A Stereocontrolled Entry to 3-Functionalized *cis*-3a-Methyloctahydroindoles: Building Blocks for *Daphniphyllum* Alkaloid Synthesis

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Abstract: A synthetic entry to *cis*-3a-methyl-3-methyleneoctahydroindol-5-ones employing ozonolysis, chemoselective methylenation, and double reductive amination of 2-(1-formylvinyl)-2-methyl-1,4-cyclohexanedione monoethylene acetal is described. The same process using a 2-methoxycarbonyl derivative gave a *trans*-diastereoselectivity in the formation of the azabicyclic compound. Diastereoselective hydroboration of the exocyclic methylene of *cis*-octahydroindole derivative gives a valuable synthetic intermediate for *Daphniphyllum* alkaloid synthesis.

Key words: alkenation, aminations, fused-ring systems, ring closure, stereoselectivity

Functionalized *cis*-3a-methyloctahydroindoles are a key architectural feature in a wide array of *Daphniphyllum* alkaloids[1] as well as dendrobine-type alkaloids[2] (Figure 1). Our interest in *Daphniphyllum* alkaloids[3] with the hexacyclic ring of daphniyunnine A,[4] its *N*-oxide calyciphilline A[5] and related congeners[6] has directed our attention to the synthesis of 3-functionalized *cis*-3a-methyloctahydroindoles with a *trans*-relationship between the substituent at C-3 and the methyl group at C-3a. Our approach to the synthesis of these building blocks involves the preparation of a 3-methylene derivative, which could then give access to several functionalities (Scheme 1) to be used in synthetic approaches to the aforementioned natural products embodying this structural motif.

As envisioned in Scheme 1, *cis*-3-methylene-3a-alkyloctahydroindoles have been previously obtained by formation of the C-3–C-3a bond from 2-alkenyl *N*-propargylaminocyclohexanes through a cyclization catalyzed by transition metals [Zr(II),[7] Pt(II),[8] or W(0)[9]].[10] In this letter, we report a different approach based on the inter- and intramolecular double reductive amination of α-(1-formylvinyl)cyclohexanones. This procedure allows the incorporation of additional functionalization at the carbocyclic ring to gain access to *cis*-3-methylene-3a-methyloctahydroindol-5-one derivatives, which could be considered valuable intermediates in the *Daphniphyllum* alkaloid synthesis, particularly if the methylene group could be stereoselectively transformed into a functionalized appendage at C-3 with the same relative configuration as that of the natural products.

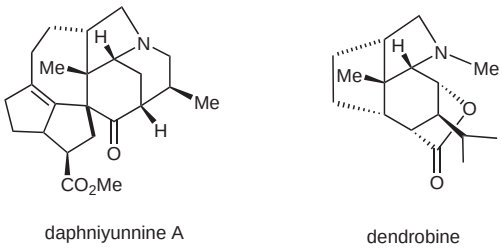
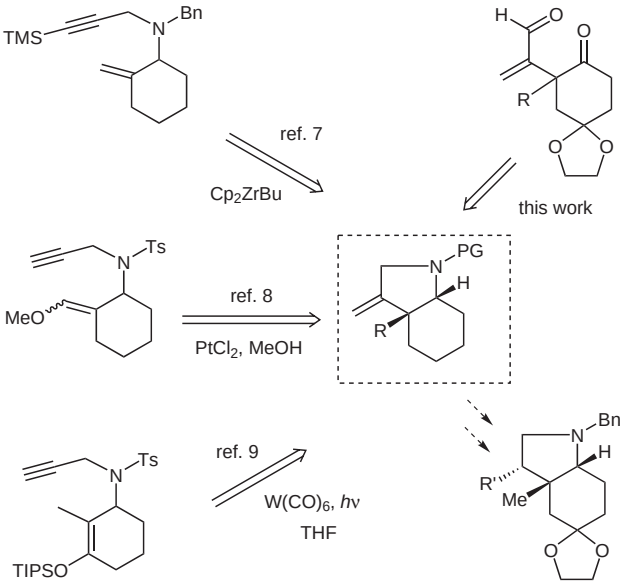


