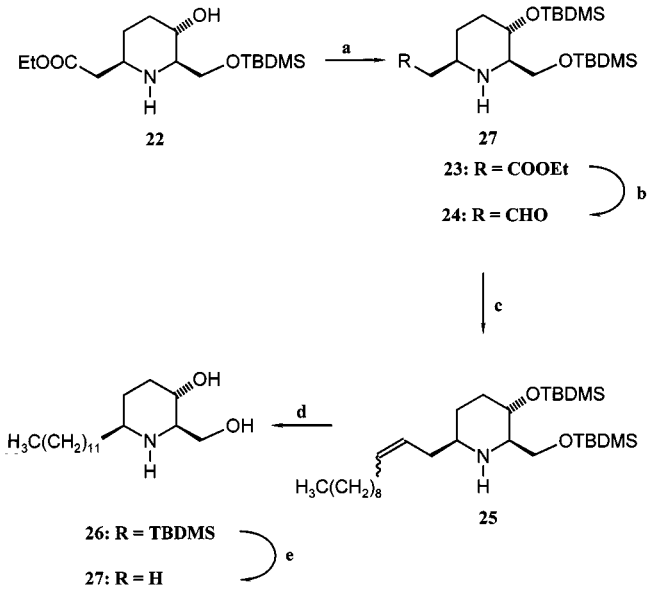
These observations suggest that conformer **A** is, despite the steric repulsion of the hydroxy and the silyloxymethyl group, the major conformer which is involved in the cycloaddition step leading to **17** (Scheme 5). Electronic effects, like the attractive gauche interaction between the azido group, and the hydroxy group might favour the formation of **B**, but on the other hand, the axial orientation of the bulky silyloxymethyl group destabilises this conformation. In summary, both chair-like conformers are not ideally suited to cycloaddition, and the reaction rate is severely retarded.



Scheme 6. a) i. Et_3N, CH_2Cl_2, 12 h, 96%, b) $Rh_2(OAc)_4$, 12 h, 97%; c) H_2, 10% Pd/C, EtOH, 48 h, 71%

Rearrangement of the triazolines to the corresponding diazo esters could be achieved by addition of triethylamine, and afforded compounds **19** and **20** in nearly quantitative yields. The diazo esters are remarkably stable towards dilute acid. Treatment of **19** with 1 M hydrochloric acid lead to the formation of a hydrochloride of **19** which could be isolated and characterized as its monohydrate. When a mixture of **19** and **20** was submitted to Rh^{II}-mediated extrusion of nitrogen,[16] the vinylogous urethane **21** was formed under very mild conditions in quantitative yield.

The introduction of the aliphatic side chain was attempted in two ways. First we alkylated the α-position of the anion of the vinylogous urethane **21** according to a modified procedure by Lhommet,[17] by deprotonating the N−H group with butyllithium in THF at −40°C and adding undecyl bromide. A small amount of alkylation product was obtained, but the yield did not exceed 16%. It must be noted that extensive decomposition occurred. Alkylation at the unprotected hydroxy function at C-5′ was not observed.



Scheme 7. a) TBDMSCl, imidazole, DMF, 84%; b) DiBAlH, *n*-pentane, −78°C, 25 min, 66%; c) $Ph_3P(CH_2)_9CH_3Br$, $NaN[Si(CH_3)_3]_2$, THF, (i) −40°C, 60 min, (ii) room temp, 160 min, 79%; d) H_2, 10% Pd/C, EtOH, 12 h, 93%; e) HCl, EtOH, 15 min, then 6 N KOH, 87%

Alternatively, in order to introduce the side chain, we hydrogenated the vinylogous urethane **21** in the presence of palladium on charcoal. This reaction proved to be completely diastereoselective as can be shown by ^{1}H-NMR analysis, and provided the 2,6-*cis*-substituted product **22**. The unprotected hydroxy group was blocked with another TBDMS group, and the ester **23** was selectively reduced to the aldehyde **24** with DIBAlH in pentane. Subsequent Wittig reaction with decylphosphonium bromide under salt-free conditions led to the olefin **25**, which was then hydrogenated .The resulting compound **26** was finally deprotected to yield (+)-desoxoprosophylline **27**, which exhibited an optical rotation identical in magnitude, but opposite in sign, to the rotation of (−)-desoxoprosophylline.[4b] Spectroscopic and physical data were in accordance with those reported in literature for (+)-desoxoprosophylline.[4i]

Experimental Section

General: ^{1}H, HH-COSY, and ^{13}C NMR: Bruker AC 200, chemical shifts relative to the solvent as internal standard. − IR: Perki-

n−Elmer 681. − MS: Finnigan MAT 8200 (70 eV). − Gas chromatography: Carlo Erba HRGC 5160 Mega Series, Macherey−Nagel SE 54 column (25 m × 0.2 mm ID, 0.1 μm film thickness), helium at 27 cm/s. − Retention indices RI_p were determined according to the method of van den Dool and Kratz[18] at 5°C/min relative to a standard of *n*-paraffins. − TLC: Merck silica gel 60 F_{254} plates. − Optical rotation: Perkin−Elmer 241. − Melting points are uncorrected. − Column chromatography: silica gel 60 (0.063−0.2 mm). − All reactions were carried out under nitrogen. − THF and ether were distilled from potassium sodium couple, acetone from calcium chloride, DMF, dichloromethane, and triethylamine from calcium hydride.

2,3-Dideoxy-2-iodo-5,6-isopropylidene-L-*talo*-hexono-1,4-lactone (11): 3-Deoxy-5,6-isopropylidene-2-mesyloxy-L-*gulo*-hexono-1,4-lactone (**10**) (15.61 g, 55.69 mmol) and sodium iodide (10.85 g, 72.40 mmol, 1.3 equivalents) were dissolved in 160 mL of acetone (abs.) and heated to reflux for 1 h. The solvent was removed in vacuo, and the oily yellow residue was taken up in ethyl acetate. The organic solution was washed with satd. sodium hydrogen carbonate solution, 0.1 M sodium thiosulfate solution, and brine. The solvent was distilled and 16.04 g (51.40 mmol, 92%) of the crude product was obtained. This material was sufficiently pure for further reaction, for analytical purposes it was chromatographed (EtOAc, R_f = 0.70) and recrystallized from *t*BuOMe. The product is light-sensitive and should not be stored in solution. − Colourless crystals, m.p. 99°C. − RI_p = 1755. − $[\alpha]_D^{20}$ = −2 (*c* = 0.7, MeOH). − IR (KBr): $\tilde{\nu}$ = 1760 cm^{-1} (C=O), 1370, 1165, 1060, 1075. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (3 H, s, CH_3), 1.27 (3 H, s, CH_3), 2.39 (1 H, ddd, $J_{2,3A}$ = 4.2, $J_{3A,4}$ = 6.7, J_{AB} = 14.5 Hz, 3_A-H), 2.61 (1 H, ddd, $J_{3B,4}$ = 7.0, $J_{2,3B}$ = 7.8, J_{AB} = 14.5 Hz, 3_B-H), 3.81 (1 H, dd, $J_{5,6A}$ = 6.4, J_{AB} = 8.4 Hz, 6_A-H), 4.00 (1 H, dd, $J_{5,6B}$ = 6.8, J_{AB} = 8.4 Hz, 6_B-H), 4.14 (1 H, ddd, $J_{4,5}$ = 3.1, $J_{5,6A}$ = 6.4, $J_{5,6B}$ = 6.8 Hz, 5-H), 4.54 (1 H, ddd, $J_{4,5}$ = 3.1, $J_{3A,4}$ = 6.7, $J_{3B,4}$ = 7.0 Hz, 4-H), 4.60 (1 H, dd, $J_{2,3A}$ = 4.2, $J_{2,3B}$ = 7.8 Hz, 2-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 10.7 (C-2), 26.0 (*C*H_3), 26.5 (*C*H_3), 38.0 (C-3), 65.8 (C-6), 76.5 (C-5), 79.8 (C-4), 111.0 [*C*$(CH_3)_2$], 174.2 (C-1). − $C_9H_{13}IO_4$ (312.12): calcd. C 34.63, H 4.20; found C 34.92, H 4.20.

