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Synthesis of Enantioenriched 2- and 2,6-Substituted Piperidin-3-ols from α-Dibenzylamino Aldehydes

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Dedicated to Professor Joan Bosch on occasion of his 60th birthday

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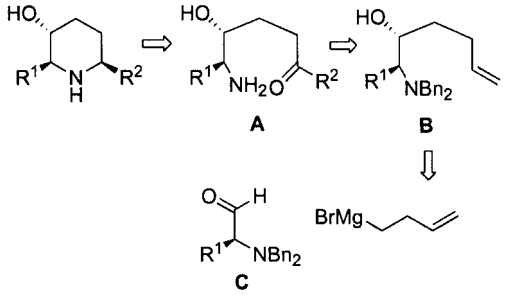
Homochiral α-dibenzylamino aldehydes react with 4-butenylmagnesium bromide in diethyl ether at 0 °C to yield *anti*-β-amino alcohols in excellent yield and *dr*. These *anti* diastereoisomers were transformed into enantioenriched 2- and 2,6-substituted 3-piperidinols in good yields.

Introduction

3-Hydroxylated piperidines are abundant in nature and some of them display potent physiological effects.[1] In this context, several synthetic methods have been developed for the synthesis of polysubstituted piperidine alkaloids.[2] Different methods that allow the formation of a piperidine ring[3] in racemic[4] or in enantioenriched forms have been described. Some of these strategies employed an asymmetric synthesis methodology,[5] but in most approaches an enantiopure substance was used as the starting material: amines,[6] amino acids,[7] and sugar derivatives[8] have been the most commonly used starting materials.

As a part of our investigations[9] exploring the chemistry of chiral α-dibenzylamino aldehydes derived from natural α-amino acids, we herein wish to disclose an efficient synthesis of enantiopure 2- and 2,6-substituted 3-hydroxypiperidines starting from this class of compound.

As summarized in the retrosynthetic analysis shown in Scheme 1, the 2-mono- (R^2 = H) or 2,6-substituted (R^2 = alkyl) 3-piperidinols can be traced back to δ-amino-γ-hydroxy carbonyl compound **A** through a stereoselective intramolecular reductive amination reaction. Compound **A** may be prepared by elaboration of olefin **B**, which in turn can be easily obtained by nucleophilic addition of 4-butenylmagnesium bromide to homochiral α-dibenzylamino aldehyde **C** derived from natural α-amino acids.



Scheme 1.

Results and Discussion

The 2- and 2,6-substituted 3-hydroxypiperidines were synthesized starting from α-dibenzylamino aldehydes **1a**–**c** readily prepared[10] from commercially available α-amino acids. These aldehydes reacted with 4-butenylmagnesium bromide in diethyl ether at 0 °C to afford the Felkin–Anh *anti*-**2a**–**c** amino alcohols in good yields and with excellent diastereoselectivities (Scheme 2 and Table 1).

Diastereoisomeric amino alcohols *anti*- and *syn*-**2a**–**c** were separated by flash chromatography and their stereochemistry determined by conversion into the corresponding oxazolidinones, as described previously for related compounds.[9c]

As summarized in Scheme 3, the synthesis of enantioenriched 2-substituted 3-hydroxypiperidines **5a**–**c** starts from amino alcohols *anti*-**2a**,[11] **2b**, or *anti*-**2c** previously protected as acetates *anti*-**3a**, **b**, and *anti*-**3c**, respectively. γ-Acetoxy-δ-dibenzylamino aldehydes *anti*-**4a**, **b**, and *anti*-**4c** were obtained in 70–75% yields by oxidative cleavage of the double bond with *N*-methylmorpholine *N*-oxide (NMO)

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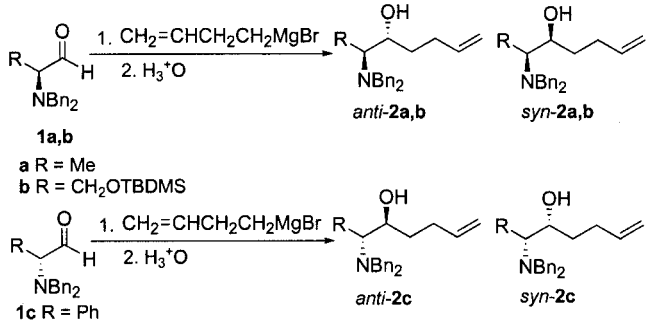


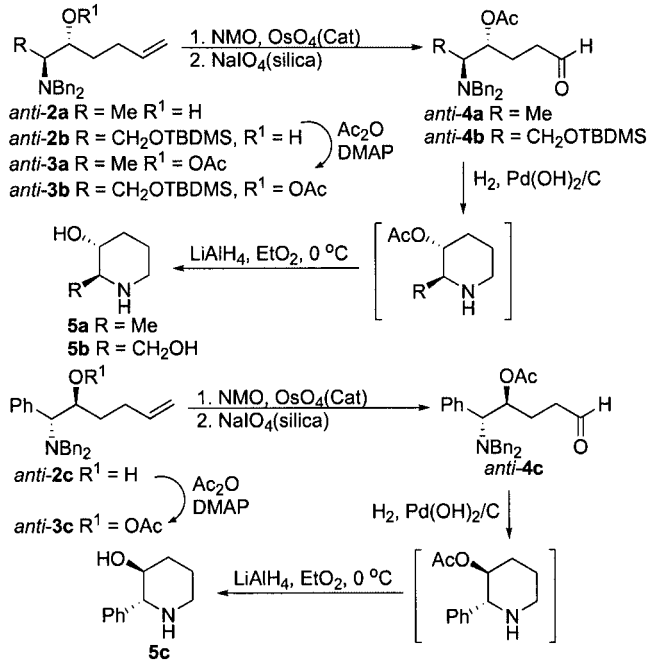
Scheme 2.

Table 1. Stereoselective addition of 4-butenylmagnesium bromide to *N*,*N*-dibenzylamino aldehydes **1a**–**c**.

R	Aldehyde	% Yield[a]	Products (% *dr*)[b]
CH_3	**1a**	70	***anti*-2a (97)** ***syn*-2a (3)**
$CH_2OTBDMS$	**1b**	75	***anti*-2b (97)** ***syn*-2b (3)**
Ph	***ent*-1c**	**85**	***anti*-2c (86)** ***syn*-2c (14)**

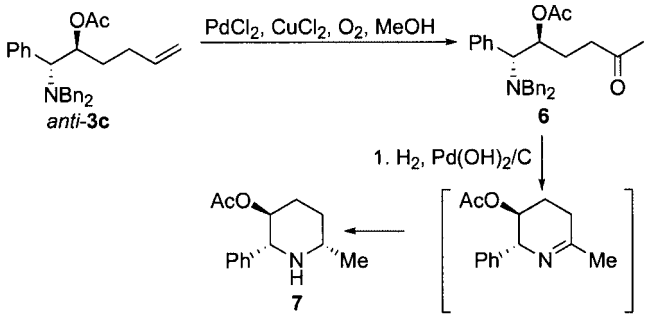
[a] Combined yield of diastereomers after purification by flash chromatography. [b] Determined by ^1H NMR analysis of the crude reaction mixture.

and a catalytic amount of osmium tetraoxide followed by treatment with sodium periodate on silica gel.[12] The aldehydes were subjected to hydrogenolysis on Pearlman's catalyst in methanol to give 2-substituted *O*-acetyl-3-piperidinols. The crude acetates were treated with lithium aluminium hydride at 0 °C to yield the final 2-substituted 3-hydroxypiperidines **5a**, **5b**,[13] and **5c**[14] in 51–55% yields over two steps.



Scheme 3.

