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Synthesis of enantiopure (2*R*,3a*S*,7a*S*)-2-ethyloctahydroindol-6-one and its Fischer indolization

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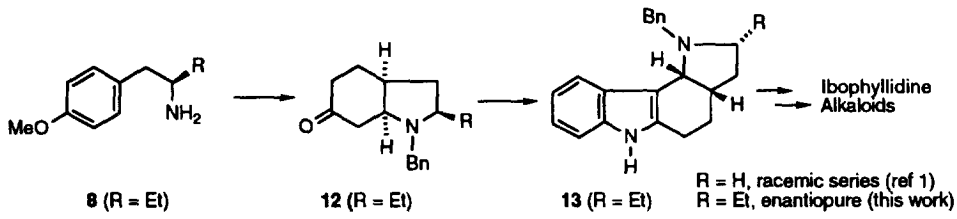
Abstract: A diastereoselective synthesis of (−)-2-ethyloctahydroindol-6-one **12** starting from *O*-methyl-L-tyrosine **1** is described. The process first involves the synthesis of enantiopure (−)-1-(4-methoxyphenyl)-2-butylamine **8**, which, after Birch reduction, *N*-benzylation and acid treatment, renders the *cis*-fused azabicyclo **12**. Studies on the Fischer indolization of **12** are also reported. © 1997 Elsevier Science Ltd

We have recently reported the synthesis of the indole alkaloid deethylibophyllidine in racemic form, in which an octahydroindol-6-one derivative was used to construct the pyrrolo[2,3-*d*]carbazole skeleton through a Fischer indolization[1] (Scheme 1). After this result, we became interested in developing the synthesis of more complex alkaloids with this skeletal-type, using the same strategy. With this objective in mind, in order to prepare intermediates for the synthesis of ibophyllidine,[2] we decided to develop a route to *cis*-fused 2-ethyl-octahydroindol-6-ones, preparing these compounds in enantiomerically pure form.



Scheme 1.

Our earlier work[1] has shown that *O*-methyltyramine can be used to synthesize the (±)-*N*-benzyl-*cis*-octahydroindol-6-one by means of Birch reduction, *N*-benzylation and acid-catalyzed isomerization followed by cyclization of the dihydroanisole formed (Scheme 1). If an optically active α-ethylphenethylamine, such as 4-(2-aminobutyl) anisole **8** were used, the three-step sequence might allow the synthesis of enantiopure compounds. We now report the implementation of this process to achieve the target 2-ethyloctahydroindol-6-one **12**, through a synthetic pathway in which L-tyrosine is used to prepare the required enantiopure α-ethylphenethylamine **8**.[3] In this paper we also describe the results obtained in the study of indolization of the β-amino ketone **12** in order to obtain pyrrolocarbazole **13**.

The synthesis starts from *O*-methyltyrosine **1**,[4] which was converted into the corresponding hydroxyethyl derivative **5** using the methodology developed by Reetz for other α-amino acids (Scheme 2).[5] Thus, after tribenzylation[6] of α-amino acid **1**, the resulting benzyl ester **2** was saponified[7] to give α-amino acid **3**, which was treated with methyllithium[8] to afford methyl ketone **4**, which, in turn, was reduced diastereoselectively to alcohol **5**. Reduction of α-amino alcohol **5** was carried out through the corresponding mesylate, which was treated with Super-Hydride® to afford the desired ethyl

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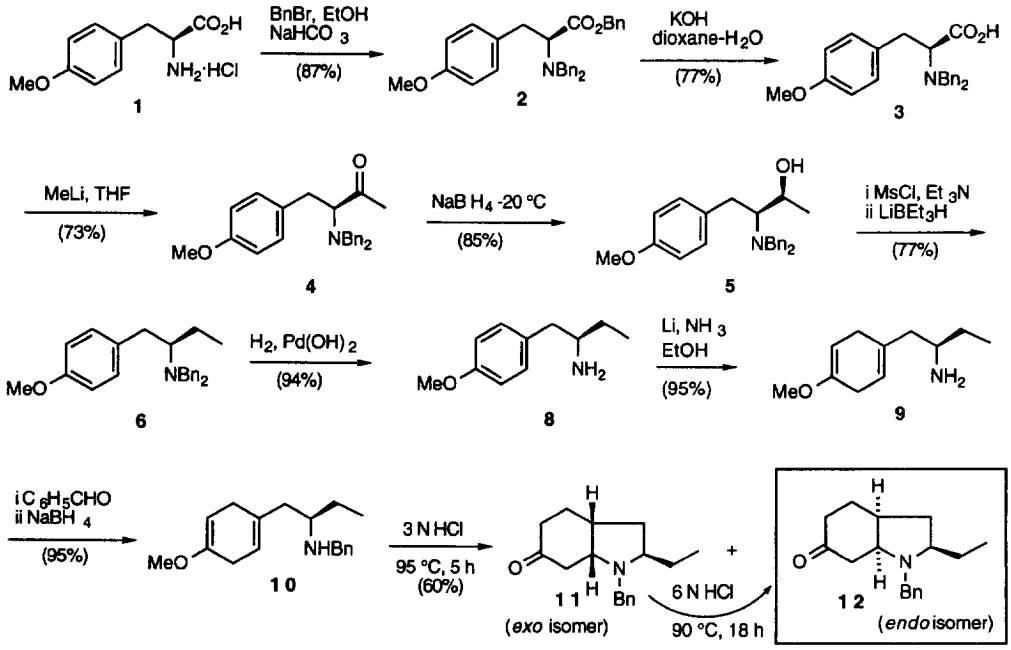
derivative **6**.[9,10] At this point, in order to ensure that the stereogenic center had not undergone partial racemization during the transformation **1**→**6**, the ^{1}H NMR spectrum of amine **6** was recorded as its (*S*)-MTPA salt,[11] both in the optically active and in the racemic series. Whereas in (±)-**6** the signals appeared duplicated for protons adjacent to the nitrogen atom, the spectrum of the corresponding optically active (−)-**6** indicated there was no enantiomeric contamination.



