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Stereodivergent reduction of enelactams embedded in hexahydroindoles. Synthesis of *trans*-3-substituted-*cis*-3a-methyloctahydroindoles

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ABSTRACT

A stereodivergent synthesis of *cis*- and *trans*-octahydroindole derivatives from the ethylene acetal of methyl 1-benzyl-3a-methyl-2,5-dioxo-2,3,3a,5,6-hexahydro-1*H*-3-indoleacetate is reported. Under ionic reduction conditions the enamide group was reduced to afford a trans-ring fused product, while a hydrogenation process led to the formation of a cis-ring fused lactam, which was transformed into a building block for *daphniphyllum* alkaloid synthesis after an epimerization at C-3.

1. Introduction

As part of our research program[1] devoted to the synthesis of *daphniphyllum* alkaloids[2] that embody a *cis*-3a-methyloctahydroindole framework with a side chain at C-3 trans to the neighboring methyl group (Fig. 1),[3–6] we turned our attention to hexahydroindole derivatives of the enelactam type with the hope of achieving some valuable building blocks.

In this context, we decided to explore the usefulness of hexahydroindole derivatives coming from the reaction of cyclohexanone-derived imines with maleic anhydride, described by Pfau some years ago[7] and subsequently applied in several synthetic processes,[8–12] but to our knowledge never used to synthesize octahydroindole derivatives.

In this paper we report our results regarding the synthesis of octahydroindole **1** (Scheme 1), which involved: (i) the stereocontrolled reduction of the double bond of a hexahydroindole adduct coming from a Pfau reaction in order to achieve the cis relationship in the ring fusion required for *daphniphyllum* alkaloid synthesis and (ii) the inversion of the relative configuration of the azabicyclic derivative at C(3) to achieve the trans relationship between the neighboring substituents at C(3) and C(3a), as found in the aforementioned natural products.[13]

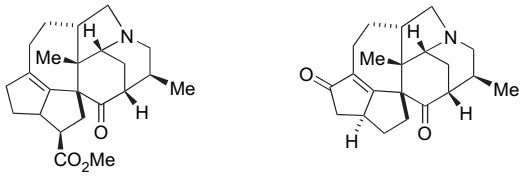
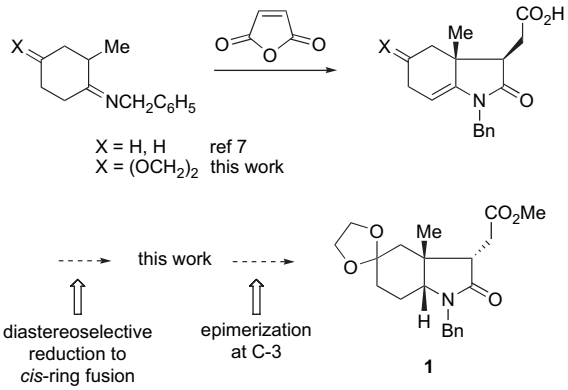


Figure 1. Structures of *daphniphyllum* alkaloids.



Scheme 1. Synthetic approach to *trans*-3-substituted-*cis*-3a-methyloctahydroindoles.

2. Results and discussion

The unknown 3a-methylhexahydroindol-5-one derivative **4** was prepared using the protocol reported by Pfau[7] (Scheme 2). Thus, ketone **2**[14] reacted with benzylamine and the resulting imine was treated with maleic anhydride to stereoselectively afford the adduct **3**, which on treatment with methyl iodide in basic medium gave the amido ester **4** required for our studies.[15] Stereochemistry of the acetate group in **4** was assigned to be cis to the neighboring methyl group, in agreement with related processes as well as NMR data (see below).

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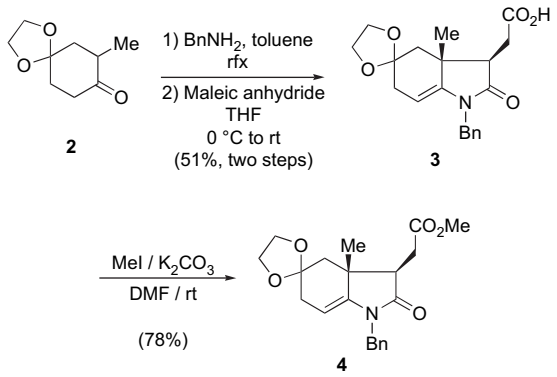


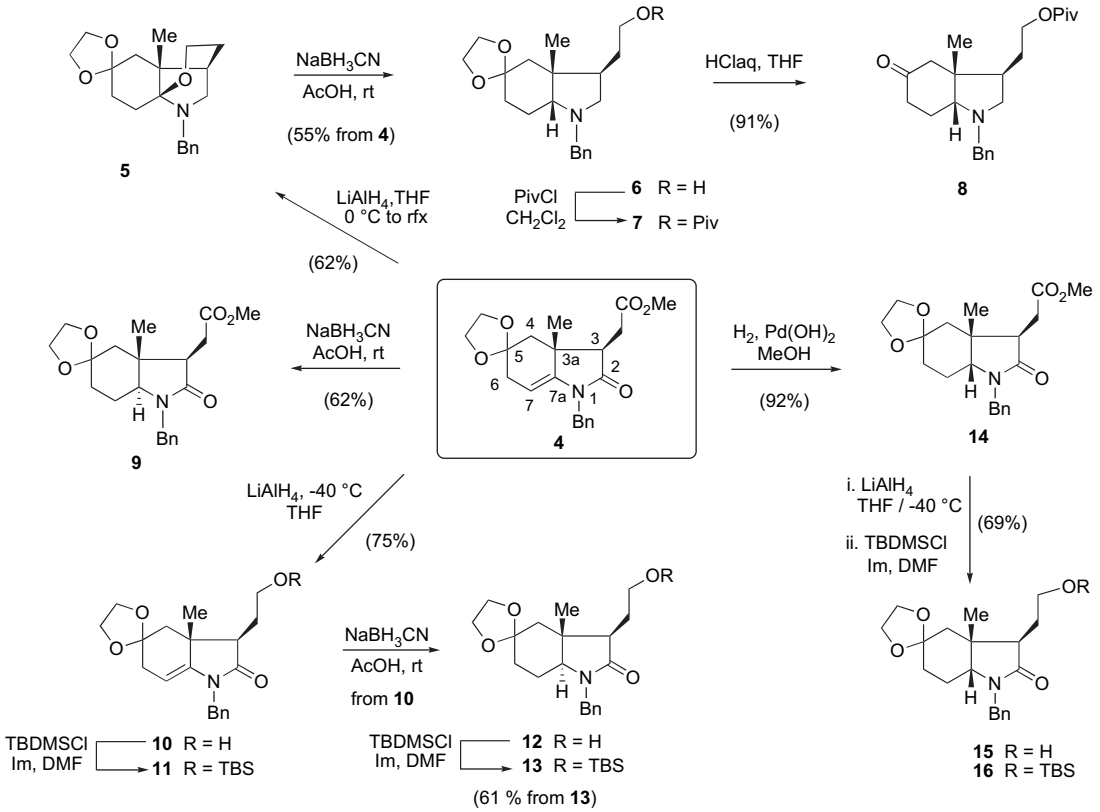
Scheme 2. Synthesis of hexahydroindole **4**.