2,3-Dideoxy-5,6-isopropylidene-L-*threo*-hexono-1,4-lactone (9): 7.00 g (22.43 mmol) of **11** were dissolved in ethyl acetate (200 mL), triethylamine (6.20 mL, 4.54 g, 44.85 mmol, 2 equivalents) and Pd/C (700 mg) were added, and the mixture was hydrogenated at 70 bar at ambient temperature (average reaction times: 20−36 h). The catalyst was removed by filtration, the filtrate was washed with 1 M HCl and brine, dried with anhydrous sodium sulfate and concentrated to dryness in vacuo. The residue was purified by chromatography (EtOAc, R_f = 0.47), to yield a colourless oil: 3.43 g (18.40 mmol, 82%), RI_p = 1426. − $[\alpha]_D^{20}$ = +30 (*c* = 1.3, MeOH). − IR (neat): $\tilde{\nu}$ = 1775 cm^{-1} (C=O), 1380, 1160, 1060. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 2.06−2.35 (2 H, m, 3-H), 2.48 (1 H, ddd, $J_{2A,3A}$ = 6.1, $J_{2A,3B}$ = 9.3, J_{AB} = 17.4 Hz, 2_A-H), 2.61 (1 H, ddd, $J_{2B,3}$ = 6.7, $J_{2B,3}$ = 7.3, J_{AB} = 17.4 Hz, 2_B-H), 3.85 (1 H, dd, $J_{5,6A}$ = 6.9, J_{AB} = 8.2 Hz, 6_A-H), 4.02 (1 H, dd, $J_{5,6B}$ = 6.7, J_{AB} = 8.2 Hz, 6_B-H), 4.11 (1 H, ddd, $J_{4,5}$ = 2.9, $J_{5,6B}$ = 6.7, $J_{5,6A}$ = 6.9 Hz, 5-H), 4.44 (1 H, ddd, $J_{4,5}$ = 2.9, $J_{3A,4}$ = 5.2, $J_{3B,4}$ = 7.9 Hz, 4-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = 24.1 (CH_2, C-3), 25.3 (CH_3, *C*H_3), 25.8 (CH_3, *C*H_3), 27.8, (CH_2, C-2), 65.1 (CH_2, C-6), 77.5 (CH, C-5), 78.0 (CH, C-4), 109.9 [*C*$(CH_3)_2$], 177.0 (C-1). − $C_9H_{14}O_4$ (186.23): calcd. C 58.05, H 7.58; found C 57.82, H 7.20.

2,3-Dideoxy-L-*threo*-hexono-1,4-lactone (12a) and 2,3-Dideoxy-L-*threo*-hexono-1,5-lactone (12b): 2.82 g (15.15 mmol) of **9** was dissolved in a mixture of 2-propanol (30 mL) and HCl (concd.) (5.0 mL). The mixture was stirred for 48 h at ambient temperature, and then the solvent was removed in vacuo and the product dried at 0.1 mbar for several days. Yield 2.17 g (14.85 mmol, 96%) of an equilibrium mixture of **12a** and **12b**, as a pale yellow hygroscopic oil. − IR (neat): $\tilde{\nu}$ = 3500−3300 cm^{-1} (OH), 1750 (C=O). − ^{1}H NMR (200 MHz, $[D_6]$acetone): δ = 2.25−2.53 (4 H, m, 2-H, 3-H), 3.79 (1 H, dd, $J_{5,6A}$ = 6.6, J_{AB} = 8.3 Hz, 6_A-H), 4.07 (1 H, dd, $J_{5,6B}$ = 6.8, J_{AB} = 8.3 Hz, 6_B-H), 4.22 (1 H, ddd., $J_{4,5}$ = 3.8, $J_{5,6A}$ = 6.6, $J_{5,6B}$ = 6.8 Hz, 5-H), 4.57 (1 H, ddd, $J_{4,5}$ = 3.8, $J_{3A,4}$ = 5.6, $J_{3B,4}$ = 7.7 Hz, 4-H), 7.99−8.03 (2 H, m, O−*H*). − ^{13}C NMR (50.3 MHz, $[D_6]$acetone) DEPT: for **12a**: δ = 23.4 (CH_2, C-3), 27.8 (CH_2, C-2), 62.6 (CH_2, C-6), 73.4 (CH, C-5), 79.6 (CH, C-4), 177.0 (C-1); for **12b**: δ = 28.0 (CH_2, C-3, 29.9 (CH_2, C-2), 63.4 (CH_2, C-6), 70.4 (CH, C-4), 73.9 (CH, C-5), 173.5 (C-1). − MS (EI); *m/z* (%): 129.1 (5.1) [M^+ − OH], 115.1 (14.61) [M^+ − CH_3O], 85.1 (100) [M^+ − $C_2H_5O_2$], 61.1 (3.14) [M^+ − $C_4H_5O_2$].

6-(*tert*-Butyldimethylsilyloxy)-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (13): 1.64 g (11.22 mmol) of **12**, DMAP (68 mg, 0.56 mmol, 0.05 equivalents) and *tert*-butyl(chloro)dimethylsilane (1.86 g, 12.32 mmol, 1.1 equivalents) were dissolved in (abs.) DMF (20 mL). Triethylamine (6.2 mL, 4.54 g, 45 mmol, 4 equivalents) was added. An exothermic reaction occurred, and the immediate formation of a colourless precipitate was observed. Within 10 min another three portions (each consisting of 844 mg, 5.6 mmol, 0.5 equivalents) of *tert*-butyl(chloro)dimethylsilane were added, then the mixture was stirred for 2 min, followed by addition of water (40 mL). The reaction mixture was extracted with two portions of ether. The combined organic extracts were washed with 1 M HCl and conc. $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. Column chromatography (Et_2O, R_f = 0.51) yielded 2.90 g, (11.14 mmol, 99%) of **13** as a colourless opaque oil that crystallized at −20°C within days. − m.p. 52°C. − RI_p = 1775. − $[\alpha]_D^{20}$ = +60 (*c* = 1.1, MeOH). − IR (neat): $\tilde{\nu}$ = 2950 cm^{-1}, 2920, 2850, 1780 (C=O), 1460, 1250, 1115, 1080. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.01 [6 H, s, Si$(CH_3)_2$], 0.82 [9 H, s, SiC$(CH_3)_3$], 2.13−2.66 (4 H, m, 2-H, 3-H), 3.03 (1 H, s, O−*H*), 3.59−3.65 (3 H, m, 5-H, 6-H), 4.55 (1 H, m, $J_{4,5}$ = 2.5, $J_{3A,4}$ = 6.9, $J_{3B,4}$ = 7.0 Hz, 4-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.7 [CH_3, Si$(CH_3)_2$], 18.0 [Si*C*$(CH_3)_3$], 23.6 (CH_2, C-3), 26.6 [CH_3, SiC$(CH_3)_3$], 28.2 (CH_2, C-2), 63.4 (CH_2, C-6), 73.2 (CH, C-5), 79.4 (CH, C-4), 177.7 (C-1). − $C_{12}H_{24}O_4Si$ (260.41): calcd. C 55.35, H 9.29; found C 54.99, H 9.14.