A different approach was used for the synthesis of 2,6-substituted piperidin-3-ol derivatives. In this way, (2*R*,3*S*,6*S*)-3-acetoxy-2-phenyl-6-methylpiperidine (**7**) was synthesized from *anti*-**3c** as outlined in Scheme 4. This amino alcohol derivative was transformed into γ-acetoxy-δ-dibenzylamino ketone (**6**) by Wacker oxidation[15] of the double bond in the presence of palladium chloride in 64% yield. Debenzylation of **6** by hydrogenolysis with palladium hydroxide in methanol, with concomitant intramolecular reductive amination, yielded **7** in 78% yield as a single diastereoisomer. The stereochemistry of **7** was established on the basis of COSY and NOESY experiments. The NOESY cross peak between proton signals arising from C-2 and C-6 revealed a *cis* relationship between the substituents at these positions.

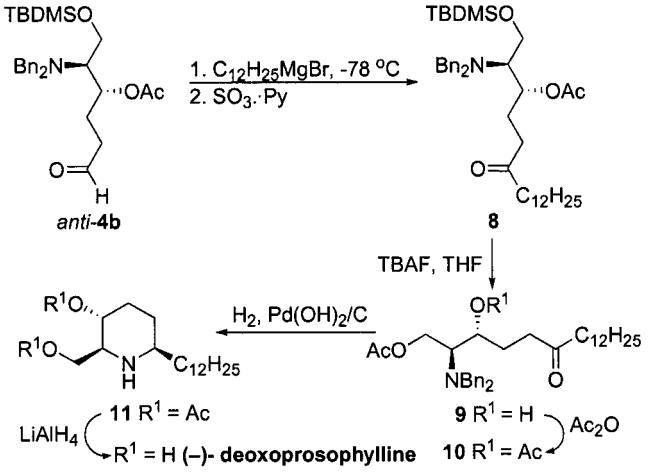


Scheme 4.

The *anti*-amino-alcohol derivative **4b** was used as the starting material for the synthesis of (–)-deoxoprosophylline. To this end, *anti*-**4b** was treated with dodecylmagnesium bromide at –78 °C in THF to give a mixture of diastereoisomeric alcohols at C-6, which, by oxidation[16] with SO_3·Py complex, led to ketone **8** in 69% yield (two steps).

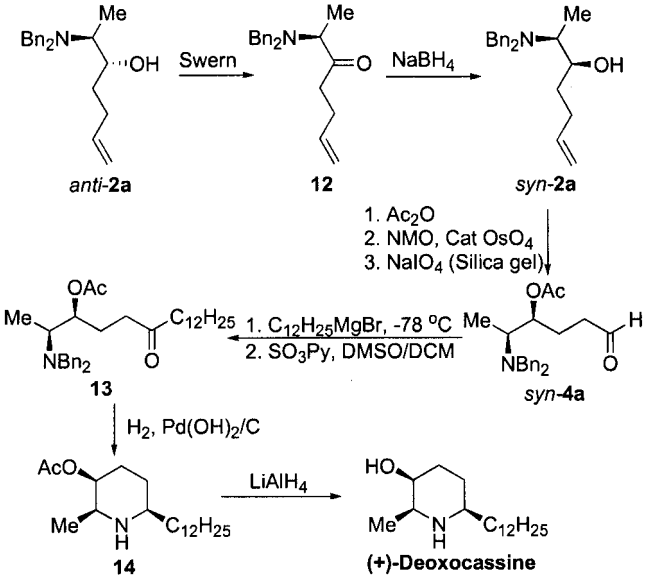
Deprotection of **8** by treatment with TBAF in THF gave the monoacetate of the dibenzylamino hydroxy ketone **9**, with the acetyl group having migrated from the secondary to the primary hydroxy group.[17] Compound **9** was protected as diacetate **10** by reaction with acetic anhydride and compound **10** was subjected to hydrogenolysis/cyclization by stirring under hydrogen in the presence of palladium hydroxide on carbon in methanol (Scheme 5). This treatment led to diacetate **11** in 80% yield as a single diastereoisomer, which was transformed into (–)-deoxoprosophylline by reduction with lithium aluminium hydride in 91% yield. The identity of the alkaloid was established by comparison of its spectral and physical characteristics with those described in the literature.[18]

Finally, the synthesis of (+)-deoxocassine is summarized in Scheme 6. The *all-cis* stereochemistry of this compound requires *syn*-**2a** as the starting amino alcohol, which, however, was obtained as the minor diastereoisomer from the reaction of **1a** with 4-butenylmagnesium bromide. Instead, *syn*-**2a** was prepared by isomerization of *anti*-**2a** in two steps. Swern oxidation of this amino alcohol yielded dibenzylamino ketone **12** in 89% yield, which was reduced with sodium borohydride in methanol[19] to a diastereomeric mixture of amino alcohols (*dr* 93:7) in which *syn*-**2a** was the major diastereoisomer. Enantiopure *syn*-**2a** was obtained by flash chromatography (silica gel, hexanes/EtOAc) of the reaction mixture and transformed into the acetate *syn*-**3a** in



Scheme 5.

89% yield by reaction with acetic anhydride. Oxidation with NMO and catalytic osmium tetraoxide, followed by reaction of the intermediate diol with sodium periodate transformed the acetate into *syn*-**4a** in 72% yield for the two steps.



Scheme 6.

Reaction of aldehyde *syn*-**4a** with an excess of dodecylmagnesium bromide at –78 °C led to an equimolar mixture of epimeric alcohols, which, without isolation, was transformed into ketone **13** in 62% yield. Debenzylation followed by intramolecular reductive amination of **13** as described above furnished trisubstituted piperidine **14** in 59% yield as a single diastereoisomer. (+)-Deoxocassine[20] was obtained in 87% yield by removal of the acetyl group in **13** by reduction with lithium aluminium hydride.

In summary, an efficient synthesis of enantiopure 2- and 2,6-substituted 3-piperidinols was successfully carried out from α-dibenzylamino aldehydes that are readily accessible from commercially available α-amino acids.

Experimental Section

General: Reactions were carried out in oven-dried glassware under argon and by using anhydrous solvents. Starting α-(dibenzylamino) aldehydes **1a**–**c** were prepared as described previously.[10] The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC 300 or AMX 300 spectrometer using TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum BX spectrometer as a film or KBr dispersion. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter in a 1-dm cell.

Reaction of Amino Aldehydes 1 with 4-Butenylmagnesium Bromide. General Method: A 1 M solution of 4-butenylmagnesium bromide in diethyl ether (2 mL, 2 mmol) was added to a solution of amino aldehydes **1** (1 mmol) in anhydrous diethyl ether (5 mL) at 0 °C under argon. The mixture was stirred at this temperature until the reaction was complete (TLC) and then quenched with a saturated solution of aqueous ammonium chloride (10 mL). The organic layer was separated and the aqueous phase extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue purified by flash chromatography (silica gel, hexane/ethyl acetate).

(2*S*,3*R*)-2-(Dibenzylamino)-6-hepten-3-ol (*anti*-2a): Yield 210 mg, 68%. Colorless oil. $[\alpha]_D^{20}$ = +17.7 (*c* = 1.1, $CHCl_3$) [ref.[11] $[\alpha]_D^{20}$ = +18.9 (*c* = 2.01, $CHCl_3$)]. IR (film): $\tilde{\nu}$ = 3367, 1640, 1603 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.10 (d, *J* = 9.4 Hz, 3 H), 1.30–1.44 (m, 1 H), 1.76–1.90 (m, 2 H), 1.95–2.21 (m, 2 H), 2.66–2.78 (q, *J* = 7.9 Hz, 1 H), 3.45 (d, *J* = 14.0 Hz, 2 H), 3.51–3.68 (m, 1 H), 3.75 (d, *J* = 14.0 Hz, 2 H), 4.92 (d, *J* = 10.8 Hz, 1 H), 4.98 (d, *J* = 17.8 Hz, 1 H), 5.70–5.90 (m, 1 H), 7.19–7.35 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 8.6 (CH_3), 30.2 (CH_2), 33.3 (CH_2), 54.7 (CH_2), 57.2 (CH), 73.1 (CH), 114.7 (CH_2), 126.9 (2 CH arom.), 128.2 (4 CH arom.), 128.8 (4 CH arom.), 138.7 (CH), 140.0 (2 C arom.) ppm.