2.1. Stereochemical and chemoselective course of the reduction of hexahydroindole 4

Our first goal, with the polyfunctionalized hexahydroindole **4** in hand, was its stereo- and chemoselective reduction. When the reduction of **4** was carried out with $LiAlH_4$ at reflux temperature, both the amide and ester group were reduced and the alkoxide generated in the reaction medium trapped the iminium salt, giving the hemiaminal **5**.[16] Further reduction of this masked iminium salt with $NaBH_3CN$ in acetic medium diastereoselectively gave the *cis*-octahydroindole **6**, in which the hydroxyl group was protected as the pivaloyl derivative (i.e., **7**), and the subsequent deprotection of the acetal group gave ketone **8**. Although the required cis-ring fused stereochemistry was achieved, the reduction of the ester and lactam would not allow the relative stereochemistry at C-3 to be corrected. We thus attempted to reduce the enamide by preserving the amide and/or ester group. When enamide **4** was treated directly with $NaBH_3CN$, under the same reaction conditions used for the reduction **5**→**6**, the *trans*-octahydroindole **9** was formed instead of a cis derivative. To check if the hydroxyethyl side chain had any influence on the cis-ring formation observed from **5**, alcohol **10** was prepared to study the stereochemical course of its double bond reduction. The ester group of lactam ester **4** was chemoselectively reduced to the alcohol **10**, which was characterized as its silyl ether **11**. Reduction of the double bond of enamide **10** using sodium cyanoborohydride gave the trans-ring fused derivative **12**.[17] Thus, the reduction of the acyliminium salt derived from **10** occurs on the opposite face to that of the reduction of the iminium salt derived from **5** (Scheme 3).

Gratifyingly, hydrogenation of **4** (H_2, $Pd(OH)_2$, MeOH)[18] diastereoselectively gave the *cis*-octahydroindole **14**. Further reduction with $LiAlH_4$ at −40 °C took place chemoselectively to give the amido alcohol **15**, which was protected as the silyl ether **16**. Thus, stereocomplementary reduction processes of enelactam **4** were observed, hydrogenation giving the cis-ring fused lactam **14** and an ionic reduction leading to the trans-ring fused lactam **9**. Interestingly, the observed stereoselectivity was the reverse of that reported in the reduction of a related 6,6-membered ring homoenelactam.[19]

In order to understand these stereoselectivity changes in the reduction of the enelactam double bond (some reduction processes gave the cis derivatives **6** and **14**, but others provided the trans derivatives **9** and **12**), we considered that: (i) the stereochemical outcome of the catalytic hydrogenation of **4** could be explained by a late transition state in which the substrate adopts a conformation resembling the end-product, with the acetal group on the bottom face and the methyl group in a pseudoequatorial disposition. This would allow the Pd-catalyst to approach the more accessible top face, thus directing the hydrogen transfer to give a cis-ring fused



Scheme 3. Reduction of hexahydroindole **4** to *cis*- and *trans*-octahydroindoles.

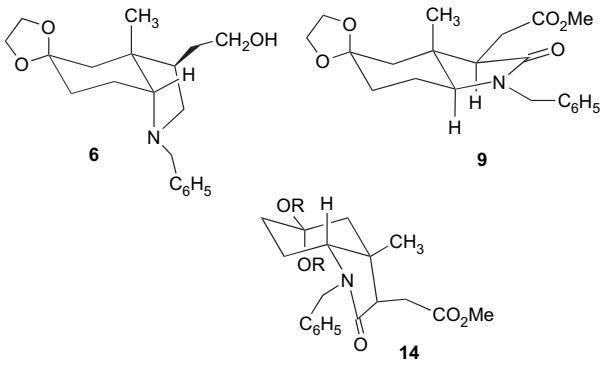


Figure 2. Preferred conformation of octahydroindoles **6**, **9**, and **14**.

lactam[20] (i.e., **14**, see Fig. 2); (ii) the reactive intermediate for the reduction of **4** using $NaBH_3CN$ in acid medium might be an acyliminium ion, which undergoes a hydride axial attack in a late transition state resembling the final trans-fused compound **9**;[21] (iii) on the contrary, the iminium salt coming from the hemiaminal **5** probably has a different preferred conformation[22] that allows a pseudoequatorial delivery of the hydride to give the cis-fused octahydroindole **6**.

The stereochemistry of the synthesized azabicyclic compounds was elucidated by 2D NMR spectra (COSY, HSQC). The ^{13}C NMR chemical shifts of carbons C-3, C-3a, and C-7a are shielded in *cis*-lactams (**14** and **16**) in comparison with those of trans derivatives (**9** and **13**) (see Table 1). The signal corresponding to the methyl group linked to the quaternary carbon C-3a is diagnostic since it appears at δ 13.8 in the trans series and at δ 23.5 in the cis series. In ^1H NMR spectra, the cis stereochemistry and its preferred conformation[23] for amine compounds **6**–**8** were apparent from the 7a-methine proton multiplicity since this appeared as a triplet (J=3.6–4.4 Hz), which is consistent only with an equatorial disposition of H-7a with respect to the cyclohexane ring (Fig. 2). On the contrary, the cis derivatives **14** and **16**, embodying a lactam group, showed a different preferred conformation, having the H-7a axially located (J=9.2–9.4, 4.2–4.5 Hz) and the methyl group (δ 0.89) in an equatorial disposition with respect to the carbocyclic ring.