6-(*tert*-Butyldimethylsilyloxy)-2,3-dideoxy-5-mesyloxy-L-*threo*-hexono-1,4-lactone (14): To a cold (−20°C) solution **13** (2.97 g, 11.39 mmol) and triethylamine (4.7 mL 34 mmol, 3 equivalents) in dichloromethane (abs.) (50 mL) was added methanesulfonyl chloride (1.1 mL, 13.66 mmol, 1.2 equivalents). The mixture was stirred for 20 min and then was allowed to warm to room temperature. After addition of water, the mixture was extracted with 4 portions of dichloromethane. The combined organic extracts were washed with 1 M HCl and concd. $NaHCO_3$ solution and dried with anhydrous Na_2SO_4. The solvent was then removed by distillation, and the colourless crystalline residue was recrystallized from *t*BuOMe to yield colourless crystals: 3.05 g (9.0 mmol, 79%), m.p. 58°C. − RI_p = 2149. − $[\alpha]_D^{20}$ = +16 (*c* = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1780 cm^{-1} (C=O), 1350, 1170, 825. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.65 (3 H, s, SiCH_3), 0.80 (3 H, s, SiCH_3), 0.89 [9 H, s, SiC$(CH_3)_3$], 2.17−2.46 (2 H, m, 3-H), 2.50−2.78 (2 H, m, 2-H), 3.12 (3 H, s, SOCH_3), 3.86 (1 H, dd, $J_{5,6A}$ = 5.0, J_{AB} = 11.2 Hz, 6_A-H), 3.95 (1 H, dd, $J_{5,6B}$ = 6.0, J_{AB} = 11.2 Hz, 6_B-H), 4.68 (1 H, ddd, $J_{4,5}$ = 3.6, $J_{5,6A}$ = 5.0, $J_{5,6\,B}$ = 6.0 Hz, 5-H), 4.76 (1 H, ddd, $J_{4,5}$ = 3.6, $J_{3A,4}$ = 6.1, $J_{3B,4}$ = 7.6 Hz, 4-H). − ^{13}C NMR

(50.3 MHz, $CDCl_3$) DEPT: δ = −5.7 [CH_3, Si(CH_3)$_2$], 18.0 [SiC(CH$_3$)$_3$], 23.6 (CH_2, C-3), 25.6 [CH_3, SiC(CH_3)$_3$], 27.5 (CH_2, C-2), 38.6 (CH_3, SO_2CH_3), 62.2 (CH_2, C-6), 77.4 (CH, C-5), 83.0 (CH, C-4), 176.1 (C-1). − $C_{13}H_{26}O_6SSi$ (338.50): calcd. C 46.13, H 7.74, S 9.47; found C 45.75, H 7.86, S 9.98.

5-Azido-6-(*tert*-butyldimethylsilyloxy)-2,3,5-dideoxy-D-*erythro*-hexono-1,4-lactone (15): A mixture of **14** (2.77 g, 8.18 mmol) and NaN_3 (883 mg, 13.58 mmol, 1.7 equivalents) dissolved in DMPU (5 mL) was stirred at 70°C for 24 h. Water was then added, and the mixture extracted with ether. The organic phase was washed with 1 M HCl, and concd. $NaHCO_3$ solution, dried with anhydrous Na_2SO_4, the solvent was evaporated and the yellow oily residue was purified by chromatography (Et_2O, R_f = 0.70). − Yield 1.51 g (5.28 mmol, 65%) as a colourless oil. − RI_p = 1857. − $[\alpha]_D^{20}$ = −3 (c = 0.88, MeOH). − IR (neat): $\tilde{\nu}$ = 2100 cm^{-1} (N_3), 1780 (C=O), 1250, 1110. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.72 [6 H, s, Si(CH_3)$_2$], 0.88 [9 H, s, SiC(CH_3)$_3$], 2.09−2.29 (2 H, m, 3-H), 2.48−2.59 (2 H, m, 2-H), 3.63 (1 H, ddd, $J_{5,6A}$ = 4.7, $J_{4,5}$ = 5.9, $J_{5,6B}$ = 6.1 Hz, 5-H), 3.75 (1 H, dd, $J_{5,6B}$ = 6.1, J_{AB} = 10.5 Hz, 6_B-H), 3.84 (1 H, dd, $J_{5,6A}$ = 4.7, J_{AB} = 10.5 Hz, 6_A-H), 4.51 (1 H, dt, $J_{4,5}$ = 5.9, $J_{3,4}$ = 6.9 Hz, 4-H); homodecoupling: HD set to 3.63 ppm: $J_{3,4}$ = 6.9 Hz, HD set to 2.19 ppm: $J_{4,5}$ = 5.9 Hz. − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.7 [CH_3, Si(CH_3)$_2$], 18.1 [SiC(CH$_3$)$_3$], 23.7 (CH_2, C-3), 25.7 [CH_3, SiC(CH_3)$_3$], 27.9 (CH_2, C-2), 63.0 (CH_2, C-6), 65.1 (CH, C-5), 77.7 (CH, C-4), 176.3 (C-1). − $C_{12}H_{23}N_3O_3Si$ (285.42): calcd. C 50.50, H 8.12, N 14.72; found C 50.11, H 7.88, N 15.06.

5-Azido-6-(*tert*-butyldimethylsilyloxy)-2,3,5-trideoxy-D-*erythro*-furanose (7): A solution of **15** (1.35 g, 4.73 mmol) in THF (abs.) (25 mL) was cooled to −78°C. DIBAlH (6.30 mL, 6.30 mmol, 1.3 equivalents of a 1 M solution in heptane) was added under vigorous stirring. The reaction mixture was stirred at −78°C for 2 h, then another portion (2.40 mL, 2.40 mmol, 0.5 equivalents) of DIBAlH solution was carefully added. The stirring was continued until no more starting material could be detected by GC. Average reaction times ranged from 4 to 6 h. After carefully controlled addition of water (10 mL) so that the temperature of the reaction mixture did not exceed −60°C, 1 M HCl (20 mL) was added. When the mixture had reached room temperature, brine was added and the product was isolated by extraction with four portions of dichloromethane. The combined organic layers were washed with conc. $NaHCO_3$, dried with Na_2SO_4 and filtered through Celite. The crude product was purified by column chromatography (Et_2O, R_f = 0.70). − Yield 941 mg (3.27 mmol, 69%) as a mixture of both anomeric lactols. − RI_p = 1767. − IR (neat): $\tilde{\nu}$ = 2095 cm^{-1} (N_3), 1470, 1460, 1255. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = −5.6 [12 H, s, Si(CH_3)$_2$], 0.89 [18 H, s, SiC(CH_3)$_3$], 1.78−2.06 (8 H, m, 2-H and 3-H), 3.44−3.89 (8 H, m, 4-H, 5-H and 8-H), 5.44 (1 H, dd, $J_{1,2A}$ = 1.5, $J_{1,2B}$ = 3.7 Hz, 1-H) and 5.55 (1 H, dd, $J_{1,2A}$ = 1.6, $J_{1,2B}$ = 4.5 Hz, 1-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.6 [CH_3, Si(CH_3)$_2$], 18.1 [SiC(CH$_3$)$_3$], 25.2 and 25.4 (CH_2, C-3), 25.7 [CH_3, SiC(CH_3)$_3$], 32.6 and 33.7 (CH_2, C-2), 63.7 and 63.9 (CH_2, C-6), 66.0 and 66.9 (CH, C-5), 77.0 and 78.7 (CH, C-4), 98.5 and 98.6 (CH, C-1). − $C_{12}H_{25}N_3O_3Si$ (287.43): calcd. C 50.15, H 8.77, N 14.62; found C 50.01, H 8.88, N 14.31.