Scheme 2.

Primary amine **8** was isolated after debenzylation of tertiary amine **6**, using $Pd(OH)_2$ as a catalyst. Birch reduction[12] of anisole **8** afforded in nearly quantitative yield dihydrobenzene **9**, which was treated with benzaldehyde followed by sodium borohydride reduction of the resulting imine to gain the *N*-benzyl derivative **10**. This was subjected to acid hydrolysis (3 N HCl at 80°C for 4 h), leading to isomerization and cyclization. The process is stereoselective, the *cis*-octahydroindole ring being formed exclusively as a mixture of isomers exo and endo **11** and **12**, respectively (a through-space correlation between the H-3a and H-7a is observed in the ROESY spectrum of **12**). Interestingly, we observed that β-amino ketone **11** in hydrochloric acid underwent clean conversion to **12** and that under these equilibrating conditions the endo isomer **12** predominated to the extent of approximately 9:1 over the exo-isomer **11**. The diastereoselective synthesis of enantiopure **12** constitutes the first synthesis of a compound of this type.[13]

Studies using NMR spectroscopy (500 MHz, COSY, HMQC, ROESY experiments) have allowed us to assign the conformational preference of *cis*-octahydroindolone **12**.[14] This compound appears to adopt a preferred conformation which locates the bond C-3a/C-3 axially with respect to the carbocyclic ring. The ROESY experiment for **12** shows, *inter alia*, (see Figure 1) interrelations between H-3α and H-5ax as well as H-2β and H-3a, which corroborates this fact. Interestingly, the coupling constants of H-7a with H-3a (9 Hz) and H-7 (4.5 Hz with both protons) suggest that the carbocyclic ring does not adopt a chair conformation. This feature seems to be common for both octahydroindol-6-one derivatives synthesized in this work, as well as for the deethyl derivative described in a previous work,[1] as is reflected by their similar ^{13}C NMR data for the carbocyclic carbon atoms.

With an efficient procedure for the synthesis of azabicyclic ketone **12**, we investigated the Fischer

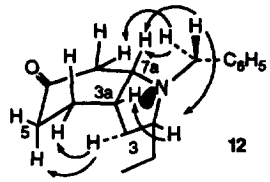
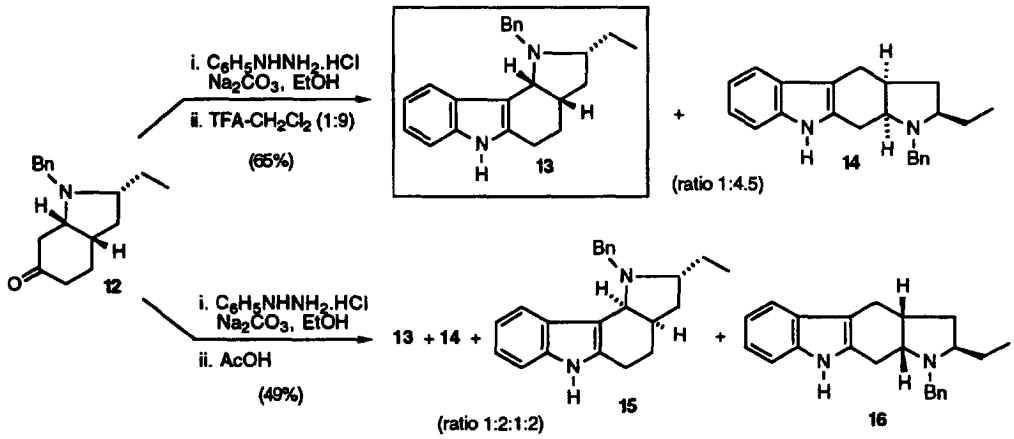


Figure 1.

indole synthesis upon **12** in order to obtain pyrrolocarbazole **13**, a valuable intermediate in our projected synthesis of ibophyllidine (Scheme 1). Unfortunately, Fischer indolization of ketone **12** proved to be troublesome. When **12** phenylhydrazone was treated with glacial acetic acid, the reaction occurred in a way that furnished a mixture of four compounds (**13–16**) in 49% overall yield, as a result of the indolization upon both methylene carbons adjacent to the original carbonyl group and the isomerization process endo→exo (Scheme 3).



Scheme 3. Fischer indolization of ketone **12**.

This latter process probably occurs via equilibration, in the hot acetic acid medium, via reverse Mannich reaction upon the β-amino phenylhydrazone intermediate.[15,16] When operating from TFA–CH_2Cl_2[17] the process was very clean, only the endo isomers being formed, but the major isomer isolated was the undesired **14** (53%), whereas tetracyclic base **13** was formed only in a 12% yield. The reason for the different behaviour in the indolization step of ketone **12** with respect to the results described in the deethyl series[1] is not clear.[18] The results reported here show that Fischer indolization of 1-benzyl-2-ethyloctahydroindol-6-one **12** does not constitute a valid method for constructing pyrrolocarbazole **13**, precursor of indole alkaloid ibophyllidine.