(2*S*,3*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(dibenzylamino)-6-hepten-3-ol (*anti*-2b): Yield 289 mg, 73%. Colorless oil. $[\alpha]_D^{20}$ = +36.5 (*c* = 2.4, $CDCl_3$). IR (film): $\tilde{\nu}$ = 3452, 2929, 1641, 1072, 838 cm^{-1}. ^{1}H NMR ($CHCl_3$): δ = 0.09 (s, 3 H), 0.11 (s, 3 H), 0.91 (s, 9 H), 1.32–1.49 (m, 1 H), 1.82–1.93 (m, 1 H), 1.98–2.20 (m, 2 H), 2,68 (dt, J_1 = 1.78, J_2 = 7.29 Hz, 1 H), 3.02 (br. s, 1 H), 3.62 (d, *J* = 13.72 Hz, 2 H), 3.88 (d, *J* = 13.72 Hz, 2 H), 3.90 (m, 1 H), 4.02 (dd, J_1 = 1.78, J_2 = 5.10 Hz, 2 H), 4.95 (dq, J_1 = 1.65, J_2 = 10.1 Hz, 1 H), 5.10 (dq, J_1 = 1.65, J_2 = 16.7 Hz, 1 H), 5.82 (m, 1 H), 7.19–7.38 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.6 (2 CH_3), 18.0 (C), 25.8 (3CH_3), 29.7 (CH_2), 34.0 (CH_2), 55.2 (2 CH_2), 61.1 (CH_2), 61.2 (CH), 71.5 (CH), 114.4 (CH_2), 126.9 (2 CH arom.), 128.2 (4 CH arom.), 128.8 (4 CH arom.), 138.9 (2 C arom.), 139.8 (CH) ppm.

(1*R*,2*S*)-1-(Dibenzylamino)-1-phenyl-5-hexen-2-ol (*anti*-2c): Yield 271 mg, 73%. Colorless solid with m.p. 82–85 °C (from EtOAc/hexane). $[\alpha]_D^{20}$ = –92.0 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3520, 1630, 1595, 750, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 1 H), 1.46–1.56 (m, 1 H), 2.16–2.28 (m, 3 H), 3.12 (d, *J* = 13.8 Hz, 2 H), 3.60 (d, *J* = 8.6 Hz, 1 H), 3.88 (d, *J* = 13.8 Hz, 2 H), 4.34 (t, *J* = 8.6 Hz, 1 H), 5.0 (d, *J* = 10.0 Hz, 1 H), 5.1 (d, *J* = 17.1 Hz, 1 H), 5.87–5.93 (m, 1 H), 7.25–7.49 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.7 (CH_2), 33.0 (CH_2), 54.6 (2 CH_2), 68.0 (CH), 69.8 (CH), 114.8 (CH_2), 126.9 (2 CH arom.), 127.7 (CH arom.), 128.3 (6 CH arom.), 128.8 (4 CH arom.), 129.9 (2 CH arom.), 135.3 (C arom.), 138.8 (CH), 139.5 (C arom.) ppm.

(1*S*,2*R*)-1-(Dibenzylamino)-1-phenyl-5-hexen-2-ol (*syn*-2c): Yield 44 mg, 12%. Colorless solid with m.p. 92–93 °C. $[\alpha]_D^{20}$ = –115.8 (*c*

= 1.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3360, 1640, 1600, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.20–1.42 (m, 2 H), 2.14–2.36 (m, 2 H), 3.11 (d, J = 13.3 Hz, 2 H), 3.60 (d, J = 10.3 Hz, 1 H), 4.05 (d, J = 13.3 Hz, 2 H), 4.30–4.36 (m, 1 H), 4.59 (br. s, 1 H), 4.92–5.04 (m, 2 H), 5.70–5.84 (m, 1 H), 7.27–7.54 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.1 (CH_2), 33.3 (CH_2), 53.6 (2 CH_2), 67.2 (CH), 67.4 (CH), 114.6 (CH_2), 127.4 (2 CH arom.), 128.0 (CH arom.), 128.4 (2 CH arom.), 128.6 (4 CH arom.), 129.1 (4 CH arom.), 130.0 (2 CH arom.), 134.0 (C arom.), 138.6 (CH), 138.7 (2 C arom.) ppm.

Preparation of Amino Alcohol *syn*-2a from Amino Alcohol *anti*-2a: DMSO (3.3 mL, 46.5 mmol) was added to a stirred solution of oxalyl chloride (1.95 mL, 22.35 mmol) in CH_2Cl_2 (50 mL) cooled to –78 °C under argon. After stirring the mixture for 15 min, a solution of the amino alcohol *anti*-**2a** (5.1 g, 16.5 mmol) in CH_2Cl_2 (50 mL) was added and the mixture was stirred for 30 min at –78 °C before addition of triethylamine (6.6 mL, 47.4 mmol). Then the reaction was warmed to room temp. whilst stirring for 45 min and the mixture was quenched with water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organic layers washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and then concentrated to yield an oil which was purified by flash chromatography (silica gel, hexane/ethyl acetate, 20:1).

(*S*)-2-(Dibenzylamino)-6-hepten-3-one (12): Yield 5.4 g, 89%. Colorless oil. $[\alpha]_D^{20}$ = –40.2 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1712, 1451, 749, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.18 (d, J = 6.7 Hz, 3 H), 2.20–2.31 (m, 2 H), 2.62 (dt, J_1 = 7.4, J_2 = 17.1 Hz, 1 H), 2.84 (dt, J_1 = 7.4, J_2 = 17.1 Hz, 1 H), 3.39 (q, J = 6.7 Hz, 1 H), 3.48 (d, J = 13.7 Hz, 2 H), 3.71 (d, J = 13.7 Hz, 2 H), 4.92–5.0 (m, 2 H), 5.70–5.83 (m, 1 H), 7.25–7.42 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.9 (CH_3), 27.8 (CH_2), 38.8 (CH_2), 54.5 (2 CH_2), 62.0 (CH), 114.9 (CH_2), 127.1 (2 CH arom.), 128.4 (4 CH arom.), 128.7 (4 CH arom.), 137.4 (CH), 139.2 (C arom.), 212.0 (C=O) ppm.

Sodium borohydride (1.04 g. 27.5 mmol, 1.5 equiv.) was added to a stirred solution of ketone **12** (2.25 g, 6.1 mmol) in MeOH/THF (9:2, 44 mL) cooled to –20 °C. After stirring for 2 h, the mixture was quenched with H_2O and extracted several times with diethyl ether. The ethereal layer was washed with NaCl solution and dried with $MgSO_4$, the solvents were removed, and the residue **2a** purified by flash chromatography (silica gel, hexane/ethyl acetate, 15:1).

