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Synthesis of Polyhydroxylated 6-N-Benzylpiperidin-2-Ones. A Novel Access to 1, 5-Dideoxy-1, 5-imino-D-xylitol

François-Didier Boyer [a] , Ange Pancrazi [b] & Jean-Yves Lallemand [b]

[a] INRA, Unité de Phytopharmacie et Médiateurs Chimiques, CNRA, route de Saint-Cyr, 78026, Versailles Cedex, France

[b] Laboratoire de Synthèse Organique, D.C.S.O. Ecole Polytechnique, 91128, Palaiseau Cedex, France

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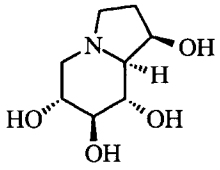
SYNTHESIS OF POLYHYDROXYLATED 6-*N*-BENZYLPIPERIDIN-2-ONES A NOVEL ACCESS TO 1, 5-DIDEOXY-1, 5-IMINO-D-XYLITOL

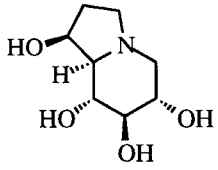
François-Didier Boyer[a], Ange Pancrazi[b], Jean-Yves Lallemand[b]*
[a]INRA, Unité de Phytopharmacie et Médiateurs Chimiques, CNRA,
route de Saint-Cyr, 78026 Versailles Cedex, France
[b]Laboratoire de Synthèse Organique, D.C.S.O.
Ecole Polytechnique, 91128 Palaiseau Cedex, France

Abstract *: The synthesis of polyhydroxylated 6-N-benzylpiperidin-2-ones is described from the corresponding N-benzylaminoglycoside. These compounds are easily reduced to the differently protected 1, 5-dideoxy-1, 5-imino-D-xylitol.*

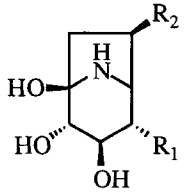
Calystegines (**1-3**) have been discovered[1] in the root secretions of *Calystegia sepium*, a member of the *Convolvulacae* and have been found to stimulate the growth of a nitrogen fixing bacterium, *Rhizobium meliloti 41* by serving as a source of carbon and nitrogen.



4
(-)-Castanospermine



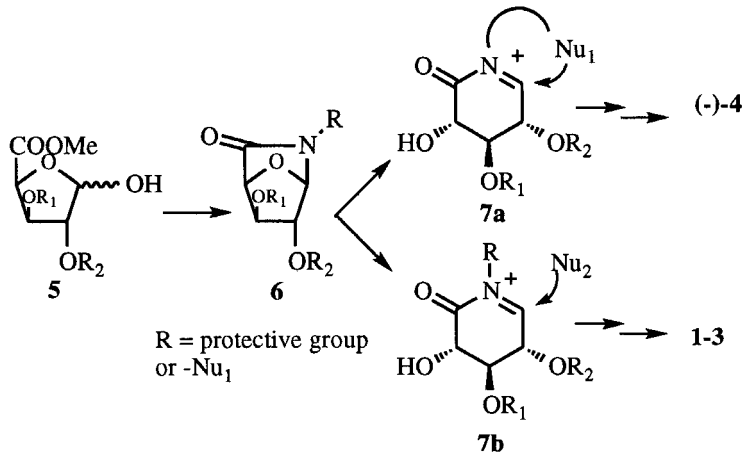
4
(+)-Castanospermine



Calystegines
A_3 **1** : $R_1 = R_2 = H$
B_2 **2** : $R_1 = OH$, $R_2 = H$
B_1 **3** : $R_1 = H$, $R_2 = OH$

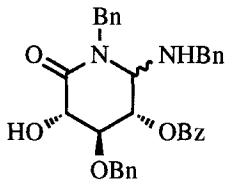
These compounds have been recently reported as displaying an inhibitory activity toward β-glucosidase and α-galactosidase[2]. (+)-Castanospermine **4** is a well known compound as a potent inhibitor of several glycosidases[3] and have also found use in anticancer, antiviral research[4].