The structural elucidation of four compounds was clearly established from their NMR spectra data. Thus, the constitution of isomers was assigned on the basis of the coupling pattern/chemical shift observed for the methine proton adjacent to the nitrogen atom: the ^1H spectra of [3,2-*c*] fused compounds **13** and **15** display a doublet at δ 4.0 and 4.3 for H-10c, while the [2,3-*b*] fused compounds **14** and **16** show a multiplet at δ lower than 3.5 for the H-10a proton. For the endo–exo pairs of tetracyclic bases **13** and **15** as well as **14** and **16**, the same signal of methine adjacent to nitrogen atom diagnosed the stereochemistry endo–exo. In the endo series this signal appears more deshielded (~0.3 ppm) than in the exo series due to the proximity of the nitrogen lone pair.

In summary, we have developed a procedure to synthesize 2-ethyloctahydroindol-6-ones in enantiomeric pure form and we have showed that Fischer indolization in this series does not provide

an adequate entry to advanced ibophyllidine synthetic intermediates because, although the desired tetracyclic base **13** has been isolated, the low yield of the process, due to the lack of the adequate regioselectivity, means that this approach to the synthesis of ibophyllidine is not worthwhile.

Experimental

General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and 75.4 MHz. In addition, 2D NMR COSY and HMQC experiments were performed on a Varian XL-500 instrument. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were determined on a Hewlett–Packard 5988 A mass spectrometer or on an Autospec-VG (HRMS). Optical rotations were taken on a Perkin–Elmer Model 241 polarimeter with a 1 ml (L=1 dm) cell. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light and a 1% $KMnO_4$ solution or hexachloroplatinate reagent. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). All reactions were carried out under an argon or nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Melting points were determined in a capillary tube on a Büchi apparatus. Microanalyses were performed by the "Centro de Investigación y Desarrollo" (CSIC), Barcelona.

Benzyl (S)-2-(N,N-dibenzyl)amino-3-(4-methoxyphenyl)propanoate 2

Benzyl bromide (54.7 ml, 257 mmol was added dropwise to a solution of amino acid hydrochloride **1** (17 g, 73.4 mmol) and K_2CO_3 (45.7 g, 330 mmol) in EtOH (400 ml). The mixture was heated to reflux for 5 h. Then, once the solution was filtered, the solvent was removed under reduced pressure, and the residue was dissolved in brine (100 ml) and extracted with CH_2Cl_2 (3×150 ml). The combined organic extracts were dried and concentrated. Chromatography (CH_2Cl_2/hexane 1:3) of the residue afforded amino ester **2** (29.7 g, 87%) as a colorless oil: $[\alpha]_D^{22}$ −58.5 (*c* 1.5, $CHCl_3$); IR (film) 1731; ^1H NMR 2.93 (dd, J=14.1, 8 Hz, 1H, H-3), 3.08 (dd, J=14.1, 7.5 Hz, 1H, H-3), 3.52 (d, J=14 Hz, 2H, NCH_2), 3.66 (t, J=7.8 Hz, 1H, H-2), 3.79 (s, 3H, OCH_3), 3.92 (d, J=14 Hz, 2H, NCH_2), 5.11 and 5.22 (2d, J=12.4 Hz, 1H each, OCH_2), 6.75 (d, J=8.7 Hz, 2H, H-2′ and H-6′), 6.92 (d, J=8.7 Hz, 2H, H-3′ and H-5′), 7.16–7.35 (m, 15H, Ar); ^{13}C NMR 34.7 (C-3), 54.3 (NCH_2), 55.1 (OCH_3), 62.5 (C-2), 65.8 (OCH_2), 113.4 (C-3′ and C-5′), 126.7, 128.0, 128.1, 128.3, 128.4, 128.5, 135.7 and 139.1 (Ar), 129.9 (C-1′), 130.2 (C-2′ and C-6′), 158.0 (C-4′), 172.0 (C-1). Anal. Calcd for $C_{31}H_{31}NO_3$: C, 79.97; H, 6.71; N, 3.01. Found: C, 79.85; H, 6.72; N, 2.98.

Benzyl (S)-2-(N,N-dibenzyl)amino-3-(4-methoxyphenyl)propanoic acid 3

A solution of amino ester 2 (29.7 g, 63.9 mmol) in a 6:1:3 dioxane–MeOH–KOH (2 N) solution (1000 ml), was stirred overnight at room temperature. When TLC indicated complete consumption of starting material, the reaction mixture was extracted with Et_2O (3×150 ml) and EtOAc (3×200 ml). The combined organic extracts were dried and concentrated. Chromatography (increasing polarity from CH_2Cl_2 to EtOAc) of the residue afforded amino acid **3** (18.5 g, 77%) as a white foam: $[\alpha]_D^{22}$ −31.4 (*c* 1, $CHCl_3$) ; IR (film) 2400–3200, 1704; ^1H NMR 2.98 (dd, J=14.4, 8.7 Hz, 1H, H-3), 3.24 (dd, J=14.4, 6.1 Hz, 1H, H-3), 3.70 (dd, J=8.7, 6.1 Hz, 1H, H-2), 3.74 and 3.80 (2d, J=14 Hz, 2H each, NCH_2), 3.81 (s, 3H, OCH_3), 6.81 (d, J=8.6 Hz, 2H, H-2′ and H-6′), 7.02 (d, J=8.6 Hz, 2H, H-3′ and H-5′), 7.16–7.26 (m, 10H, Ar), ^{13}C NMR 33.9 (C-3), 54.3 (NCH_2), 55.1 (OCH_3), 62.9 (C-2), 113.6 (C-3′ and C-5′), 127.2 (*p*-Ar), 128.2 and 128.8 (*o* and *m*-Ar), 130.0 (C-1′), 130.3 (C-2′ and C-6′), 138.0 (*ipso*-Ar), 158.1 (C-4′), 176.5 (C-1), Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73; Found: C, 76.39; H, 6.73; N, 3.72.

