Desymmetrization of Cyclohexa-2,5-dienes through a Diastereoselective Protonation–Hydroamination Cascade

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General:

^{1}H NMR and ^{13}C NMR were recorded on a Brüker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), Brüker AC-250 FT (^{1}H: 250 MHz, ^{13}C: 62.9 MHz), using solvent peak as internal reference. The chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and hertz respectively.

InfraRed (IR) spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. Melting points were uncorrected and determined by using a Büchi-Totolli apparatus.

Rotational optical activities were determined using a Perkin-Elmer polarimeter, model 341, using a sodium lamp (589 nm) in a chloroform solution (*iso* reagent, stabilized with 0.6% of EtOH).

Merck silica gel (0.043-0.063 mm) was used for flash chromatography. In some cases, silica gel was preliminary deactivated by mixing with 5% (v/v) of triethylamine. CH_2Cl_2 was distilled under CaH_2. THF, toluene and Et_2O were distilled from sodium and benzophenone. Acetone was distilled over calcium sulfate. Ethanol was dried over magnesium turnings.

All reactions were carried out under nitrogen. All reagents and starting materials, unless noted, were directly used as obtained commercially.

3-Hydroxy-5-methoxybiphenyl[1] and 2-(1-phenyl-2,5-cyclohexadien-1-yl)acetate[2] were synthesized according to previously reported procedures. The chiral amines, (*R*)-2-methoxy-1-phenyl-ethylamine, (-)-*R*-2-methoxymethoxy-1-phenyl-ethylamine, 2-(*R*)-triethylsilanyloxy-1-phenyl-ethylamine, (*1S*,*2R*)-2-methoxy-indan-1-ylamine, were prepared by adaptation of a published procedure[3].

For Birch reductions, lithium wire (3.2mm diameter, 0.01% sodium content) was cut into small pieces and hammered before use. NH_3 gas was dried by passing through potassium hydroxide pellets.

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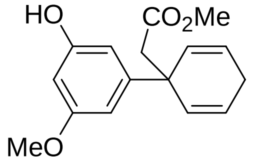
[1] Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.*, **2005**, *7*, 4557-4560.

[2] Müller, P. M.; Pfister, R. *Helv. Chim. Acta* **1973**, *66*, 771-779.

[3] Bream, R. N.; Ley, S. V.; McDermott, B.; Procopiou, P. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2237-2242.

Synthesis:

[1-(3-Hydroxy-5-methoxy-phenyl)-cyclohexa-2,5-dienyl]-acetic acid methyl ester (precursor of **1b**):



In a dry three-necked flask equipped with a dry-ice condenser was introduced 3-hydroxy-5-methoxybiphenyl[1] (2.25 g, 11.25 mmol, 1 eq.) in THF (50 mL). A solution of *n*-BuLi (2.5 M in hexane, 5.0 mL, 12.5 mmol, 1.1 eq.) was added dropwise at -78°C. After 15 minutes, ammonia (approx. 100 mL) was condensed with the dry-ice condenser filled with an acetone/liquid nitrogen mixture placed at -78°C. Lithium wire (0.173 g, 24.71 mmol, 2.2 eq.) was added. The cold bath was replaced by a room-tempered one to reflux ammonia for one hour. The red-brown mixture was then cooled to -78°C and methyl chloroacetate (3.1 mL, 34 mmol, 3 eq.) in THF (10 mL) was added in one portion. The mixture turned immediately brown. After 10 minutes, ammonia was evaporated and a half-saturated ammonium chloride solution was added. Extraction with ether, washing with brine, drying with sodium sulfate and evaporation of the solvents gave a brown paste, which was purified by flash chromatography (petroleum ether/EtOAc, 75:25) to give the product (1.51 g, 5.52 mmol, 49%) as a yellow oil.

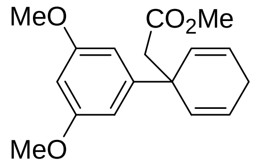
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.45-6.44 (m, 1H, aromatic H), 6.42-6.41 (m, 1H, aromatic H), 6.27-6.25 (m, 1H, aromatic H), 5.87-5.76 (m, 4H, olefinic H), 3.73(s, 3H, $ArOCH_3$), 3.59 (s, 3H, CO_2CH_3), 2.81 (s, 2H, $C\underline{H}_2CO_2Me$), 2.63 (broad s, 2H, bis-allylic CH_2).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 172.0 (C=O), 160.9 (aromatic C), 157.1 (aromatic C), 149.4 (aromatic C), 131.1 (2 olefinic CH), 124.2 (olefinic CH), 106.2 (aromatic CH), 105.1 (aromatic CH), 99.2 (aromatic CH), 55.4 ($ArO\underline{C}H_3$), 51.7 ($CO_2\underline{C}H_3$), 45.6 ($\underline{C}H_2CO_2Me$), 42.7 (aliphatic C), 25.9 (bis-allylic CH_2).

IR (film, NaCl): ν_{max} = 3404, 2952, 1715, 158, 1434, 1195, 1159, 1059, 967, 841, 715 cm^{-1}.

HRMS (EI): $[M]^{+\bullet}$ $C_{16}H_{18}O_4$: calcd. 274.1205; found 274.1212 (2 ppm).

[1-(3,5-Dimethoxy-phenyl)-cyclohexa-2,5-dienyl]-acetic acid methyl ester (1b):



In a dry two-necked flask equipped with a condenser, [1-(3-hydroxy-5-methoxy-phenyl)-cyclohexa-2,5-dienyl]-acetic acid methyl ester (1.40 g, 5.11 mmol) was dissolved in acetone (50 mL). Potassium carbonate (4.23 g, 30.66 mmol, 6 eq.) and dimethylsulfate (1.94 mL, 20.44 mmol, 4 eq.) were added and the mixture was warmed to 60°C for 16 hours. Acetone was evaporated and the residue was diluted in water and extracted with ether. The organic layer was washed with brine, dried over sodium sulfate and solvent was evaporated. After purification by flash chromatography (petroleum ether/EtOAc 93/7) the product **1b** (1.18 g, 4.09 mmol, 80%) was obtained as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.49 (d, *J* = 2.2 Hz, 2H, 2 aromatic H), 6.31 (t, *J* = 2.2 Hz, 1H, aromatic H), 5.91-5.79 (m, 4H, olefinic H), 3.77 (s, 6H, 2 OCH_3), 3.59 (s, 3H, CO_2CH_3), 2.84 (s, 2H, $C\underline{H}_2CO_2Me$), 2.68-2.65 (m, 2H, bis-allylic CH_2).

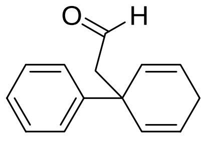
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 171.4 (C=O), 160.9 (2 aromatic C), 149.2 (aromatic C), 131.3 (2 olefinic CH), 124.1 (2 olefinic CH), 104.9 (2 aromatic CH), 97.8 (aromatic CH), 55.3 (2 OCH_3), 51.4 ($CO_2\underline{C}H_3$), 45.5 ($\underline{C}H_2CO_2Me$), 42.8 (aliphatic C), 25.9 (bis-allylic CH_2).

IR (film, NaCl): ν_{max} = 2951, 2837, 1738, 1595, 1456, 1425, 1311, 1205, 1157, 1065, 835 cm^{-1}.

MS (EI, 70 eV) m/z (%): 288 $[M]^+$ (5), 215 $[M-CH_2OMe]^+$ (100).

HRMS (EI): $[M]^+$ $C_{17}H_{20}O_4$: calcd. 288.1362; found 288.1360 (0 ppm).

(1-Phenyl-cyclohexa-2,5-dienyl)-acetaldehyde (2a):



In a dry three-necked flask equipped with a thermometer was introduced 2-(1-phenyl-2,5-cyclohexadien-1-yl)acetate[2] (3.013 g, 13.21 mmol) in toluene (40 mL). The solution was cooled to –78°C and a solution of DIBAL-H (1 M in hexane, 13.9 mL, 1.05 eq.) was added dropwise over 20 minutes in such a manner that the temperature was maintained between –80°C to –75°C. After 30 minutes, the mixture was allowed to warm slightly to –20°C in 3 hours. Methanol (1 mL) was added followed by a concentrated solution of potassium tartrate (20 mL). After stirring 1 hour at room temperature, the organic layer was separated. The aqueous layer was extracted twice with ether and the organic phases were combined, washed with brine, and dried over sodium sulfate. Evaporation of the solvent, and purification by flash chromatography (petroleum ether/EtOAc 95:5) gave **2a** (2.055 g, 10.4 mmol, 78%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.73 (t, *J* = 3.0 Hz, 1H, CHO), 7.38-7.35 (m, 4H, aromatic H), 7.27-7.22 (m, 1H, aromatic H), 5.99-5.93 (m, 2H, 2 olefinic CH), 5.82-5.76 (m, 2H, 2 olefinic CH), 2.83 (d, *J* = 3.0 Hz, 2H, $C\underline{H}_2CHO$), 2.76-2.72 (m, 2H, CH*a*H*b*).