Figure 1



Scheme 1 Synthetic approaches to *cis*-3-methylene-3a-methyloctahydroindoles

The starting material for the synthetic entry to our azabicyclic target was ketone **1** (Scheme 2), which was prepared from the monoethylene acetal of 1,4-cyclohexanedione by α-methylation (LiHMDS, MeI, THF, 70%)[11] followed by regioselective allylation under thermodynamic conditions using sodium hydride as the base (NaH, $BrCH_2CH{=}CH_2$, NaI, THF, r.t., 66%). This alternative to our previously reported procedure[3] for the α,α-disubstituted cylohexanedione **1**,[12] although giving a lower overall yield, requires only two steps instead of five. Ketone **1** was submitted to a one-pot procedure reductive ozonolysis–methylenation process, using the protocol developed by Hon[13] (CH_2Br_2–Et_3N) in the second step, giving keto aldehyde **2** in 42% yield.[14,15] The double reductive

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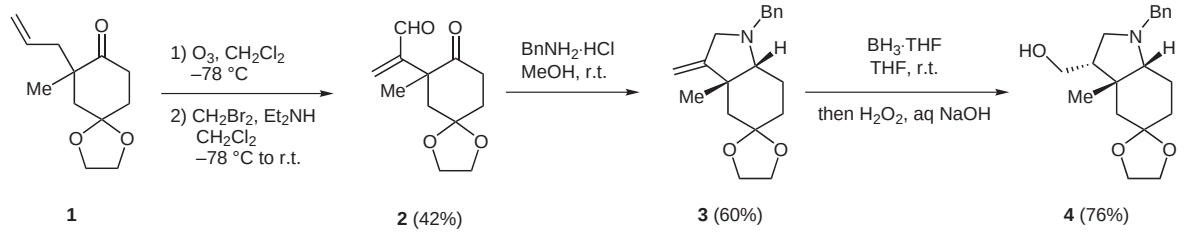
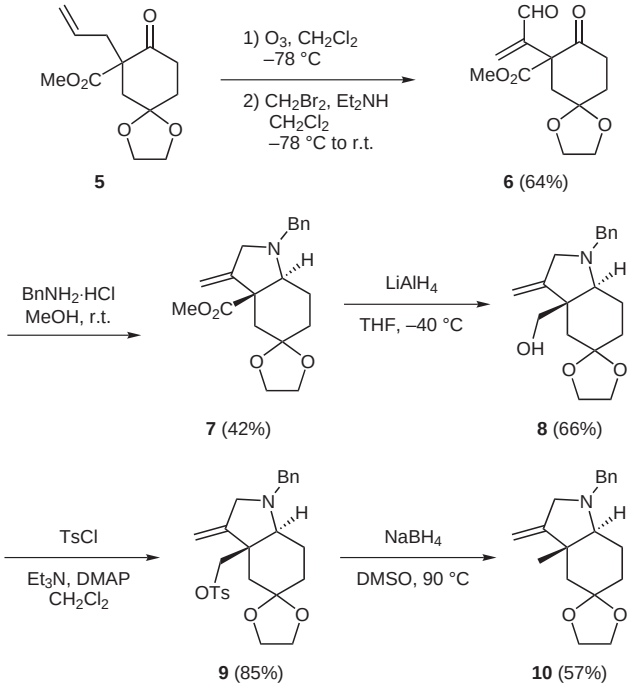


Scheme 2 Stereoselective synthesis of 3-hydroxymethyl-3a-methyloctahydroindolone **4**

amination of **2** using benzylamine hydrochloride and sodium cyanoborohydride diastereoselectively furnished *cis*-octahydroindole **3** in 60% overall yield.[16,17] Diastereoselective hydroboration of **3** allowed alcohol **4** to be obtained with the desired relative configuration at the three stereogenic centers.[18] The synthetic sequence herein described is the first for octahydroindole derivatives with this stereochemical arrangement and tetrasubstitution pattern of great interest for the development of a *Daphniphyllum* synthetic approach.

This promising result prompted us to extend the methodology to the synthesis of compounds embodying a different substituent at C-3a. Under the same reaction conditions used for the aminocyclization of **2**, keto aldehyde **6** did not give a *cis*-octahydroindole, the *trans*-octahydroindole **7** being formed instead (Scheme 3). For conclusive evidence of the structural assignment, ester **7** was reduced to alcohol **8**,[19] which in turn was reduced again to give the 3a-methyl derivative **10**,[20] epimer of **3**. This result shows that the methyl- and methoxycarbonyl-substituted derivatives behave differently, probably due to a different preferred conformation of the bicyclic iminium salt intermediates (see below).