(S)-3-(N,N-Dibenzyl)amino-4-(4-methoxyphenyl)-2-butanone 4

To a solution of amino acid **3** (22.6 g, 60.3 mmol) in THF (500 ml) at 0°C was added a 1.6 M solution of MeLi (100 ml), and then the solution was stirred for 7 h. At this time, saturated aqueous NH_4Cl (400 ml) was added very slowly. The aqueous layer was separated and extracted with CH_2Cl_2 (3×300 ml), and the combined organic extracts were washed with brine, dried and concentrated. Chromatography (hexane/EtOAc 9:1) provided ketone **4** (16.2 g, 73%) as a white solid and 930 mg (4%) of 3-(*N,N*-dibenzyl)amino-2-methyl-4-(4-methoxyphenyl)-2-butanol (**17**) as a by-product. Compound **4**: mp 81–83°C (hexane); $[\alpha]_D^{22}$ −44.5 (*c* 1.8, $CHCl_3$); IR (KBr) 1715; ^{1}H NMR 2.08 (s, 3H, H-1), 2.83 (dd, *J*=13.5, 3.8 Hz, 1H, H-4), 3.09 (dd, *J*=13.5, 9.5 Hz, 1H, H-4), 3.49 (dd, *J*=9.5 and 3.8 Hz, 1H, H-3), 3.56 (d, *J*=13.6 Hz, 2H, NCH_2), 3.72 (s, 3H, OCH_3), 3.79 (d, *J*=13.6 Hz, 2H, NCH_2), 6.76 (d, *J*=8.6 Hz, 2H, H-2′ and H-6′), 7.03 (d, *J*=8.6 Hz, 2H, H-3′ and H-5′), 7.20–7.30 (m, 10H, Ar); ^{13}C NMR 28.0 (C-4), 28.9 (C-1), 54.5 (NCH_2), 55.1 (OCH_3), 68.7 (C-3), 113.6 (C-3′ and C-5′), 127.2 (*p*-Ar), 128.3 and 128,8 (*o* and *m*-Ar), 130.3 (C-2′ and C-6′), 131.4 (C-1′), 139.1 (*ipso*-Ar), 157.7 (C-4′), 208.3 (C-2); Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75; Found: C, 80.35; H, 7.32; N, 3.83. Compound **17**: $[\alpha]_D^{22}$ +50.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR 1.00 and 1.26 (2s, 3H each, CH_3), 2.83 (dd, *J*=12.5, 3 Hz, 1H), 2.98–3.10 (m, 2H), 3.4 (br, 1H, OH), 3.84 (s, 3H, OCH_3), 3.75–3.90 (br, 4H, NCH_2), 6.92 (d, *J*=8.5 Hz, 2H), 7.23–7.31 (m, 12H); ^{13}C NMR 26.0 and 29.4 ($2CH_3$), 31.2 (CH_2), 55.1 (OCH_3), 55.9 (NCH_2), 67.7 (CH), 71.1 (C), 113.8 (2CH), 127.1, 128.3, 128.7, 128.9, 129.1, 130.1, 132.6, 139.1, 158.0 (Ar).

(2S,3S)-3-(N,N-Dibenzyl)amino-4-(4-methoxyphenyl)-2-butanol 5

To a solution of amino ketone **4** (15 g, 40.2 mmol) in MeOH (500 ml) at −23°C was added $NaBH_4$ (3.15 g, 80.4 mmol) in small portions. The resulting mixture was maintained at this temperature for 8 h. Then, water (200 ml) was added and the mixture was extracted with Et_2O (3×250 ml). The organic extracts were washed with brine, dried, and concentrated, yielding alcohol **5** as a pure powder (15 g, quantitative), which was recrystallized from MeOH (12.75 g, 85%): mp 113–115°C (MeOH); $[\alpha]_D^{22}$ +47.3 (*c* 2, $CHCl_3$); IR (KBr) 3396; ^{1}H NMR 0.97 (d, *J*=6 Hz, 3H, H-1), 2.61 (dd, *J*=14.4, 6.2 Hz, 1H, H-4), 2.75 (dt, *J*=8.9, 6.4 Hz, 1H, H-3), 3.04 (dd, *J*=14.3, 6.3 Hz, 1H, H-4), 3.38 (d, *J*=13.4 Hz, 2H, NCH_2), 3.73 (dq, *J*=8.9, 6.1 Hz, 1H, H-2), 3.83 (s, 3H, OCH_3), 3.88 (d, *J*=13.2 Hz, 2H, NCH_2), 4.39 (s, 1H, OH), 6.87 (d, *J*=8.6 Hz, 2H, H-2′ and H-6′), 7.13 (d, *J*=8.5 Hz, 2H, H-3′ and H-5′), 7.19–7.30 (m, 10H, Ar); ^{13}C NMR 20.3 (C-1), 31.2 (C-4), 53.7 (NCH_2), 55.2 (OCH_3), 66.0 (C-3), 66.6 (C-2), 113.9 (C-3′ and C-5′), 127.2 (*p*-Ar), 128.4 and 129.0 (*o*- and *m*-Ar), 130.0 (C-2′ and C-6′), 132.3 (C-1′), 138.9 (*ipso*-Ar), 158.0 (C-4′), Anal. Calcd for $C_{25}H_{29}NO_2$: C, 79.95; H, 7.79, N, 3.73; Found: C, 79.97; H, 7.87; N, 3.74.

In some runs, after the addition of water in the work-up, a precipitate appeared, which was filtered and corresponded to pure alcohol **5**.