2.2. The epimerization question

Attempts to induce the epimerization of lactam **15** at C(3) under basic conditions failed, the starting material being recovered when LDA was used as the base in a THF solution at −78 °C. We then turned our attention to the formation of the ester enolate from **14** with the aim of changing the configuration of its β-position. Thus, phenylselanyl derivative **17** (4:1 mixture of epimers) was obtained by treating ester **14** with LHMDS and trapping the formed enolate with PhSeCl. Oxidation of **17** with H_2O_2 furnished a 3:1 *Z*/*E* mixture of α,β-unsaturated derivatives **18**, which was diastereoselectively reduced through hydrogenation to give the diastereoisomerically homogeneous lactam **1**. Interestingly, lactam **1** showed a different conformational preference to that of its C-3 epimer **14**, as is evidenced by the multiplicity of H-7a in their NMR spectra (Scheme 4).

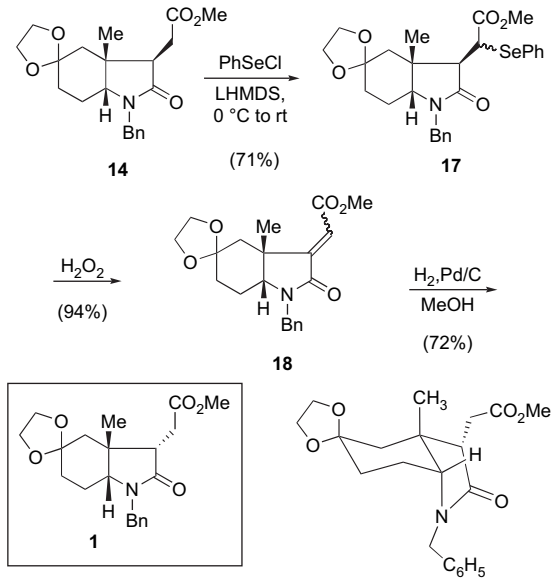
In summary, reduction of hexahydroindole **4** can be controlled by an appropriate choice of reducing agent, leading to either *cis*- or *trans*-octahydroindoles with absolute diastereoselectivity. In this way, and after an epimerization process, the polyfunctionalized octahydroindole **1**, a possible valuable building block for *daphniphyllum* alkaloid synthesis, was achieved.

Table 1
^{13}C NMR data for octahydroindol-5-one derivatives

	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	NCH_2	Me	CH_2	Other
1	175.8	52.2	41.1	37.0	107.8	28.6	20.3	59.3	44.0	22.1	28.8	[a]
3	175.3	50.4	41.2	42.5	108.1	35.1	96.5	143.6	43.9	20.4	30.1	[b]
4	174.3	50.8	43.7	40.9	108.2	35.1	95.6	143.9	42.8	20.5	29.5	[c]
5	55.0	40.6	44.8	40.4	109.1	25.1	32.0	94.2	50.0	16.9	27.1	[d]
6	58.2	41.4	43.1	43.5	109.3	29.6	22.5	67.5	58.0	21.8	33.3	[e]
7	58.4	42.6	43.4	43.8	109.3	29.5	22.2	67.5	57.8	21.4	29.5	[f]
8	57.0	44.2	43.7	50.6	213.1	34.2	23.8	69.2	58.4	24.0	26.9	[g]
9	176.1	52.2	43.4	42.1	108.3	34.6	20.4	64.1	44.6	13.8	29.4	[h]
10	177.1	55.8	41.4	42.4	108.2	35.1	95.7	144.4	43.8	20.6	27.5	[i]
11	176.2	50.5	41.0	43.0	108.5	35.0	94.5	144.7	43.5	20.6	28.0	[j]
13	178.1	52.0	42.1	43.7	108.6	34.6	20.5	64.3	44.5	13.7	28.2	[k]
14	174.4	45.5	40.4	40.8	107.6	31.0	24.3	60.4	44.5	23.5	30.0	[l]
16	176.0	44.9	40.6	40.8	107.8	30.9	24.1	60.2	44.2	23.5	28.4	[m]
17	172.9	42.8	42.1	25.1	107.7	31.8	41.7	61.1	44.7	23.7	48.1	[n]
(*Z*)18	166.0	153.7	41.1	23.0	108.2	29.3	38.3	61.2	45.0	24.8	120.1	[o]
(*E*)18	166.0	148.1	41.7	22.5	107.4	29.1	41.3	59.7	44.4	23.9	119.8	[p]

All spectra were recorded in $CDCl_3$ (at 100 MHz,[a] 75 MHz[b] or 50 MHz[c]) and the assignments were aided by gHSQC experiments for compounds **1**, **5**, **7**, **8**, and **11**–**13**, and DEPT in all cases.