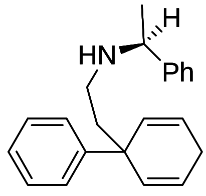
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 203.1 (CHO), 146.2 (aromatic C), 131.2 (2 olefinic CH), 128.6 (aromatic CH), 126.5 (aromatic CH), 126.2 (2 aromatic CH), 124.5 (2 olefinic CH), 52.2 ($\underline{C}H_2CHO$), 25.9 (CH_2).

IR (film, NaCl): ν_{max} = 3025, 2816, 1715, 1492, 1420, 1044, 1032, 946, 746, 697 cm^{-1}.

MS (SIMS) *m/z* (%): 221 $[M+Na]^+$ (03), 155 $[M-CH_2CHO]^+$ (100).

HRMS (SIMS): $[M+Na]^+$ $C_{14}H_{14}ONa$: calcd. 221.0942; found 221.0941 (0.7 ppm).

[2-(1-Phenyl-cyclohexa-2,5-dienyl)-ethyl]-(1-phenyl-ethyl)-amine (4):



To a solution of **2a** (0.237 g, 1.20 mmol) in CH_2Cl_2 (12 mL) and sodium sulfate (1.70 g, 12.0 mmol, 10 eq.) was added (*L*)-(-)-α-phenylethylamine (0.160 g, 1.32 mmol, 1.1 eq.). After stirring 4 hours at room temperature, the solution was filtered and salt washed with CH_2Cl_2. Evaporation of the solvent gave an oily product. This oil was diluted in methanol (12 mL) and $NaBH_4$ was added in one portion at 0°C. After stirring 2h at room temperature, water (0.5 mL) was added at 0°C and methanol was evaporated. The residue was partitioned between a 10% NaOH solution and ether. The organic layer was separated and the aqueous layer extracted twice with ether. The organic layers were combined, dried over sodium sulfate, filtered and evaporated. After purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 85:15) the product **4** (0.307 g, 1.01 mmol, 85%) was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36-7.15 (m, 10H, aromatic H), 5.83-5.77 (m, 2H, olefinic H), 5.61-5.57 (m, 2H, olefinic H), 5.76 (q, *J* = 6.4 Hz, 1H, CH), 2.72-2.48 (m, 4H, bis-allylic CH_2 and CH_2N), 2.12-1.95 (m, 2H, $C\underline{H}_2CH_2N$), 1.35 (d, *J* = 6.4 Hz, CH_3), 1.36 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 148.1 (aromatic C), 146.0 (aromatic C), 132.6 (2 olefinic CH), 128.5 (2 aromatic CH), 128.4 (2 aromatic CH), 126.9 (aromatic CH), 126.6 (2x2 aromatic CH), 126.0 (aromatic CH), 123.7 (olefinic CH), 123.6 (olefinic CH), 58.5 (CH), 44.6 (CH_2N), 43.3 (aliphatic C), 40.2 ($\underline{C}H_2CH_2N$), 26.1 (bis-allylic CH_2), 24.4 (CH_3).

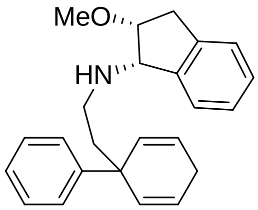
IR (film, NaCl): ν_{max} = 3023, 2815, 1492, 1446, 1128, 947, 762, 698 cm^{-1}.

MS (SIMS) *m/z* (%): 304 $[M+H]^+$ (100), 288 $[M-CH_3]^+$ (08), 155 $[M-CH_2CH_2NH(CH(CH_3)Ph)]^+$ (25).

HRMS (SIMS): $[M+H]^+$ $C_{22}H_{26}N$: calcd. 304.2065; found 304.2071 (-1.8 ppm).

$[\alpha]_D^{20}$ = -47° (C = 0.9, $CHCl_3$).

(2-Methoxy-indan-1-yl)-[2-(1-phenyl-cyclohexa-2,5-dienyl)-ethyl]-amine (5):



To a solution of **2a** (0.125 g, 0.632 mmol) in CH_2Cl_2 (6 mL) and 4Å molecular sieves (0.52 g) was added (*1S*,*2R*)-2-methoxy-indan-1-ylamine (0.103 g, 0.632 mmol, 1 eq.). After stirring at room temperature overnight, the solution was filtered. Evaporation of the solvent gave an oil which was diluted in methanol (6 mL). $NaBH_4$ (53 mg, 1.40 mmol, 2.2 eq.) was then added in one portion at 0°C. After stirring 2 hours at room temperature, water (0.5 mL) was added at 0°C and methanol was evaporated. The residue was partitioned between a 10% NaOH solution and ether. The organic layer was separated and the aqueous layer extracted ether. The organic layers were combined, dried over sodium sulfate, filtered and evaporated. After purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 95:5), the product **5** (164 mg, 0.475 mmol, 75%) was obtained as an oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.44-7.31 (m, 5H, aromatic CH), 7.24-7.18 (m, 4H, aromatic H), 5.92-5.85 (m, 2H, 2 olefinic CH), 5.74-5.67 (m, 2H, 2 olefinic CH), 4.12 (broad s, 2H, CHN and $C\underline{H}OCH_3$), 3.41 (s, 3H, OCH_3), 3.12-2.90 (m, 2H, benzylic CH_2), 2.85-2.78 (m, 2H, $C\underline{H}_2NH$), 2.75-2.71 (m, 2H, bis-allylic CH_2), 2.26-2.03 (m, 2H, $C\underline{H}_2CH_2N$), 1.94 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 148.1 (aromatic C), 143.8 (aromatic C), 140.1 (aromatic C), 132.7 (2 olefinic CH), 128.4 (aromatic CH), 127.6 (aromatic CH), 126.7 (aromatic CH), 126.6 (aromatic CH), 126.0 (aromatic CH), 125.2 (aromatic CH), 124.7 (aromatic CH), 123.6 (olefinic CH), 123.5 (olefinic CH), 82.0 ($\underline{C}HOMe$), 65.3 (CHNH), 57.2 (OCH_3), 44.7 (CH_2NH), 43.3 (aliphatic C), 40.4 ($\underline{C}H_2CH_2N$), 35.5 (benzylic CH_2), 26.2 (bis allylic CH_2).

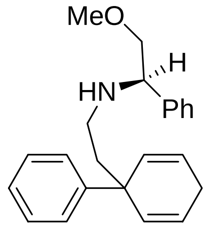
IR (film, NaCl): ν_{max} = 3022, 2927, 2819, 1462, 1095, 752, 722, 697 cm^{-1}.

MS (SIMS) *m/z* (%) : 368 $[M+Na]^+$ (10), 346 $[M+H]^+$ (100), 314 $[M-OCH_3]^+$ (05).

HRMS (SIMS): $[M+H]^+$ $C_{24}H_{28}NO$: calcd. 346.2171; found 346.2167 (1.0 ppm)

$[\alpha]_D^{20}$ = -41° (C = 1.04, $CHCl_3$).

(2-Methoxy-1-phenyl-ethyl)-[2-(1-phenyl-cyclohexa-2,5-dienyl)-ethyl]-amine (6):



To a solution of **2a** (0.163 g, 0.823 mmol) in CH_2Cl_2 (8 mL) with sodium sulfate (1.170 g, 8.23 mmol, 10 eq.) was added (*R*)-2-methoxy-1-phenyl-ethylamine (0.213 g, 0.861 mmol, 1.05 eq.). After stirring 3 hours at room temperature, the solution was filtered and the salts washed with CH_2Cl_2. Evaporation of the solvent gave an oil which was diluted in methanol (8mL). $NaBH_4$ was added in one portion at 0°C.After stirring 2h at room temperature, water (0.5 mL) was added at 0°C and the methanol was evaporated. The residue was partitioned between a 10% NaOH solution and ether. The organic layer was separated and the aqueous layer extracted twice with ether. The organic layers were combined, dried over sodium sulfate, filtered and evaporated to give a oily product which was purified by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 95:5) to give **6** (0.234 g, 0.703 mmol, 85%) as an oil.

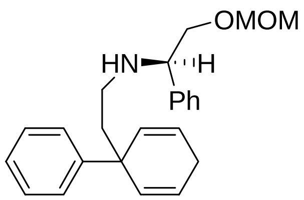
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38-7.26 (m, 9H, aromatic H), 7.21-7.15 (m, 1H, aromatic H), 5.83-5.77 (m, 2H, 2 olefinic H), 5.64-5.56 (m, 2H, 2 olefinic H), 3.94-3.89 (m, 1H, CHN), 3.51-3.38 (m, 2H, CH_2O), 3.39 (s, 3H, OCH_3), 2.65-2.63 (m, 2H, bis-allylic CH_2), 2.59-2.52 (m, 2H, CH_2N), 2.07 (t, J = 8.5Hz, 2H, $C\underline{H}_2CH_2N$).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 148.1 (aromatic C),141.0 (aromatic C), 132.7 (olefinic CH), 132.4 (olefinic CH), 128.4 (2 aromatic CH), 128.3 (2 aromatic CH), 127.6 (2 aromatic CH), 127.4 (aromatic CH), 126.6 (2 aromatic CH), 126.0 (aromatic CH), 123.6 (olefinic CH), 123.5 (olefinic CH), 78.0 (CH_2O), 63.0 (CHN), 58.9 (OCH_3), 44.3 (CH_2N), 43.2 (aliphatic C), 40.2 ($\underline{C}H_2CH_2N$), 26.0 (bis allylic CH_2).