(R)-N,N-Dibenzyl-1-(4-methoxyphenyl)-2-butanamine 6

A solution of **5** (3.75 g, 10 mmol) in THF (200 ml) was cooled to 0°C and triethylamine (1.5 ml, 11 mmol) and mesyl chloride (0.95 ml, 10 mmol) were added. The reaction was allowed to warm to room temperature and stirred for 1 h (until the complete disappearance of starting material was observed by TLC). The crude reaction mixture was filtered and the solution was concentrated to a volume of 50 ml at 0°C. Then, a 1 M solution of Super-Hydride® (100 ml) was added dropwise. The reaction was warmed to 65°C for 3 h. At this time, it was cooled and quenched with brine (25 ml). The aqueous layer was extracted with Et_2O (4×40 ml), and the combined organic layers dried. Evaporation of the solvent and chromatography of the residue (EtOAc/Hexane 1:19) afforded a mixture of amines (3.08 g, 88%) identified as amine **6** and (*R*)-*N,N*-(dibenzyl)-4-(4-methoxyphenyl)-2-butanamine **7** in a 7:1 ratio. After an additional chromatography both compounds were isolated in a pure form. Compound **6**: mp 79°C (hexane); $[\alpha]_D^{22}$ +29.7 (*c* 0.9, $CHCl_3$); IR (neat) 1613, 1515, 1247; ^{1}H NMR 0.86 (t, *J*=7.3 Hz, 3H, H-4), 1.24–1.38 (m, 1H, H-3), 1.49–1.61 (m, 1H, H-3), 2.38 (dd, *J*=13.3, 8.7 Hz, 1H,

H-1), 2.62 (m, 1H, H-2), 2.99 (dd, *J*=13.3, 4.5 Hz, 1H, H-1), 3.55 and 3.78 (2d, *J*=14 Hz, 2H each, NCH_2), 3.78 (s, 3H, OCH_3), 6.77 (d, *J*=8.5 Hz, 2H, H-2′ and H-6′), 6.95 (d, *J*=8.5 Hz, 2H, H-3′ and H-5′), 7.20–7.34 (m, 10H, Ar); ^{13}C NMR 11.8 (C-1), 22.7 (C-2), 34.3 (C-4), 53.3 (NCH_2), 55.2 (OCH_3), 61.3 (C-2), 113.5 (C-3′ and C-5′), 126.6 (*p*-Ar), 128.1 and 128.7 (*o*- and *m*-Ar), 130.1 (C-2′ and C-6′), 133.0 (C-1′), 140.5 (*ipso*-Ar), 157.6 (C-4′). Anal. Calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90. Found: C, 83.55; H, 8.17; N, 3.90. Compound **7**: IR (film) 1611, 1511, 1245; ^1H NMR 1.03 (d, *J*=6.6 Hz, 3H, H-1), 1.50 (ddt, *J*=13.6, 10.4, 6 Hz, 1H, H-3), 1.81–1.94 (m, 1H, H-3), 2.44 (ddd, *J*=10.4, 6, 5.8 Hz, 1H, H-4), 2.68–2.79 (m, 2H, H-2 and H-4), 3.42 and 3.72 (2d, *J*=14 Hz, 2H each, NCH_2), 3.76 (s, 3H, OCH_3), 6.75 (d, *J*=8.7 Hz, 2H, H-2′ and H-6′), 6.97 (d, *J*=8.6 Hz, 2H, H-3′ and H-5′), 7.21–7.39 (m, 10H, Ar), ^{13}C NMR 13.3 (C-1), 32.3 (C-3), 36.7 (C-4), 52.1 (C-2), 53.3 (NCH_2), 55.2 (OCH_3), 113.6 (C-3′ and C-5′), 126.6 (*p*-Ar), 128.1 and128.7 (*o*- and *m*-Ar), 129.2 (C-2′ and C-6′), 135.0 (C-1′), 140.7 (*ipso*-Ar), 157.5 (C-4′). Anal Calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90; Found: C, 83.60; H, 8.19; N, 3.87.

(R)-1-(4-Methoxyphenyl)-2-butanamine ***8***

A mixture of amine **6** (11.2 g, 6.74 mmol), EtOH (600 ml) and 20% $Pd(OH)_2$ (1.12 g) was stirred under H_2 at room temperature until the complete disappearance of starting material was observed by TLC (2 days). Additional $Pd(OH)_2$ (600 mg) was added during the process. The mixture then was filtered through Celite®, and the Celite® was washed with a large quantity of CH_2Cl_2. The filtrate was concentrated, affording 5.25 g (94%) of primary amine **8** as a white solid, which required no additional purification: mp 168–170°C; $[\alpha]_D^{22}$ −9.25 (*c* 1.15, $CHCl_3$); IR (KBr): 3403; ^1H NMR 0.98 (t, *J*=7.4 Hz, 3H, H-4), 1.34–1.58 (m, 2H, H-3), 2.54 (dd, *J*=13.5, 8 Hz, 1H, H-1), 2.77 (dd, *J*=13.5, 5.5 Hz, 1H, H-1), 2.94 (m, 1H, H-2), 3.13 (br s, 2H, NH_2), 3.78 (s, 3H, OCH_3), 6.84 (d, *J*=8.5 Hz, 2H, H-2′ and H-6′), 7,12 (d, *J*=8.5 Hz, 2H, H-3′ and H-5′); ^{13}C NMR 10.4 (C-4), 29.0 (C-3), 42.1 (C-1), 54.4 (C-2), 55.1 (OCH_3), 113.8 (C-3′ and C-5′), 130.1 (C-2′ and C-6′), 130.9 (C-1′), 158.1 (C-4′). HRMS Calcd for $C_{11}H_{17}NO$: 179.1310, found 179.1312.