[a] 51.5, 173.2 (CO_2Me); 63.8, 64.6 (OCH_2).
[b] 63.7, 64.4 (OCH_2); 127.2, 127.5, 128.6, 135.7 (Ar); 175.7 (CO_2H).
[c] 51.9, 172.6 (CO_2Me); 63.7, 64.4 (OCH_2); 127.2, 127.3, 128.5, 136.1 (Ar).
[d] 60.2 (CH_2OR); 63.4, 64.3 (OCH_2); 126.4, 127.6, 128.3, 140.2 (Ar).
[e] 61.6 (CH_2OH); 63.8, 63.9 (OCH_2); 126.8, 128.1, 128.4, 139.5 (Ar).
[f] 27.2 $(CH_3)_3$; 38.6 (C); 63.6, 63.7 (OCH_2); 64.0 (CH_2OPiv); 126.6, 128.1, 128.4, 139.9 (Ar); 178.5 (CO).
[g] 27.1 $(CH_3)_3$; 38.6 (C); 63.7 (CH_2OPiv); 126.9, 128.2, 128.5, 139.1 (Ar); 178.4 (CO).
[h] 51.8, 172.9 (CO_2Me); 63.6, 64.6 (OCH_2); 127.6, 128.1, 128.5, 137.3 (Ar).
[i] 62.1 (CH_2OH); 63.7, 64.5 (OCH_2); 127.3, 127.4, 128.6, 136.0 (Ar).
[j] −5.4, −5.3, 18.2, 25.9 (TBDMS); 61.2 (CH_2OSi); 63.7, 64.4 (OCH_2); 127.2, 127.3, 128.5, 136.5 (Ar).
[k] −5.3, −5.2, 18.3, 27.0 (TBDMS); 61.4 (CH_2OSi); 63.6, 64.6 (OCH_2); 127.2, 127.6, 128.5, 137.6 (Ar).
[l] 51.8, 173.0 (CO_2Me); 64.0, 64.4 (OCH_2); 127.6, 128.3, 128.6, 136.5 (Ar).
[m] −5.3, −5.2, 18.4, 26.0 (TBDMS); 62.1 (CH_2OSi); 63.9, 64.3 (OCH_2); 127.5, 128.3, 128.6, 136.9 (Ar).
[n] 52.0, 172.5 (CO_2Me); 64.1, 64.5 (OCH_2); 127.6, 128.5, 128.6, 128.7, 129.1, 135.0, 136.2 (Ar).
[o] 51.7, 167.3 (CO_2Me); 64.0, 64.1 (OCH_2); 127.8, 128.1, 128.8, 135.9 (Ar).
[p] 52.3, 167.4 (CO_2Me); 64.0, 64.3 (OCH_2); 127.6, 128.1, 128.7, 136.1 (Ar).



Scheme 4. The epimerization at C(3): from **14** to its epimer **1**.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) and the spots were located with iodoplatinate reagent or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. IR spectra were carried out in a Nicolet Avatar 320 FT-IR apparatus. ^1H and ^{13}C NMR spectra were recorded either on a Varian Gemini 300 or using a Varian Mercury 400 instrument. Chemical shifts are reported in parts per million downfield (δ) from Me_4Si.

3.1.1. (3RS,3aRS)-1′-Benzyl-3a′-methyl-2′-oxo-1′,2′,3′,3a′,4′,6′-hexahydrospiro[1,3-dioxolane-2,5′-[5H]indole]-3′-acetic acid ***3***

The title compound was prepared according to Pfau's method. A solution of 2-methyl-1,4-cyclohexanedione monoethylene acetal (**2**, 6.3 g, 37.0 mmol) and benzylamine (4.4 mL, 4.36 g, 40.7 mmol) in toluene (37 mL) was refluxed overnight with a Dean–Stark apparatus. The solvent was then evaporated and the crude imine was dissolved in THF (30 mL). To this cooled solution (0 °C) maleic anhydride (4 g, 40.7 mmol) in THF (37 mL) was added. The reaction was allowed to warm to rt and stirred for 2 h. The reaction mixture was concentrated and the residue was partitioned between H_2O and Et_2O. The organic layers were separated and the aqueous phase was then acidified with 2 N HCl and extracted with ether. The combined organic extracts were dried, filtered, and concentrated to yield acid **3** as a yellow solid, which was used for the next step without further purification (51% yield for two steps). ^1H NMR (300 MHz, $CDCl_3$, COSY) 1.14 (s, 3H, Me), 1.89 and 2.03 (2d, J=13.4 Hz, 1H each, H-4), 2.38–2.55 (m, 3H, H-3 and H-6), 2.79–2.93 (m, 2H, CH_2), 3.86–4.02 (m, 4H, OCH_2), 4.50 and 4.81 (2d, J=15.5 Hz, 1H each, CH_2Ph), 4.84 (t, J=3.9 Hz, 1H, H-7), 7.18–7.35 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

3.1.2. (3RS,3aRS)-1′-Benzyl-3′-(methoxycarbonyl)methyl-3a′-methyl-2′-oxo-1′,2′,3′,3a′,4′,6′-hexahydrospiro-[1,3-dioxolane-2,5′-[5H]indole] ***4***

Iodomethane (0.87 mL, 1.98 g, 14.0 mmol) was slowly added to a mixture of acid **3** (2 g, 5.6 mmol) and K_2CO_3 (1.55 g, 11.2 mmol) in DMF (28 mL) at rt. The reaction mixture was stirred for 2 h and extracted with Et_2O. The organic layers were dried, filtered, and concentrated. After purification by chromatography (hexane/EtOAc 2:1 to 1:1), compound **4** (1.62 g, 78% yield) was obtained as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) 1.14 (s, 3H, Me), 1.92 and 1.99 (2d, J=13.6 Hz, 1H each, H-4), 2.41–2.50 (m, 3H, CH_2 and H-6), 2.89–2.98 (m, 2H, CH_2 and H-3), 3.73 (s, 3H, OMe), 3.85–3.97 (m, 4H, OCH_2), 4.47 and 4.79 (d, J=15.4 Hz, 1H each, CH_2Ph), 4.75 (t, J=3.9 Hz, 1H, H-7), 7.18–7.32 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1. HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO_5$: 372.1805 (M^++1), found: 372.1801.

3.1.3. (4RS,4aRS,8aSR)-9-Benzyl-4a-methyl-3,4,4a,8,8a-hexahydro-8a,3-(iminomethano)-2H-chromen-6(7H)-one ethylene acetal ***5***

To a well-stirred suspension of $LiAlH_4$ (80 mg, 2.07 mmol) in THF (3 mL) at 0 °C was added a solution of enamide **4** (0.22 g, 0.59 mmol) in THF (3 mL). The resulting solution was refluxed for 2 h, quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate, dried, and concentrated to give a yellow oil that was used in the next step without further purification. An analytical sample could be obtained by chromatography (CH_2Cl_2/MeOH 95:5) to yield **5** (120 mg, 62% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, gCOSY)—the numbering of the indole nucleus is maintained—1.20 (m, 1H, CH_2), 1.30 (s, 3H, Me), 1.41 (dd, J=13.4, 2.4 Hz, 1H, H-4), 1.56 (ddd, J=12.6, 5.6, 2.9 Hz, 1H, H-7), 1.69–1.73 (m, 2H, H-6), 1.88 (d, J=12.6 Hz, H-4), 1.88–1.94 (m, 2H, H-3 and H-7), 2.20 (m, 1H, CH_2), 2.52 (d, J=9.4 Hz, 1H, H-2), 3.47 (ddd, J=9.6, 4.6, 1.5 Hz, 1H, H-2), 3.63 (td, J=12.0, 5.2 Hz, 1H, CH_2O), 3.78 (d, J=15 Hz, 1H, CH_2Ph), 3.80–3.88 (m, 3H, OCH_2), 3.97–4.01 (m, 2H, OCH_2), 4.22 (d, J=15 Hz, 1H, CH_2Ph), 7.19–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, gHSQC), see Table 1.

