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Synthetic Applications of 2-Aryl-4-piperidones. XI[1] A New Synthesis of the E-Azaeburnamine Skeleton

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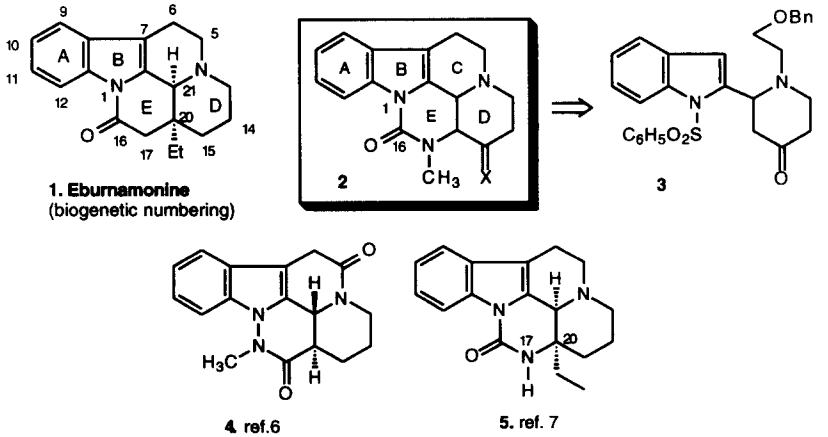
Abstract: 17-Azaeburnamine type compound **2** is synthesized by closure of ring E on 1-aminoindolo[2,3-*a*]quinolizidine **8**. Compound **8** is obtained by a Neber rearrangement on the corresponding indolo[2,3-*a*]quinolizidin-2-one, or by K^{t}BuO cyclisation of 3-amino-2-(2-indolyl)piperidin-4-one **16**. In both cases the starting substrate is 4-piperidone **3**. The synthesis of the new [ABED] ring system **6** is also described. Copyright © 1996 Elsevier Science Ltd

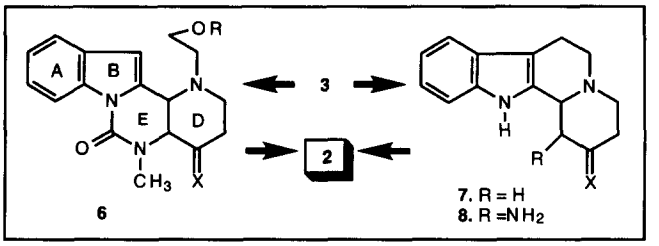
INTRODUCTION

In the context of our studies on the synthesis of indolo[2,3-*a*]quinolizidine alkaloids[2] and biologically active 3-aminopiperidines[1] from 2-aryl-4-piperidones,[3] we have now focused our attention on the preparation of 17-aza[4] derivatives of eburnamonine.[5] So far, only two E-azaeburnamine compounds have been described, the 16-azaderivative **4**[6] and the 17-azaeburnamonine derivative **5**.[7] Winterfeld described the synthesis of the basic skeleton of 17-azaeburnamonine (**5**) through a nucleophilic opening of a cyclopropane ring with generation of ring E by formation of the N17-C20 bond.



Scheme 1

In our case, we envisaged the synthesis of compound **2** either by formation of the C ring on an [ABED] tetracycle **6**, which would be a new heterocyclic system, or by closure of ring E on a 1-aminoindolo[2,3-*a*]quinolizidine **8**. Both of the key structures **6** and **8** could be prepared from 2-(2-indolyl)-4-piperidone **3**, by use of the Neber rearrangement[1] for the amination, and the K^{t}BuO cyclisation[2] for the indoloquinolizidine formation.



Scheme 2

The first syntheses of 1-aminoindolo[2,3-*a*]quinolizidines as potential intermediates to E-azaeburnamine derivatives have been described recently. They were achieved either by closure of the piperidine ring,[8] or by introduction of the amino group on an indoloquinolizidine *via* reduction of an oxime.[9] In the latter case, the 1-aminoindoloquinolizidines obtained were used to prepare E-homoazaeburnane systems, whose biological activities were tested on the tyrosine hydroxylases of rats and mice.[9]

Finally, the synthesis of 1-amino-9,10-dimethoxybenzo[*a*]quinolizidines[10] and of 2,3-dihydro-1*H*-pyrimidino[3,4,5-*l,m*]β-carbolines ([ABCE] ring system),[11] both related to our target structure, have also been described.