IR (film, NaCl): ν_{max} = 3336, 3024, 2883, 2817, 1599, 1492, 1454, 1194, 1105, 948, 761, 699 cm^{-1}.

MS (SIMS) *m/z* (%): 356 $[M+Na]^+$ (07), 334 $[M+H]^+$ (100), 288 $[M-CH_2OCH_3]^+$ (66).
HRMS (SIMS): $[M+H]^+$ $C_{23}H_{28}NO$: calcd. 334.2171; found 334.2167 (1.2 ppm).
$[\alpha]_D^{20}$ = -48° (C = 0.94, $CHCl_3$).

(2-Methoxymethoxy-1-phenyl-ethyl)-[2-(1-phenyl-cyclohexa-2,5-dienyl)-ethyl]-amine (7):



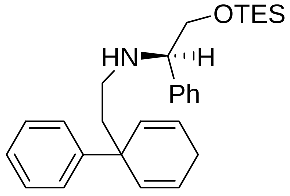
Compound **2a** (363 mg, 1.83 mmol) and (-)-*R*-2-methoxymethoxy-1-phenyl-ethylamine (332 mg, 1.83 mmol, 1 eq.) were condensed in CH_2Cl_2 (18 mL) with sodium sulfate (2.60 g, 18.3 mmol, 10 eq.) for 4 hours. After filtration and evaporation of the solvent, the oil was diluted with MeOH (18 mL) and $NaBH_4$ (139 mg, 3.66 mmol, 2 eq.) was added in portions at 0°C. After stirring for 2 hours at room temperature, ether was added followed by a 10% NaOH solution. After stirring for 30 minutes, the aqueous layer was extracted with ether, the combined organic layers were washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Solvents were evaporated and after purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 90:10), **7** (523 mg, 1.46 mmol, 80% yield), was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38-7.23 (m, 9H, aromatic H), 7.19-7.14 (m, 1H, aromatic H), 5.83-5.74 (m, 2H, 2 olefinic H), 5.63-5.53 (m, 2H, 2 olefinic H), 4.66-4.61 (AB system, *J* = 15.0Hz, 2H, OCH*a*H*b*O), 3.88 (dd, *J* = 4.1 and 8.7Hz, 1H, CHN), 3.67-3.50 (ABX system, *J* = 9.8 and 53.5Hz, 2H, $CH\underline{H}_a\underline{H}_bO$), 3.33 (s, 3H, OCH_3), 2.72-2.79 (m, 2H, bis-allylic CH_2), 2.59-2.50 (m, 2H, CH_2N), 2.08-2.00 (m, 2H, $C\underline{H_2}CH_2N$), 1.93 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 148.1 (aromatic C), 141.1 (aromatic C), 132.6 (olefinic CH), 132.5 (olefinic CH), 128.5 (2 aromatic CH), 128.4 (2 aromatic CH), 127.7 (2 aromatic CH), 127.5 (aromatic CH), 126.7 (2 aromatic CH), 126.0 (aromatic CH), 123.6 (2 olefinic CH), 96.8 (OCH_2O), 73.0 ($CH\underline{C}H_2O$), 63.2 ($N\underline{C}HPh$), 55.5 (OCH_3), 44.4 (CH_2N), 43.3 (aliphatic C), 40.3 ($C\underline{H_2}CH_2N$), 26.1 (bis-allylic CH_2).

IR (film, KBr): ν_{max} = 3023, 2927, 2818, 1492, 1453, 1152, 1107, 1039, 948, 761, 733, 699 cm^{-1}.
MS (ESI) *m/z* (%): 364 $[M+H]^+$ (100).
HRMS (SIMS): $[M+H]^+$ $C_{24}H_{30}NO_2$: calcd 364.2277; found 364.2279.
$[\alpha]_D^{20}$ = -42° (C = 1.55, $CHCl_3$).

[2-(1-Phenyl-cyclohexa-2,5-dienyl)-ethyl]-(1-phenyl-2-triethylsilanyloxy-ethyl)-amine (8):



To a solution of **2a** (1.02 g, 4.07 mmol) in CH_2Cl_2 (20 mL) and sodium sulfate (5.78 g, 40.7 mmol, 10 eq.), was added 2-(*R*)-triethylsilanyloxy-1-phenyl-ethylamine (0.81 g, 4.07 mmol). After stirring at room temperature overnight, the solution was filtered and salts were washed with CH_2Cl_2. After evaporation of the solvent, the oily residue was diluted in methanol (20 mL) and $NaBH_4$ (0.31 g, 8.14 mmol, 2 eq.) was added in portions at 0°C. After stirring 3 hours at room temperature, a half-saturated Na2CO3 solution was added at 0°C. After stirring 30 minutes, the solution was extracted twice with ether. A 10% NaOH solution was added to the aqueous layer which was again extracted twice with ether. The combined organic layers were dried over sodium sulfate. After filtration and evaporation of the solvent, the product was purified by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 98:2) to give **8** (1.08 g, 2.49 mmol, 61%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36-7.21 (m, 9H, aromatic H), 7.19-7.13 (m, 1H, aromatic H), 5.83-5.73 (m, 2H, 2 olefinic H), 5.63-5.53 (m, 2H, 2 olefinic H), 3.76 (dd, *J* = 4.2 and 9.1Hz, 1H, PhCHN), 3.66 (dd, *J* = 4.2 and 9.8Hz, 1H, $C\underline{H}_aH_xO$), 3.53 (dd, *J* = 9.1 and 9.8Hz, 1H, $CH_a\underline{H}_xO$), 2.71-2.54 (m, 2H, bis-allylic CH_2), 2.56-2.49 (m, 2H, CH_2N), 2.09-1.96 (m, 2H, $C\underline{H}_2CH_2N$), 1.88 (broad s, 1H, NH), 0.95 (t, J = 7.9Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.59 (q, J = 7.9Hz, 6H, $Si(C\underline{H}_2CH_3)_3$).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 148.2 (aromatic C), 141.4 (aromatic C), 132.7 (olefinic CH), 132.6 (olefinic CH), 128.4 (2 aromatic CH), 128.3 (2 aromatic CH), 127.8 (2 aromatic CH), 127.3 (aromatic CH), 126.7 (2 aromatic CH), 126.0 (aromatic CH), 123.6 (olefinic CH), 123.5 (olefinic CH), 68.4 (CH_2O), 65.5 (PhCHN), 44.4 (CH_2N), 43.4 (aliphatic C), 40.4 ($C\underline{H}_2CH_2N$), 26.1 (bis-allylic CH_2), 6.9 (3 $SiCH_2\underline{C}H_3$), 4.5 (3 $Si\underline{C}H_2CH_3$).

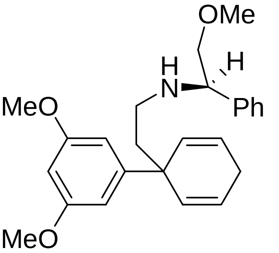
IR (film, KBr): ν_{max} = 3024, 2954, 2875, 1492, 1454, 1239, 1078, 1008, 730, 699 cm^{-1}.

MS (ESI) m/z (%): 434 $[M+H]^+$ (100).

HRMS (SIMS): [M+H]+ $C_{28}H_{40}NOSi$: calcd 434.2879; found 434.2867 (2.8 ppm).

Element. Anal. Calcd. for $C_{28}H_{39}NOSi$ (433): C 77.54, H 9.06, N 3.23; found: C 77.66, H 9.06, N 3.10.

{2-[1-(3,5-Dimethoxy-phenyl)-cyclohexa-2,5-dienyl]-ethyl}-(2-methoxy-1-phenyl-ethyl)-amine (9):



In a dry three necked flask equipped with a thermometer, **1b** (1.108 g, 3.85 mmol) was dissolved in toluene (11 mL). DIBAL-H (1 M in hexane, 4 mL, 4 mmol, 1.05 eq.) was added dropwise in such a manner that temperature never exceeded –70°C. After addition, the temperature was allowed to rise slowly to –40°C during 2 hours. Then, methanol (1 mL) was added followed by a concentrated solution of potassium tartrate. After 2 hours stirring, the two phases were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated. The intermediate aldehyde was used as a crude mixture without further purification.