(R)-1-(4-Methoxy-2,5-dihydrophenyl)-2-butanamine ***9***

To a solution of amine **8** (5.41 g, 30.2 mmol) in EtOH (30 ml) was added at −78°C ammonia (100 ml). Small chips of lithium (1.75 g, 0.25 g-atom) were added (*ca.* 1 h) with vigorous stirring until the solution was a persistent deep blue, and then stirring was maintained for 90 min. The cooling bath was removed, the ammonia was allowed to evaporate overnight, and the reaction mixture was concentrated. Brine (100 ml) was added to the residue, and the mixture was extracted with Et_2O (3×100 ml). The dried organic extract was concentrated to give **9** (5.2 g, 96%) as an oil, which was deemed suitably pure to carry through to subsequent steps without purification: ^1H NMR 0.94 (t, *J*=7.4 Hz, 3H, H-4), 1.20–1.45 (m, 2H, H-3), 1.46 (br s, 2H, NH_2), 1.88 (dd, *J*=13.6, 9.2 Hz, 1H, H-1), 2.15 (dd, *J*=13.6, 4.4 Hz, 1H, H-1), 2.72–2.94 (m, 1H, H-2), 2.73 (brs, 4H, H-2′ and H-5′), 3.54 (s, 3H, OCH_3), 4.62 (brs, 1H, H-3′), 5.46 (brs, 1H, H-6′); ^{13}C NMR 10.4 (C-4), 29.0 and 29.2 (C-2′ and C-5′), 30.4 (C-3), 45.2 (C-1), 49.9 (C-2), 53.7 (OCH_3), 90.2 (C-3′), 119.9 (C-6′), 132.9 (C-1′), 152.8 (C-4′).

(2R,3aR,7aR)- and (2R,3aS,7aS)-1-Benzyl-2-ethyloctahydroindole-6-one ***11*** *and* ***12***

To a solution of amine **9** (5.2 g, 28.7 mmol) in CH_2Cl_2 (30 ml), were added benzaldehyde (3.03 g, 30 mmol) and molecular sieves (4 Å, 5 g). The mixture was stirred at room temperature for 4 h, filtered, and concentrated to give the crude imine as a yellowish oil: IR (film) 1704, 1664, 1644. To a stirred solution of this imine in MeOH (30 ml) was slowly added $NaBH_4$ (1.085 g, 28.7 mmol) at room temperature. The reaction mixture was stirred for 3 h, quenched by addition of water (100 ml) and then extracted with CH_2Cl_2 (3×100 ml). The organic extract was dried and concentrated to provide (2*S*)-*N*-benzyl-2-(4-methoxy-3,6-dihydrophenyl)-2-butanamine (**10**) in a quantitative yield (8 g) as a yellow oil, which was used directly in the next step: IR (film) 3303, 1695, 1664; ^1H NMR 0.90 (t, *J*=7.4 Hz, 3H, H-4), 1.30–1.58 (m, 2H, H-3), 1.90–2.10 (m, 3H, NH and H-1), 2.54–2.71 (m, 5H, H-2, H-2′ and H-5′), 3.55 (s, 3H, OCH_3), 3.68 and 3.83 (2d, *J*=13.2 Hz, 1H each, CH_2Ar), 4.58 (br

t, *J*=1.5 Hz, 1H, H-3′), 5.42 (br s, 1H, H-6′), 7.25–7.44 (m, 5H, Ar); ^{13}C NMR 9.8 (C-4), 26.4 (C-3), 29.2 and 29.2 (C-2′ and C-5′), 41.6 (C-1), 51.1 (NCH_2), 53.9 (OCH_3), 55.1 (C-2), 90.4 (C-3′), 120.3 (C-6′), 126.8 (*p*-Ar). 128.1 and 128.3 (*o* and *m*-Ar), 133.0 (C-1′), 140.7 (*ipso*-Ar), 152.8 (C-4′).