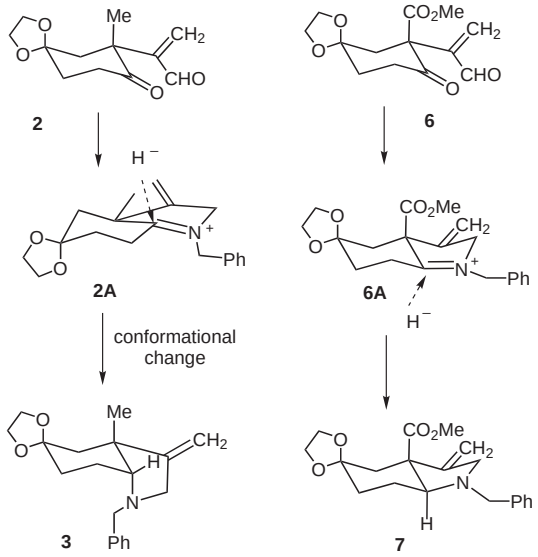


Scheme 3 Synthesis of *trans*-3-methylene-3a-methyloctahydroindoles

The relative stereochemistry of **3** and **10** was elucidated by 2D NMR spectra (COSY and HSQC). The key evidence for the stereochemical and, in the *cis*-series, conformational elucidation of these octahydroindoles was found in the ^{1}H NMR coupling pattern for the methine proton at C-7a, which appears as a triplet (J = 2.7 Hz) for the *cis*-isomer **3** and a doublet of doublets (J = 11.9 and 3.4 Hz) for the *trans*-isomer. The chemical shifts of C-6 and C-7a are of diagnostic value for the assignment of *cis*/*trans* configuration in this series of compounds, their signals appearing deshielded (δ = 34.6 and 71.8 ppm for **10**) in the *trans*-series compared with the *cis*-derivatives (δ = 28.6 and 67.8 ppm for **3**).

The results reported here constitute an example of the influence of the substituent at C-3a on the iminium salt reduction process in 3a-substituted hexahydro-2*H*-indoles.[21] The diastereoselectivity observed could be explained by the different conformational behavior of bicyclic iminium intermediates **2A** and **6A** (Scheme 4), formed when keto aldehydes **2** and **6** were submitted to the double reductive amination.[22] Thus, in order to avoid the steric crowding between the C-3a–Me and C-5–O bond of the acetal group, as well as to diminish the A^{1,3} strain between the exocyclic methylene at C-3 and the methylene at C-4, compound **2A** could adopt a conformation in which the B ring is located below the quasiplanar ring A, implying that the acetal group blocks the bottom face of **2a**. Consequently, the hydride approach takes place from the top face, giving the reduced compound **3** with a *cis*-diastereoselectivity (Scheme 4). In contrast, the methoxycarbonyl group at C-3a in **6A** is less sterically demanding, allowing a conformation with the acetal group located above. The hydride attack thus occurs from the more accessible bottom face and the resulting reduced octahydroindole **7** has a *trans*-relationship in the azabicyclic ring. Although electronic effects, as observed by Woerpel in oxacarbenium ions,[23] cannot be discarded when trying to understand the stereoselectivity in the reduction involving a cyclic iminium ion bearing an electron-withdrawing substituent such as the methoxycarbonyl group, it should be mentioned that in our previous study[3] a *cis*-diastereoselectivity was found in the octahydroindole ring formation from **5**, which lacks the methylene group.

In summary, the synthesis of *cis*-3a-methyl-3-methyleneoctahydroindol-5-one derivative **3** and alcohol **4**, bearing the same relative configuration in its three stereogenic centers as daphniyunnine A, has been reported. The



Scheme 4 Reaction pathways for the reduction of *N*-benzylhexahydroindole iminium salts

usefulness of these new building blocks in the total synthesis of *Daphniphyllum* alkaloids is currently being studied.