[1-(3,5-Dimethoxy-phenyl)-cyclohexa-2,5-dienyl]-acetaldehyde (564 mg, maximum 2.19 mmol), was diluted in CH_2Cl_2 (20 mL), and sodium sulfate (3.10 g, 21.9 mmol) was added followed by (R)-(-)-(2-methoxy-1-phenyl-ethyl)-amine (330 mg, 2.19 mmol). After stirring for 4 hours at room temperature, salts were filtered and solvent evaporated. The oil was diluted in methanol (20 mL) and $NaBH_4$ (165 mg, 4.36 mmol) was added at 0°C. After 2 hours at room temperature, water (1 mL) was added and methanol was evaporated. The residue was partitioned between a 10% sodium hydroxide solution and ether. The 2 phases were separated and the aqueous layer extracted with ether. The combined extracts were washed with saturated Na_2CO_3 solution, dried over sodium sulfate and filtered. Solvent was evaporated, and after purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 85:15), **9** was obtained as a colorless oil (473 mg, 0.120 mmol, 45% over two steps, 54% corrected yield, some ester **1b**, 177 mg, 0.615 mmol, being also recovered).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36-7.24 (m, 5H, aromatic H), 6.49 (d, J = 3.3Hz, 2H, 2 aromatic H), 6.28 (t, J = 3.3Hz, 1H, aromatic H), 5.80-5.72 (m, 2H, 2 olefinic H), 5.60-5.50 (m, 2H, 2 olefinic H), 3.86 (dd, J = 4.1 and 9.0Hz, 1H, PhCHN), 3.76 (s, 6H, 2 OCH_3), 3.48-3.34 (m, 2H, CH_2O), 3.36 (s, 3H, OCH_3), 2.62-2.57 (m, 2H, bis-allylic CH_2), 2.52-2.46 (m, 2H CH_2N), 2.01-1.96 (m, 2H, $C\underline{H}_2CH_2N$), 1.81 (broad s, 1H, NH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 160.8 (2 aromatic C), 150.8 (aromatic C), 141.0 (aromatic C), 132.4 (olefinic CH), 132.1 (olefinic CH), 128.5 (2 aromatic CH), 127.7 (2 aromatic CH), 127.5 (aromatic CH), 123.9 (olefinic CH), 123.8 (olefinic CH), 105.2 (2 aromatic CH), 97.8 (aromatic CH), 80.0 (CH_2O), 63.1 (PhCHN), 59.0 (OCH_3), 55.4 (2 OCH_3), 44.4 (CH_2N), 43.5 (aliphatic C), 40.3 ($\underline{C}H_2CH_2N$), 26.0 (bis-allylic CH_2).

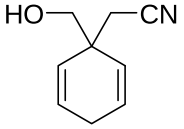
IR (film, KBr): ν_{max} = 3023, 2932, 1592, 1454, 1424, 1308, 1203, 1152, 1063, 926, 834, 760, 702 cm^{-1}.

MS (ESI) m/z (%): 394 $[M+H]^+$ (100).

HRMS (EI): $[M]^{+\cdot}$ $C_{25}H_{31}NO_3$: calcd. 393.2304; found: 393.2306 (0 ppm)

$[\alpha]_D^{23}$ = -36° (C = 1.04, $CHCl_3$).

(1-Hydroxymethyl-cyclohexa-2,5-dienyl)-acetonitrile (precursor of **11**):



In a three-necked flask equipped with a dry-ice condenser, was introduced lithium benzoate (1.92 g, 15 mmol) and THF (50 mL). Ammonia (around 100 mL) was condensed at -78°C and lithium wire (0.23 g, 33 mmol, 2.2 eq.) was added. The cold bath was removed and ammonia allowed to reflux for 1 hour (-33°C). Chloroacetonitrile (2.9 mL, 45 mmol, 3 eq.) diluted in THF (7 mL) was added at –78°C in one portion. The media turned brown immediately. Ammonia was evaporated after 5 minutes and the mixture was acidified by a 1 M HCl solution. The aqueous layer was extracted with ether. The combined extracts were washed with brine, dried over sodium sulfate and solvents were evaporated. The dark brown paste was filtered through celite and eluted with CH_2Cl_2. After evaporation of the solvent, the paste was filtered through a short plug of silica gel and eluted with ethyl acetate. The compound **10** (2.31 g) was used without further purification (NMR analysis shows a mixture of 12% of benzoic acid and 88% of product).

To the crude mixture of **10** (684 mg, around 4.2 mmol) diluted in THF (12 mL) was added triethylamine (590 µL, 4.2 mmol, 1 eq.) and ethyl chloroformate (400 µL, 4.2 mmol, 1 eq.) at –10°C. After 30 minutes, the mixture was filtered and salts were washed with THF. $NaBH_4$ (476 mg, 3 eq.) was added at 0°C followed by methanol (2.6 mL) dropwise. After 2 hours at room temperature, the media was acidified with a 1 M HCl solution and extracted with ether. The combined organic layers were washed with brine, dried over sodium sulfate and solvents were evaporated. The crude was purified by flash chromatography (petroleum ether/EtOAc 70/30) to give the product (348 mg, 2.33 mmol, 56% over 2 steps) as a white solid (m.p. = 41.3-42.8°C).

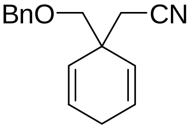
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.05 (dt, *J* = 10.2 and 3.4Hz, 2H, 2 olefinic H), 5.57 (dt, *J* = 10.2 and 1.9Hz, 2H, 2 olefinic H), 3.51 (s, 2H, CH_2O), 2.84-2.61 (m, 2H, bis-allylic CH_2), 2.45 (s, 2H, CH_2CN), 1.79 (broad s, 1H, OH).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 129.1 (2 olefinic CH), 126.5 (2 olefinic CH), 117.7 (CN), 68.9 (CH_2O), 40.7 (aliphatic C), 26.8 (bis-allylic CH_2), 26.7 ($\underline{C}H_2CN$).

IR (solid, KBr): ν_{max} = 3477, 3022, 2865, 2258 (CN), 1298, 1081, 1038, 947, 733, 707 cm^{-1}.

Element. Anal. Calcd for $C_9H_{11}NO$ (149.2): C 72.46, H : 7.43, N 9.39.; found: C 72.80, H 7.75, N 9.11.

(1-Benzyloxymethyl-cyclohexa-2,5-dienyl)-acetonitrile (11):



In a two-necked flask, sodium hydride (60% in mineral oil, 162 mg, 4.05 mmol, 1.2 eq.) was washed three times with pentane and dissolved in THF (15 mL). (1-hydroxymethyl-cyclohexa-2,5-dienyl)-acetonitrile (502 mg, 3.37 mmol) diluted in THF (15 mL) was added dropwise at 0°C. The mixture was stirred at this temperature for 30 minutes. Tetrabutylammonium iodide (62 mg, 0.17 mmol, 0.05 eq.) was added and then benzyl bromide (806 mg, 4.72 mmol, 1.4 eq.). The solution was stirred 1 hour at 0°C then 4 hours at room temperature. Excess of sodium hydride was then destroyed with a small amount of water at 0°C. After filtration over celite, eluting with ether, evaporation of solvent and purification by flash chromatography (petroleum ether/EtOAc 95/5) the product **11** (697 mg, 2.92 mmol, 86%) was obtained as a colorless oil.

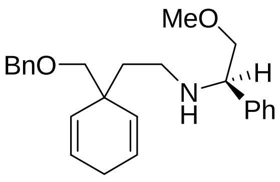
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40-7.27 (m, 5H, aromatic H), 6.00-5.93 (m, 2H, 2 olefinic H), 5.69-5.64 (m, 2H, 2 olefinic H), 4.54 (s, 2H, OCH_2Ph), 3.38 (s, 2H, $CqC\underline{H}_2O$), 2.83-2.61 (m, 2H, bis-allylic CH_2), 2.54 (s, 2H, CH_2CN).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 138.0 (aromatic C), 128.5 (2 aromatic CH), 127.8 (aromatic CH), 127.7 (2 olefinic CH), 127.6 (2 aromatic CH), 127.0 (2 olefinic CH), 118.0 (CN), 76.1 ($Cq\underline{C}H_2O$), 73.6 ($O\underline{C}H_2Ph$), 39.5 (aliphatic C), 27.1 ($\underline{C}H_2CN$), 26.8 (bis-allylic CH_2).

IR (film, KBr): ν_{max} = 3030, 2860, 2244 (CN), 1454, 1418, 1361, 1106, 1075, 738, 716, 699 cm^{-1}.

HRMS (EI): $[M\text{-}BzOCH_2]^{+\cdot}$ C_8H_8N: calcd. 118.0657; found 118.0664 (5 ppm).

[2-(1-Benzyloxymethyl-cyclohexa-2,5-dienyl)-ethyl]-(2-methoxy-1-phenyl-ethyl)-amine (13):



In a dry three-necked flask equipped with a thermometer, (1-benzyloxymethyl-cyclohexa-2,5-dienyl)-acetonitrile (445 mg, 1.86 mmol, 1 eq.) was introduced in toluene (9 mL). DIBAL-H (1 M solution in hexane, 1.95 mL, 1.05 eq.) was added dropwise, and the temperature kept below –70°C. After addition, the temperature was allowed to rise slowly to –0°C during 4 hours. Methanol was added (1 mL) followed by a 1 M solution of HCl. After 15 minutes, the 2 phases were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated. After purification by flash chromatography (petroleum ether/EtOAc 95/5) an inseparable mixture of starting material and **13** (326 mg) was obtained which was used in the next step.