(2*S*,3*S*)-2-(Dibenzylamino)-6-hepten-3-ol (*syn*-2a): Yield 1.76 g, 78%. Colorless oil. $[\alpha]_D^{20}$ = +24.1 (c = 1.0, EtOAc). IR (film): $\tilde{\nu}$ = 3410, 1639 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.03 (d, J = 6.6 Hz, 3 H), 1.18–1.31 (m, 1 H), 1.50–1.62 (m, 1 H), 1.95–2.20 (m, 1 H), 2.20–2.35 (m, 1 H), 2.59 (dq, J_1 = 6.55, J_2 = 9.60 Hz, 1 H), 3.32 (d, J = 13.3 Hz, 2 H), 3.51 (dt, J_1 = 3.10, J_2 = 9.33 Hz, 1 H), 3.84 (d, 13.3 Hz, 2 H), 4.49 (br. s, 1 H), 4.93 (d, J = 10.35 Hz, 1 H), 5.10 (dq, J_1 = 2.65, J_2 = 17.40 Hz, 1 H), 5.80–5.89 (m, 1 H), 7.22–7.35 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 8.0 (CH_3), 30.1 (CH_2), 33.2 (CH_2), 53.2 (2 CH_2), 58.3 (CH), 70.1 (CH), 114.4 (CH_2), 127.2 (2 CH arom.), 128.5 (4 CH arom.), 128.9 (4 CH arom.), 138.7 (2 C arom.), 138.8 (CH) ppm.

Acetylation of Amino Alcohols 2. General Method: Ac_2O (0.15 mL, 1.52 mmol) and DMAP (28.0 mg, 0.23 mmol) was added to a solution of **2** (0.92 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 1.5 h and quenched with water (5 mL). After separation, the organic layer was washed with a saturated $NaHCO_3$ solution (2 × 5 mL) and brine (5 mL) and then dried with anhydrous $MgSO_4$. The solvent was distilled and the residue purified by flash chromatography.

(2*S*,3*R*)-2-(Dibenzylamino)-6-hepten-3-yl Acetate (*anti*-3a): Yield 290 mg, 90%. Colorless oil. $[\alpha]_D^{20}$ = +13.8 (c = 1.2, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1736, 1454, 1244, 749, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.04 (d, J = 6.7 Hz, 3 H), 1.48–1.57 (m, 1 H), 1.79–1.97 (m, 3 H), 2.02 (s, 3 H), 2.78 (dq, J_1 = 6.9, J_2 = 7.2 Hz, 1 H), 3.42 (d, J = 13.7 Hz, 2 H), 3.74 (d, J = 13.7 Hz, 2 H), 4.90–4.97 (m, 2 H), 5.09 (td, J_1 = 3.13, J_2 = 7.90 Hz, 1 H), 5.69–5.80 (m, 1 H), 7.19–7.39 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 8.5 (CH_3), 21.1 (CH_3), 29.0 (CH_2), 31.1 (CH_2), 54.1 (2 CH_2), 54.8 (CH), 74.6 (CH), 114.6 (CH_2), 126.8 (2 CH arom.), 128.1 (4 CH arom.), 128.7 (4 CH arom.), 138.0 (2 C arom.), 139.8 (CH), 170.7 (CO_2) ppm. $C_{23}H_{29}NO_2$ (351.48): calcd. C 78.59, H 8.32, N 3.99; found C 78.71, H 8.23, N 3.87.

(2*S*,3*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(dibenzylamino)-6-hepten-3-yl Acetate (*anti*-3b): Yield 351 mg, 87%. Colorless oil. $[\alpha]_D^{20}$ = +8.45 (c = 1.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1741, 1241, 1028, 839, 748, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.08 (s, 3 H), 0.1 (s, 3 H), 0.95 (s, 9 H), 1.51–1.67 (m, 1 H), 1.68–1.93 (m, 3 H), 1.96 (s, 3 H), 2.83–2.90 (m, 1 H), 3.68 (d, J = 13.72 Hz, 2 H), 3.87 (d, J = 13.72 Hz, 2 H), 3.83–3.94 (m, 1 H), 4.87–4.96 (m, 2 H), 5.2 (dt, J_1 = 3.6, J_2 = 7.3 Hz, 1 H), 5.64–5.79 (m, 1 H), 7.15–7.34 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.8 (2 CH_3), 18.1 (C), 21.2 (CH_3), 25.9 (3 CH_3), 28.7 (CH_2), 30.9 (CH_2), 55.1 (2 CH_2), 59.4 (CH), 59.5 (CH_2), 72.0 (CH), 114.4 (CH_2), 126.8 (2 CH arom.), 128.1 (4 CH arom.), 128.9 (4 CH arom.), 138.1 (CH), 140.0 (2 C arom.), 170.1 (CO_2) ppm. $C_{29}H_{43}NO_2Si$ (465.74): calcd. C 74.79, H 9.31, N 3.01; found C 74.92, H 9.23, N 2.89.

(1*R*,2*S*)-1-(Dibenzylamino)-1-phenyl-5-hexen-3-yl Acetate (*anti*-3c): Yield 346 mg, 91%. Colorless oil. $[\alpha]_D^{20}$ = –90.75 (c = 1.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1736, 1460, 1224, 749, 698 cm^{-1}. ^1H NMR ($CHCl_3$): δ = 1.68 (s, 3 H), 1.73–1.85 (m, 1 H), 2.04–2.11 (m, 2 H), 2.37–2.45 (m, 1 H), 3.13 (d, J = 13.6 Hz, 2 H), 3.85 (d, J = 10.1 Hz, 1 H), 3.95 (d, J = 13.6 Hz, 2 H), 5.04–5.15 (m, 2 H), 5.80–5.99 (m, 2 H), 7.27–7.47 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.7 (CH_3), 29.0 (CH_2), 31.6 (CH_2), 54.3 (2 CH_2), 64.8 (CH), 71.9 (CH), 114.9 (CH_2), 127.0 (2 CH arom.), 127.4 (CH arom.), 127.8 (2 CH arom.), 128.4 (4 CH arom.), 128.9 (4 CH arom.), 129.7 (2 CH arom.), 134.5 (C arom.), 138.1 (CH), 139.4 (2 CH arom.), 170.3 (CO_2) ppm. $C_{28}H_{31}NO_2$ (413.55): calcd. C 81.32, H 7.56, N 3.39; found C 81.46, H 7.44, N 3.27.

(2*S*,3*S*)-2-(Dibenzylamino)-6-hepten-3-yl Acetate (*syn*-3a): Yield 287 mg, 89%. Colorless oil. $[\alpha]_D^{20}$ = –13.11 (c = 0.4, AcOEt). IR (film): $\tilde{\nu}$ = 1735, 1494, 1452, 1370, 749, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.02 (d, J = 7.2 Hz, 3 H), 1.61–1.72 (m, 2 H), 1.80–1.92 (m, 2 H), 2.08 (s, 3 H), 2.82 (dq, J_1 = 6.9, J_2 = 7.2 Hz, 1 H), 3.35 (d, J = 13.6 Hz, 2 H), 3.88 (d, J = 13.6 Hz, 2 H), 4.87–4.96 (m, 2 H), 5.02 (q, J = 6.3 Hz, 1 H), 5.65–5.81 (m, 1 H), 7.18–7.38 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.2 (CH_3), 21.3 (CH_3), 29.5 (CH_2), 31.1 (CH_2), 54.3 (2 CH_2), 54.8 (CH), 75.8 (CH), 114.6 (CH_2), 126.7 (2 CH arom.), 128.1 (4 CH arom.), 128.8 (4 CH arom.), 138.0 (CH), 140.2 (2 C arom.), 170.6 (CO_2) ppm. $C_{23}H_{29}NO_2$ (351.48): calcd. C 78.59, H 8.32, N 3.99; found C 78.43, H 8.43, N 4.12.