Acknowledgment

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References and Notes

(1) Kobayashi, J.; Morita, H. *The Alkaloids* **2003**, *60*, 165.
(2) Morita, H.; Fujiwara, M.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 5801.
(3) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461.
(4) Zhang, H.; Yang, S.-P.; Fan, C.-Q.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 533.
(5) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895.
(6) (a) Saito, S.; Kubota, T.; Fukushi, E.; Kawabata, J.; Zhang, H.; Kobayashi, J. *Tetrahedron Lett.* **2007**, *48*, 1587. (b) Li, C.; He, H.; Wang, Y.; Mu, S.; Li, S.; Gao, Z.; Gao, Z.; Hao, X. *Tetrahedron Lett.* **2007**, *48*, 2737; and references therein.
(7) By Zr-promoted reductive cyclization: Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 5643.
(8) By intramolecular reaction of enol ethers with alkynes catalyzed by Pt(II): Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627.
(9) By $W(CO)_5(L)$-catalyzed cyclization of ω-acetylenic silyl enol ethers: Grandmarre, A.; Kusama, H.; Iwasawa, N. *Chem. Lett.* **2007**, *36*, 66.
(10) For the synthesis of 3a-unsubstituted *cis*-3-methylenehydoindoles, see: (a) Solé, D.; Cancho, Y.; Llebaría, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895. (b) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Tetrahedron Lett.* **1996**, *37*, 2003. (c) Berteina, S.; De Mesmaeker, A.; Wendeborn, S. *Synlett* **1999**, 1121. (d) Gordon, G. J.; Luker, T.; Tuckett, M. W.; Whitby, R. J. *Tetrahedron* **2000**, *56*, 2113.
(11) Carcache, D. A.; Cho, Y. S.; Hua, Z.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1016.
(12) For the enantioselective synthesis of **1**, see: (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924.
(13) Hon, Y.-S.; Chang, F.-J.; Liu, L.; Lin, W.-C. *Tetrahedron* **1998**, *54*, 5233.
(14) This was higher than the 30% yield obtained when the intermediate aldehyde was submitted to methylenation with the Eschenmoser reagent.
(15) **2-[(1-Methylene)formylmethyl]-2-methylcyclohexane-1,4-dione Monoethylene Acetal (2)**
A stirred solution of ketone **1** (1.1 g, 5.23 mmol) in CH_2Cl_2 (105 mL) at –78 °C was treated with a constant stream of ozone. When the solution turned a characteristic pale blue, it was purged with oxygen. To this solution (at –78 °C) was added a mixture of CH_2Br_2 (1.84 mL, 4.54 g, 26.15 mmol) and Et_2NH (8.15 mL, 5.74 g, 78.47 mmol; preheated to 55 °C for 1.5 h and then cooled to r.t.) and the resulting yellow solution was stirred at r.t. for 2.5 h. The reaction mixture was concentrated, Et_2O was added (most of the ammonium salts precipitated), and the mixture was filtered and washed with Et_2O. The residue was purified by flash column chromatography (silica gel, hexane–EtOAc, 2:1 to 1:1) to give aldehyde **2** (42% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.62 (dd, *J* = 13.9, 2.9 Hz, 1 H, H-3), 2.00 (dm, *J* = 12.8 Hz, 1 H, H-5eq), 2.32 (td, 1 H, *J* = 12.8, 5.1 Hz, H-5ax), 2.42 (d, *J* = 13.9 Hz, 1 H, H-3), 2.59 (dt, *J* = 16.5, 4.8 Hz, 1 H, H-6eq), 2.75 (ddd, *J* = 16.6, 12.4, 5.7 Hz, 1 H, H-6ax), 4.05–3.91 (m, 4 H, OCH_2), 6.16 (s, 1 H, =CH), 6.35 (s, 1 H, =CH), 9.46 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5 (Me), 32.8 (C-5), 35.9 (C-6), 43.7 (C-3), 49.5 (C-2), 64.2 and 64.6 (OCH_2), 107.4 (C-4), 134.8 ($=CH_2$), 140.3 (=C), 193.3 (CHO), 211.1 (C-1). IR (NaCl, neat): 2969, 2888, 1711, 1688, 1282, 1114, 1072, 1036 cm^{-1}.
(16) ***cis*-1-Benzyl-3a-methyl-3-methyleneoctahydroindol-5-one Ethylene Acetal (3)**
To a solution of aldehyde **2** (0.4 g, 1.78 mmol) in MeOH (9 mL) were added first benzylamine hydrochloride (1.13 g, 7.85 mmol) and then $NaBH_3CN$ (0.09 g, 1.43 mmol). After stirring for 30 min, an additional portion of $NaBH_3CN$ (0.09 g, 1.43 mmol) was added and stirring was continued for 1 h. A third portion of $NaBH_3CN$ (0.25 g, 3.92 mmol) was then added, and stirring was continued overnight. After removing the MeOH, CH_2Cl_2 was added and the resulting organic solution was washed with sat. aq $NaHCO_3$ solution, dried and concentrated. The resulting mixture was purified by column chromatography (silica gel, hexane–EtOAc, 4:1 to 2:1) to give amine **3** (60% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, gCOSY): δ = 1.21 (s, 3 H, H-9), 1.35 (dd, *J* = 13.7, 2.5 Hz, 1 H, H-4), 1.46 (ddd, *J* = 12.5, 6.0, 2.9 Hz, 1 H, H-7), 1.77–2.10 (m, 4 H, H-4, H-6, and H-7), 2.23 (t, *J* = 2.7 Hz, 1 H, H-7a), 2.79 (dt, *J* = 13.7, 2.5 Hz, 1 H, H-2), 3.02 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 3.64 (dt, *J* = 14.5, 1.8 Hz, 1 H, H-2), 3.88–4.01 (m, 4 H, OCH_2), 4.10 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 4.66 (t, *J* = 2.1 Hz, 1 H, =CH), 4.69 (t, *J* = 2.6 Hz, 1 H, =CH), 7.21–7.35 (m, 5 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (C-7), 21.8 (CH_3), 28.6 (C-6), 42.3 (C-4), 45.5 (C-3a), 57.5 (NCH_2Ar), 57.9 (C-2), 63.6 and 64.3 (OCH_2), 67.8 (C-7a), 101.5 ($=CH_2$), 102.1 (C-5), 123.7 (ArH), 128.3 (ArH), 128.4 (ArH), 139.7 (Ar), 157.4 (C-3).
(17) For the isolation of the 5-desoxo derivative, see: Mori, M.; Saitoh, F.; Uesaka, N.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4993.