Despite the great number of synthetic approaches toward natural (+)-castanospermine **4**[5] and some of its epimers, only one synthesis for (-)-**4** has been reported[6]. The published syntheses[7] of calystegines seemed difficult to generalize to other natural polyhydroxylated alkaloids. Due to their similar structures, our plan was to develop a same strategy for the synthesis of polyhydroxylated alkaloids, natural calystegines (**1-3**) and (-)-castanospermine **4**.

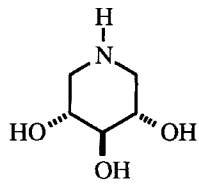


Scheme 1

This strategy is illustrated in scheme 1 and involved preparation of the alkylation initiator, *N*-acyliminium ion (**7a**, **7b**), from sugar-derived[8] bicyclic precursor **6**. Cyclisation of acyliminium ion **7a** by attack of an internal nucleophile could furnish the indolizidine skeleton of (-)-castanospermine. On the other hand, alkylation of acyliminium **7b** could initiate the preparation of the carbon chain, precursor of the five membered ring of calystegines. Our attemps to synthetize lactam **6** led us unexpectedly to obtain selectively protected polyhydroxylated 6-*N*-benzylpiperidin-2-one **8**. We show a novel access to 1, 5-dideoxy-1, 5-imino-D-xylitol **9**, an other inhibitor of β-glycosidases[9] from compound **8**.

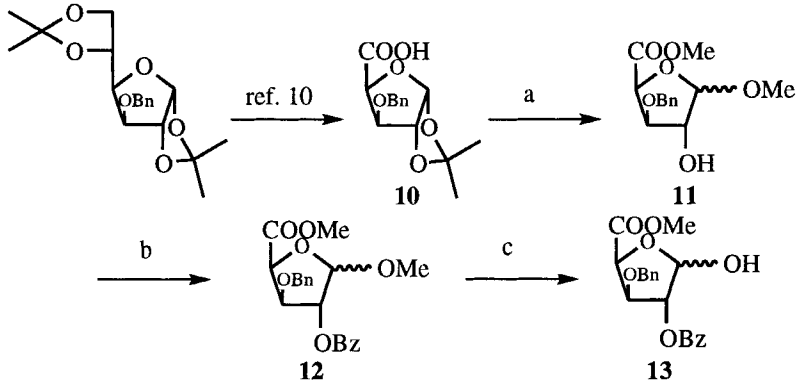


8



9

The starting material **10** was readily prepared by Dhalave's procedure[10] from diacetone-D-glucose. Acid **10** was converted to **11** with MeOH in presence of acid Amberlite resin (yield 71% over 5 steps from diacetone-D-glucose). After benzoylation of hydroxyl at C-2 position (BzCl, DMAP) the hydrolysis of the methoxy group at anomeric position was achieved in aqueous trifluoroacetic acid (36h) leading to **13** (scheme 2).

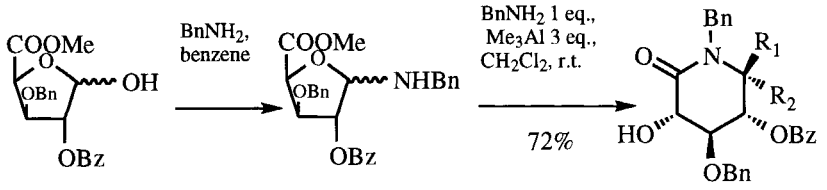


10 **11** **12** **13**

Scheme 2 : a) Amberlite IR 120-H, MeOH, reflux, 24h, b) BzCl, DMAP, CH_2Cl_2, 0°C, (97%), c) CF_3COOH, THF, H_2O, 48h, r.t. (66%).