A solution of crude **10** (4.89 g) in 3 N HCl (10 ml) was heated at 95°C for 5 h. The reaction mixture was basified with 2 N aqueous NaOH and extracted with CH_2Cl_2 (3×20 ml). Purification of the dried organic extract by chromatography (15:85 EtOAc–CH_2Cl_2) gave **11** (320 mg, 7%) and **12** (2.49 g, 53%). Compound **11**: $[\alpha]_D^{22}$ −59.9 (*c* 2, $CHCl_3$); IR (film) 1713; ^{1}H NMR (COSY) 0.83 (t, *J*=7.4 Hz, 3H, CH_3), 1.23 (ddq, *J*=12, 11, 7 Hz, 1H, CH_2CH_3), 1.66 (dqd, *J*=12, 7, 3.5 Hz, 1H, CH_2CH_3), 1.77–1.81 (m, 3H, H-3 and H-4), 1.91–2.03 (m, 1H, H-4), 2.14 (dt, *J*=17.1, 5.4 Hz, 1H, H-5), 2.40–2.47 (m, 3H, H-5 and H-7), 2.49–2.58 (m, 1H, H-3a), 2.84 (m, 1H, H-2), 3.29 (dt, *J*=9.1, 5.7 Hz, 1H, H-7a), 3.47 and 3.82 (2d, *J*=14 Hz, 1H each, CH_2Ar), 7.20–7.30 (Ar); ^{13}C NMR (HMQC) 10.4 (CH_3), 22.2 (CH_2), 25.8 (C-4), 33.1 (C-3), 34.3 (C-3a), 36.2 (C-5), 40.1 (C-7), 51.0 (CH_2Ar), 59.5 (C-7a), 60.8 (C-2), 126.7 (*p*-Ar), 128.0 (*m*-Ar), 128.7 (*o*-Ar), 138.7 (*ipso*-Ar), 212.9 (C-6). Compound **12**: $[\alpha]_D^{22}$ −52.5 (*c* 1.25, $CHCl_3$); IR (film) 1716; ^{1}H NMR (COSY, 500 MHz) 0.83 (t, *J*=7.5 Hz, 3H, CH_3), 1.15–1.26 (m, 2H, CH_2CH_3 and H-3), 1.63–1.75 (m, 2H, CH_2CH_3 and H-4_{eq}), 1.93 (dddd, *J*=13, 10, 5.5, 4.5 Hz, 1H, H-4_{ax}), 2.13 (m, 1H, H-3), 2.16 (ddd, *J*=18, 7.5, 4.5 Hz, 1H, H-5_{eq}), 2.35 (m, 1H, H-3a), 2.34 and 2.41 (2dd, *J*=15.5, 4.5 Hz, 1H each, H-7), 2.43–2.50 (m, 2H, H-2 and H-5_{ax}), 2.99 (ddd *J*=9, 4.5, 4.5 Hz, 1H, H-7a), 3.66 and 3.71 (2d, *J*=14.5 Hz, 1H each, CH_2Ar), 7.20 (d, *J*=7.5, 2H, *o*-Ar), 7.21 (td, *J*=7.5, 1 Hz, 1H, *p*-Ar), 7.27 (td, *J*=7.5, 1 Hz, 1H, *m*-Ar); ^{13}C NMR (HMQC) 10.2 (CH_3), 26.5 (CH_2CH_3), 26.6 (C-4), 33.2 (C-3a), 35.9 (C-3), 36.3 (C-5), 42.7 (C-7), 55.1 (CH_2Ar), 61.9 (C-7a), 64.8 (C-2), 126.7 (*p*-Ar), 128.2 (*m*-Ar), 128.4 (*o*-Ar), 139.5 (*ipso*-Ar), 213.0 (C-6). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.31; H, 9.11; N, 5.45.

When a solution of **11** in 6 N HCl was heated at 90°C for 18 h, after the usual work-up, azabicyclic ketone **12** was obtained as the major product (9:1 ratio with respect to **11**).

Fischer indolization of ketone 12

Method A. To a solution of ketone **12** (176 mg, 0.68 mmol) in EtOH (6 ml) were added phenylhydrazine hydrochloride (127 mg, 0.88 mmol) and Na_2CO_3 (86 mg, 0.81 mmol). The mixture was heated at reflux for 3 h (until disappearance of carbonyl absorption in IR spectrum), filtered, and concentrated. The crude hydrazone was dissolved in 25 ml of a mixture of TFA–CH_2Cl_2 (1:10) and heated at 35–40°C for 17 h. The reaction mixture was quenched by addition of Na_2CO_3 solution. The organic layer was dried, concentrated and the residue chromatographed twice. On elution with CH_2Cl_2–EtOAc (10:1) (2*R*,3a*R*,10a*R*)-1-benzyl-2-ethyl-1,2,3,3a,4,9,10,10a-octahydropyrrolo[2,3-*b*]carbazole (**14**, 117 mg, 53%) was isolated. Further elution (CH_2Cl_2/EtOAc, 4:1) gave (2*R*,3a*S*,10c*R*)-1-benzyl-2-ethyl-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3,2-*c*]carbazole (**13**, 26 mg, 12%). Compound **13**: $[\alpha]_D^{22}$ −16.3 (*c* 0.6, $CHCl_3$); IR (neat) 3408; ^{1}H NMR (COSY, 500 MHz) 0.64 (t, *J*=7 Hz, 3H, CH_3), 0.85 and 1.30 (2m, 1H each, CH_2CH_3), 1.15 (m, 1H, H-4), 1.25 (m, 1H, H-3), 1.80 (m, 1H, H-4), 2.22–2.40 (m, 2H, H-3 and H-3a), 2.66–2.72 (m, 2H, H-2 and H-5), 2.82 (dm, *J*=14 Hz, 1H, H-5), 3.68 (d, *J*=14 Hz, 1H, CH_2Ar), 3.98 (d, *J*=4.2 Hz, 1H, H-10c), 4.47 (d, *J*=14 Hz, 1H, CH_2Ar), 7.00 (dt, *J*=7.5, 1.2 Hz, 1H, H-8), 7.06 (dt, *J*=7.5, 1.2 Hz, 1H, H-9), 7.15–7.32 (m, 6H, H-7 and Ar), 7.59 (d, *J*=7.5 Hz, 1H, H-10), 7.78 (br s, 1H, NH); ^{13}C NMR (HMQC) 10.6 (CH_3), 22.4 (C-5), 27.1 (C-4), 29.0 (CH_2CH_3), 35.4 (C-3), 36.2 (C-3a), 58.5 (CH_2Ar), 61.8 (C-10c), 67.1 (C-2), 110.4 (C-7), 111.1 (C-10b), 118.8 (C-10), 119.3 (C-9), 120.8 (C-8), 126.2 (*p*-Ar), 127.6 (*o*-Ar), 128.3 (C-10a), 128.7 (*m*-Ar), 135.8 (C-5a), 135.9 (C-6a), 141.9 (*ipso*-Ar). Anal. Calcd for $C_{23}H_{26}N_2$: C, 83.36; H, 7.93; N, 8.47. Found: C, 83.05; H, 8.02; N, 8.39. Compound **14**: $[\alpha]_D^{22}$ +37.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (COSY, 500 MHz) 0.86 (t, *J*=7 Hz, 3H, CH_3), 1.33 and 1.64 (2m, 1H each, CH_2CH_3), 1.42 and 2.11 (2dt, *J*=12, 7.5 Hz, 1H each, H-3), 2.45 (six-line, *J*=6.5 Hz, 1H, H-3a), 2.6–2.7 (m, 3H, H-2 and H-10), 2.70 (dd, *J*=16, 5.5 Hz, 1H, H-4), 2.90 (dd, *J*=16, 7.5 Hz, 1H, H-4), 3.10 (brd, *J*=5.5 Hz, 1H, H-10a), 3.72 and 3.90 (2d, *J*=15 Hz, 1H each, NCH_2), 7.04 (dt, J=7.5, 1.2