Oxidative Cleavage of the Olefin 3a–c to Aldehydes 4a–c: A catalytic amount of OsO_4 in toluene (5% solution, 5 mol-%) was added to a stirred solution of olefin **3** (4.08 mmol) and NMO (2.38 g, 20.35 mmol) in acetone (10 mL) and water (2 mL) at room temperature. After stirring for 8 h, a saturated aqueous solution of Na_2SO_3 (5 mL) was added to the mixture and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried with Na_2SO_4 and the solvent removed under vacuum to afford a crude dihydroxylated compound which was used without purification in the next step. The crude dihydroxylated product was dissolved in CH_2Cl_2 (20 mL) and added in one portion to a vigorously stirred

suspension of $NaIO_4$ supported on silica gel (8 g, 20% $NaIO_4$) in CH_2Cl_2 (20 mL) at 0 °C. After stirring at the same temperature for 1 h, the solid was removed by filtration and washed with CH_2Cl_2 (3 × 30 mL). The filtrate was concentrated under vacuum and the residue purified by column chromatography (silica gel, hexane/EtOAc).

(2*S*,3*R*)-2-(Dibenzylamino)-6-oxo-3-hexyl Acetate (*anti*-4a): Yield 1.02 g, 71%. Colorless oil. IR (film): $\tilde{\nu}$ = 1728, 1246, 749, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.06 (d, J = 9.1 Hz, 3 H), 1.72–1.89 (m, 1 H), 1.97 (s, 3 H), 1.97–2.06 (m, 1 H), 2.11–2.27 (m, 2 H), 2.78 (dq, J_1 = 6.2, J_2 = 6.5 Hz, 1 H), 3.35 (d, J = 13.76 Hz, 2 H), 3.76 (d, J = 13.76 Hz, 2 H), 5.04–5.14 (m, 1 H), 7.19–7.37 (m, 10), 9.58 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 8.3 (CH_3), 20.9 (CH_3), 23.7 (CH_2), 38.8 (CH_2), 54.0 (2 CH_2), 54.1 (CH), 73.9 (CH), 126.9 (2 CH arom.), 128.2(4 CH arom.), 128.9 (CH arom.), 139.5 (2 C arom.), 170.6 (CO_2), 201.6 (C=O) ppm. $C_{22}H_{27}NO_3$ (353.45): calcd. C 74.76, H 7.70, N 3.96; found C 74.69, H 7.53, N 3.81.

(2*S*,3*S*)-2-(Dibenzylamino)-6-oxo-3-hexyl Acetate (*syn*-4a): Yield 1.04 g, 72%. Colorless oil. $[\alpha]_D^{20}$ = –18.1 (c = 0.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1729, 1243, 749, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.08 (d, J = 6.9 Hz, 3 H), 1.78–2.21 (m, 4 H), 2.1 (s, 3 H), 2.81–2.92 (m, 1 H), 3.32 (d, J = 13.6 Hz, 2 H), 3.92 (d, J = 13.6 Hz, 2 H), 4.90–5.0 (m, 1 H), 7.20–7.40 (m, 10 H), 9.52 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.1 (CH_3), 21.1 (CH_3), 24.1 (CH_2), 39.8 (CH_2), 54.3 (2 CH_2), 54.4 (CH), 75.5 (CH), 126.9 (2 CH arom.), 128.1 (4 CH arom.), 128.9 (CH arom.), 140.0 (2 C arom.), 170.7 (CO_2), 201.4 (C=O) ppm. $C_{22}H_{27}NO_3$ (353.45): calcd. C 74.76, H 7.70, N 3.96; found C 74.88, H 7.58, N 4.09.

(2*S*,3*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(dibenzylamino)-6-oxo-3-hexyl Acetate (*anti*-4b): Yield 1.26 g, 70%. Colorless oil. $[\alpha]_D^{20}$ = +12.6 (c = 0.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1729, 1243, 749, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 3 H), 0.13 (s, 3 H), 0.95 (s, 9 H), 1.82–1.98 (m, 2 H), 1.97 (s, 3 H), 2.01–2.28 (m, 2 H), 2.85 (ddd, J_1 = 3.0, J_2 = 6.1, J_3 = 9.4 Hz, 1 H), 3.65 (d, J = 13.6 Hz, 2 H), 3.83 (dd, J_1 = 6.1, J_2 = 10.7 Hz, 1 H), 3.91 (d, J = 13.6 Hz, 2 H), 3.97 (dd, J_1 = 3.0, J_2 = 10.7 Hz, 1 H), 5.22 (dt, J_1 = 5.7, J_2 = 9.4 Hz, 1 H), 7.22–7.41 (m, 10 H), 9.5 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.6 (2 CH_3), 18.1 (C), 21.1 (CH_3), 23.4 (CH_2), 25.8 (3 CH_3), 38.5 (CH_2), 55.1 (2 CH_2), 58.6 (CH), 59.0 (CH_2), 70.7 (CH), 126.9 (2 CH arom.), 128.3 (4 CH arom.), 129.1 (4 CH arom.), 139.8 (C arom.), 170.2 (CO_2), 201.8 (C=O) ppm. $C_{28}H_{41}NO_4Si$ (483.71): calcd. C 69.52, H 8.54, N 2.90; found C 69.66, H 8.67, N 2.81.

(1*R*,2*S*)-1-(Dibenzylamino)-5-oxo-1-phenyl-2-pentyl Acetate (*anti*-4c): Yield 1.27 g, 75%. Colorless oil. IR (film): $\tilde{\nu}$ = 1726, 750, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.63 (s, 3 H), 1.90–2.07 (m, 1 H), 2.16–2.31 (m, 1 H), 2.34–2.49 (m, 1 H), 2.58–2.69 (m, 1 H), 3.08 (d, J = 13.3 Hz, 2 H), 3.80 (d, J = 10.3 Hz, 1 H), 3.91 (d, J = 13.3 Hz, 2 H), 5.75–5.87 (m, 1 H), 7.15–7.52 (m, 15 H), 9.70 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5 (CH_3), 28.3 (CH_2), 35.6 (CH_2), 54.8 (2 CH_2), 65.8 (CH), 72.9 (CH), 126.9 (2 CH arom.), 127.1 (CH arom.), 127.8 (2 CH arom.), 128.1 (4 CH arom.), 128.6 (4 CH arom.), 129.4 (2 CH arom.), 134.5 (C arom.), 139.4 (2 CH arom.), 170.8 (CO_2), 201.5 (C=O) ppm. $C_{27}H_{29}NO_3$ (415.52): calcd. C 78.04, H 7.03, N 3.37; found C 78.17, H 7.11, N 3.26.

Synthesis of 2-Substituted 3-Piperidinols 5a–c: 20% $Pd(OH)_2$/C (100 mg) was added in one portion to a solution of the appropriate dibenzylamino aldehyde **4** (1.5 mmol) in methanol (20 mL). The mixture was stirred under 1 atm of hydrogen and the reaction monitored by TLC. After completion of the reaction, the catalyst was removed by filtration through Celite. The Celite was washed with methanol (20 mL) and the solvent evaporated under reduced pressure to afford a yellowish residue which was used without purification in the next step. The residue (0.92 mmol) was dissolved in anhydrous diethyl ether (4 mL) and added to a suspension of $LiAlH_4$ (35.0 mg, 0.92 mmol) in Et_2O (4 mL) at 0 °C. The mixture was stirred for 1 h at this temperature and then quenched by addition of a 15% NaOH aqueous solution. The mixture was filtered off and the solids washed with Et_2O. The solvent was eliminated under vacuum and the residue purified by flash chromatography (silica gel, CH_2Cl_2/MeOH).