3.1.4. (3RS,3aRS,7aRS)-1′-Benzyl-3′-(2-hydroxyethyl)-3a′-methyloctahydrospiro[1,3-dioxolane-2,5′-[5H]indole] ***6***

To a solution of the above crude **5** (0.59 mmol) in acetic acid (6 mL) was added portionwise sodium cyanoborohydride (0.15 g, 0.237 mmol) and the resulting solution was stirred overnight at rt. The reaction was quenched by careful addition of saturated aqueous solution of Na_2CO_3 and extracted with ethyl acetate. The organic phase was dried, filtered, concentrated, and purified by chromatography (CH_2Cl_2/MeOH 98:2 to 95:5) to afford **6** (106 mg, 55% yield from **4**) as a colorless oil. IR (NaCl, neat) 3420, 2934, 2786, 1493, 1452, 1360, 1221, 1100, 1052, 983, 949, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, gCOSY) 1.04 (s, 3H, Me), 1.25–1.50 (m, 2H, H-7), 1.51 (dd, J=13.9, 1.4 Hz, 1H, H-4), 1.64–1.80 (m, 4H, H-3, H-6, and CH_2), 1.82 (d, J=14.1 Hz, 1H, H-4), 1.91–2.07 (m, 2H, H-2 and CH_2), 2.34 (t, J=4.4 Hz, 1H, H-7a), 3.11 (dd, J=8.7, 7.1 Hz, 1H, H-2), 3.30 (d, J=13.3 Hz, 1H, CH_2Ph), 3.47–3.65 (m, 2H, CH_2OH), 3.88–3.93 (m, 4H, OCH_2), 3.97 (d, J=13.4 Hz, 1H, CH_2Ph), 7.20–7.35 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

3.1.5. (3RS,3aRS,7aRS)-1′-Benzyl-3′-[2-(tert-butoxy-carbonyloxy)ethyl]-3a′-methyloctahydrospiro-[1,3-dioxolane-2,5′-[5H]indole] ***7***

To a solution of alcohol **6** (90 mg, 0.266 mmol) and triethylamine (0.08 mL, 0.055 g, 0.543 mmol) in CH_2Cl_2 (2.7 mL) at rt was added trimethylacetyl chloride (0.05 mL, 0.048 g, 0.40 mmol) and the reaction mixture was stirred for 2 h at rt. Water was added and the solution was extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The residue was purified by chromatography (hexane/EtOAc 4:1 to 2:1) to yield **7** (65 mg, 58% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$, gCOSY) 1.05 (s, 3H, Me), 1.15 (s, 9H, $C(CH_3)_3$), 1.19–1.50 (m, 2H, H-6), 1.46 (d, J=13.6 Hz, 1H, H-4), 1.68–1.86 (m, 4H, H-3, H-7 and CH_2), 1.82 (d, J=14.1 Hz, 1H, H-4), 1.90–1.99 (m, 2H, H-2 and CH_2),

2.24 (t, J=3.6 Hz, 1H, H-7a), 3.11 (t, J=8.5 Hz, 1H, H-2), 3.19 (d, J=13.3 Hz, 1H, CH_2Ph), 3.88–4.00 (m, 7H, CH_2OPiv, OCH_2, and CH_2Ph), 7.18–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1.

3.1.6. (3RS,3aRS,7aRS)-1-Benzyl-3-[2-(tert-butoxycarbonyloxy)-ethyl]-3a-methyloctahydroindol-5-one **8**

To a solution of acetal **7** (65 mg, 0.156 mmol) in THF (1.8 mL) was added 10% aqueous HCl (2.5 mL). After being stirred overnight, the mixture was basified with saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The organic extracts were dried, concentrated, and the residue was purified by chromatography (hexane/EtOAc 4:1 to 2:1) to afford ketone **8** (53 mg, 91% yield) as a yellow oil. IR (NaCl, cm^{-1}): 2959, 2794, 1723, 1478, 1455, 1398, 1370, 1284, 1243, 1157; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 0.95 (s, 3H, Me), 1.11 (s, 9H, $C(CH_3)_3$), 1.45 (m, 1H, CH_2), 1.60–1.72 (m, 2H, H-3 and CH_2), 1.84–1.98 (m, 3H, H-2 and H-7), 2.16 (dm, J=18 Hz, 1H, H-6eq), 2.19 (d, J=14.7 Hz, 1H, H-4), 2.33 (d, J=14.7 Hz, 1H, H-4), 2.45 (t, J=3.7 Hz, 1H, H-7a), 2.55 (ddd, J=18.2, 11.4, 5.4 Hz, 1H, H-6ax), 2.97 (dd, J=8.9, 5.7 Hz, 1H, H-2), 3.25 (d, J=13.1 Hz, 1H, CH_2Ph), 3.92–3.97 (m, 3H, CH_2OPiv and CH_2Ph), 7.25–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, gHSQC), see Table 1. HRMS (ESI-TOF) calcd for $C_{23}H_{34}NO_3$: 372.2533 (M^++1), found: 372.2535.