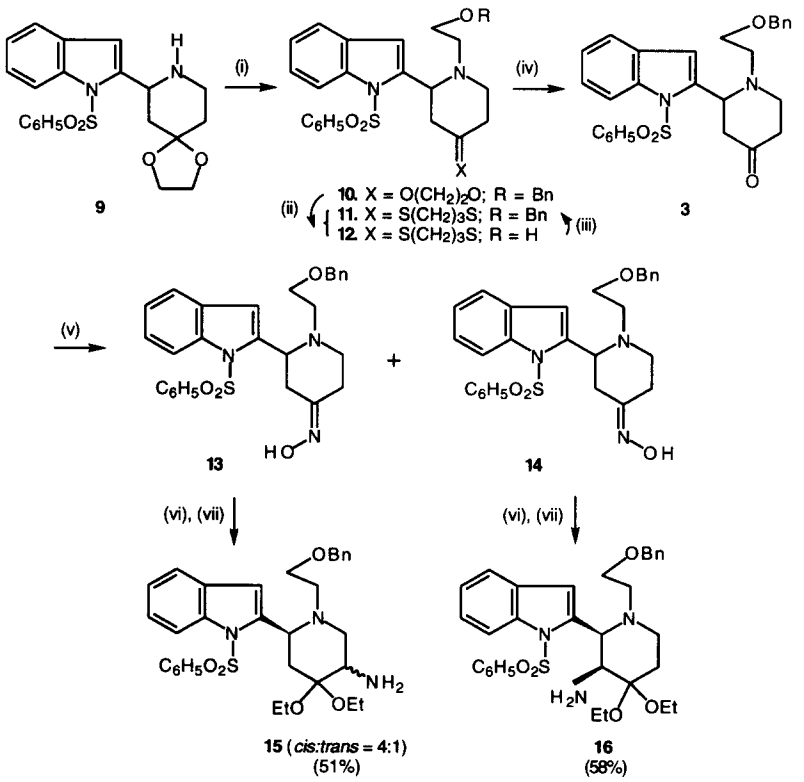
RESULTS AND DISCUSION

In view of the novelty of tetracycle **6**, we first planned to obtain compound **2** by closure of ring C in the last step. The starting 2-indolylpiperidine **9**[12] was alkylated with benzyl iodoethyl ether[13] to give piperidine **10** (Scheme 3). Surprisingly, the usual aqueous acid treatment to hydrolyse these acetals[1,14] led only to complex mixtures.[15] Therefore, the acetal function of compound **10** was converted to the corresponding dithioacetal **11** by treatment with propanedithiol in the presence of $BF_3.Et_2O$. As expected in these conditions, the hydroxy group was partially deprotected[16] yielding a variable proportion of alcohol **12**, which was benzylated back to **11**. Treatment of dithioacetal **12** with $(CF_3COO)_2IC_6H_5$ in CH_3CN-H_2O (9:1)[17] led to 2-indolyl-4-piperidone **3** in 96% yield.

The most characteristic spectroscopic data of compound **3** were an absorption at 1703 cm^{-1} in its IR register, and a signal at δ 208.5 in the ^{13}C NMR spectrum, due to the carbonyl function. In addition, the methine proton geminal to the indolyl group appeared as a deshielded triplet (δ 5.00, J = 3 Hz) in its ^1H NMR spectrum, which implies an axial disposition for the indolyl substituent. We had observed this unusual conformation previously as being characteristic of 2-(1-phenylsulfonyl-2-indolyl)-4-piperidones.[18]

Reaction of piperidone **3** with $NH_2OH.HCl$ in DME in the presence of K_2CO_3 afforded a 1:1 mixture of oximes **13** and **14**, which were isolated by column chromatography. The stereochemistry of compounds **13** and **14** was deduced from the ^{13}C NMR data. Thus, oxime (*Z*)-**13** presented signals at δ 29.1 and 29.2 for C-3 and C-5, and (*E*)-**14** at δ 36.7 (C-3) and 23.6 (C-5) as a consequence of the shielding effect of the oxime

hydroxy group on six-membered rings.[1] Both oximes showed a triplet at δ ~4.60 corresponding to 2-H in their ^{1}H NMR spectra, which indicated again the axial disposition of the indolyl substituent. Oximes **13** and **14** were tosylated independently with TsCl and K_2CO_3 in THF. After completion of the reaction was verified by tlc and NMR, the tosyloximes were made to react with 2 equivalents of KOEt in dry EtOH in the presence of a dessicating agent (anhydrous Na_2SO_4 or $MgSO_4$). Tosyloxime *(Z)*-**13** gave a 4:1 mixture of 5-aminopiperidines *cis*- and *trans*-**15**, which were isolated by column chromatography. In the ^{13}C NMR spectra, the most significant data for the 5-aminopiperidines **15** were two methine carbons corresponing to C-2 (δ 57.4 for *cis*-**15** and δ 57.3 for the *trans* isomer) and to C-5 (δ 50.1 for *cis*-**15** and δ 53.6 for *trans*-**15**), and the quaternary acetal signal for C-4 (δ 100.5 for *cis*-**15** and δ 98.4 for *trans*-**15**). The ^{1}H NMR complete signal assignment of both isomers was inferred from 2D NMR experiments (Table 1). In both cases, the indolyl substituent was equatorially disposed, and the main difference between the two isomers was the signal multiplicity of 5-H, which indicated that the amino group was axial in the major *cis*-isomer and equatorial in *trans*-**15**.