The mixture was diluted in CH_2Cl_2 (6 mL), and sodium sulfate (950 mg, 6.70 mmol) was added followed by (*R*)-(-)-(2-methoxy-1-phenyl-ethyl)-amine (121 mg, 0.80 mmol). After stirring for 4 hours, the salts were filtered and solvents evaporated. The oil was diluted in methanol (6 mL) and $NaBH_4$ (51 mg, 1.24 mmol) was added at 0°C. After 2 hours at room temperature, a 10% sodium hydroxide solution was added. The media was stirred with ether 30 minutes. The 2 phases were separated and the aqueous layer extracted with ether. The combined organic layer were washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Solvents were evaporated to give an oil which was purified by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 9:1). Starting material (147 mg, 0.615 mmol, 33%) was eluted first then **13** (262 mg, 0.695 mmol, 37%, 56% corrected yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36-7.23 (m, 10H, aromatic H), 5.82-5.73 (m, 2H, 2 olefinic H), 5.54-5.43 (m, 2H, 2 olefinic H), 4.50 (s, 2H, $PhCH_2O$), 3.83 (dd, *J* = 9.1 and 4.1Hz, 1H, PhCHN), 3.45-3.33 (m, 2H, $C\underline{H_2}OCH_3$), 3.35 (s, 3H, OCH_3), 3.22 (s, 2H, $CqC\underline{H_2}O$), 2.68-2.47 (m, 2H, bis-allylic CH_2), 2.44-2.38 (m, 2H, CH_2N), 1.66-1.61 (m, 2H, $C\underline{H_2}CH_2N$).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 141.0 (aromatic C), 138.8 (aromatic C), 130.6 (olefinic CH), 130.3 (olefinic CH), 128.4 (aromatic CH), 128.3 (aromatic CH), 127.6 (aromatic CH), 127.5 (aromatic CH), 127.4 (aromatic CH), 125.6 (olefinic CH), 125.5 (olefinic CH), 78.7 ($Cq\underline{C}H_2O$), 77.9 ($\underline{C}H_2OMe$), 73.4 ($PhCH_2O$), 63.1 (PhCHN), 58.9 (OCH_3), 44.0 (CH_2N), 40.8 (aliphatic C), 37.8 ($\underline{C}H_2CH_2N$), 26.6 (bis-allylic CH_2).

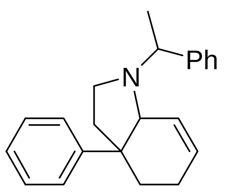
IR (film, KBr): ν_{max} = 3026, 2852, 1454, 1360, 1195, 1102, 1028, 757, 735, 700 cm^{-1}.

MS (ESI) m/z (%): 378 $[M+H]^+$ (100).

HRMS (EI): $[M-CH_2OMe]^+$ $C_{23}H_{26}NO$: calcd 332.2014; found: 332.2026 (3 ppm).

$[\alpha]_D^{20}$ = -53° (C = 0.89, $CHCl_3$).

3a-Phenyl-1-(1-phenyl-ethyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole (14):



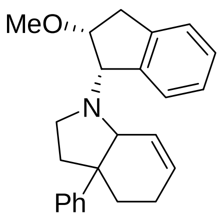
The compound **4** (110 mg, 0.363 mmol) dissolved in THF (0.7 mL) and *n*-BuLi (2.5 M in hexane, 30 µL, 0.2 eq.) was added at room temperature. The reaction was stirred for 4 hours during which the solution turned from orange to yellow. One drop of water was added and the organic layer was diluted with ether, washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Solvents were evaporated to give a pale yellow oil of **14** (102 mg, 0.336 mmol, 93%) as a mixture of diastereoisomer in a 63:37 ratio.

^{13}C NMR ($CDCl_3$, aliphatic signals, 75.5 MHz):

Major product: 61.9 (NCHPh), 47.7 ($N\underline{C}H$-CH=), 42.5 (CH_2), 40.3 (CH_2), 38.0 (aliphatic C), 34.2 (CH_2), 23.9 (CH_2), 22.4 (CH_3).

Minor product: 61.0 (NCHPh), 48.9 ($N\underline{C}H$-CH=), 42.5 (CH_2), 40.0 (CH_2), 37.9 (aliphatic C), 34.8 (CH_2), 23.8 (CH_2), 22.9 (CH_3).

1-(2-Methoxy-indan-1-yl)-3a-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-indole (15):



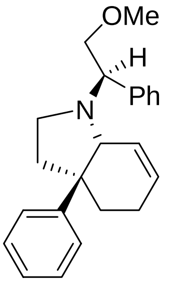
The compound **5** (137 mg, 0.397 mmol) was dissolved in THF (2 mL) and *n*-BuLi (2.5 M in hexane, 60 µL, 0.4 eq.) was added at room temperature. After 3 hours, one drop of water was added and the organic layer was diluted with ether, washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Solvents were evaporated to give an oil which was purified by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 98:2 to 95:5). The compound **15** (35 mg, 0.101 mol, 26%), was eluted first as a 9:1 mixture of 2 isomers, then starting material (57 mg, 0.165 mmol, 42%).

^{1}H NMR (Major isomer, $CDCl_3$, 300 MHz): δ = 7.36-7.14 (m, 9H, aromatic H), 6.42-6.30 (m, 1H, olefinic H), 6.06-6.01 (m, 1H, olefinic H), 4.67 (d, *J* = 7.2Hz, 1H, NCHPh), 4.24-4.16 (m, 1H, CHOMe), 3.55 (s, 3H, OCH_3), 3.48 (s, 1H, allylic CH), 3.19-2.95 (m, 4H, CH_2N and CH_2Ph), 2.28 (td, *J* = 12.4 and 4.9Hz, 1H), 2.16-1.81 (m, 5H), 1.73-1.63 (m, 1H), 1.61-1.46 (m, 1H).

^{13}C NMR (Major isomer, $CDCl_3$, 62.9 MHz): δ = 147.9 (aromatic C), 141.1 (aromatic C), 138.7 (aromatic C), 132.8 (olefinic CH), 128.1 (aromatic CH), 127.8 (2 aromatic CH), 126.7 (2 aromatic CH), 126.6 (2 aromatic CH), 125.6 (aromatic CH), 125.0 (2 aromatic CH and 1 olefinic CH), 81.3 (CHOMe), 60.4 (allylic CH), 60.1 (NCHPh), 57.8 (OCH_3), 45.7 (aliphatic C), 44.6 (CH_2), 39.4 (CH_2), 38.1 (CH_2), 34.7 (CH_2), 24.4 (CH_2).

MS (ESI) *m/z* (%): 346 $[M+H]^+$ (100).

1-(2-Methoxy-1-phenyl-ethyl)-3a-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole (16):



The compound **6** (490 mg, 1.47 mmol) was dissolved in THF (1.5 mL) and *n*-BuLi (2.5 M in hexane, 120 µL, 0.2 eq.) was added at room temperature. The reaction was stirred for 4 hours during which the solution turned from orange to yellow. A drop of water was added and the organic layer was diluted with ether, washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Solvents were evaporated and **16** was obtained as a colorless oil in a nearly quantitative yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.42-7.25 (m, 9H, aromatic H), 7.21-7.15 (m, 1H, aromatic H), 6.22-6.16 (m, 1H, olefinic H), 6.05-5.99 (m, 1H, olefinic H), 4.23 (t, *J* = 6.6Hz, 1H, PhCHN), 3.90-3.78 (m, 2H, CH_2O), 3.38 (s, 3H, OCH_3), 3.23-3.21 (m, 1H, allylic CH), 3.06-2.98 (m, 1H, CH*a*H*x*N), 2.65-2.98 (m, 1H, CH*a*H*x*N), 2.17-1.96 (m, 4H), 1.75-1.56 (m, 2H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 148.3 (aromatic C), 138.0 (aromatic C), 131.4 (olefinic CH), 128.9 (2 aromatic CH), 128.1 (2 aromatic CH), 127.9 (2 aromatic CH), 127.3 (olefinic CH), 126.6 (2 aromatic CH), 126.2 (aromatic CH), 125.6 (aromatic CH), 75.3 (CH_2O), 62.3 (PhCHN), 60.8 (allylic CH), 58.9 (OCH_3), 46.5 (aliphatic C), 45.8 (CH_2N), 37.9 (CH_2), 34.7 (CH_2), 23.6 (CH_2).

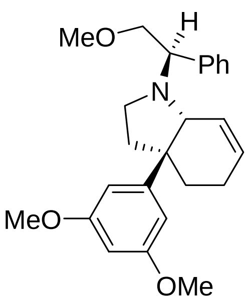
IR (film, NaCl): ν_{max} = 3025, 2924, 2826, 1495, 1452, 1192, 1112, 764, 700 cm^{-1}.

MS (EI, 70 eV) m/z (%): 288 $[M-CH_2OCH_3]^{+\cdot}$ (80), 91 $[tropylium]^{+\cdot}$ (100).

HRMS (EI): $[M-CH_2OMe]^+$ $C_{21}H_{22}N$: calcd. 288.1752; found 288.1756 (1 ppm).

$[\alpha]_D^{20}$ = -102° (C = 1.20, $CHCl_3$).