(18) **(3*RS*,3a*RS*,7a*RS*)-1-Benzyl-3-hydroxymethyl-3a-methyloctahydroindol-5-one Ethylene Acetal (4)**
To a solution of **3** (0.9 g, 3.0 mmol) in anhyd THF (30 mL) at r.t. was added dropwise BH_3·THF complex (15 mL, 15.0 mmol; 1 M solution in THF). When the starting material was completely consumed, the reaction was cooled to 0 °C and 3 N NaOH (6 mL) and H_2O_2 (3 mL of an 30% aq solution) were carefully added to the solution. After stirring for an hour, brine was added to the reaction and extracted with EtOAc. The organic layers were dried, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2–EtOAc, 98:2 to 95:5) to afford alcohol **4** (705 mg, 76%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, gCOSY): δ = 1.21 (s, 3 H, CH_3), 1.28 (dd, *J* = 13.1, 2.2 Hz, 1 H, H-4), 1.45 (ddd, *J* = 12.4, 5.9, 3.2 Hz, 1 H, H-7), 1.87–1.76 (m, 2 H, H-4 and H-6), 1.91–2.11 (m, 2 H, H-6 and H-7), 2.38 (t, *J* = 2.6 Hz, 1 H, H-7a), 2.52 (t, *J* = 10.1 Hz, 1 H, H-2), 2.74 (dd, *J* = 10.1, 8.2 Hz, 1 H, H-2), 3.19 (d, *J* = 13.4 Hz, 1 H, CH_2Ph), 3.47 (dd, *J* = 10.4, 8.4 Hz, 1 H, CH_2OH), 3.69 (dd, *J* = 10.4, 5.9 Hz, 1 H, CH_2OH), 3.87–3.99 (m, 4 H, OCH_2), 4.02 (d, *J* = 13.5 Hz, 1 H, CH_2Ph), 7.20–7.32 (m, 5 H, ArH). ^{13}C NMR (300 MHz, $CDCl_3$, gHSQC): δ = 21.5 (C-6), 21.9 (Me), 28.6 (C-7), 36.5 (C-4), 43.0 (C-3a), 51.0 (C-3), 55.1 (C-2), 57.9 (NCH_2Ar), 62.6 (CH_2OH), 63.5 and 64.4 (OCH_2), 68.5 (C-7a), 109.6 (C-5), 126.6 (ArH), 128.1 (ArH), 128.3 (ArH), 140.2 (Ar). IR (NaCl, neat): 3440, 2926, 2877, 2788, 1359, 1091 cm^{-1}.