Ethyl (6*S*,7*R*)-7-Azido-8-(*tert*-butyldimethylsilyloxy)-6-hydroxyoct-2-enoate (16), Ethyl (2*R*,3*S*,6*R*,7*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,8,9-triazabicyclo[4.3.0]non-8-ene-7-carboxylate (17), and Ethyl (2*R*,3*S*,6*S*,7*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,8,9-triazabicyclo[4.3.0]non-8-ene-7-carboxylate (18): 1.22 g (4.24 mmol) of **7** was dissolved in dry toluene (15 mL) and (ethoxycarbonylmethylene)triphenylphosphorane (1.48 g, 4.24 mmol, 1 equivalent) was added. The mixture was stirred at room temperature for 48 h, the solvent was evaporated at ambient temperature in vacuo into a cooling trap and the residue was subjected to column chromatography (EtOAc) to give a mixture of all three products (1.49 g, 4.16 mmol, 98%). If the reaction mixture was stirred at room temperature for 5 d instead of 48 h, 98% of the diastereomeric triazolines were obtained, and no α,β-unsaturated ester **16** could be detected. − $C_{16}H_{31}N_3O_4Si$ (357.53) calcd. C 53.75, H 8.74, N 11.75; found C 53.70, H 8.69, N 11.44. − For spectroscopic purposes, pure samples of all three products could be obtained by column chromatography (EtOAc).

Ethyl (6*S*,7*R*)-7-Azido-8-(*tert*-butyldimethylsilyloxy)-6-hydroxyoct-2-enoate (16): R_f = 0.73 (EtOAc). − $[\alpha]_D^{20}$ = +1 (c = 0.8, MeOH). − IR (neat): $\tilde{\nu}$ = 3450 cm^{-1} (OH), 2095 (N=N=N), 1715 (C=O), 1650 (C=C), 1460, 1250, 1100. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = −0.01 [6 H, s, Si(CH_3)$_2$], 0.80 [9 H, s, SiC(CH_3)$_3$], 1.16 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 1.48−1.62 (2 H, m, 5-H), 2.16−2.37 (2 H, m, 4-H), 3.22−3.32 (1 H, m, 7-H), 3.52−3.58 (1 H, m, 6-H), 4.06 (2 H, q, J = 7.1, OCH_2CH_3), 5.74 (1 H, d, $J_{2,3}$ = 15.6 Hz, 2-H), 6.86 (1 H, dd, $J_{3,4}$ = 7.0, $J_{2,3}$ = 15.6 Hz, 3-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.9 [CH_3, Si(CH_3)$_2$], 13.9 (CH_3, OCH_2CH_3), 17.8 [SiC(CH$_3$)$_3$], 25.4 [CH_3, SiC(CH_3)$_3$], 27.9 and 31.4 (CH_2, C-4 and C-5), 59.9 (CH_2, OCH_2CH_3), 63.4 (CH_2, C-8), 66.8 (CH, C-7), 70.3 (CH, C-6), 121.4 (CH, C-2), 148.2 (CH, C-3), 166.3 (C-1).

Ethyl (2*R*,3*S*,6*R*,7*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,8,9-triazabicyclo[4.3.0]non-8-ene-7-carboxylate (17): R_f = 0.62 (EtOAc), $[\alpha]_D^{20}$ = +213 (c = 0.74, MeOH). − IR (neat): $\tilde{\nu}$ = 3500−3350 cm^{-1} (OH), 1730 (C=O), 1460, 1250, 830. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 [6 H, s, Si(CH_3)$_2$], 0.89 [9 H, s, SiC(CH_3)$_3$], 1.31 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 1.38−2.16 (4 H, m, 4-H, 5-H), 3.41 (1 H, ddd, $J_{1'B,2}$ = 4.1, $J_{2,3}$ = 9.1, $J_{1'A,2}$ = 9.1 Hz, 2-H), 3.59−3.76 (2 H, m, 3-H, 6-H), 4.21 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 4.34 (1 H, dd, $J_{1'A,2}$ = 9.1, J_{AB} = 10.3 Hz, $1'_A$-H), 4.51 (1 H, d, $J_{6,7}$ = 8.2 Hz, 7-H), 4.55 (1 H, dd, $J_{1'B,2}$ = 4.1, J_{AB} = 10.3 Hz, $1'_B$-H); homodecoupling: HD set to 1.45 ppm: 4.21 (2 H, s, OCH_2CH_3), 4.34 (1 H, dd, $J_{1'A,2}$ = 9.2, J_{AB} = 9.7 Hz, $1'_A$-H), HD set to 4.52 ppm: 3.40 (1 H, dd, $J_{1'B,2}$ = 3.4, $J_{2,3}$ = 9.1 Hz, 2-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = −5.7 [CH_3, Si(CH_3)$_2$], 14.0 (CH_3, OCH_2CH_3), 17.9 [SiC(CH$_3$)$_3$], 25.6 [CH_3, SiC(CH_3)$_3$], 26.4 and 31.3 (CH_2, C-4 and C-5), 58.4 (CH, C-2), 62.6 (CH_2, OCH_2CH_3), 63.6, (CH, C-6), 65.5 (CH_2, C-1′), 72.9 (CH, C-3), 80.8 (CH, C-7), 167.9 (COOEt).