Hz, H-7), 7.07 (dt, J=7.5, 1.2 Hz, 1H, H-6), 1.19–7.26 (m, 5H, ArH), 7.30 (brd, J=7.5 Hz, 1H, H-8), 7.42 (dd, J=7.5, 1.2 Hz, 1H, H-5), 7.50 (br, 1H, NH); ^{13}C NMR (HMQC) 10.9 (CH_3), 23.9 (C-4), 27.2 (C-10), 28.9 (CH_2CH_3), 35.0 (C-3a), 36.5 (C-3), 58.1 (CH_2Ar), 62.6 (C-10a), 66.3 (C-2), 108.3 (C-4a), 110.3 (C-8), 117.5 (C-5), 118.9 (C-6), 120.6 (C-7), 126.5 (*p*-Ar), 127.4 (C-4b), 127.9(*o*-Ar), 128.5 (*m*-Ar), 132.5 (C-9a), 135.9 (C-8a), 140.8 (*ipso*-Ar). Anal. Calcd for $C_{23}H_{26}N_2$: C, 83.36; H, 7.93; N, 8.47. Found: C, 83.16; H, 7.97; N, 8.42.

Method B. Operating from ketone **12** (190 mg, 0.74 mmol) and warming its corresponding phenylhydrazone in acetic acid (14 ml) at 110°C for 4 h, a crude reaction mixture was obtained, which was concentrated, taken up with Na_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (3×15 ml). The organic extracts were dried, concentrated and the residue chromatographed twice. On elution with CH_2Cl_2–EtOAc (4:1) a mixture of **14** and **16** (80 mg, 33%) in nearly equal ratio was isolated. Further elution gave 22 mg (9%) of **13**, and then 18 mg (7%) of **15**. (2*R*,3a*R*,10c*S*)-1-benzyl-2-ethyl-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3,2-*c*]carbazole (**15**): IR (neat) 3401; ^{1}H NMR 0.74 (t, *J*=7.2 Hz, 3H, CH_3), 1.26 (quint, *J*=7.1, 2H, CH_2CH_3); 1.50–1.70 (m, 1H, H-3), 1.80–1.90 (m, 2H, H-4), 1.98–2.12 (m, 1H, H-3), 2.26–2.32 (m, 1H, H-3a), 2.66–2.90 (m, 2H, H-5), 2.93–3.03 (m, 1H, H-2), 3.79 and 3.92 (2d, *J*=14 Hz, 1H each, CH_2Ar), 4.34 (d, *J*=5.7 Hz, 1H, H-10c), 7.04 (dt, *J*=8, 1.3 Hz, 1H, H-8), 7.09 (t, *J*=8 Hz, 1H, H-9), 7.20–7.32 (m, 6H, H-7 and Ar), 7.60 (d, *J*=8 Hz, 1H, H-10), 7.85 (br s, 1H, NH); ^{13}C NMR 10.7 (CH_3), 22.8 (C-5), 24.6 (CH_2CH_3), 28.0 (C-4), 35.2 (C-3), 37.6 (C-3a), 53.3 (CH_2Ar), 56.9 (C-10c), 61.3 (C-2), 110.4 (C-7), 110.4 (C-10b), 118.7 (C-10), 119.5 (C-9), 120.0 (C-8), 126.1 (*p*-Ar), 127.8 (*o*-Ar), 127.8 (C-10a), 128.3 (*m*-Ar), 135.8 (C-5a), 136.8 (C-6a), 141.8 (*ipso*-Ar). (2*R*,3a*S*,10a*S*)-1-Benzyl-2-ethyl-1,2,3,3a,4,9,10,10a-octahydropyrrolo[2,3-*b*]carbazole (**16**): ^{1}H NMR 0.94 (t, J=7 Hz, 3H, CH_3), 3.38 (m, 1H, H-10a); ^{13}C NMR 10.5 (CH_3), 26.4 (C-4), 28.7 (CH_2CH_3), 30.6 (C-10), 34.2 (C-3), 41.0 (C-3a), 57.7 (CH_2Ar), 66.2 (C-10a), 68.3 (C-2), 110.4 (C-8), 117.7 (C-5), 119.1 (C-6), 121.0 (C-7), 126.8 (*p*-Ar), 128.0 (*o*-Ar), 128.0 (C-4b), 129.0 (*m*-Ar), 132.8 (C-9a), 133.5 (C-8a).

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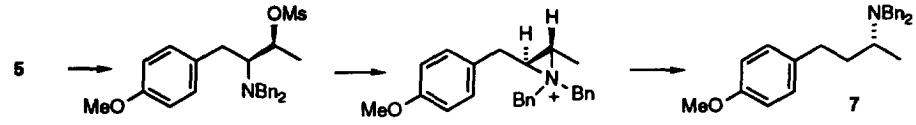

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