(2*S*,3*R*)-2-Methyl-3-piperidinol (5a): Yield 90 mg, 51%. Colorless solid with m.p. 130–131 °C (from CH_2Cl_2/hexane). $[\alpha]_D^{20}$ = –11.5 (c = 0.6, $CHCl_3$) [ref.[21]: m.p. 130 °C, $[\alpha]_D^{20}$ = +16.2 (c = 0.92, $CHCl_3$) for the (2*R*,3*S*) enantiomer]. IR (KBr): $\tilde{\nu}$ = 3402, 3275, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.18 (d, J = 6.3 Hz, 3 H), 1.21–1.38 (m, 1 H), 1.43–1.60 (m, 1 H), 1.68–1.77 (m, 1 H), 1.96–2-06 (m, 1 H), 2.34 (br. s, 2 H), 2.37–2.49 (m, 1 H), 2.56 (dt, J_1 = 2.9, J_2 = 12.2 Hz, 1 H), 2.91–2.98 (m, 1 H), 3.14 (ddd, J_1 = 4.3, J_2 = 8.2, J_3 = 12.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.5 (CH_3), 25.4 (CH_2), 33.6 (CH_2), 45.6 (CH_2), 58.4 (CH), 73.3 (CH) ppm. $C_6H_{13}NO$ (115.17): calcd. C 62.57, H 11.38, N 12.16; found C 62.71, H 11.26, N 12.08.

(2*S*,3*R*)-2-(Hydroxymethyl)-3-piperidinol (5b): Yield 104 mg, 53%. Colorless solid with m.p. 120–121 °C (MeOH/Et_2O). $[\alpha]_D^{20}$ = –44.5 (c = 0.4, MeOH) [ref.[13]: $[\alpha]_D^{21}$ = +58.3 (c = 1.06, MeOH) for the (2*R*,3*S*) enantiomer]. IR (KBr): $\tilde{\nu}$ = 3420, 1050 cm^{-1}. ^{1}H NMR (CD_3OD): δ = 1.25–1.41 (m, 1 H), 1.43–1.58 (m, 1 H), 1.68–1.77 (m, 1 H), 1.98–2.06 (m, 1 H), 2.38 (td, J_1 = 3.1, J_2 = 9.8 Hz, 1 H), 2.52 (td, J = 2.5, 12.1 Hz, 1 H), 2.93–3.02 (m, 1 H), 3.23–3.34 (m, 1 H), 3.55 (dd, J_1 = 7.2, J_2 = 10.7 Hz, 1 H), 3.88 (dd, J_1 = 3.1, J_2 = 10.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.1 (CH_2), 34.9 (CH_2), 46.5 (CH_2), 63.7 (CH_2), 65.0 (CH), 69.6 (CH) ppm. $C_6H_{13}NO_2$ (131.17): calcd. C 54.94, H 9.99, N 10.86; found C 55.06, H 10.10, N 10.74.

(2*R*,3*S*)-2-Phenyl-3-piperidinol (5c): Yield 146 mg, 55%. Colorless solid with m.p. 144–146 °C (MeOH/Et_2O). $[\alpha]_D^{20}$ = –32.4 (c = 1.0, $CHCl_3$) [ref.[14]: m.p. 143–144 °C, $[\alpha]_D^{22}$ = –23.0 (c = 1.5, MeOH)]. IR (KBr): $\tilde{\nu}$ = 3250, 750, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.32–1.48 (m, 1 H), 1.55–1.79 (m, 2 H), 1.90 (br. s, 2 H), 2.08–2.15 (m, 1 H), 2.62 (td, J_1 = 3.0, J_2 = 11.6 Hz, 1 H), 2.91–2.99 (m, 1 H), 3.24 (d, J = 8.8 Hz, 1 H), 3.48 (ddd, J_1 = 4.4, J_2 = 8.8, J_3 = 10.7 Hz, 1 H), 7.15–7.37 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.2 (CH_2), 33.2 (CH_2), 46.7 (CH_2), 69.3 (CH), 72.5 (CH), 127.8 (CH arom.), 128.1 (2 CH arom.), 128.5 (2 CH arom.), 141.4 (C arom.) ppm. $C_{11}H_{15}NO$ (177.24): calcd. C 75.54, H 8.53, N 7.90; found C 75.62, H 8.66, N 7.79.

Synthesis of 2,6-Substituted 3-Piperidinol Derivative 7

(1*R*,2*S*)-1-(Dibenzylamino)-5-oxo-1-phenyl-2-hexyl Acetate (6): Oxygen was bubbled through a solution of *ent*,*anti*-**3c** (372 mg, 0.92 mmol), palladium chloride bis(acetonitrile) complex (34 mg, 0.13 mmol, 0.14 equiv.), and cupric chloride (176 mg, 1.3 mmol, 1.4 equiv.) in methanol (7 mL) at room temperature. After stirring for 25 h, the reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue was treated with ethyl acetate (15 mL), water (15 mL), and an aqueous ammonia solution (3 mL). The organic layer was separated, dried with anhydrous Na_2SO4, evaporated under reduced pressure, and purified by column chromatography on silica gel (hexane/ethyl acetate, 8:1) to give **6** (308 mg, 78%) as a colorless oil. $[\alpha]_D^{20}$ = +97.7 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1736, 1718, 1241, 735, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 3 H), 1.82–1.95 (m, 1 H), 2.11 (s, 3 H), 2.20–2.32 (m, 1 H), 2.38–2.50 (m, 1 H), 2.59–2.68 (m, 1 H), 3.06 (d, J = 13.5 Hz, 2 H), 3.79 (d, J = 10.5 Hz, 1 H), 3.95 (d, J = 13.5 Hz, 2 H), 5.75 (ddd, J_1 = 3.0, J_2 = 7.9, J_3 = 10.5 Hz, 1 H), 7.22–7.44 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.5 (CH_3), 25.6 (CH_2), 29.9

(CH_3), 38.3 (CH_2), 54.1 (2 CH_2), 64.4 (CH), 71.4 (CH), 127.0 (2 CH arom.), 127.4 (CH arom.), 127.8 (2 CH arom.), 128.3 (4 CH arom.), 129.0 (4 CH arom.), 129.5 (2 CH arom.), 134.3 (C arom.), 139.3 (2 C arom.), 170.4 (CO_2), 207.8 (C=O) ppm. $C_{28}H_{31}NO_3$ (429.55): calcd. C 78.29, H 7.27, N 3.26; found C 78.16, H 7.38, N 3.21.

(2*R*,3*S*,6*S*)-6-Methyl-2-phenyl-3-piperidinyl Acetate (7): 20% $Pd(OH)_2$/C (55 mg) was added in one portion to a solution of the dibenzylamino ketone **6** (180 mg, 0.42 mmol) in methanol (10 mL). The mixture was stirred under 1 atm of hydrogen and the reaction monitored by TLC. After completion of the reaction, the catalyst was removed by filtration through Celite and washed with methanol (20 mL). The solvent was evaporated under reduced pressure to afford piperidine **7** (76 mg, 78%) as a colorless solid, m.p. 52–54 °C (diethyl ether). $[\alpha]_D^{20}$ = –6.9 (*c* = 0.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3446, 1736, 1247, 1039 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.11 (d, *J* = 6.4 Hz, 3 H), 1.30–1.60 (m, 2 H), 1.62 (br. s, 1 H), 1.70–1.75 (m, 1 H), 1.78 (s, 3 H), 2.10–2.21 (m, 1 H), 2.78–2.91 (m, 1 H), 3.65 (d, *J* = 10.2 Hz, 1 H), 4.81 (ddd, *J* = 4.2, 8.8, 10.2 Hz, 1 H), 7.17–7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.9 (CH_3), 22.1 (CH_3), 30.8 (CH_2), 32.9 (CH_2), 52.3 (CH), 65.9 (CH), 74.2 (CH), 127.6 (CH arom.), 127.7 (2 CH arom.), 128.1 (2 CH arom.), 141.0 (C arom.), 169.9 (CO_2) ppm. $C_{14}H_{19}NO_2$ (233.31): calcd. C 72.07, H 8.21, N 6.00; found C 72.19, H 8.30, N 6.11.