Reagents and conditions: (i) $ICH_2CH_2OCH_2Ph$ (1.1 equivalents), K_2CO_3, acetone, reflux, 48 h (98%); (ii) $HS(CH_2)_3SH$, $BF_3.Et_2O$, CH_2Cl_2, r.t., 5 days (82%); (iii) BnBr (1.2 equivalents), NaH (1.2 equivalents), THF, room temperature, 16 h (65%); (iv) $(CF_3CO_2)_2IC_6H_5$, CH_3CN:H_2O (1:1), r.t., 1 h (96%); (v) $NH_2OH.HCl$, K_2CO_3, DME, reflux, 1.5 h (71%); (vi) TsCl, K_2CO_3, THF, r.t., 48 h; (vii) KOEt, dry EtOH, Na_2SO_4, r.t., 2 h.

Scheme 3

Table 1. ^{1}H NMR (500MHz) data of aminopiperidines **15** and **16**.[a,b,c]

Compound	*cis*-**15**	*trans*-**15**	*cis*-**16**
2-H_a	4.17 dd (11,2)	4.26 dd (12,3)	4.60 s
3-H_a	1.72 dd (12,11)	1.70 dd (13,12)	----
3-H_e	2.15 dt (12,2)	2.42 dd (13,3)	2.95 s
5-H_a	----	3.03 dd (11,4)	1.83 br t (11)
5-H_e	2.98 br s	----	1.90-2.00 m
6-H_a	2.65 dd (12, 3)	2.31 t (11)	2.28 td (11,3)
6-H_e	3.11 dd (12, 2)	3.15 dd (11, 4)	3.05 ddd (11,4,2)
NH_2	masked	1.85 br s	1.50 br s
NCH_2	1.90 dt (12,3) 2.56 ddd (12,11,6)	1.95 m 2.55 ddd (12,11,6)	1.90-2.00 m 2.65 ddd (12,11,6)
CH_2OBn	3.30-3.50 m	3.30-3.35 m 3.35-3.45 m	3.30-3.60 m
CH_2Ph	4.37 s	4.38 s	4.35 s
CH_3CH_2O	1.15 t (7) 1.30 t (7)	1.05 t (7) 1.30 t (7)	1.15 t (7) 1.35 t (7)
CH_3CH_2O	3.30-3.50 m 3.70-3.80 m	3.44, 3.53, 3.63, and 3.77 (4 m)	3.50-3.60 m

a. Aromatic protons were about the same for the three compounds: 6.85 ± 0.5 (s, 1H, In-3H); 7.20-7.53 (m, 11H), 7.75 ± 0.5 (d, J = 7 Hz, 2H); 8.30 ± 0.5 (d, J = 7 Hz, In-7H).
b. Assignments are confirmed by COSY experiments.
c. Coupling constants are given in brackets (Hz).

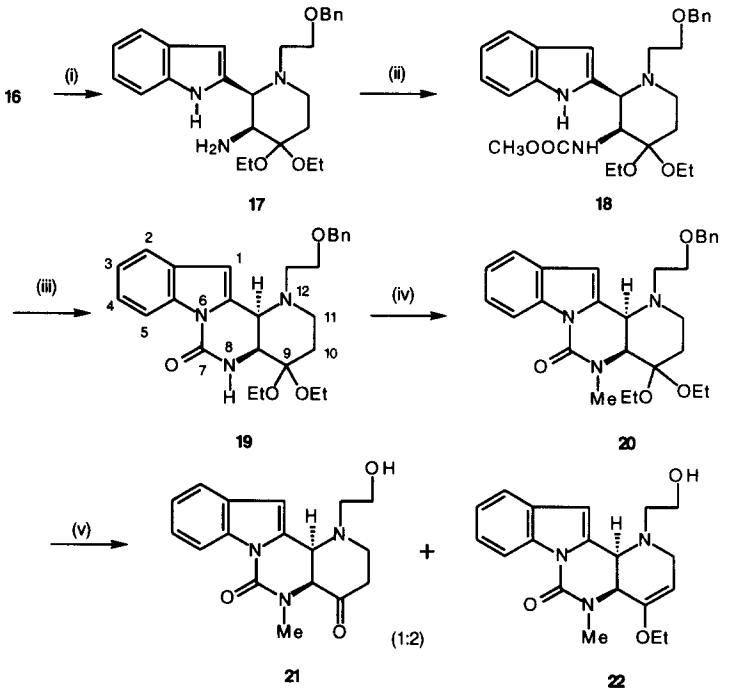
When tosyloxime (*E*)-**14** was used as the reaction substrate, usually only *cis*-3-aminopiperidine **16** was isolated, which was identified on the basis of its spectral data and by comparison with the data previously obtained for **15**. In this case the amino group was axial and the indolyl substituent equatorial, as expected.[1] However, in one experiment the formation of 3-aminopiperidine ***trans*-16** was detected.