Ethyl (2*R*,3*S*,6*S*,7*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,8,9-triazabicyclo[4.3.0]non-8-ene-7-carboxylate (18): R_f = 0.51 (EtOAc), $[\alpha]_D^{20}$ = −206 (c = 1.96, MeOH). − IR (neat): $\tilde{\nu}$ = 3400−3300 cm^{-1} (OH), 1730 (C=O), 1460, 1100, 830. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 [6 H, s, Si(CH_3)$_2$], 0.87 [9 H, s, SiC(CH_3)$_3$], 1.28 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 1.40−1.48 (1 H, m, 5_A-H), 1.60−1.95 (3 H, 5_B-H, 4-H), 2.26 (1 H, s, O−H), 3.80 (2 H, d, $J_{1',2}$ = 5.7, 1′-H), 3.96 (1 H, ddd, $J_{5A,6}$ = 4.6, $J_{6,7}$ = 6.5, $J_{5B,6}$ = 11.6 Hz, 6-H), 4.20 (2 H, q, J = 7.1, OCH_2CH_3), 4.34 (1 H, m,, 2-H), 4.69 (1 H, d, $J_{6,7}$ = 6.5 Hz, 7-H); homodecoupling: HD set to 3.96 ppm: 1.44 (ddd, $J_{4,5}$ < 2, J_{AB} = 12.4 Hz, 5_A-H), HD set to 1.27 ppm: 4.20 (2 H, s, OCH_2CH_3), 4.15 (1 H, m, 3-H), HD set to 4.34 ppm: 3.79 (2 H, s, 1′-H), HD set to 4.70 ppm: 3.96 (1 H, dd, $J_{5A,6}$ = 4.4, $J_{5B,6}$ = 11.6 Hz, 6-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.6 [CH_3, Si(CH_3)$_2$], 14.1 (CH_3, OCH_2CH_3), 18.1 [SiC(CH$_3$)$_3$], 22.7 and 26.6 (CH_2, C-4 and C-5), 25.8 [CH_3, SiC(CH_3)$_3$], 54.9 (CH, C-2), 61.8 (CH_2, OCH_2CH_3), 62.8 (CH_2, C-1′), 63.0 and 65.9 (CH, C-3 and C-6), 82.2 (CH, C-2), 168.4 (COOEt).

Ethyl (2′*R*,3′*S*,6′*R*)-2-Diazo-2-[2′-(*tert*-butyldimethylsilyloxymethyl)-3′-hydroxypiperid-6′-yl]acetate (19) and Ethyl (2′*R*,3′*S*,6′*S*)-2-Diazo-2-[2′-(*tert*-butyldimethylsilyloxymethyl)-3′-hydroxypiperid-6′-yl]acetate (20): A mixture of diastereomeric triazolines (1.49 g, 4.17 mmol) and triethylamine (0.64 mL, 4.6 mmol, 1.1 equivalents) was dissolved in dichloromethane (20 mL). The mixture was stirred and left to stand overnight. Removal of the solvent and triethylamine in vacuo followed by filtration through silica gel with ethyl acetate afforded 1.43 g of a mixture of diastereomeric diazo esters **19** and **20** (4.00 mmol, 96%). − $C_{16}H_{31}N_3O_4Si$ (357.53): calcd. C 53.75, H 8.74, N 11.75; found C 53.56, H 8.51, N 11.90. − For spectroscopic purposes pure samples of both diastereomers could be obtained by column chromatography (EtOAc).

Ethyl (2′*R*,3′*S*,6′*R*)-2-Diazo-2-[2′-(*tert*-butyldimethylsilyloxymethyl)-3′-hydroxypiperid-6′-yl]acetate (19): R_f = 0.55 (EtOAc), $[\alpha]_D^{20}$ = +44 (*c* = 1.1, MeOH). − IR (neat): $\tilde{\nu}$ = 3400−3300 cm^{-1} (OH), 2080 (N=N), 1690 (C=O), 830. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.08 [6 H, s, Si(CH_3)$_2$], 0.89 [9 H, s, SiC(CH_3)$_3$], 1.27 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.35−1.59 (2 H, m, 4′-H), 1.78−2.16 (2 H, m, 5′-H), 2.71 (1 H, ddd, $J_{1''A,2'}$ = 6.4, $J_{1''B,2'}$ = 6.7, $J_{2',3'}$ = 8.8 Hz, 2′-H), 3.38−3.53 (1 H, m, 3′-H), 3.45−3.70 (2 H, m, 1′′$_A$-H, 6′-H), 3.85 (1 H, dd, $J_{1''B,2'}$ = 6.7, J_{AB} = 9.7 Hz, 1′′$_B$-H), 4.22 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.5 [CH_3, Si(*C*H$_3$)$_2$], 14.5 (CH_3, OCH$_2$*C*H$_3$), 18.1 [Si*C*(CH$_3$)$_3$], 25.8 [CH_3, SiC(*C*H$_3$)$_3$], 28.1 (CH_2, C-5′), 33.0 (CH_2, C-4′), 50.3 (CH, C-2′), 60.1 (CH_2, O*C*H$_2$CH$_3$), 62.4 (CH, C-6′), 66.8 (CH_2, C-1′′), 71.1 (CH, C-3′), 166.5 (C-1).

Ethyl (2′*R*,3′*S*,6′*S*)-2-Diazo-2-[2′-(*tert*-butyldimethylsilyloxymethyl)-3′-hydroxypiperid-6′-yl]acetate (20): R_f = 0.35 (EtOAc), $[\alpha]_D^{20}$ = −36 (*c* = 1.39, MeOH). − IR (neat): $\tilde{\nu}$ = 3400−3300 cm^{-1} (OH), 2075 (N=N), 1685 (C=O), 830. −^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.07 [6 H, s, Si(CH_3)$_2$], 0.89 [9 H, s, SiC(CH_3)$_3$], 1.28 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.20−2.04 (4 H, m, 4′-H, 3′-H), 2.70 (1 H, ddd, $J_{2',3'}$ = $J_{1''A,2'}$ = $J_{1''B,2'}$ = 6.6 Hz, 2′-H), 3.54 (1 H, ddd, $J_{3',4'}$ = 4.6, $J_{2',3'}$ = 6.6, $J_{3',4'}$ = 9.9 Hz, 3′-H), 3.59 (1 H, dd, $J_{1'',2'}$ = 6.6, J_{AB} = 9.7 Hz, 1′′$_A$-H), 3.82 (1 H, dd, $J_{1'',2'}$ = 6.6, J_{AB} = 9.7 Hz, 1′′$_B$-H), 4.19 (1 H, m, 6′-H), 4.23 (2 H, q, *J* = 7.1, OCH_2CH$_3$). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = −5.8 [Si(*C*H$_3$)$_2$], 14.3 (OCH$_2$*C*H$_3$), 17.9 [Si*C*(CH$_3$)$_3$], 24.6 (C-5′), 25.6 [SiC(*C*H$_3$)$_3$], 29.1 (C-4′), 46.5 (C-2′), 57.8 (O*C*H$_2$CH$_3$), 60.4 (C-6′), 65.1 (C-1′′), 69.7 (C-3′), 166.9 (C-1).