Synthesis of Compounds 8 and 13: Dodecylmagnesium bromide (2.8 mL, 1 M in Et_2O, 2.0 equiv.) was added at –78 °C to a solution of the corresponding amino aldehydes *anti*-**4b** or *syn*-**4a** (1.4 mmol) in anhydrous diethyl ether (40 mL). The mixture was stirred at that temperature until the reaction was complete (TLC) and then quenched with a solution of aqueous saturated ammonium chloride (50 mL). The organic layer was separated and the aqueous phase extracted with diethyl ether (2 × 40 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue used in the next reaction. A solution of sulfur trioxide–pyridine complex (1.13 g, 7.1 mmol) in DMSO/CH_2Cl_2 (10 mL/10 mL) was added to a stirred solution of the amino alcohol (2.36 mmol) and triethylamine (0.99 mL, 7.1 mmol) in DMSO/CH_2Cl_2 (5 mL/5 mL) over 20 min. The reaction vessel was maintained at 20 °C by immersion in a water bath and the reaction was monitored by TLC analysis. After completion of the reaction the mixture was poured into saturated NaCl (50 mL) at 0 °C and the mixture extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 1% HCl, H_2O, saturated $NaHCO_3$, and saturated NaCl and then dried with $MgSO_4$, filtered, and concentrated to afford a clear oil that was purified by flash chromatography.

(2*S*,3*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(dibenzylamino)-6-oxo-3-octadecyl Acetate (8): Yield 993 mg, 69%. Colorless oil. $[\alpha]_D^{20}$ = –28.5 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1739, 1710, 1241, 747, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.09 (s, 3 H), 0.13 (s, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H), 0.96 (s, 9 H), 1.10–1.35 (m, 18 H), 1.42–1.56 (m, 2 H), 1.71–1.92 (m, 2 H), 1.96 (s, 3 H), 2.06–2.21 (m, 2 H), 2.23 (t, *J* = 7.4 Hz, 2 H), 2.82 (ddd, J_1 = 3.1, J_2 = 6.8, J_3 = 9.7 Hz, 1 H), 3.68 (d, *J* = 13.6 Hz, 2 H), 3.83 (dd, J_1 = 6.8, J_2 = 10.8 Hz, 1 H), 3.90 (d, *J* = 13.6 Hz, 2 H), 3.96 (dd, J_1 = 3.1, J_2 = 10.8 Hz, 1 H), 5.18–5.27 (m, 1 H), 7.21–7.40 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.7 (2 CH_3), 14.1 (CH_3), 18.1 (C), 21.1 (CH_3), 22.6 (CH_2), 23.7 (CH_2), 25.1 (CH_2), 25.8 (3 CH_3), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (2 CH_2), 31.9 (CH_2), 37.3 (CH_2), 42.7 (CH_2), 53.3 (CH_2), 55.1 (2 CH_2), 59.0 (CH), 59.2 (CH_2), 71.4 (CH), 126.9 (2 CH arom.), 128.2 (4 CH arom.), 129.1 (4 CH arom.), 139.9 (2 CH arom.), 170.2 (CO_2), 210.3 (C=O) ppm.

(2*S*,3*S*)-2-(Dibenzylamino)-6-oxo-3-octadecyl Acetate (13): Yield 763 mg, 62%. Colorless oil. $[\alpha]_D^{20}$ = –16.8 (*c* = 0.3, EtOAc). IR (film): $\tilde{\nu}$ = 1736, 1715, 1241, 747, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.4 Hz, 3 H), 1.08 (d, *J* = 6.7 Hz, 3 H), 1.15–1.40 (m, 18 H), 1.45–1.58 (m, 2 H), 1.70–1.82 (m, 1 H), 1.88–2.02 (m, 1 H), 2.10 (s, 3 H), 2.03–2.21 (m, 2 H), 2.27 (t, *J* = 7.4 Hz, 2 H), 2.82 (dq, J_1 = 6.7, J_2 = 6.9 Hz,1 H), 3.34 (d, *J* = 13.5 Hz, 2 H), 3.87 (d, *J* = 13.5 Hz, 2 H), 4.91–4.97 (m, 1 H), 7.20–7.36 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.2 (CH_3), 14.1 (CH_3), 21.2 (CH_3), 22.7 (CH_2), 23.7 (CH_2), 25.6 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (2 CH_2), 31.9 (CH_2), 38.3 (CH_2), 42.7 (CH_2), 53.4 (CH_2), 54.3 (2 CH_2), 54.7 (CH), 75.6 (CH), 126.8 (2 CH arom.), 128.1 (4 CH arom.), 128.9 (4 CH arom.), 140.1 (2 C arom.), 170.7 (CO_2.), 210.2 (C=O) ppm. $C_{34}H_{51}NO_3$ (521.77): calcd. C 78.26, H 9.85, N 2.68; found C 78.39, H 9.75, N 2.61.

Synthesis of (–)-Deoxoprosophylline

(2*S*,3*R*)-2-(Dibenzylamino)-3-hydroxy-6-oxooctadecyl Acetate (9): nBu_4NF (1.30 g, 4.41 mmol, 3 equiv.) was added to a solution of **8** (0.89 g, 1.47 mmol) in THF (30 mL) at room temp. The solution was stirred for 1 h and then an aqueous NH_4Cl solution (40 mL) was added. The mixture was extracted with chloroform (2 × 50 mL). The organic layer was washed with brine, dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel using hexane/EtOAc (8:1) as eluent to afford **9** (584 mg, 74%) as a colorless oil. $[\alpha]_D^{20}$ = +14.6 (*c* = 0.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3447, 1739, 1712, 1245, 748, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.3 Hz, 3 H), 1.18–1.43 (m, 18), 1.44–1.87 (m, 4 H), 2.13 (s, 3 H), 2.33 (t, *J* = 7.6 Hz, 2 H), 2.32–2.55 (m, 1 H), 2.72–2.86 (m, 2 H), 3.64 (d, *J* = 13.5 Hz, 2 H), 3.66–3.81 (m, 1 H), 3.84 (d, *J* = 13.5 Hz, 2 H), 4.35–4.48 (m, 1 H), 4.52 (d, *J* = 4.8 Hz, 2 H), 7.24–7.40 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 21.1 (CH_3), 22.6 (CH_2), 23.8 (CH_2), 27.9 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (3 CH_2), 31.8 (CH_2), 38.5 (CH_2), 42.8 (CH_2), 55.0 (2 CH_2), 60.0 (CH), 61.4 (CH_2), 69.6 (CH), 127.0 (2 CH arom.), 128.3 (4 CH arom.), 128.9 (4 CH arom.), 139.4 (2 C arom.), 171.2 (CO_2), 212.5 (C=O) ppm.

(2*S*,3*R*)-3-Acetoxy-2-(dibenzylamino)-6-oxooctadecyl Acetate (10): Ac_2O (0.35 mL, 3.54 mmol) and a crystal of DMAP were added to a solution of **9** (118 mg, 0.22 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 1.5 h and quenched with water (5 mL). After separation, the organic layer was washed with a saturated $NaHCO_3$ solution (2 × 5 mL) and brine (5 mL), and then dried with anhydrous $MgSO_4$. The solvent was distilled and the residue purified by chromatography (silica gel, hexane/EtOAc: 10:1) to afford **10** (99 mg, 78%) as a colorless oil. $[\alpha]_D^{20}$ = +13.02 (*c* = 0.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1741, 1242, 749, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.20–1.38 (m, 18 H), 1.45–1.61 (m, 2 H), 1.68–1.85 (m, 1 H), 1.97 (s, 3 H), 1.98–2.22 (m, 3 H), 2.09 (s, 3 H), 2.25 (t, *J* = 7.1 Hz, 2 H), 2.93–2.99 (m, 1 H), 3.57 (d, *J* = 13.5 Hz, 2 H), 3.81 (d, *J* = 13.5 Hz, 2 H), 4.31 (dd, J_1 = 3.4, J_2 = 11.9 Hz, 1 H), 4.41 (dd, J_1 = 6.2, J_2 = 11.9 Hz, 1 H), 5.24 (m, 1 H), 7.21–7.40 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 20.9 (2 CH_3), 22.6 (CH_2), 23.6 (CH_2), 25.5 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (3 CH_2), 31.8 (CH_2), 37.2 (CH_2), 42.7 (CH_2), 54.5 (2 CH_2), 57.4 (CH), 60.3 (CH_2), 70.8 (CH), 127.1 (2 CH arom.), 128.2 (4 CH arom.), 128.9 (4 CH arom.), 139.1 (2 C arom.), 170.3 (CO_2), 170.7 (CO_2), 209.8 (C=O) ppm.