In order to achieve the closure of ring E, the indole protecting group of aminopiperidine *cis*-**16** was removed (Scheme 4), the resulting aminopiperidine **17** was methoxycarbonylated, and the carbamate **18** was treated with NaH. The formation of the tetracyclic compound **19** was demonstrated by the loss of the indole NH proton and of the methoxy group signals in the NMR spectra. The most characteristic data of compound **19** were: i) the shielding of the carbonyl signal in the ^{13}C NMR spectrum ($\Delta\delta$ = +5.6); ii) the deshielding of the indole 3-H proton ($\Delta\delta$ = -0.15), and the presence of two methine protons as broad singlets at δ 3.73 (8a-H) and δ 3.82 (12a-H) in the ^{1}H NMR spectrum.

Methylation of **19** with NaH and CH_3I yielded compound **20**, which was treated with excess $BF_3.Et_2O$ and Me_2S to achieve the debenzylation and the carbonyl deprotection. From the reaction, two compounds were isolated, which were identified as the hydroxy ketone **21** and the hydroxy enol ether **22**. Thus, piperidone **21** showed two carbonyl absorption bands at 1723 (C-9) and 1693 (NCON) cm^{-1} in its IR spectrum, and signals at δ 150.8 (NCON) and 203.0 (C-9) in its ^{13}C NMR spectrum. In the ^{1}H NMR spectrum, the methine protons of the E/D ring junction appeared as two doublets (J = 6 Hz) at δ 4.12 (8a-H) and δ 4.91 (12a-H). Compound **22** showed an intense absorption at 1688 cm^{-1}, corresponding to both the

carbonyl group (NCON) and the enol ether double bond, and an alcohol band in its IR spectrum. The presence of an olefine proton (δ 4.58) in the ^1H NMR spectrum, together with a methine carbon (δ 93.8) in the ^{13}C NMR record were diagnostic of the structure of **22**, which was corroborated by the molecular peak at *m/z* 341 in the MS register.

The cyclisation of compounds **21** and **22** to obtain the target pentacyclic structure type **2** was assayed by tosylation of the hydroxy group and subsequent base treatment. The formation of the tosylate was checked by tlc before addition of LDA under a variety of experimental conditions. Unfortunately, in every case the base treatment led only to decomposition products.

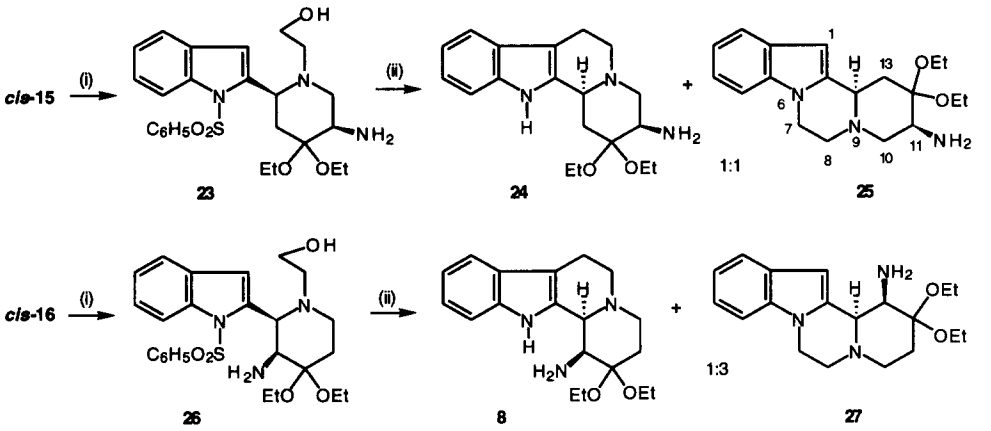


Reagents and conditions: (i) 10% aqueous NaOH, EtOH, reflux, 5 h (39%); (ii) 1. NaH, THF, 0°C, 15 min. 2. $ClCO_2CH_3$, 0°C, 3h (quantitative); (iii) NaH, THF, 0°C, 3 h (quantitative); (iv) 1. NaH, THF, 0°C, 15 min. 2. CH_3I (0.1 equivalents), room temperature, 2 h (quantitative); (v) Me_2S (30 equivalents), $BF_3.Et_2O$ (10 equivalents), CH_2Cl_2, 30°C, 18 h (46%).