3.1.7. (3RS,3aRS,7aSR)-1′-Benzyl-3′-(methoxycarbonyl)methyl-3a′-methyl-2′-oxo-octahydrospiro[1,3-dioxolane-2,5′-[5H]indole] **9**

Sodium cyanoborohydride (0.34 g, 5.38 mmol) was added portionwise to a solution of enamide **4** (0.5 g, 1.34 mmol) in acetic acid (13 mL) and the resulting solution was stirred overnight at rt. The reaction was then quenched by careful addition of saturated aqueous solution of Na_2CO_3 and extracted with ethyl acetate. The organic phase was dried, filtered, concentrated, and purified by chromatography (hexane/EtOAc 4:1 to 2:1) to afford **9** (308 mg, 62% yield) as a yellow oil. IR (NaCl, cm^{-1}) 2950, 1737, 1693, 1434, 1296, 1258, 1166, 1069; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 0.94 (s, 3H, Me), 1.43–1.61 (m, 2H, H-6 and H-7), 1.69–1.87 (m, 4H, H-4, H-6, and H-7), 2.36 (dd, J=16.2, 8.4 Hz, 1H, CH_2), 2.69 (dd, J=8.5, 5.6 Hz, 1H, H-3), 2.86 (d, J=16.2 and 5.6 Hz, 1H, CH_2), 3.12 (dd, J=12.1, 3.3 Hz, 1H, H-7a), 3.71 (s, 3H, CO_2Me), 3.78–3.96 (m, 4H, OCH_2), 4.32 and 4.57 (2d, J=15.2 Hz, 1H each, CH_2Ph), 7.18–7.33 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRMS (ESI-TOF) calcd for $C_{21}H_{28}NO_5$: 374.1961 (M^++1), found: 374.1963.

3.1.8. (3RS,3aRS)-1′-Benzyl-3′-(2-hydroxyethyl)-3a′-methyl-2′-oxo-1′,2′,3′,3a′,4′,6′-hexahydrospiro[1,3-dioxolane-2,5′-[5H]indole] **10**

To a well-stirred suspension of $LiAlH_4$ (0.04 g, 1.08 mmol) in anhydrous THF (3 mL) at −40 °C was added a solution of ester **4** (0.20 g, 0.54 mmol) in THF (2.5 mL). The resulting solution was stirred for 4 h at −40 °C, quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, dried, and concentrated. The residue was purified by chromatography (hexane/EtOAc 1:1 to 1:3) to afford alcohol **10** (140 mg, 75% yield) as a yellow oil. IR (NaCl, cm^{-1}) 3398, 3030, 2919, 1720, 1677, 1406, 1149, 1079, 1047; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 1.15 (s, 3H, Me), 1.71 (ddd, J=14.2, 8.3, 3.7 Hz, 1H, CH_2), 1.83 (d, J=13.3 Hz, 1H, H-4), 1.95 (m, 1H, CH_2), 2.02 (d, J=13.3 Hz, 1H, H-4), 2.42 (d, J=3.8 Hz, 2H, H-6), 2.46 (dd, J=9.9, 3.7 Hz, 1H, H-3), 3.72 (dt, J=10.8, 2.9 Hz, 1H, CH_2OH), 3.86–3.99 (m, 5H, OCH_2 and CH_2OH), 4.49 (d, J=15.4 Hz, 1H, CH_2Ph), 4.76 (t, J=3.9 Hz, 1H, H-7), 4.79 (d, J=15.4 Hz, 1H, CH_2Ph), 7.19–7.32 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRMS (ESI-TOF) calcd for $C_{20}H_{26}NO_4$: 344.1856 (M^++1), found: 344.1855.

3.1.9. (3RS,3aRS)-1′-Benzyl-3′-[2-(tert-butyldimethylsilanyloxy)-ethyl]-3a′-methyl-2′-oxo-1′,2′,3′,3a′,4′,6′-hexahydrospiro-[1,3-dioxolane-2,5′-[5H]indole] **11**

To a solution of alcohol **10** (0.14 g, 0.40 mmol) in DMF (1 mL) at rt were added imidazole (0.055 g, 0.80 mmol) and *tert*-butyldimethylchlorosilane (0.09 g, 0.60 mmol). After having been stirred overnight at rt, water was added, the mixture was extracted with Et_2O, and the organic phase washed with brine and water. The organic extracts were dried and concentrated and the residue was purified by chromatography (hexane/EtOAc 4:1) to afford compound **11** (126 mg, 69% yield) as a yellow oil. IR (NaCl, cm^{-1}) 2929, 2857, 1723, 1684, 1402, 1360, 1304, 1254, 1098, 836; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 0.07 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.14 (s, 3H, Me), 1.75–1.60 (m, 1H, CH_2), 1.85 (d, J=13.4 Hz, 1H, H-4), 2.05 (d, J=13.4 Hz, 1H, H-4), 2.03–2.11 (m, 1H, CH_2), 2.40 (d, J=4.0 Hz, 2H, H-6), 2.49 (t, J=6.9 Hz, 1H, H-3), 3.76–4.00 (m, 6H, OCH_2 and CH_2OSiR), 4.46 (d, J=15.4 Hz, 1H, CH_2Ph,), 4.69 (t, J=3.9 Hz, 1H, H-7), 4.78 (d, J=15.4 Hz, 1H, CH_2Ph), 7.19–7.31 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT), See Table 1. HRMS (ESI-TOF) calcd for $C_{26}H_{40}NO_4Si$: 458.2721 (M^++1), found: 458.2721.

3.1.10. (3RS,3aRS,7aSR)-1′-Benzyl-3′-[2-(tert-butyldimethyl-silyloxy)]ethyl-3a′-methyl-2′-oxo-octahydrospiro-[1,3-dioxolane-2,5′-[5H]indole] **13**

A solution of alcohol **10** (0.1 g, 0.29 mmol) in glacial acetic acid (3 mL) was treated with $NaBH_3CN$ (0.036 g, 0.58 mmol). After being stirred overnight at rt, the reaction was quenched by careful addition of saturated aqueous solution of Na_2CO_3 and extracted with ethyl acetate. The organic phase was dried, filtered, and concentrated. The crude amine **12** was then dissolved in DMF (0.6 mL) and imidazole (0.040 g, 0.58 mmol) and *tert*-butyldimethylchlorosilane (0.66 g, 0.44 mmol) were added to the solution. After stirring overnight at rt, water was added, the mixture was extracted with Et_2O, and the organic phase washed with brine and water. The organic extracts were dried and concentrated and the residue was purified by chromatography (hexane/EtOAc 4:1) to afford compound **13** (81 mg, 61% yield from **10**) as a yellow oil. IR (NaCl, cm^{-1}) 2929, 2855, 1693, 1433, 1402, 1358, 1254, 1099, 945, 836, 776, 700; ^1H NMR (300 MHz, $CDCl_3$) 0.06 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 3H, Me), 1.50–1.72 (m, 4H, H-4 and H-6), 1.80–2.05 (m, 4H, H-7 and CH_2), 2.18 (t, J=6.7 Hz, 1H, H-3), 3.04 (dd, J=12.0, 3.3 Hz, 1H, H-7a), 3.73–3.89 (m, 6H, OCH_2 and CH_2OSi), 4.31 and 4.57 (2d, J=15.2 Hz, 1H each, CH_2Ph), 7.11–7.26 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1. HRMS (ESI-TOF) calcd for $C_{26}H_{42}NO_4Si$: 460.2877 (M^++1), found: 460.2886.