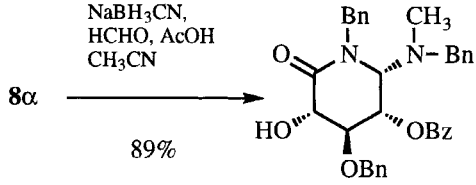
13 was reacted with benzylamine overnight to form the *N*-benzylaminoglycoside **14**. All attemps to form lactam **6** in acid or basic medium (AcOH, K_2CO_3 or PhMgBr) failed. On the contrary, treatment of this crude material with trimethylaluminium[11] with addition of one more equivalent of benzylamine furnished the piperidin-2-one **8** as a mixture of diastereoisomers (**8α/8β**) easily separated by chromatography on silica gel (scheme 3). Structure of **8** was assigned by NMR studies and confirmed by methylation[12] of secondary amine group to afford compound **15**.

A mechanism for the formation of **8** is proposed on scheme 4. Opening of the tetrahydrofuran ring by Me_3Al, formation of the aluminium amide derivatived



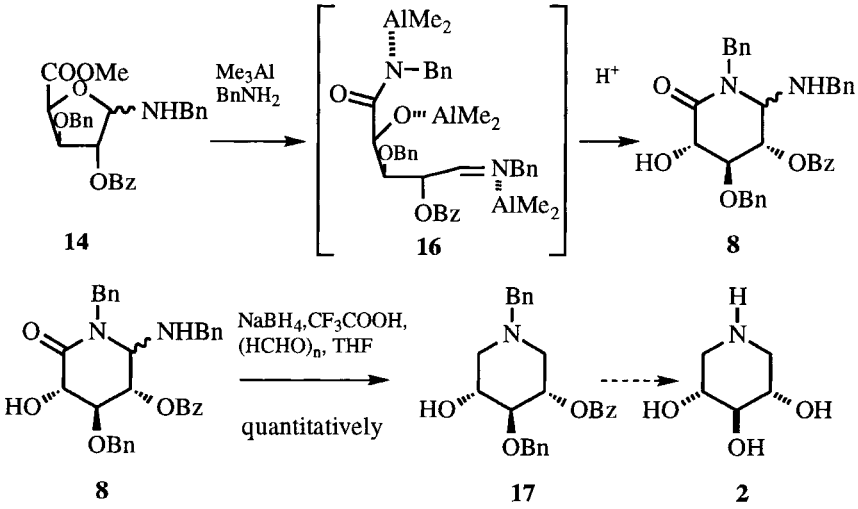
13 **14**

8α : 55% , R_1 = H, R_2 = NHBn
8β : 17% , R_1 = NHBn, R_2 = H



15

Scheme 3



14 **16** **8**

8 **17** **2**

Scheme 4

16 and intramolecular cyclisation on imine group could afford after acid hydrolysis the epimers **8**α and **8**β. Formation of acyliminium ion intermediate **7b** seems unlikely not to happen as reaction with other nucleophiles like thiophenol was unsuccessful. In addition it was found that one equivalent of benzylamine was necessary to bring the reaction to completion and consequently the lactam ring seems be formed from benzylamine present in the reaction mixture and not from *N*-benzyl group of the *N*-benzylglycoside **14**.

Diastereoisomers **8**α and **8**β were easily reduced by $NaBH_4$ in acid medium to yield quantitatively the selectively protected polyhydroxylated 1, 5-dideoxy-1, 5-imino-D-xylitol **17.**

Experimental

Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1-dm cell. IR spectra were recorded on a Perkin Elmer 1600 instrument. NMR spectra were recorded on Bruker WP 200 and AM 400 spectrometers. Chemical shifts are reported in δ ppm relative, in most cases, to $CHCl_3$ as internal reference (7.27 ppm for ^1H and 77.14 ppm for ^{13}C). Occasionnaly, Me_4Si (0.0 ppm for ^1H) was used as internal reference. Coupling constants (J) are given in Herzt (Hz). Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quadruplet) and m (multiplet) and br. (broad).

Methyl (methyl-3-*O*-benzyl-α, β-D-xylofuranoside) uronate 11.