Scheme 4

In view of this result, we turned our attention to the preparation of 1-aminoindolo[2,3-*a*]quinolizidine **8** (X = OEt, OEt). We first tested on the 5-aminopiperidine series whether the K^{t}BuO direct cyclisation of *N*-hydroxyethyl-2-[1-(phenylsulfonyl)-2-indolyl]piperidines[2] would work in the presence of the primary amino group. Thus, piperidine *cis*-**15** was debenzylated, and the resulting aminoalcohol **23** was made to react with 2 equivalents of K^{t}BuO in dry THF at 0°C for 30 min. As expected, a 1:1 mixture of 3-aminoindolo[2,3-

a]quinolizidine **24** and 11-amino-7,8,9,10,11,12,13,13a-octahydropyrido[1′,2′;1,2]pyrazino[4,3-*a*]indole **25** was obtained, in 50% yield (Scheme 5). However, using the same reaction sequence, 3-aminopiperidine *cis*-**16** gave a 1:3 mixture of 1-aminoindolo[2,3-*a*]quinolizidine **8** and pyridopyrazinoindole **27** in only 33% yield.



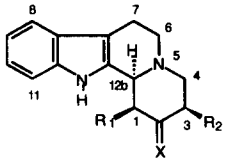
Reagents and conditions: (i) Me_2S, $BF_3.Et_2O$, CH_2Cl_2, 30°C, 18h (**23**, 40% yield; **26** 43% yield). (ii) K^{t}BuO, THF, 0°C, 30 min (**24:25** = 1:1, 50%; **8:27** = 1:3, 33%).

Scheme 5

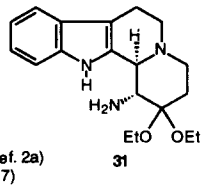
Indoloquinolizidines **24** and **8** had a *trans* C/D relationship, and the amino group of each was in a *cis* orientation with respect to the C12a-C12b bond, as shown by their spectral data. Thus, Bohlman bands were observed in the IR registers; the chemical shift of the angular 12b-H was below δ 3.8 (δ 3.45 for **24**; δ 3.74 for **8**) in the ^{1}H NMR spectra, indicating its *anti* relationship with the nitrogen lone pair; and C-7 ^{13}C NMR chemical shift was δ 21.9 for compound **24**, and δ 21.7 for **8**.[19] The axial orientation of the amino group in compound **8** was shown both by the ^{1}H NMR signal multiplicity of the geminal proton 1-H, which was a broad singlet (δ 3.30), and by a "γ-gauche" effect exerted by the axial C-1 amino group on carbon C-3 (Δδ = -6.5) in the ^{13}C NMR spectrum (see Table 2). A similar ^{13}C NMR shielding effect was observed on C-1 in 3-aminoquinolizidine **24** (Δδ = -6.1), which proved the axial orientation of the amino group in compound **24**.

The most important ^{1}H NMR datum used for the structural determination of pyridopyrazinoindoles **25** and **27** was a singlet at δ 6.20 (**25**) and δ 6.26 (**27**) corresponding to the C-3 indole proton (1-H). The axial orientation of the amino group provoked a ^{13}C NMR shielding effect on C-13 (Δδ = -6.5) in compound **25**, and on C-11 (Δδ = -6.9) in **27**, as shown by comparison to their unsubstituted analogue **III**.

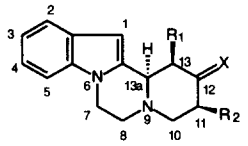
Table 2. ^{13}C NMR data of aminoindoloquinolizidines **8**, **24**, **31**, and of aminopyridopyrazinoindoles **25** and **27**.



I. $R_1 = R_2 = H$; $X = OCH_2CH_2O$ (ref. 2a)
II. $R_1 = NH_2$; $R_2 = H$; X = H,H (ref. 7)
24. $R_1 = H$; $R_2 = NH_2$; X = OEt,OEt
8. $R_1 = NH_2$; $R_2 = H$; X = OEt,OEt

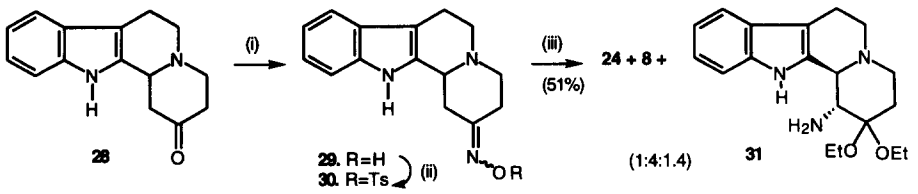


31



III. $R_1 = R_2 = H$; $X = OCH_2CH_2O$ (ref. 2a)
25. $R_1 = H$; $R_2 = NH_2$; X = OEt,OEt
27. $R_1 = NH_2$; $R_2 = H$; X = OEt,OEt