Ethyl (2′*R*,3′*S*,6′*R*)-2-Diazo-2-[2′-(*tert*-butyldimethylsilyloxymethyl)-3′-hydroxypiperid-6′-yl]acetate Hydrochloride Monohydrate: A solution of **17** (396 mg, 1.11 mmol) and triethylamine (150 µL, 110 mg, 1.11 mmol, 1 equivalent) in chloroform (15 mL) was left to stand overnight until the diazo ester was formed quantitatively. The mixture was then washed with 1 M HCl. The intense yellow colour of the diazo ester immediately changed to pale yellow. The organic phase was dried with Na_2SO_4 and the solvent was evaporated to yield the product as a pale yellow solid (366 mg, 0.89 mmol, 80%), m.p. 55°C (decomposition). − $[\alpha]_D^{20}$ = +11 (*c* = 1.36, MeOH). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (OH, NH), 2100 (N=N), 1670 (C=O), 1580, 1530, 1250, 830. − ^{1}H NMR (200 MHz,$CDCl_3$): δ = 0.08 [6 H, s, Si(CH_3)$_2$], 0.89 [9 H, s, SiC(CH_3)$_3$], 1.28 (3 H, t, *J* = 7.2 Hz, OCH$_2$CH_3), 1.60−2.49 (4 H, m, 4′-H, 5′-H), 3.05−3.23 (1 H, m, 2′-H), 4.04−4.18 (3 H, m, 3′-H, 1′′-H), 4.24 (3 H, t, *J* = 7.2 Hz, OCH$_2$CH_3). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.5 [CH_3, Si(*C*H$_3$)$_2$], 14.2 (CH_3, OCH$_2$*C*H$_3$), 18.0 [Si*C*(CH$_3$)$_3$], 23.9 (CH_2, C-5′), 25.7 [CH_3, SiC(*C*H$_3$)$_3$], 31.9 (CH_2, C-4′), 53.1 (CH, C-2′), 60.2 (CH_2, C-1′′), 63.0 (CH, C-6′), 64.1 (CH, C-3′), 166.1 (C-1). − $C_{16}H_{34}ClN_3O_5Si$ (412.01): calcd. C 46.64, H 8.32, N 10.12; found C 46.48, H 8.36, N 10.11.

Ethyl (2′*R*,3′*S*)-2-[2′-(*tert*-Butyldimethylsilyloxymethyl)-3′-hydroxypiperidyliden-6′-yl]acetate (21): 1.43 g (4.00 mmol) of diazo esters **19** and **20** was dissolved in dichloromethane (20 mL) and rhodium(II) acetate dimer (9 mg, 0.02 mmol, $5\cdot10^{-3}$ equivalents) was suspended in the solution. The solution was stirred for 24 h at room temperature. It was then twice extracted with brine, dried with Na_2SO_4 and the solvent evaporated to yield 1.28 g (3.88 mmol, 97%), of a pale yellow oil, $[\alpha]_D^{20}$ = −30 (*c* = 1.1, MeOH). − IR (neat): $\tilde{\nu}$ = 3420 cm^{-1} (OH), 1740, 1650, 1600 (C=O, C=C), 1460, 1250. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 [6 H, s, Si(CH_3)$_2$], 0.88 [9 H, s, SiC(CH_3)$_3$], 1.18 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.50−2.46 (4 H, m, 4′-H, 5′-H), 3.20 (1 H, ddd, $J_{1''A,2'}$ = $J_{1''B,2'}$ = $J_{2',3'}$ = 6.7 Hz, 2′-H), 3.38 (1 H, s, O−*H*), 3.64−3.78 (3 H, m, 3′-H, 1′′-H), 4.02 (2 H, q, *J* = 7.1, OCH_2CH$_3$), 4.38 (1 H, s, 2-H), 8.45 (1 H, s, N−*H*). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.6 [CH_3, Si(*C*H$_3$)$_2$], 14.5 (CH_3, OCH$_2$*C*H$_3$), 18.0 [Si*C*(CH$_3$)$_3$], 27.2, 27.8 (CH_2, C-4′, C-5′), 58.3 (CH_2, O*C*H$_2$CH$_3$), 58.5 (CH, C-2′), 66.6 (CH_2, C-1′′), 69.1 (CH, C-3′), 81.3 (CH, C-2), 160.6 (C-6′), 170.4 (C-1). − $C_{16}H_{31}NO_4Si$ (329.52): calcd. C 58.32, H 9.48, N 4.25; found C 57.89, H 9.75, N 4.11.

Ethyl (2′*R*,3′*S*,6′*R*)-2-[2′-(*tert*-Butyldimethylsilyloxymethyl)-3′-hydroxypiperid-6′-yl]acetate (22): 1.42 g (4.30 mmol) of **21** was dissolved in ethanol (60 mL) (p.a.), 10% Pd/C (750 mg) was added and the mixture was hydrogenated at 50 bar for 48 h. The catalyst was removed by filtration and the solvent evaporated in vacuo. After column chromatography (EtOAc/MeOH, 9:1), **22** was obtained as colourless oil, R_f = 0.22, yield 1.02 g (3.06 mmol, 71%), $[\alpha]_D^{20}$ = +20 (*c* = 1.4, MeOH). − IR (neat): $\tilde{\nu}$ = 3600−3300 cm^{-1} (NH, OH), 1750 (C=O), 1480, 1205, 900. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03 [6 H, s, Si(CH_3)$_2$], 1.12 [9 H, s, SiC(CH_3)$_3$], 1.44 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.32−1.69 (2 H, m, 4′-H), 1.80−1.93 (1 H, m, 5′$_A$-H), 2.15−2.25 (1 H, m, 5′$_B$-H), 2.52 (1 H, dd, $J_{2A,6'}$ = 9.1, J_{AB} = 16.3 Hz, 2$_A$-H), 2.69 (1 H, dd, $J_{2B,6'}$ = 4.0, J_{AB} = 16.3 Hz, 2$_B$-H), 2.67−2.77 (1 H, m, 2′-H), 3.03−3.16 (1 H, m, 6′-H), 3.40 (1 H, ddd, $J_{3'A,4'}$ = 4.5, *J* = 9.6, *J* = 10.6, 3′-H), 3.70 (1 H, dd, $J_{2',1''A}$ = 8.9, J_{AB} = 9.9 Hz, 1′′$_A$-H), 4.25 (1 H, dd, $J_{2',1''B}$ = 3.3, J_{AB} = 9.9 Hz, 1′′$_B$-H), 4.32 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.3, −5.2 [CH_3, Si(*C*H$_3$)$_2$], 14.6 (CH_3, OCH$_2$*C*H$_3$), 19.1 [Si*C*(CH$_3$)$_3$], 26.4 [CH_3, SiC(*C*H$_3$)$_3$], 31.7 (CH_2, C-5′), 34.5 (CH_2, C-4′), 41.0 (CH_2, C-2), 53.5 (CH, C-6′), 61.6 (CH_3, OCH$_2$*C*H$_3$), 65.0 (CH, C-2′), 65.3 (CH_2, C-1′′), 69.5 (CH, C-3′), 173.5 (C-1). − $C_{16}H_{33}NO_4Si$ (331.53): calcd. C 57.97, H 10.03, N 4.22; found C 57.82, H 9.84, N 4.14.