The crude product **10** (16.5 g, 56 mmol) prepared by Dhalave's procedure[10] was dissolved in MeOH (200 mL) with Amberlite IR 120-H and the mixture refluxed for 24h. After cooling to room temperature, the mixture was filtered and evaporated under reduced pressure. The residue was purified by column chromatography (petroleum ether, AcOEt 1 : 1) to give **11** (15.6 g, 71% from diacetone-D-glucose, α/β = 66/33) as a colorless oil.
$[\alpha]_D$ = +35.4 (c = 1.1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) α major anomer δ(ppm) = 7.37-7.26 (m, 5H, Ar-H, 5.15 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1), 4.79 (d, 1H, $J_{3,4}$ = 6.0 Hz, H-4), 4.70 (AB, 2H, O-CH_2-Ph), 4.29 (br. t, 1H, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 4.3 Hz, H-2), 4.20 (dd, 1H, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 6.0 Hz, H-3), 3.74 (s, 3H,

OCH_3), 3.50 (s, 3H, CO_2CH_3), 2.85 (br. m, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) = 169.4 (C-5), 137.3 (arom.), 128.1; 127.5; 127.2 (arom.), 102.6 (C-1), 83.4 ; 77.3; 75.2 (C-2, C-3, C-4), 72.0 (O-CH_2-Ph)), 55.9 (O$\underline{C}H_3$), 51.8 ($CO_2\underline{C}H_3$). IR ($CDCl_3$) : 3468, 3087, 3065, 3030, 2991, 2950, 1756 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_6$: C : 59.56, H : 6.43. Found : C : 59.68, H : 6.42.

Methyl (methyl-2-*O*-benzoyl-3-*O*-benzyl-α, β-D-xylofuranoside) uronate 12.

To a solution of **11** (4.05 g, 10.5 mmol) in CH_2Cl_2 (30 mL) at 0°C was added DMAP (3.6 g, 21 mmol) and dropwise benzoylchloride (2.1 mL, 21 mmol). The resulting mixture was stirred at 0°C for 1h, at room temperature 1h and hydrolysed with aqueous $NaHCO_3$ (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure to afford the crude product. Chromatography provided pure **12** (4.1 g, 97%, α/β = 66/33) as a colorless oil.

^{13}C NMR (50 MHz, $CDCl_3$) α major anomer δ(ppm) = 170.1 (C-5), 167.3 (CO_2 (Bz)), 136.5; 133.7; 133.5; 129.9; 129.8; 128.9, 128.5, 127.9; 127.7 (arom.), 102.4 (C-1β), 96.1 (C-1α), 81.3 (2C), 79.2 (C-2, C-3, C-4 β), 80.6; 77.0; 76.5 (C-2, C-3, C-4 α), 72.8; 72.6 (O-CH_2-Ph α and β), 52.4; 52.1 ($CO_2\underline{C}H_3$). IR (film) : 3455, 3087, 3063, 3032, 3005, 2952, 2874, 1724 cm^{-1}.

Methyl (2-*O*-benzoyl-3-*O*-benzyl-α,β-D-xylofuranoside) uronate 13.

Compound **12** (14.58 g, 36.6 mmol) in THF (14 mL) was mixed with CF_3COOH (108 mL) at room temperature for 48h. The resulting mixture was basified with $NaHCO_3$ solid. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure leaving a crude product chromatographed to give **13** (9.38 g, 66%, α/β : 25/75) as a white solid.

$[\alpha]_D$ = +40.9 (c = 0.77, CH_2Cl_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) = 170.1 (C-5), 165.3 (CO_2 (Bz)), 136.5; 133.7; 133.5; 129.9; 129.8; 128.9, 128.5, 127.9; 127.7 (arom.), 102.4 (C-1β), 96.1 (C-1α), 81.3 (2C), 79.2 (C-2, C-3, C-4 β), 80.6; 77.0; 76.5 (C-2, C-3, C-4 α), 72.8; 72.6 (O-CH_2-Ph α and β), 52.4; 52.1 ($CO_2\underline{C}H_3$). IR (film) : 3455, 3087, 3063, 3032, 3005, 2952, 2874, 1724 (bl) cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6$: C : 64.51, H : 5.41. Found : C : 64.82, H : 5.51.

Methyl (*N*-benzyl-2-*O*-benzoyl-3-*O*-benzyl-α, β-D-xylofuranosylamine) uronate 14.