Compound	I (ref. 2a)	II (ref. 7)	24	8	31	III (ref. 2a)	25	27
C-1	39.1	48.9	33.0	52.5	55.9	95.4	95.4	95.0
C-2	107.2	30.9	100.5	100.6	100.0	119.7	119.8	119.7
C-3	34.8	20.9	50.7	28.3	29.2	120.1	120.3	120.2
C-4	52.8	52.9	57.2	53.4	53.2	120.7	120.8	120.5
C-5	----	----	----	----	----	108.6	108.6	108.5
C-5a	----	----	----	----	----	138.0	128.0	128.3
C-6	52.3	52.8	52.3	51.9	51.5	----	----	----
C-7	21.6	21.2	21.9	21.7	21.9	42.0	42.0	41.7
C-7a	127.2	127.4	127.3	127.3	masked	----	----	----
C-7b	108.1	110.4	108.7	110.3	masked	----	----	----
C-8	118.1	118.0	118.1	117.8	117.7	51.7	51.4	51.2
C-9	119.4	119.1	119.5	119.3	118.5	----	----	----
C-10	121.4	121.3	121.5	121.3	120.7	53.1	57.2	52.2
C-11	110.8	111.1	110.7	111.1	110.9	34.8	50.6	27.9
C-11a	134.1	136.3	134.3	132.9	masked	----	----	----
C12	----	-----	----	----	----	106.9	100.1	100.3
C-12a	136.0	133.2	136.0	136.4		----	----	----
C-12b	57.0	63.6	55.9	60.1	60.9	----	----	----
C-13	----	----	----	----	----	39.4	32.9	53.0
C-13a	----	----	----	----	----	57.7	56.6	61.3
C-13b	----	----	----	----	----	135.9	136.0	135.2
CH_3CH_2O	----	----	15.4 15.6	15.3 15.5	15.5 16.0	----	15.3, 15.6	15.3 15.6
OCH_2	64.4	----	55.2 55.5	55.0 55.7	57.8 58.5	----	54.9 55.2	54.9 55.2

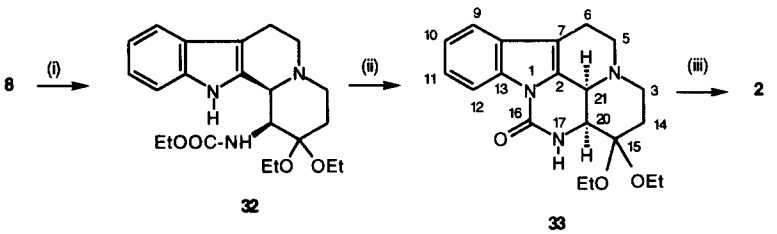


Reagents and conditions: (i) $NH_2OH.HCl$, K_2CO_3, DME, reflux, 1.5 h (93%); (ii) TsCl, K_2CO_3, THF, r.t., 48 h; (iii) KOEt, dry EtOH, Na_2SO_4, r.t., 2 h.

Scheme 6

Alternatively, we performed the Neber rearrangement on indolo[2,3-*a*]quinolizidin-2-one **28**[2] (Scheme 6). The oximination of compound **28** followed by tosylation of the resulting 1:1 mixture of *(E)* and *(Z)*-**29**,[20] and final KOEt treatment of the tosyloximes **30**, yielded a 1:4:1.4 mixture of aminoindoloquinolizidines **24**, *cis*-**8**, and *trans*-**31** (Scheme 6). The equatorial disposition of the amino group in the new 1-aminoindolo[2,3-*a*]quinolizidine **31** was inferred from the *trans* diaxial coupling constant ($J_{12b\text{-}1}$= 10 Hz) of the doublet at δ 3.30 in the ^1H NMR spectrum, corresponding to the angular methine proton 12b-H.

As for tetracycle **19**, compound **8** was methoxycarbonylated to give the carbamate **32**, which was cyclized by means of NaH to yield the pentacyclic 17-azaeburnane compound **33**. The closure of ring E was made evident by the loss of the signals corresponding to the indole NH proton and to the carbamate methoxy group in the NMR spectra. The angular protons 20-H and 21-H get deshielded (Δδ = + 0.68 and + 0.89, respectively), as a consequence of the increased rigidity of the molecule. Finally, compound **33** was methylated to yield the target structure **2**. The complete spectral characterization of 17-azaeburna derivatives **33** and **2** is shown in table 3.



Reagents and conditions: (i) 1. NaH, THF, 0°C, 15 min. 2. $ClCO_2CH_3$, 0°C, 3h (quantitative); (ii) NaH, THF, 0°C, 3 h (quantitative); (iii) 1. NaH, THF, 0°C, 15 min. 2. CH_3I (0.1 equivalents), room temperature, 2 h (quantitative).