3a-(3,5-Dimethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole (17):



The compound **9** (362 mg, 0.92 mmol) was dissolved in THF (1.8 mL) and *n*-BuLi (2.5 $\underline{\mathrm{M}}$ in hexane, 110 µL, 0.3 eq.) was added at room temperature. The reaction was stirred for 4 hours during which the solution turned from orange to yellow. A drop of water was added and the organic layer was diluted with ether, washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Solvents were evaporated and the crude product was purified by flash chromatography (deactivated silica gel petroleum ether/EtOAc 95/5 to 90/10). Compound **17** (180 mg, 0.458 mmol, 46%) was obtained as a white solid (m.p. = 112.2-113.2°C) which was crystallized with ethyl acetate and hexane, to give crystals suitable for X-Ray analysis.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.35-7.21 (m, 5H, aromatic H), 6.39 (d, J = 2.3Hz, 2H ,2 aromatic H), 6.26 (t, J = 2.3Hz, 1H, aromatic H), 6.13-6.05 (m, 1H, olefinic H), 6.00-5.92 (m, 1H, olefinic H), 4.16 (t, J = 6.6Hz, 1H, $\mathrm{NC\underline{H}Ph}$), 3.82-3.71 (m, 2H, CH_2OMe), 3.75 (s, 6H, 2 OCH_3), 3.32 (s, 3H, OCH_3), 3.32 (d, J = 3.4Hz, 1H, allylic CH), 2.97-2.90 (m, 1H, $\mathrm{C\underline{H}}a\mathrm{H}x\mathrm{N}$), 2.59-2.51 (m, 1H, $\mathrm{CH}\underline{a}\underline{\mathrm{H}}x\mathrm{N}$), 2.08-1.9 (m, 4H), 1.70-1.58 (m, 2H).

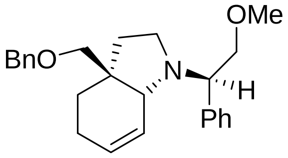
^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 160.3 (2 aromatic C), 151.0 (aromatic C), 137.9 (aromatic C), 131.5 (olefinic CH), 128.9 (2 aromatic CH), 128.2 (2 aromatic CH), 127.4 (aromatic CH), 126.1 (olefinic CH), 105.4 (2 aromatic CH), 96.9 (aromatic CH), 75.3 (CH_2O), 62.3 (PhCHN), 60.9 ($\mathrm{Cq\underline{C}HN}$), 59.0 ($OCH_3$), 55.3 (2 OCH_3), 46.9 (aliphatic C), 45.8 (CH_2), 37.8 (CH_2), 34.6 (CH_2), 23.7 (allylic CH_2).

IR (solid, KBr): ν_{max} = 2925, 1618, 1583, 1452, 1337, 1197, 1157, 1113, 1047, 841, 702 cm^{-1}.

MS (ESI) *m/z* (%): 394 $[M+H]^+$ (100).

$[\alpha]_D^{20}$ = -122° (C = 1.54, $CHCl_3$).

3a-Benzyloxymethyl-1-(2-methoxy-1-phenyl-ethyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole (18):



The compound **13** (82 mg, 0.218 mmol) was dissolved in THF (0.4 mL) and *n*-BuLi (2.5 $\underline{\mathrm{M}}$ in hexane, 40 µL, 0.4 eq.) was added at room temperature. The reaction was stirred for 2 hours during which the solution turned from orange to yellow. A drop of water was added and the organic layer was diluted with ether, washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Solvents were evaporated and after purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 97:3), the product 18 (67 mg, 0.178 mmol, 82%) was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40-7.28 (m, 10H, aromatic H), 5.97-5.88 (m, 1H, olefinic H), 5.81-5.75 (m, 1H, olefinic H), 4.56-4.47 (AB system, J_{AB} = 27.2Hz, 2H, $PhCH_2O$), 3.93 (t, J = 6.0Hz, 1H, PhCHN), 3.79-3.74 (m, 1H, $\mathrm{C\underline{H}}a\mathrm{H}b\mathrm{OMe}$), 3.66-3.60 (m, 1H, $\mathrm{CH}\underline{a}\underline{\mathrm{H}}b\mathrm{OMe}$), 3.40-3.18 (AB system, J_{AB} = 85.1Hz, 2H, $\mathrm{C\underline{H}_2OBn}$), 3.32 (s, 3H, OCH_3), 2.96 (s, 1H, allylic H), 2.82-2.68 (m, 2H, CH_2N), 2.18-1.89 (m, 2H, allylic H), 1.83-1.60 (m, 2H), 1.68 (t, J = 7.1Hz, 2H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 140.0 (aromatic C), 139.0 (aromatic C), 130.1 (olefinic CH), 128.6 (2 aromatic CH), 128.3 (2 aromatic CH), 128.2 (2 aromatic CH), 127.5 (2 aromatic CH), 127.4 (aromatic CH), 127.3 (aromatic CH), 125.4 (olefinic CH), 76.8 ($\mathrm{\underline{C}H_2OMe}$), 76.8 ($\mathrm{Cq\underline{C}H_2O}$), 73.3 ($CH_2OPh$), 64.0 (NCHPh), 59.3 (allylic CH), 59.0 (OCH_3), 47.3 (CH_2N), 43.2 (aliphatic C), 31.1 (CH_2), 28.4 (CH_2), 22.0 (CH_2).

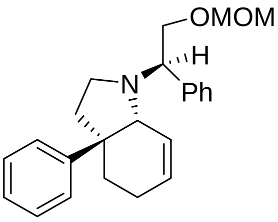
IR (film, KBr): ν_{max} = 3026, 2854, 1495, 1453, 1361, 1192, 1109, 1028, 735, 696 cm^{-1}.

MS (ESI) *m/z* (%): 378 $[M+H]^+$ (100).

HRMS (EI): $[M-CH_2OMe]^+$ $C_{23}H_{26}NO$: calcd 332.2014; found: 332.2026 (3 ppm).

$[\alpha]_D^{20}$ = -100° (C = 1.56, $CHCl_3$).

1-(2-Methoxymethoxy-1-phenyl-ethyl)-3a-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole (19):



The compound **7** (652 mg, 1.82 mmol) was dissolved in THF (1.8 mL) and *n*-BuLi (2.5 M in hexane, 145 µL, 0.2 eq.) was added at room temperature. The reaction was stirred for 3 hours during which the solution turned from orange to yellow. Water (0.5 mL) was added and the organic layer was diluted with ether, washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. Evaporation of solvents gave **19** (625 mg, 96%) which was used without purification.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.37-7.10 (m, 10H, aromatic H), 6.21-6.13 (m, 1H olefinic H), 6.03-5.94 (m, 1H, olefinic H), 4.65-4.56 (AB system, J_{AB} = 22.4Hz, 2H, OCH_2O), 4.22 (t, J = 7.3Hz, 1H, PhCHN), 3.97 (d, J = 7.3Hz, 2H, $CHC\underline{H_2}O$), 3.25 (s, 3H, OCH_3), 3.14-3.08 (m, 1H, allylic H), 3.02-2.93 (m, 1H, $C\underline{H}aHxN$), 2.58-2.48 (m, 1H, $CHa\underline{H}xN$), 2.14-1.89 (m, 4H), 1.71-1.46 (m, 2H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 148.3 (aromatic C), 137.4 (aromatic C), 131.8 (olefinic CH), 129.0 (2 aromatic CH), 128.2 (2 aromatic CH), 127.8 (2 aromatic CH), 127.4 (aromatic CH), 12.6 (2 aromatic CH), 125.9 (olefinic CH), 125.7 (aromatic CH), 96.6 (OCH_2O), 69.8 ($CH\underline{C}H_2O$), 62.1 (PhCHN), 60.7 (allylic CH), 55.4 (OCH_3), 46.4 (aliphatic C), 45.5 (CH_2), 38.0 (CH_2), 34.8 (CH_2), 23.7 (CH_2).

IR (film, KBr): ν_{max} = 3024, 2926, 2822, 1601, 1495, 1452, 1150, 1111, 1042, 917, 764, 700 cm^{-1}.

MS (ESI) *m/z* (%): 364 $[M+H]^+$ (100).

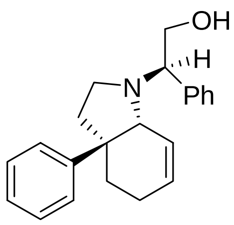
HRMS (SIMS): $[M+H]^+$ $C_{24}H_{30}NO_2$: calcd 364.2277; found 364.2279 (-0.6 ppm).

$[\alpha]_D^{20}$ = -100° (C = 1.26 $CHCl_3$).

Preparation of 20a and 20b:

The compound **19** (625 mg, 1.746 mmol), used as a crude, was dissolved in isopropanol (10 mL, HPLC grade). A concentrated solution of hydrochloric acid (0.4 mL) was then added and the media was warmed to 55°C for 16 hours. The solution was extracted with EtOAc. The organic layer was washed with a saturated Na_2CO_3 solution and dried over sodium sulfate. After purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 90/10), the compound **20b** (17 mg, 0.054 mmol, 3%) was eluted first then **20a** (406 mg, 1.27 mmol, 70% over two steps).