A mixture of **13** (0.947 g, 2.5 mmol), benzylamine (0.415 mL, 3.8 mmol) in dry benzene was stirred at room temperature overnight and evaporated under reduced pressure to give quantitatively the crude product **14** (1.2 g, α/β : 33/66) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) β major anomer δ(ppm) = 8.04-7.24 (m, 15H, Ar-H), 5.46 (s, 1H, H-1), 5.05 (s, 1H, H-2)), 4.89 (d, 1H, $J_{4,3}$ = 5.6 Hz, H-4), 4.75 (AB, 2H, J = 12.0 Hz, O-CH_2-Ph), 4.35 (d, 1H, $J_{4,3}$ = 5.6 Hz, H-3), 4.27 (d, 1H, J = 13.1 Hz, N-CH_2-Ph), 3.97 (d, 1H, J = 13.1 Hz, N-CH_2-Ph), 3.75 (s, 3H, CO_2Me), α minor anomer δ(ppm) = 5.46 (m, 2H, H-1, H-2), 4.87 (m, 2H, H-3, H-4), 4.75 (AB, 2H, J = 12.0 Hz, O-CH_2-Ph), 4.24 (d, 1H, J = 10.7 Hz, N-CH_2-Ph), 4.05 (d, 1H, J = 10.7 Hz, N-CH_2-Ph), 3.74 (s, 3H, CO_2Me). ^{13}C NMR (50 MHz, $CDCl_3$) β major anomer δ(ppm) = 170.0 (C-5), 165.5 (CO_2 (Bz)), 139.7; 133.6; 129.8; 129.3; 128.4; 127.9, 126.9 (arom.), 95.0 (C-1), 81.9, 80.1; 79.3 (C-2, C-3, C-4), 72.6 (CH_2 (O-CH_2-Ph)), 52.0 ($CO_2\underline{C}H_3$), 49.5 (CH_2 (N-CH_2Ph)). α minor anomer δ(ppm) = 91.4; 78.0; 75.9; 50.7. IR (film) : 3400, 3334, 3062, 3030, 2950, 1764, 1724, 1601 cm^{-1}.

***N*-Benzyl-(3S,4S,5S,6S)-5-benzoyloxy-4-benzyloxy-3-hydroxy-6-*N*-benzyl piperidin-2-one 8α.**

***N*-Benzyl-(3S,4S,5S,6R)-5-benzoyloxy-4-benzyloxy-3-hydroxy-6-*N*-benzyl piperidin-2-one 8β.**

To a mixture of crude product **14** (0.523 g, 1.09 mmol), and benzylamine (0.123 mL, 1.09 mmol) in CH_2Cl_2 (10 mL) was added dropwise at room temperature Me_3Al (1.6 mL, 3.2 mmol, 2 M solution in toluene). The resulting mixture was maintained at room temperature for 1h30 and carefully acidified with 1 M HCl to ca pH 2, stirred 30 min and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Flash chromatography (petroleum ether, AcOEt 80 : 20) gave pure **8α** (0.327 g, 55%) and **8β** (0.095 g, 17%) as colorless oils.

8α : $[\alpha]_D$ = -24.3 (c = 0.72 CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) = 7.68-6.98 (m, 20H, Ar-H), 5.34 (t, 1H, $J_{4,5}$ = 2.7 Hz, $J_{5,6}$ = 2.7 Hz, H-5), 5.04 (d, 1H, J = 14.4 Hz, N-CH_2-Ph), 4.85 (AB, 2H, J = 11.9 Hz, O-CH_2-Ph), 4.76 (d, 1H, $J_{3,4}$ = 6.9 Hz, H-3), 4.33 (dd, 1H, $J_{5,6}$ = 2.7 Hz, $J_{4,6}$ = 1.1 Hz, H-6), 4.10

(br. m, 1H, OH), 4.01 (d, 1H, J = 14.4 Hz, N-CH_2-Ph), 3.86 (m, 3H, H-4 and NH-CH_2-Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) = 171.1 (C-2), 165.2 (CO_2 (Bz)), 139.1, 137.8, 136.2 (arom.), 133.4; 129.9; 128.8; 128.7; 128.6; 128.5; 128.4; 128.0; 127.9; 127.7; 127.5 (arom.), 82.4 ; 72.5; 72.3 (C-4, C-5, C-6), 72.8 (O-CH_2-Ph), 71.2 (C-3), 50.3; 49.7 (CH_2 (N-CH_2-Ph)). IR (film) : 3424, 3354, 3087, 3061, 3028, 2918, 1721, 1643, 1602 cm^{-1}.