Scheme 7

ACKNOWLEDGEMENTS

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Table 3. NMR Data of compounds **33**[a] and **2**

^{1}H NMR[b]			^{13}C NMR		
Compound	**33**	**2**	**Compound**	**33**	**2**
3-H_a	2.70 td (13,3)	2.79 td (13,3)	C-3	41.7	41.7
3-H_e	2.54 dt (13,3)	2.56 dt (13,3)	C-5	50.1	50.1
5-H_a	3.30 m	3.25-3.35 m	C-6	16.1	16.1
5-H_e	3.30 m	3.25-3.35 m	C-7	128.7	128.7
6-H_a	2.47 dm	2.47 dm	C-8	108.6	108.1
6-H_e	2.90 m	2.85-3.00 m	C-9	117.9	117.9
9-H	7.40 d (7)	7.40 d (7)	C-10	122.2	122.2
10-H	7.17 t (7)	7.10 t (7)	C-11	123.7	123.7
11-H	7.24 t (7)	7.15 t (7)	C-12	114.7	114.7
12-H	8.20 d (7)	8.20 d (7)	C-13	masked	135.0
14-H_a	1.70 td (13,3)	1.80 td (13,3)	C-14	30.0	30.0
14-H_e	1.98 dt (13,3)	2.02 dt (13,3)	C-15	97.1	97.1
20-H	3.74 d (7)	3.69 d (7)	C-16	152.1	152.1
21-H	4.69 br d (7)	4.71 dt (7,2)	C-20	51.7	51.7
OCH_2CH_3	0.41 t (7) 1.16 t (7)	0.38 t (7) 1.19 t (7)	C-21	58.7	58.5
OCH_2CH_3	3.01, 3.19 (2m) 3.63, 3.71 (2m)	3.13 q (7) 3.52 q (7)	OCH_2CH_3	14.3 15.9	14.3 15.9
17-NH	5.20 br s	----	OCH_2CH_3	56.7 58.6	55.7 58.6
17-NCH_3	----	3.26 (s)	17-NCH_3	---	37.9

a. All signal assignments for compound **33** were confirmed by COSY (H,H) and (H,C) experiments.
b. Coupling constants are given in brackets (Hz).

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 mm, SDS). TLC was performed on SiO_2 (silica gel 60 F254, Macherey-Nagel) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Dragendorff or hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over

anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica and Biològica, CID, Barcelona.

1-(Benzyloxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (10). Benzyl iodoethyl ether[13] (3.49 g, 13.33 mmol) was added dropwise to a mixture of piperidine **9**[12] (4.42 g, 11.11 mmol) and anhydrous K_2CO_3 (5 g) in dry acetone (100 ml). The resulting mixture was refluxed under N_2 for 48 h. The crude reaction mixture was filtered over Celite® and the filtrate was evaporated to give a residue which was flash chromatographed (Et_2O-hexane, 80:20) to give pure piperidine **10** (4.01 g, 70%): ^{1}H NMR 1.71 (dm, J =12 Hz, 1H, 5-H_a), 1.90-2.10 (m, 3H, 3-H and 5-H_e), 2.49 (td, J = 12 and 3 Hz, 1H, 6-H_a), 2.60-2.70 (m, 1H, NCH_A), 3.21 (ddd, J = 12, 5, and 3 Hz, 1H, 6-H_e), 3.30-3.40 (m, 1H, NCH_B), 3.60 (m, 1H, CH_AOBn), 3.75 (m, 1H, CH_BOBn), 3.87-4.10 (m, 4H, OCH_2), 4.28 (dd, J = 12 and 3 Hz, 1H, 2-H_a), 4.38 (s, 4H, OCH_2Ph), 6.77 (s, 1H, In-3H), 7.20-7.50 (m, 11 H, Ar-H), 7.79 (d, J = 7 Hz, 2H, Ar-H), 8.30 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 34.3 (C-5), 42.6 (C-3), 51.2 (NCH_2), 53.1 (C-6), 58.2 (C-2), 64.1 (OCH_2), 68.4 (CH_2OBn), 72.6 (OCH_2Ph), 106.4 (C-4), 109.5 (In-C3), 114.7 (In-C7), 120.6 (In-C4), 123.5 (In-C5), 124.2 (In-C6), 126.6, 127.2, 128.1, 129.0, and 133.6 (Ph-H); MS *m/z* (%) 533 (M^+, 0.1), 411 (16), 285 (10), 128 (61), 91 (100). Anal. Calcd for $C_{30}H_{32}N_2O_5S$: C, 67.65; H, 6.06; N, 5.30. Found: C, 67.85; H, 6.29; N, 5.29.