3.1.11. (3RS,3aRS,7aRS)-1′-Benzyl-3′-(methoxycarbonyl)methyl-3a′-methyl-2′-oxo-octahydrospiro[1,3-dioxolane-2,5′-[5H]indole] **14**

To a solution of enamide **4** (0.27 g, 0.73 mmol) in MeOH (7.3 mL) was added $Pd(OH)_2$ (0.18 g). The resulting suspension was stirred at rt under a H_2 atmosphere (1 atm) until the starting material was completely consumed. The reaction mixture was then filtered over Celite, washed with ethyl acetate, and concentrated. The residue was purified by chromatography (hexane/EtOAc 4:1) to afford compound **14** (250 mg, 92% yield) as a yellow oil. IR (NaCl, cm^{-1}) 2948, 1738, 1687, 1434, 1269, 1165, 1165, 1113, 1062; ^1H NMR (400 MHz, $CDCl_3$, gCOSY) 0.89 (s, 3H, Me), 1.45 (d, J=14.5 Hz, 1H, H-4), 1.46 (td, J=14, 4 Hz, 1H, H-6ax), 1.63 (dm, J=13.5 Hz, H-6eq), 1.70 (m, 1H, H-7), 1.80 (dd, J=14.5, 1.9 Hz, 1H, H-4), 1.93 (m, 1H, H-7), 2.31 (dd, J=15.6, 7.6 Hz, 1H, CH_2CO_2Me), 2.67 (dd, J=15.6, 6.9 Hz, 1H, CH_2CO_2Me), 2.90 (dd, J=9.2, 4.5 Hz, 1H, H-7a), 3.43 (t, J=7.2 Hz, 1H, H-3), 3.73 (s, 3H, OMe), 3.85–3.95 (m, 5H, OCH_2 and CH_2Ph), 4.95 (d, J=14.8 Hz, 1H, CH_2Ph), 7.18–

7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, gHSQC), see Table 1. HRMS (ESI-TOF) calcd for $C_{21}H_{28}NO_5$: 374.1961 (M^++1), found: 374.1953.

3.1.12. (3RS,3aRS,7aRS)-1′-Benzyl-3′-[2-(tert-butyldimethylsilyloxy)]ethyl-3a′-methyl-2′-oxo-octahydrospiro-[1,3-dioxolane-2,5′-[5H]indole] **16**

To a stirred suspension of $LiAlH_4$ (38 mg, 1 mmol) in THF (3 mL) at −40 °C was added a solution of amide **14** (250 mg, 0.67 mmol) in THF (3 mL). After 1 h at −40 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate, dried, and concentrated to give the alcohol **15**. To a solution of this crude alcohol in DMF (5 mL) were added imidazole (91 mg, 1.34 mmol) and TBDMSCl (151 mg, 1 mmol). The solution was stirred overnight at rt and partitioned between Et_2O and H_2O. The organic phase was washed with H_2O, dried, concentrated, and purified by chromatography (hexane/EtOAc 9:1 to 4:1) to give 212 mg of **16** (69% from **14**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 0.093 and 0.096 (2s, 3H each, $Si(CH_3)_2$), 0.89 (s, 3H, Me), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.42 (d, J=14.4 Hz, 1H, H-4), 1.45 (m, 1H, H-6), 1.55–1.75 (m, 4H, H-6, H-7, and CH_2), 1.84 (dd, J=14.4, 1.9 Hz, 1H, H-4), 1.88 (m, 1H, H-7), 2.78 (dd, J=9.4, 4.2 Hz, 1H, H-7a), 2.89 (dd, J=8.7, 5.2 Hz, 1H, H-3), 3.93–3.81 (m, 6H, OCH_2, CH_2Ph, and CH_2OSiR), 4.00 (ddd, J=9.9, 8.5, 4.9 Hz, 1H, CH_2OSiR), 4.96 (d, J=14.8 Hz, 1H, CH_2Ph), 7.34–7.19 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1.

3.1.13. (3RS,3aRS,7aRS)-1′-Benzyl-3a′-methyl-2′-oxo-3-[(α-phenylselanyl)methoxycarbonyl]octahydrospiro-[1,3-dioxolane-2,5′-[5H]indole] **17**

To a cold (−78 °C) solution of ester **14** (0.09 g, 0.24 mmol) in THF (1.4 mL) was slowly added 0.48 mL of LiHMDS (0.48 mmol, 1 M solution in THF). The reaction mixture was stirred at 0 °C for 30 min and then a solution of PhSeCl (0.07 g, 0.36 mmol) in THF (1 mL) was added. The temperature was allowed to rise to rt and the stirring was maintained for a further 3 h, after which the reaction was quenched with saturated aqueous NH_4Cl solution, extracted with dichloromethane, dried, and concentrated. The residue was purified by chromatography (hexane/EtOAc 4:1 to 2:1) to afford **17** (90 mg, 71% yield) as a 4:1 mixture of diastereoisomers (yellow oil). IR (NaCl, cm^{-1}) 2948, 1732, 1686, 1435, 1265; ^{1}H NMR (300 MHz, $CDCl_3$, COSY)—major isomer—0.97 (s, 3H, Me), 1.44–1.54 (m, 3H, H-4 and H-6), 1.67–1.74 (m, 2H, H-6 and H-7), 1.92–1.99 (m, 1H, H-7), 2.68 (dd, J=14.7, 2.1 Hz, 1H, H-3), 2.80 (dd, J=10.1, 5.5 Hz, 1H, H-7a), 3.63 (s, 3H, OMe), 3.73–4.03 (m, 6H, OCH_2, CH_2OSi, and CH_2Ph), 4.89 (d, J=14.7 Hz, 1H, CH_2Ph), 7.22–7.67 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT), see Table 1. HRMS (ESI-TOF) calcd for $C_{27}H_{32}NO_5Se$: 530.1440 (M^++1), found: 530.1435.