8β : ^1H NMR(400 MHz, $CDCl_3$) δ(ppm) = 7.96-7.16 (m, 20H, Ar-H, 7.02 (br. s, 1H, NH), 5.42 (dd, 1H, $J_{4,5}$ = 6.8 Hz, $J_{5,6}$ = 3.8 Hz, H-5), 5.12 (d, 1H, J = 14.7 Hz, N-CH_2-Ph), 4.87 (AB, 2H, J = 11.8 Hz, O-CH_2-Ph), 4.59 (d, 1H, $J_{5,6}$ = 3.8 Hz, H-6), 4.44 (dd, 1H, J = 14.7 Hz, N-CH_2-Ph), 4.32 (d, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 4.13 (t, 1H, $J_{3,4}$ = 6.8 Hz, $J_{4,5}$ = 6.8 Hz, H-4), 3.87 (d, 1H, OH), 3.78 (AB, 2H, NH-CH_2-Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) = 170.9 (C-2), 165.5 (CO_2 (Bz)), 139.1, 138.2, 137.4 (arom.), 133.6; 130.0; 129.5; 128.9; 128.8; 128.7; 128.4; 128.2; 127.7; 127.6 (arom.), 78.5; 73.5; 72.9 (C-4, C-5, C-6), 73.3 (O-CH_2-Ph) 69.8(C-3), 51.8 (NH-CH_2-Ph); 47.8 (N-CH_2-Ph).

_N_-Benzyl-(3S,4S,5S,6S)-5-benzoyloxy-4-benzyloxy-3-hydroxy-6-(_N_-benzyl,_N_-methyl) piperidin-2-one 15.

To a stirred mixture of **8α** (0.2 g, 0.37 mmol), and formaldehyde (0.4 mL, 37% aqueous solution) in CH_3CN (2 mL) was added in one portion sodium cyanoborohydride (0.095 g, 1 mmol) and dropwise AcOH (0.05 mL). The resulting mixture was stirred at room temperature for 1h and poured in Et_2O (15 mL). The organic layer was washed with 1 N NaOH, brine, dried (Na_2SO_4) and concentrated. Flash chromatography (petroleum ether, AcOEt 70 : 30) gave the pure product **15** (0.177 g, 86%) as a white solid (m.p. = 36-37°C, petroleum ether, AcOEt).

$[\alpha]_D$ = -1.5 (c = 0.59 CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ(ppm) = 8.06-7.21 (m, 20H, Ar-H), 5.81 (dd, 1H, $J_{4,5}$ = 7.3 Hz, $J_{5,6}$ = 5.1 Hz, H-5), 5.35 (d, 1H, J = 14.4 Hz, N-CH_2-Ph), 4.95 (AB, 2H, J = 11.7 Hz, O-CH_2-Ph), 4.73 (d, 1H, J = 11.7 Hz, O-CH_2-Ph), 4.60 (d, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 4.30 (d, 1H, J = 14.4 Hz, N-CH_2-Ph), 4.31 (d, 1H, $J_{5,6}$ = 5.1 Hz, H-6), 3.79 (dd, 1H, $J_{4,5}$ = 7.3 Hz, $J_{3,4}$ = 9.6 Hz, H-4), 3.74 (AB, 2H, J = 13.4 Hz, CH_3N-C$\underline{H}_2$-Ph), 2.37 (s, 3H, NCH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) = 171.2 (C-2), 165.2 (CO_2 (Bz)), 138.0, 137.7, 135.9 (arom.), 133.4; 129.8; 128.7; 128.5; 128.4; 128.1; 127.9; 127.6; 127.5; 127.3 (arom.), 79.7; 77.3; 71.0; 69.8 (C-3, C-4, C-5, C-6), 73.6 (O-CH_2-