2-Phenyl-2-(3a-phenyl-2,3,3a,4,5,7a-hexahydro-indol-1-yl)-ethanol (20a):



^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40-7.12 (m, 10H, aromatic H), 6.33-6.25 (m, 1H, olefinic H), 6.11-6.03 (m, 1H, olefinic H), 4.25 (dd, J = 4.9 and 10.5Hz, 1H, NCHPh), 4.03 (t, J = 10.5Hz, 1H, $C\underline{H}aHxOH$), 3.70 (dd, J = 4.9 and 10.5Hz, 1H, $CHa\underline{H}xOH$), 3.30 (broad s, 1H, OH), 3.17 (d, J = 4.1Hz, 1H, allylic H), 3.05 (td, J = 8.7 and 3.4Hz, 1H, $C\underline{H}aHxN$), 2.33 (td, J = 9.03 and 8.7Hz, 1H, $CHa\underline{H}xN$), 2.17-1.92 (m, 4H), 1.78-1.69 (m, 1H), 1.60-1.45 (m, 1H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 147.5 (aromatic C), 134.9 (aromatic C), 133.2 (olefinic CH), 129.2 (2 aromatic CH), 128.3 (2 aromatic CH), 128.0 (aromatic CH), 127.9 (2 aromatic CH), 126.6 (2 aromatic CH), 125.8 (aromatic CH), 124.6 (olefinic), 61.4 (NCHPh), 60.9 (CH_2OH), 59.7 (allylic CH), 46.2 (aliphatic C), 42.6 (CH_2N), 38.6 (CH_2), 35.5 (allylic CH_2), 24.0 (CH_2).

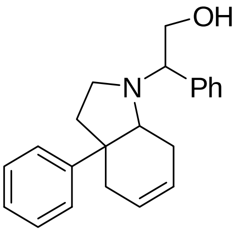
IR (film, NaCl): ν_{max} = 3432, 3025, 2930, 1494, 1058, 1031, 910, 765, 700 cm^{-1}.

MS (ESI) *m/z* (%): 320 $[M+H]^+$ (100).

HRMS (SIMS): $[M+H]^+$ $C_{22}H_{26}NO$: calcd 320.2014; found 320.2030 (-4.9 ppm).

$[\alpha]_D^{20}$ = -178° (C = 0.83, $CHCl_3$).

2-Phenyl-2-(3a-phenyl-2,3,3a,4,7,7a-hexahydro-indol-1-yl)-ethanol (20b):



^{1}**H NMR** (CDCl$_3$, 300 MHz): δ = 7.41-7.13 (m, 10H, aromatic H), 5.91-5.82 (m, 1H, olefinic H), 5.74-5.65 (m, 1H, olefinic H), 4.11 (dd, *J* = 4.5 and 10.5Hz, 1H, C$\underline{\mathrm{H}}$*a*H*x*O), 3.98 (dd, *J* = 9.8 and 10.5Hz, 1H, CH*a*$\underline{\mathrm{H}}$*x*O), 3.68 (dd, *J* = 4.5 and 9.8Hz, 1H, PhCHN), 3.14-3.04 (m, 2H, Cq-CHN and C$\underline{\mathrm{H}}$*a*H*x*N), 2.98 (broad s, 1H, OH), 2.72 (ddd, *J* = 10.2, 9.4 and 4.2Hz, 1H, CH*a*$\underline{\mathrm{H}}$*x*N), 2.54-2.40 (m, 3H, allylic H), 2.10-1.98 (m, 1H, allylic H), 1.97-1.79 (m, 2H, C$\underline{\mathrm{H}}_2$CH$_2$N).

^{13}**C NMR** (CDCl$_3$, 62.9 MHz): δ = 146.1 (aromatic C), 135.6 (aromatic C), 129.1 (2 aromatic CH), 128.4 (2 aromatic CH), 128.3 (2 aromatic CH), 127.9 (aromatic CH), 126.4 (2 aromatic CH), 126.2 (aromatic CH), 126.2 (olefinic CH), 123.8 (olefinic CH), 62.6 (Cq$\underline{\mathrm{C}}$HN), 61.0 (PhCHN), 60.6 (CH$_2$O), 45.9 (aliphatic C), 41.3 (CH$_2$N), 37.2 ($\underline{\mathrm{C}}$H$_2$CH$_2$N), 33.8 (allylic CH$_2$), 24.0 (allylic CH$_2$).

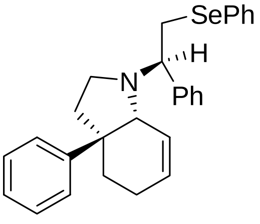
IR (film, KBr): ν_{max} = 3427, 3026, 2883, 1600, 1495, 1445, 1223, 1138, 1060, 1028, 761, 700, 660 cm^{-1}.

MS (SIMS) *m/z* (%): 320 [M+H]$^+$ (100), 288 [M-CH$_2$OH]$^+$ (45), 265 (65), 234 (32).

HRMS (SIMS): [M+H]$^+$ C$_{22}$H$_{26}$NO: calcd 320.2014; found 320.2025 (-3.2 ppm).

$[\alpha]_D^{23}$ = -120° (C = 0.81, CHCl$_3$).

3a-Phenyl-1-(1-phenyl-2-phenylselanyl-ethyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole (21):



To a solution of **20a** (618 mg, 1.94 mmol) in CH$_2$Cl$_2$ (20 mL) was added triethylamine (235 mg, 2.33 mmol, 1.2 eq.) and mesyl chloride (244 mg, 2.13 mmol, 1.1 eq.) at 0°C. After stirring for 4 hours at room temperature, the mixture was diluted with CH$_2$Cl$_2$, washed with a saturated Na$_2$CO$_3$ solution, dried over sodium sulfate and filtered. Evaporation of the solvents gave an oil. This product was diluted in ethanol (10 mL) and added, at 0°C, to a PhSeNa solution formed by heating sodium borohydride (155 mg, 4.07 mmol, 2.1 eq.) and diphenyldiselenide (604 mg, 1.94 mmol, 1 eq.) in ethanol (10 mL) at 80°C for 30 minutes. The resulting solution was then heated to 80°C for 2 hours. After concentration of the solution, a saturated Na$_2$CO$_3$ solution was added. Extraction with ethyl acetate, drying over sodium sulfate and evaporation of solvents gave a paste which was purified by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 100/0 to 99/1) to give **21** (716 mg, 1.56 mmol, 80%) as a colorless oil

^{1}**H NMR** (CDCl$_3$, 300 MHz): δ = 7.49-7.46 (m, 2H, aromatic H), 7.30-7.15 (m, 13H, aromatic H), 5.97-5.86 (m, 2H, olefinic H), 4.55 (dd, *J* = 5.5 and 10.1Hz, 1H, PhCHN), 3.63 (dd, *J* = 10.1 and 12.7Hz, 1H, C$\underline{\mathrm{H}}$*a*H*x*Se), 3.10-3.02 (m, 2H, allylic CH and C$\underline{\mathrm{H}}$*a*H*x*N), 2.97 (dd, *J* = 5.5 and 12.7Hz, 1H, CH*a*$\underline{\mathrm{H}}$*x*Se), 2.30 (dt, *J* = 8.7 and 8.7Hz, 1H, CH*a*$\underline{\mathrm{H}}$*x*N), 2.02-1.97 (m, 2H, C$\underline{\mathrm{H}}_2$CH$_2$N), 1.93-1.81 (m, 2H), 1.59-1.40 (m, 2H).

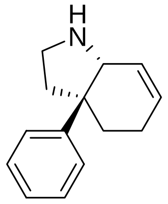
^{13}**C NMR** (CDCl$_3$, 75.5 MHz): δ = 148.0 (aromatic C), 141.1 (aromatic C), 135.4 (2 aromatic CH), 131.8 (olefinic CH), 129.8 (aromatic C), 128.9 (2 aromatic CH), 128.3 (2 aromatic CH), 128.1 (2 aromatic CH), 127.9 (2 aromatic CH), 127.8 (aromatic CH), 126.8 (aromatic CH), 126.6 (2 aromatic CH), 125.7 (aromatic CH), 125.2 (olefinic CH), 64.5 (allylic CH), 58.2 (CH$_2$Se), 51.2 (CH$_2$N), 47.0 (aliphatic C), 46.9 (PhCHN), 38.9 (CH$_2$), 34.6 (CH$_2$), 23.6 (CH$_2$).

IR (film, NaCl): ν_{max} = 3058, 3023, 2929, 2790, 1600, 1579, 1495, 1476, 1437, 910, 739, 693 cm^{-1}.

MS (SIMS) *m/z* (%): 460 [M+H (^{80}Se)]$^+$ (30), 302 [M -PhSeH]$^+$ (23), 212 (100).

HRMS (SIMS): [M+H (^{80}Se)]$^+$ C$_{28}$H$_{30}$N^{80}Se: calcd 460.1543; found 460.1539 (1.0 ppm).