Ethyl (2′*R*,3′*S*,6′*R*)-2-[2′-(*tert*-Butyldimethylsilyloxymethyl)-3′-(*tert*-butyldimethylsilyloxy)piperid-6′-yl]acetate (23): Imidazole (817 mg, 12.00 mmol, 4 equivalents) and *tert*-butyl(chloro)dimethylsilane (905 mg, 6.00 mmol, 2 equivalents) were added to a solution of **22** (1.0 g, 3.02 mmol) in 10 mL of DMF (abs.). The reaction mixture was stirred at 60°C for 24 h; another portion of imidazole (905 mg, 6.00 mmol, 2 equivalents) and *tert*-butyl(chloro)dimethylsilane (817 mg, 12.00 mmol, 4 equivalents) was added. The mixture was stirred at 60°C until no more starting material could be detected by TLC. Water was then added and the mixture extracted with 4 portions of ether, the combined organic layers were dried with Na_2SO_4, the solvent was distilled, and the residue was purified by column chromatography (Et_2O/petroleum ether, 2:1, R_f = 0.64). The product was dried at 0.1 mbar for 3 d to yield 1.13 g (2.54 mmol, 84%) of a colourless oil. − $[\alpha]_D^{20}$ = +33 (*c* = 0.9, *t*BuOMe). − IR (neat): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 1760 (C=O), 1480, 1270, 1100. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00, 0.01, 0.02, 0.03 [12 H, 4 s, Si(CH_3)$_2$], 0.84 [9 H, s, SiC(CH_3)$_3$], 0.86 [9 H, s, SiC(CH_3)$_3$], 1.22 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.15−1.48 (2 H,

m, 4′$_A$-H, 5′$_A$-H), 1.59−1.69 (1 H, m, 5′$_B$-H), 1.84−1.92 (1 H, m, 4′$_B$-H), 2.32−2.40 (2 H, m, 2-H), 2.43 (1 H, s, N−*H*), 2.54 (1 H, ddd, $J_{1''B,2'}$ = 3.0, $J_{1''A,2'}$ = 9.0, $J_{2',3'}$ = 9.0 Hz, 2′-H), 2.85−2.95 (1 H, m, 6′-H), 3.24 (1 H, ddd, $J_{3',4'}$ = 4.5, $J_{2',3'}$ = 9.0, $J_{3',4'}$ = 10.0 Hz, 3′-H), 3.39 (1 H, dd, $J_{1''A,2'}$ = 9.0, J_{AB} = 9.5 Hz, 1′′$_A$-H), 3.95 (1 H, dd, $J_{1''B,2'}$ = 3.0, J_{AB} = 9.5 Hz, 1′′$_B$-H), 4.01 (2 H, q, J = 7.1, OC*H*$_2$CH$_3$). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.5, −5.0, −4.1, −3.0 [CH$_3$, Si(*C*H$_3$)$_2$], 14.1 (CH$_3$, OCH$_2$*C*H$_3$), 17.8, 18.2 [Si*C*(CH$_3$)$_3$], 25.6, 25.7 [CH$_3$, SiC(*C*H$_3$)$_3$], 31.0 (CH$_2$, C-5′), 34.1 (CH$_2$, C-4′), 41.0 (CH$_2$, C-2), 52.1 (CH, C-6′), 60.3 (CH$_2$, O*C*H$_2$CH$_3$), 63.9 (CH, C-2′), 64.5 (CH$_2$, C-1′′), 69.9 (CH, C-3′), 171.9 (C-1). − $C_{22}H_{47}NO_4Si_2$ (445.80): calcd. C 59.27, H 10.63, N 3.10; found C 58.95, H 10.38, N 3.14.

(2′*R*,3′*S*,6′*R*)-2-[3′-(*tert*-Butyldimethylsilyloxy)-2′-(*tert*-butyldimethylsilyloxymethyl)piperid-6′-yl]ethanal (24): A solution of **23** (850 mg, 1.91 mmol) in of pentane (abs.) (10 mL) was cooled to −78°C. DIBAlH (2.30 mL, 2.30 mmol, 1.2 equivalents of a 1 M solution in hexane) was slowly added, and the reaction stirred at −78°C for 25 min. Then, 10 mL of a methanol/water (1:1) mixture was cautiously added, while avoiding warming of the reaction above −60°C. When the evolution of gas had stopped and the water was entirely frozen, the mixture was warmed to room temperature and diluted with brine. It was extracted with four portions of dichloromethane, the combined organic extracts were dried with Na_2SO_4, filtered through a layer of Celite, and the solvent was evaporated. The crude product was purified by column chromatography through silica gel (Et_2O, R_f = 0.45) to yield 504 mg (1.25 mmol, 66%) of a colourless oil. The aldehyde could not be stored for more than a few hours because even at −20°C the compound decomposed rapidly. Immediate conversion into **25** is strongly recommended. − IR (neat): ṽ = 1740 cm^{-1} (C=O), 1480, 1270, 1110, 850. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.02, 0.03, 0.04, 0.05 [12 H, 4 s, Si(C*H*$_3$)$_2$], 0.87 [9 H, s, SiC(C*H*$_3$)$_3$], 0.93 [9 H, s, SiC(C*H*$_3$)$_3$], 1.18−1.96 (4 H, m, 4′-H, 5′-H), 2.47−2.53 (2 H, m, 2-H), 2.51−2.60 (1 H, m, 2′-H), 3.03−3.08 (1 H, m, 6′-H), 3.28 (1 H, ddd, $J_{3',4'}$ = 4.5, $J_{3',4'}$ = 9.2, $J_{2',3'}$ = 9.2 Hz, 3′-H), 3.42 (1 H, dd, $J_{1''A,2'}$ = 8.5, J_{AB} = 9.5 Hz, 1′′$_A$-H), 3.93 (1 H, dd, $J_{1''B,2'}$ = 3.0, J_{AB} = 9.5 Hz, 1′′$_B$-H), 9.79 (1 H, t, J = 1.6 Hz, 1-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = −5.4, −4.9, −4.1 [CH$_3$, Si(*C*H$_3$)$_2$], 17.9 [Si*C*(CH$_3$)$_3$], 18.3 [Si*C*(CH$_3$)$_3$], 25.7 [CH$_3$, SiC(*C*H$_3$)$_3$], 25.9 [CH$_3$, SiC(*C*H$_3$)$_3$], 31.8 (CH$_2$, C-5′), 34.2 (CH$_2$, C-4′), 50.4 (CH$_2$, C-2), 50.5 (CH, C-6′), 63.4 (CH, C-2′), 64.4 (CH$_2$, C-1′′), 69.9 (CH, C-3′), 201.3 (CH, C-1).