(2*S*,3*R*,6*R*)-2-(Acetoxymethyl)-6-dodecyl-3-piperidinyl Acetate (11): 20% $Pd(OH)_2$/C (63 mg) was added in one portion to a solution of amino ketone **10** (237 mg, 0.410 mmol) in dry methanol (10 mL). The mixture was stirred under 1 atm of hydrogen and the

reaction monitored by TLC. After completion of the reaction (45 h) the catalyst was removed by filtration through Celite and washed with methanol (20 mL). The solvent was evaporated under reduced pressure to afford **11** (126 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ = –31.0 (*c* = 0.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1740, 1231, 1037, 785 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.05–1.50 (m, 22 H), 1.71–1.82 (m, 2 H), 1.84–2.21 (m, 3 H), 2.02 (s, 3 H), 2.07 (s, 3 H), 2.48–2.57 (m, 1 H), 2.89 (ddd, J_1 = 2.7, J_2 = 6.9, J_3 = 9.7 Hz, 1 H), 4.02 (dd, *J* = 6.9, 11.1 Hz, 1 H), 4.19 (dd, J_1 = 2.7, J_2 = 11.1 Hz, 1 H), 4.53 (td, J_1 = 4.6, J_2 = 9.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 20.8 (CH_3), 21.1 (CH_3), 22.6 (CH_2), 26.1 (CH_2), 29.3 (2 CH_2), 29.6 (4 CH_2), 30.2 (CH_2), 31.0 (CH_2), 31.8 (CH_2), 36.5 (CH_2), 55.8 (CH), 58.5 (CH), 65.2 (CH_2), 71.1 (CH), 170.2 (CO_2), 170.8 (CO_2), 211.9 (C=O) ppm. $C_{22}H_{41}NO_4$ (383.57): calcd. C 68.89, H 10.77, N 3.65; found C 69.00, H 10.84, N 3.53.

(–)-Deoxoprosophylline: A solution of **11** (138 mg, 0.36 mmol) in anhydrous THF (1 mL) was added dropwise to a suspension of $LiAlH_4$ (14.0 mg, 0.36 mmol) in THF (2 mL) at 0 °C. The mixture was stirred for 1 h at that temperature and then quenched by addition of a 15% aqueous solution of NaOH. The mixture was filtered off and the solids washed with THF. The solvent was eliminated under vacuum to afford the titled compound (98 mg, 91%) as a colorless solid. M.p. 89–91 °C (from EtOAc). $[\alpha]_D^{20}$ = –10.3 (*c* = 0.1, $CHCl_3$) [ref.[7a] m.p. 91.0–91.5 °C, $[\alpha]_D^{20}$ = –11.4 (*c* = 0.24, $CHCl_3$)]. IR (film): $\tilde{\nu}$ = 3267, 1465, 1060, 800 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.3 Hz, 3 H), 1.02–1.51 (m, 22 H), 1.52–1.85 (m, 2 H), 1.95–2.10 (m, 2 H), 2.50–2.61 (m, 2 H), 3.20 (br. s, 3 H), 3.41 (dt, J_1 = 5.3, J_2 = 9.6 Hz, 1 H), 3.70 (dd, J_1 = 5.3, J_2 = 10.9 Hz, 1 H), 3.84 (dd, J_1 = 5.0, J_2 = 10.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.9 (2 CH_2), 26.5 (CH_2), 29.3 (2 CH_2), 29.6 (4 CH_2), 31.9 (2 CH_2), 33.8 (CH_2), 36.2 (CH_2), 56.1 (CH), 63.4 (CH), 63.9 (CH_2), 69.7 (CH) ppm.

Synthesis of (+)-Deoxocassine

(2*S*,3*S*,6*R*)-6-Dodecyl-2-methyl-3-piperidinyl Acetate (14): 20% $Pd(OH)_2$/C (80 mg) was added in one portion to a solution of the dibenzylamino ketone **13** (1.0 mmol) in methanol (20 mL). The mixture was stirred under 1 atm of hydrogen and the reaction monitored by TLC. After completion of the reaction, the catalyst was removed by filtration through Celite and washed with methanol (20 mL). The solvent was evaporated under reduced pressure to afford piperidine **14** as an oil which was purified by flash chromatography. Yield 191 mg, 59%. Colorless oil. $[\alpha]_D^{20}$ = +19.9 (*c* = 0.4, EtOAc). IR (film): $\tilde{\nu}$ = 1736, 1243, 1019, 752 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.5 Hz, 3 H), 1.05 (d, *J* = 6.5 Hz, 3 H), 1.15–1.40 (m, 22 H), 1.40–1.70 (m, 4 H), 1.95–2.10 (m, 1 H), 2.11 (s, 3 H), 2.52–2.61 (m, 1 H), 2.87 (q, *J* = 6.5 Hz, 1 H), 4.81 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 18.6 (CH_3), 21.3 (CH_3), 22.7 (CH_2), 25.9 (CH_2), 26.8 (CH_2), 29.3 (3 CH_2), 29.6 (4 CH_2), 29.7 (CH_2), 31.9 (CH_2), 37.0 (CH_2), 53.9 (CH), 56.6 (CH), 70.6 (CH), 171.1 (CO_2) ppm. $C_{20}H_{39}NO_2$ (325.53): calcd. C 73.79, H 12.08, N 4.30; found C 73.66, H 11.99, N 4.41.

(+)-Deoxocassine: A solution of **14** (299 mg, 0.92 mmol) in anhydrous THF (4 mL) was added dropwise to a suspension of $LiAlH_4$ (35.0 mg, 0.92 mmol) in THF (4 mL) at 0 °C. The mixture was stirred for 1 h at that temperature and then quenched by addition of 15% aqueous solution of NaOH. The mixture was filtered off and the solids washed with THF. The solvent was eliminated under vacuum and the residue purified by flash chromatography. Yield 227 mg, 87%. Colorless solid. M.p. 48–50 °C (from MeOH/Et_2O). $[\alpha]_D^{20}$ = +11.8 (*c* = 1.0, $CHCl_3$) [ref.[20] m.p. 47.5–48.5 °C, $[\alpha]_D^{20}$ = –12.3 (*c* = 0.19, $CHCl_3$) for (–)-deoxocassine]. IR (film): $\tilde{\nu}$ = 3126, 1466, 1018, 867 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.10 (d, *J* = 6.5 Hz, 3 H), 1.18–1.45 (m, 22 H), 1.45–1.65 (m, 4 H), 1.85–1.95 (m, 1 H), 2.43–2.68 (m, 2 H), 2.75 (q, *J* = 6.5 Hz, 1 H), 3.5 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 18.7 (CH_3), 22.6 (CH_2), 25.8 (CH_2), 26.1 (CH_2), 29.3 (CH_2), 29.6 (5 CH_2), 29.7 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 37.0 (CH_2), 55.7 (CH), 57.1 (CH), 67.9 (CH) ppm.

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