3a-Phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole (22):



To a solution of **21** (60 mg, 0.131 mmol) in methanol (2 mL) was added sodium periodate (29 mg, 0.138 mmol, 1.05 eq.) and water (0.5 mL) at 0°C. After stirring at room temperature for 18 hours, the mixture was acidified with a 1 $\underline{M}$ solution of HCl. After stirring for additional 2 hours, the media was basified with a 10% sodium hydroxide solution and extracted with ether. After washing the organic layer with saturated Na_2CO_3 solution and drying over sodium sulfate, the paste was purified by flash chromatography (deactivated silica gel, CH_2Cl_2/MeOH 9/1) to give **22** as a oil (14 mg, 0.070 mmol, 51%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34-7.19 (m, 5H, aromatic H), 6.17-6.06 (m, 2H, 2 olefinic H), 5.93 (broad s, 1H, NH), 3.93 (s, 1H, CHN), 3.45 (ddd, *J* = 7.9, 8.3 and 11.7Hz, 1H, C$\underline{H}$*a*H*x*N), 3.27-3.18 (m, 1H, CH*a*$\underline{H}$*x*N), 2.37-2.19 (m, 2H), 2.06-1.91 (m, 2H), 1.79-1.72 (m, 1H, 1.62-1.50 (m, 1H).

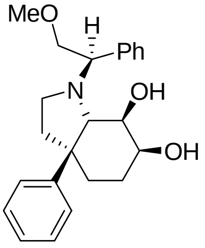
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 144.8 (aromatic C), 134.5 (CH), 128.4 (2 aromatic CH), 126.6 (CH), 126.3 (2 aromatic CH), 123.3 (CH), 59.2 (CHN), 47.3 (aliphatic C), 43.0 (CH_2), 39.9 (CH_2), 31.8 (CH_2), 22.9 (CH_2).

IR (solid, KBr): ν_{max} = 3424, 2880, 2780, 2725, 2454, 1601, 1497, 1408, 767, 701 cm^{-1}.

MS (SIMS) m/z (%): 200 $[M+H]^+$ (100).

HRMS (SIMS): $[M+H]^+$ $C_{14}H_{18}N$: calcd 200.1439; found : 200.1436 (1.7 ppm).

1-(2-Methoxy-1-phenyl-ethyl)-3a-phenyl-octahydro-indole-6,7-diol (precursor of 23):



To a crude solution of **16** (345 mg, 1.04 mmol) in *t*-BuOH (5 mL) and water (5 mL) was added $K_3Fe(CN)_6$ (1.022 g, 3.12 mmol, 3 eq.), potassium carbonate (429 mg, 3.12 mmol, 3 eq.), methanesulfonamide (98 mg, 1.04 mmol, 1 eq.), quinuclidine (4.6 mg, 0.04 mmol, 0.04 eq.), and potassium osmate dihydrate (11.4 mg, 0.03 mmol, 0.03 eq.). After stirring at room temperature for 24 hours, sodium sulfite (1.31 g, 10.4 mmol, 10 eq.) was added and the media was stirred for 30 minutes. The solution was basified with a 10% NaOH solution and extracted with ethyl acetate (4 times). A paste was obtained after drying over sodium sulfate, filtration and evaporation of solvent, which was sufficiently pure (by NMR) to be used directly in the next step (purification gave substantial lost of product).

Purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 50/50) gave the title compound as a colorless oil in moderate yield (around 50%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48-7.44 (m, 2H, aromatic H), 7.35-7.30 (m, 2H, aromatic H), 7.26-7.15 (m, 4H, aromatic H), 7.08-7.04 (m, 2H, aromatic H), 4.96 (broad s, 1H, OH), 4.16-4.13 (m, 1H), 3.79 (d, *J* = 8.3 Hz, 1H), 3.70 (dd, *J* = 10.2 and 3.4 Hz, 1H), 3.60 (dd, *J* = 8.7 and 2.6 Hz, 1H), 3.29-3.24 (m, 1H), 3.26 (s, 3H, OCH_3), 3.10 (t, *J* = 3.4 Hz, 1H), 2.92 (t, *J* = 8.7 Hz, 1H, C$\underline{H}$*a*H*x*N), 2.58 (broad s, 1H, OH), 2.41-2.32 (m, 1H, CH*a*$\underline{H}$*x*N), 2.56-2.09 (m, 3H), 1.95-1.85 (m, 1H), 1.72-1.62 (m, 2H).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 147.9 (aromatic C), 141.4 (aromatic C), 128.6 (2 aromatic CH), 128.4 (2 aromatic CH), 127.8 (2 aromatic CH), 127.0 (aromatic CH), 126.3 (2 aromatic CH), 126.2 (aromatic CH), 75.7 (CH_2O), 75.6 (CH), 69.0 (CH), 68.5 (CH), 68.0 (CH), 59.0 (OCH_3), 50.4 (CH_2), 50.2 (aliphatic C), 31.7 (CH_2), 31.6 (CH_2), 26.4 (CH_2).

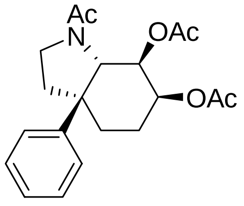
IR (film, NaCl): ν_{max} = 3405, 2928, 2892, 1452, 1099, 1060, 910, 733, 702 cm^{-1}.

MS (ESI) *m/z* (%): 368 $[M+H]^+$ (100).

HRMS (EI): $[M-CH_2OMe]^+$ $C_{21}H_{24}NO_2$: calcd 322.1807; found : 322.1836 (9 ppm).

$[\alpha]_D^{20}$ = -39° (C = 0.8, $CHCl_3$).

Acetic acid 7-acetoxy-1-acetyl-3a-phenyl-octahydro-indol-6-yl ester (23):



The solution of crude mixture of 1-(2-methoxy-1-phenyl-ethyl)-3a-phenyl-octahydro-indole-6,7-diol with palladium (10% wt. on activated carbon, 220 mg, 0.2 eq.) and a small amount of perchloric acid in ethanol (3 mL) and water (2 mL) was purged first with nitrogen then hydrogen through freeze-pump-thaw cycles. The solution was stirred for 2 days at room temperature under an atmosphere of hydrogen.

A 10% sodium hydroxide solution (1 mL) was added and the solution was filtered over celite and eluted with ethyl acetate. After evaporation of the solvents, the resulting paste was diluted in CH_2Cl_2 (10 mL). Triethylamine (2.2 mL, 15.5 mmol, 15 eq.), a small amount of DMAP then anhydride acetic acid (0.98 mL, 10.4 mmol, 10 eq.) were added at 0°C. After stirring overnight at room temperature, the organic phase was washed with brine and dried over sodium sulfate. Purification by flash chromatography (deactivated silica gel, petroleum ether/EtOAc 30/70) gave **23** as an oil (141 mg, 0.393 mmol, 38%, four steps). NMR in $CDCl_3$ shows a 1:1 mixture of two rotamers but deuterated benzene gives a 2:1 ratio and spaces out signals.

Major rotamer:

^{1}H NMR (C_6H_6, 300 MHz, only characteristic signals are noted): δ = 5.49-5.41 (m, 2H), 5.20 (dd, *J* = 9.2 and 2.8 Hz, 1H), 3.15 (t, *J* = 9.4 Hz, 1H, C$\underline{\text{H}}$*a*H*x*N), 2.74 (ddd, *J* = 7.9, 9.8 and 10.2 Hz, 1H, CH*aHx*N), 2.08 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H).

^{13}C NMR (C_6H_6, 75.5 MHz): δ = 171.0 (C=O), 169.9 (C=O), 169.2 (C=O), 146.6 (aromatic C), 129.1 (2 aromatic CH), 127.1 (aromatic CH), 125.6 (2 aromatic CH), 72.6 (CH), 70.4 (CH), 59.3 (CH), 49.4 (aliphatic C), 44.3 (CH_2), 33.2 (CH_2), 29.7 (CH_2), 25.0 (CH_2), 21.9 (CH_3), 21.3 (CH_3), 20.6 (CH_3).

Minor rotamer:

^{1}H NMR (C_6H_6, 300 MHz, only characteristic signals are noted): 5.68-5.64 (m, 1H), 5.00 (dd, *J* = 9.8 and 2.6 Hz, 1H), 4.55 (d, *J* = 9.8 Hz, 1H), 3.82-3.70 (m, 1H, C$\underline{\text{H}}$*a*H*x*N), 3.49-3.39 (m, 1H, CH*aHx*N), 2.08 (s, 3H), 1.83 (s, 3H), 1.75 (s, 3H).

^{13}C NMR (C_6H_6, 75.5 MHz): δ = 169.6 (C=O), 169.2 (C=O), 168.6 (C=O), 146.1 (aromatic C), 129.2 (2 aromatic CH), 127.3 (aromatic CH), 125.5 (2 aromatic CH), 74.0 (CH), 69.8 (CH), 63.5 (CH), 50.8 (aliphatic C), 43.2 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 24.8 (CH_2), 21.9 (CH_3), 21.3 (CH_3), 20.6 (CH_3).

IR (film, NaCl): ν_{max} = 3460, 2952, 1732, 1651, 1454, 1225, 1047, 954, 764, 702 cm^{-1}.

MS (SIMS) *m/z* (%): 382 $[M+Na]^+$ (60), 360 $[M+H]^+$ (100).

HRMS (SIMS): $[M+H]^+$ $C_{20}H_{26}NO_5$: calcd 360.1811; found : 360.1810 (0.3 ppm).

$[\alpha]_D^{23}$ = +198° (C = 1.45, $CHCl_3$).