3.1.14. (Z)- and (E)-(3aRS,7aRS)-1′-Benzyl-3a′-methyl-2′-oxo-3-(2-methoxy-2-oxoethylidene)octahydrospiro-[1,3-dioxolane-2,5′-[5H]indole] ***18a*** and ***18b***

To a solution of **17** (50 mg, 0.095 mmol) in THF (1 mL) at rt was added $NaHCO_3$ (0.024 g, 0.28 mmol) followed by H_2O_2 (0.3 mL of a 30% aqueous solution). The reaction mixture was stirred at rt for 4 h and extracted with ethyl acetate. The organic extracts were dried and concentrated and the residue was purified by chromatography (hexane:EtOAc 2:1 to 1:1) to afford **18** as a mixture of *E* and *Z* isomers (34 mg, 94% combined yield, colorless oil).

18a *(E-minor isomer)*: IR (NaCl, cm^{-1}) 2923, 1724, 1693, 1655, 1433, 1357, 1269, 1175, 1024; ^{1}H NMR (300 MHz, $CDCl_3$) 1.34 (s, 3H, Me), 1.43–1.61 (m, 2H, H-6 and H-7), 1.67–1.88 (m, 2H, H-6 and H-7), 1.95 (d, J=14.6 Hz, 1H, H-4), 2.36 (d, J=14.6 Hz, 1H, H-4), 3.16 (t, J=4.4 Hz, 1H, H-7a), 3.77 (s, 3H, OMe), 3.79–3.94 (m, 4H, OCH_2), 4.11 and 5.10 (2d, J=15.0 Hz, 1H each, CH_2Ph), 6.74 (s, 1H, =CH), 7.24–7.36 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT), see Table 1. HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO_5$: 372.1805 (M^++1), found: 372.1801.

18b *(Z-major isomer)*: IR (NaCl, cm^{-1}) 2948, 1733, 1694, 1431, 1362, 1332, 1239, 1123, 1092, 1014; ^{1}H NMR (300 MHz, $CDCl_3$) 1.25 (s, 3H, Me), 1.50–1.39 (m, 2H, H-6 and H-7), 1.57 (dd, J=14.5, 1.4 Hz, 1H, H-4), 1.81 (d, J=14.4 Hz, 1H, H-4), 1.82–1.89 (m, 2H, H-6 and H-7), 3.16 (t, J=4.2 Hz, 1H, H-7a), 3.86 (s, 3H, OMe), 3.84–3.93 (m, 4H, OCH_2), 4.13 and 4.95 (2d, 1H each, J=15.0 Hz, CH_2Ph), 5.92 (s, 1H, =CH), 7.24–7.34 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT), see Table 1. HRMS (ESI-TOF) calcd for $C_{21}H_{26}NO_5$: 372.1805 (M^++1), found: 372.1802.

3.1.15. (3RS,3aSR,7aSR)-1′-Benzyl-3′-(methoxycarbonyl)methyl-3a′-methyl-2′-oxo-octahydrospiro[1,3-dioxolane-2,5′-[5H]indole] **1**

A mixture of either **18a** or **18b** (18 mg, 0.048 mmol) and 10% palladium on charcoal (2 mg) in methanol (0.5 mL) was stirred under H_2 (1 atm) at rt. When the starting material was completely consumed, the reaction mixture was filtered over Celite, washed with ethyl acetate, and concentrated. The residue was purified by chromatography (hexane/EtOAc 2:1) to afford **1** (13 mg, 72% yield) as a single isomer (yellow oil). IR (NaCl, cm^{-1}) 2948, 1738, 1694, 1433, 1366, 1326, 1291, 1171, 1122, 1089; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.20 (s, 3H, Me), 1.15–1.50 (m, 4H, H-4 and H-6), 1.85 (tt, J=14.5, 3.2 Hz, 1H, H-7ax), 1.94 (dq, J=14.5, 3.2 Hz, 1H, H-7eq), 2.29 (dd, J=18.2, 9.4 Hz, 1H, CH_2), 2.79 (m, 2H, H-3 and CH_2), 3.13 (t, J=2.7 Hz, 1H, H-7a), 3.73 (s, 3H, CO_2Me), 3.94–3.86 (m, 5H, OCH_2 and CH_2Ph), 5.03 (d, J=15.2 Hz, 1H, CH_2Ph), 7.34–7.20 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), see Table 1. HRMS (ESI-TOF) calcd for $C_{21}H_{28}NO_5$: 374.1961 (M^++1), found: 374.1956.

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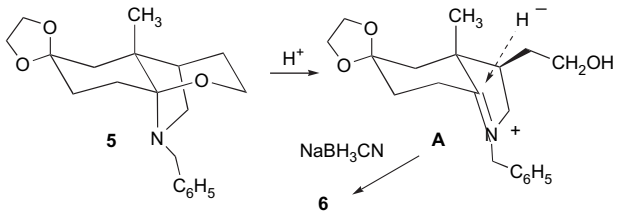
22. Although a coordination of the hydroxyethyl group with the reducing agent could be considered to justify the cis diastereoselectivity in the reduction of iminium **A** to **6**, the same substrate-directable effect should be observed in the reduction of alcohol **10**, but in this case, and under the same reaction conditions, it resulted in a trans diastereoselectivity (**10**→**12**).



23. For NMR studies about *cis*- and *trans*-**3a**-substituted octahydroindole derivatives, see: (a) Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013–4028; (b) Bonjoch, J.; Solé, D.; Cuesta, X. *Heterocycles* **1997**, *45*, 315–322; (c) Bonjoch, J.; Solé, D.; Carrillo, R.; Peidró, E.; Bosch, J. *Tetrahedron* **2001**, *57*, 6011–6017; (d) Solé, D.; Urbaneja, X.; Cordero-Vargas, A.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 10177–10184.