(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butyldimethylsilyloxymethyl)-6-(*n*-dodec-2-enyl)piperidine (25): A solution of *n*-decylphosphonium bromide (904 mg, 1.87 mmol, 1.5 equivalents) in THF (abs.) (20 mL) was cooled to −40°C, followed by slow addition of sodium bis(trimethylsilyl)amide (1 M in THF, 3.70 mL, 3.7 mmol, 3 equivalents). Immediately after the addition, the mixture turned to an intense orange colour. After stirring the Wittig reagent at −40°C for 1 h, a previously cooled solution of **24** (500 mg, 1.24 mmol) in THF (abs.) (10 mL) was added. The reaction mixture was left at −40°C for 40 min, and then it was warmed to room temperature and stirred for 2 h. The solvent was evaporated and the residue treated with Et_2O/petroleum ether (1:6) which led to immediate precipitation of triphenylphosphane oxide. The product was purified by column chromatography (Et_2O/petroleum ether, 1:6, R_f = 0.52), yield 515 mg (0.98 mmol, 79%) as a colourless oil. − $[\alpha]_D^{20}$ = +57 (c = 2.0, *t*BuOMe). − IR (neat): ṽ = 1480 cm^{-1}, 1270, 1100. − ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 0.04−0.08 [12 H, m, Si(C*H*$_3$)$_2$], 0.85−0.95 [18 H, m, SiC(C*H*$_3$)$_3$], 1.03−1.46 [17 H, m, (C*H*$_2$)$_7$C*H*$_3$], 1.56−1.69 (2 H, m), 1.88−2.18 (6 H, m), 2.41−2.56 (2 H, m, 2-H, 6-H), 2.81 (1 H, s, N−*H*), 3.35 (1 H, ddd, $J_{3,4}$ = 4.6, J = 8.8, J = 10.4 Hz, 3-H), 3.43 (1 H, dd, $J_{1'A,2}$ = 8.9, J_{AB} = 9.4 Hz, 1′$_A$-H), 4.00 (1 H, dd, $J_{1'B,\,2}$ = 2.9, J_{AB} = 9.4 Hz, 1′$_B$-H), 5.27−5.55 (2 H, m, 2′′-H, 3′′-H). − ^{13}C NMR (50.3 MHz, [D$_6$]acetone) DEPT: δ = −5.5, −5.1, −4.2 [CH$_3$, Si(*C*H$_3$)$_2$], 14.0 (CH$_3$, C-12′′), 18.1 [Si*C*(CH$_3$)$_3$], 18.5 [Si*C*(CH$_3$)$_3$], 23.0 (CH$_2$), 25.8 [CH$_3$, SiC(*C*H$_3$)$_3$], 25.9 [CH$_3$, SiC(*C*H$_3$)$_3$], 27.7 (CH$_2$), 28.3 (CH$_2$), 28.7 (CH$_2$), 29.7 (CH$_2$), 29.9 (CH$_2$), 30.2 (CH$_2$), 31.9 (CH$_2$), 32.3 (CH$_2$), 34.8 (CH$_2$), 56.1 (CH, C-6), 65.1 (CH, C-2), 65.5 (CH$_2$, C-1′), 70.9 (CH, C-3), 127.0 and 132.5 (CH, C-2′′and C-3′′). − $C_{30}H_{63}NO_2Si_2$ (526.01): calcd. C 68.50, H 12.07, N 2.66; found C 68.51, H 11.78, N 2.41.

(2*R*,3*S*,6*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butyldimethylsilyloxymethyl)-6-(*n*-dodecyl)piperidine (26): 10% Pd/C (80 mg) was added to a solution of **25** (392 mg, 0.75 mmol) in of ethanol (p.a.) (15 mL) and the mixture was hydrogenated at 50 bar overnight. The catalyst was then removed by filtration, the filtrate was concentrated to dryness, and the residue was purified by column chromatography (Et_2O/petroleum ether, 1:6, R_f = 0.54). Yield 369 mg (0.70 mmol, 93%) as a colourless oil. − $[\alpha]_D^{20}$ = +39 (c = 1.3, *t*BuOMe). − IR (neat): ṽ = 1440 cm^{-1}, 1230, 1070, 820. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.02, 0.03, 0.05 [12 H, 3 s, Si(C*H*$_3$)$_2$], 0.87 [9 H, s, SiC(C*H*$_3$)$_3$], 0.89 [9 H, s, SiC(C*H*$_3$)$_3$], 0.90−1.70 (25 H, m, (C*H*$_2$)$_{11}$C*H*$_3$), 1.58−1.94 (4 H, m, 4-H, 5-H), 2.43−2.50 (1 H, m, 6-H), 2.51 (1 H, ddd, $J_{1'B,2}$ = 3.1, $J_{1'A,2}$ = 9.1, $J_{2,3}$ = 9.3 Hz, 2-H), 3.28 (1 H, ddd, $J_{3,4}$ = 4.5, $J_{2,3}$ = 9.3, $J_{3,4}$ = 10.4 Hz, 3-H), 3.43 (1 H, dd, $J_{1'A,2}$ = 9.1, J_{AB} = 9.5 Hz, 1′$_A$-H), 3.97 (1 H, dd, $J_{1'B,2}$ = 3.1, J_{AB} = 9.5 Hz, 1′$_B$-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = −5.4, −4.9, −4.1 [CH$_3$, Si(*C*H$_3$)$_2$], 14.1 [CH$_3$, (CH$_2$)$_{11}$*C*H$_3$], 18.0 [Si*C*(CH$_3$)$_3$], 18.2 [Si*C*(CH$_3$)$_3$], 22.7 (CH$_2$), 25.8 [CH$_3$, SiC(*C*H$_3$)$_3$], 25.9 [CH$_3$, SiC(*C*H$_3$)$_3$], 26.1 (CH$_2$), 29.6 (CH$_2$), 31.6 (CH$_2$), 31.9 (CH$_2$), 34.5 (CH$_2$), 36.6 (CH$_2$), 55.5 (CH, C-6), 64.3 (CH, C-2), 64.8 (CH$_2$, C-1′), 70.6 (CH, C-3). − $C_{30}H_{65}NO_2Si_2$ (528.03): calcd. C 68.24, H 12.41, N 2.65; found C 68.57, H 12.57, N 2.74.

(2*R*,3*S*,6*S*)-6-(*n*-Dodecyl)-3-hydroxy-2-(hydroxymethyl)piperidine [(+)-Desoxoprosophylline, 27]: 369 mg (0.70 mmol) of **26** was dissolved in 30 mL of freshly prepared ethanolic HCl. The solution was stirred at ambient temperature for 1 h, and the solvent was removed by distillation in vacuo. The residue was dissolved in 50 mL of 6 M aqueous KOH, and extracted with four portions of dichloromethane. The combined organic extracts were concentrated to dryness and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 9:1, R_f = 0.16) and recrystallized from acetone to give **27** (182 mg 0.61 mmol, 87%) as colourless crystals, m.p. 83°C. − $[\alpha]_D^{20}$ = +13 (c = 0.22, $CHCl_3$) {ref.[4b]: $[\alpha]_D^{20}$ = −14.0 (c = 0.24, $CHCl_3$)}. − IR (KBr): ṽ = 2980 cm^{-1}, 2880, 1490, 1480, 1280, 1080. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 [3 H, t, J = 6.7 Hz, (CH$_2$)$_{11}$C*H*$_3$], 1.0−1.4 [22 H, m, C*H*$_2$)$_{11}$], 1.65−1.80 (2 H, m, 5-H), 1.96−2.09 (2 H, m, 4-H), 2.42−2.61 (2 H, m, 2-H, 6-H), 2.93 (3 H, br s, N−*H*, O−*H*), 3.45 (1 H, ddd, $J_{3,4}$ = 4.5, J = 8.6, J = 9.2 Hz, 3-H), 3.70 (1 H, dd, $J_{1'A,2}$ = 5.3, J_{AB} = 10.7 Hz, 1′$_A$-H), 3.82 (1 H, dd, $J_{1'B,2}$ = 4.4, J_{AB} = 10.7 Hz, 1′$_B$-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ = 14.1 [CH$_3$, (CH$_2$)$_{11}$*C*H$_3$], 22.7 (CH$_2$), 26.2 (CH$_2$), 29.3 (CH$_2$), 29.6 (CH$_2$), 29.8 (CH$_2$), 31.0 (CH$_2$), 33.8 (CH$_2$), 36.4 (CH$_2$), 56.1 (CH, C-6), 63.2 (CH, C-2), 64.2 (CH$_2$, C-1′), 70.2 (CH, C-3). − $C_{18}H_{37}NO_2$ (299.50): calcd. C 72.19, H 12.45, N 4.68; found C 71.94, H 12.17, N 4.72.

Acknowledgments

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support and the Merck KG Darmstadt for donating chemicals.

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Received November 2, 1998
[O98492]