Ph), 57.1 (CH_3N-$\underline{C}H_2$-Ph), 47.7 (N-CH_2-Ph), 35.4 (NCH_3). IR ($CDCl_3$) : 3460 , 3089, 3066, 3032, 2956, 2866, 1731 , 1662 cm^{-1}. Anal. Calcd for $C_{34}H_{34}N_2O_5$: C : 74.16, H : 6.22, N : 5.09. Found: C : 74.31, H : 6.13, N : 5.06.

_N_-Benzyl-(3S,4S,5R)-3-benzoyloxy-4-benzyloxy-5-hydroxy piperidine 17.

To a stirred mixture of **8α** (0.2 g, 0.37 mmol), paraformaldehyde (0.110 g, 3.6 mmol), $NaBH_4$ (0.072 g, 1.87 mmol) in THF (3.5 mL) was added dropwise CF_3COOH (1.75 mL). The resulting mixture was stirred at room temperature for five minutes and basified to pH = 11 with 5 N NaOH. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers dried and concentrated under reduced pressure. Flash chromatography (petroleum ether, AcOEt 80 : 20) gave the pure product **17** (0.177 g) quantitatively as a white solid m.p. = 80-81°C (petroleum ether, AcOEt).
$[\alpha]_D$ = +15.7 (c = 0.21 CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ(ppm) = 8.05-7.22 (m, 15H, Ar-H), 5.27 (ddd, 1H, $J_{2eq,\ 3}$ = 3.7 Hz, $J_{2ax,\ 3}$ = 8.2 Hz, $J_{3,\ 4}$ = 7.1 Hz, H-3), 4.81 (d, 1H, J = 11.6 Hz, H_a (O-CH_2-Ph)), 4.68 (d, 1H, J = 11.6 Hz, $H_{a'}$ (O-CH_2-Ph)), 3.83 (ddd, 1H, $J_{4,\ 5}$ = 7.1 Hz, $J_{5,\ 6eq}$ = 3.4 Hz, $J_{5,\ 6ax}$ = 10.4 Hz, H-5), 3.64 (d, 1H, J = 13.3 Hz, $H_{b'}$, N-CH_2-Ph), 3.58 (dd, 1H, $J_{3,\ 4}$ = 7.1 Hz, $J_{4,\ 5}$ = 7.1 Hz, H-4), 3.56 (d, 1H, J = 13.3 Hz, H_b, N-CH_2-Ph), 3.06 (dd, 1H, $J_{2ax,\ 2eq}$ = 11.2, $J_{2eq,\ 3}$ = 3.7 Hz, H-2eq), 2.94 (dd, 1H, $J_{5,\ 6eq}$ = 3.4 Hz, $J_{6ax,\ 6eq}$ = 10.4 Hz, H-6eq), 2.42 (dd, 1H, $J_{2ax,\ 3}$ = 8.2 Hz, $J_{2ax,\ 2eq}$ = 11.2 Hz, H-2ax), 2.32 (dd, 1H, $J_{5,\ 6ax}$ = 10.4 Hz, $J_{6ax,\ 6eq}$ = 10.4 Hz, H-6ax), ^{13}C NMR (50 MHz, $CDCl_3$) δ(ppm) = 165.6 (CO_2 (Bz)), 138.2, 137.5 (arom.), 133.1; 130.1; 129.6; 128.7; 128.5; 128.4; 127.6; 127.3 (arom.), 81.6 (C-3), 73.6 (O-CH_2-Ph), 72.0; 69.3 (C-4, C-5), 61.6; 56.3 (C-2, C-6), 54.5 (N-CH_2-Ph). IR ($CDCl_3$) : 3586, 3080, 3066, 3031, 2951, 2819, 1719 cm^{-1}. Anal. Calcd for $C_{26}H_{27}N_2O_4$: C : 74.80, H : 6.52, N : 3.36. Found : C : 74.88, H : 6.48, N : 3.34.

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