(19) ***trans*-1-Benzyl-3a-hydroxymethyl-3-methylene-octahydroindol-5-one Ethylene Acetal (8)**
^{1}H NMR (300 MHz, $CDCl_3$, NOESY): δ = 1.57–1.60 (m, 2 H, H-4 and H-7), 1.74–1.89 (m, 2 H, H-4 and H-6), 1.89–2.01 (m, 2 H, H-6 and H-7), 2.40 (dd, *J* = 11.9, 3.4 Hz, 1 H, H-7a), 2.82 (td, *J* = 14.4, 2.4 Hz, 1 H, H-2), 3.12 (d, *J* = 12.9 Hz, 1 H, NCH_2Ar), 3.44 (d, *J* = 11.0 Hz, 1 H, CH_2OH), 3.69 (d, *J* = 14.4 Hz, 1 H, H-2), 3.86–4.00 (m, 4 H, OCH_2), 4.04 (d, *J* = 13 Hz, 1 H, NCH_2Ar), 4.40 (d, *J* = 11.0 Hz, 1 H, CH_2OH), 4.80 (t, *J* = 2.5 Hz, 1 H, $=CH_2$), 4.88 (t, *J* = 2.0 Hz, 1 H, $=CH_2$), 7.26–7.30 (m, 5 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, gHSQC): δ = 21.1 (C-7), 34.5 (C-6), 40.3 (C-4), 49.5 (C-3a), 58.0 (CH_2Ph), 59.9 (C-2), 63.9 and 64.7 (OCH_2), 66.3 (CH_2OH), 72.3 (C-7a), 103.7 ($=CH_2$), 109.0 (C-5), 127.1 (ArH), 128.3 (ArH), 128.5 (ArH), 138.0 (Ar), 152,1 (C-3). IR (NaCl, neat): 3410, 3300, 2947, 2881, 2804, 1452, 1359, 1252, 1206, 1142, 1110, 1059, 1011 cm^{-1}.

(20) ***trans*-1-Benzyl-3a-methyl-3-methyleneoctahydroindol-5-one Ethylene Acetal (10)**
^{1}H NMR (300 MHz, $CDCl_3$, gCOSY): δ = 1.18 (s, 3 H, CH_3), 1.56–1.62 (m, 3 H, H-4 and H-7), 1.72–1.75 (m, 1 H, H-7), 1.91–1.96 (m, 2 H, H-6), 1.97 (dd, *J* = 13.2, 2.4 Hz, 1 H, H-7), 2.04–2.12 (m, 1 H, H-7a), 2.73 (dt, *J* = 14.8, 2.1 Hz, 1 H, H-2), 3.18 (d, *J* = 13.5 Hz, 1 H, CH_2Ph), 3.70 (dt, *J* = 15.2, 1.9 Hz 1 H, H-2), 3.86–4.07 (m, 5 H, OCH_2 and CH_2Ph), 4.58 (t, *J* = 2.3 Hz 1 H, $=CH_2$), 7.22–7.37 (m, 5 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (CH_3), 21.5 (C-7), 34.6 (C-6), 42.6 (C-4), 45.4 (C-3a), 58.1 (NCH_2Ar), 58.6 (C-2), 63.6 and 63.6 (OCH_2), 71.8 (C-7a), 100.0 ($=CH_2$), 109.8 (C-5), 126.7 (ArH), 128.1 (ArH), 128.3 (ArH), 139.8 (Ar), 156.7 (C-3).

(21) For the influence of the substituent at C-3a in the reduction of *N*-Boc-hexahydro-1*H*-indoles, see: Brodney, M. A.; Cole, M. L.; Freemont, J. A.; Kyi, S.; Junk, P. C.; Padwa, A.; Riches, A. G.; Ryan, J. H. *Tetrahedron Lett.* **2007**, *48*, 1939.

(22) Both precursors **2** and **6** seem to have the same preferred conformation, according to their NMR data. For methyl derivative **2**, see ref. 15. For **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (ddd, *J* = 13.1, 6.5, 3.3 Hz, 1 H, H-5), 2.26 (dt, *J* = 13.5, 5.2 Hz, 1 H, H-5), 2.51 (d, *J* = 13.0 Hz, 1 H, H-3), 2.56 (d, *J* = 13.7 Hz, 1 H, H-3), 2.63 (ddd, *J* = 15.9, 5.2, 3.0 Hz, 1 H, H-6), 3.04 (ddd, *J* = 15.9, 13.7, 6.5 Hz, 1 H, H-6), 3.79 (s, 3 H, OMe), 3.91–4.04 (m, 4 H, OCH_2), 6.23 and 6.28 (2 s, 1 H each, $=CH_2$), 9.47 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.9 (C-5), 37.6 (C-6), 39.7 (C-3), 53.0 (OMe), 61.4 (C-2), 64.3 and 64.8 (OCH_2), 106.4 (C-4), 135.9 ($=CH_2$), 147.5 (=C), 170.4 (CO_2Me), 192.0 (CHO), 203.1 (C-1). IR (NaCl, neat): 2956, 2894, 1740, 1710, 1695, 1434, 1279, 12361121, 1089, 1040 cm^{-1}.

(23) (a) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521. (b) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063. (c) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195.

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