1-(Benzyloxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Propylenedithio Acetal (11). Method A: To solution of piperidine **10** (1.23 g, 2.31 mmol) in dry CH_2Cl_2 (10 ml), 1,3-propanedithiol (0.32 ml, 4.62 mmol) and $BF_3.Et_2O$ (1.16 ml, 9.24 mmol) were added. The solution was stirred at 40 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (25 ml), and washed with aqueous $NaHCO_3$. The organic extracts were dried and evaporated, and the residue was flash chromatographed to yield dithiane **11** and hydroxyethylpiperidine **12** . **Dithiane 11** (Et_2O-hexane, 60:40; 554 mg, 41%): ^{1}H NMR 1.71 (dt, J = 12 and 6 Hz, 1H, NCH_A), 1.80-2.00 (m, 2H, 3-H_a and SCH_2CH_2), 2.00-2.15 (m, 3H, 5-H_a, 5-H_e, and SCH_2CH_2), 2.47 (dt, J = 12 and 6 Hz, NCH_B), 2.60-2.80 (m, 3H, SCH_A, SCH_A' and 6-H_a), 2.95-3.05 (m, 3H, 6-H_e, 3-H_e, and SCH_B), 3.10-3.40 (m, 3H, SCH_B', and CH_2OBn), 4.36 (br s, 3H, OCH_2Ph and 2-H_a), 6.80 (s, 1H, In-3H), 7.23-7.53 (m, 11H, Ar-H), 7.84 (d, J = 7 Hz, 2H, Ar-H), 8.30 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 25.5 (SCH_2), 25.9 (SCH_2CH_2), 26.2 (SCH_2'), 37.7 (C-5), 45.6 (C-3), 48.1 (C-4), 48.6 (C-6), 54.0 (NCH_2), 57.3 (C-2), 68.4 (CH_2OBn), 72.7 (OCH_2Ph), 109.7 (In-C3), 114.7 (In-C7), 120.7 (In-C4), 123.6 (In-C5), 124.2 (In-C6), 126.6, 127.3, 128.2, 129.3, and 133.9 (Ph), 137.1 (In-C7a), 138.3 (In-C2), 139.4, 143.4. Anal. Calcd for $C_{31}H_{34}N_2O_3S$: C, 64.33; H, 5.92; N, 4.84; S, 16.62. Found: C, 64.20; H, 6.19; N, 4.42; S, 16.54. **Aminoalcohol 12** (Et_2O-MeOH, 98:2; 460 mg, 40%): IR 3500-3350 (OH) cm^{-1};^{1}H NMR 1.60 (br d, J = 12 Hz, 1H, NCH_A), 1.95-2.20 (m, 4H, 5-H, 3-H_a, and SCH_2CH_A), 2.45-2.55 (m, 1H, NCH_B), 2.58-2.80 (m, 3H, 3-H_e, SCH_e, and SCH_2CH_B), 2.90-3.05 (m, 4H, 6-H_a, CH_2OH, and SCH_e'), 3.15 (td, J = 12 and 6 Hz, 1H, SCH_a), 3.20-3.30 (dm, J = 12 Hz, 1H, 6-H_e), 3.55 (td, J = 12 and 6 Hz, 1H, SCH_a'), 4.55 (br d, J = 12 Hz, 1H, 2-H_a), 6.75 (br s, 1H, In-3H), 7.20-7.60 (m, 6H, Ar-H), 7.85 (d, J = 7 Hz, 1H, Ar-H), 8.32 (d, J = 7 Hz, 1H, In-7H).

Method B: A dispersion of NaH (60% in oil, 69 mg, 1.7 mmol) was washed twice with dry Et_2O and once with dry THF under inert atmosphere, and cooled at 0°C before addition of a solution of aminoalcohol **12** (700 mg, 1.4 mmol) in dry THF (25 ml). Benzyl bromide (0.2 ml, 1.7 mmol) was added immediately, and the reaction mixture was stirred at room temperature overnight. The crude was poured on iced H_2O, and

extracted once with Et_2O and then with CH_2Cl_2. The organic extracts, dried and evaporated yielded compound **11** (665 mg, 82%).

1-(2-Benzyloxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone (3). Method A: A solution of ethylene acetal **10** (500 mg, 0.94 mmol) in 4N HCl-MeOH (1:1, 50 ml) was refluxed for 12 h. The reaction mixture was poured on iced H_2O, basified with Na_2CO_3 and extracted with CH_2Cl_2. The dried organic extracts were evaporated and flash chromatographed (Et_2O-hexane, 60:40) to give piperidone **3** (oil, 87 mg, 19% yield). Method B: To a solution of dithiane **11** (1.45 g, 2.51 mmol) in MeCN-H_2O 9:1 (100 ml), $(CF_3COO)_2IC_6H_5$ (1.51 g, 3.512 mmol) was added, and the resulting mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue, dissolved in CH_2Cl_2, was washed with saturated aqueous Na_2CO_3. The organic extracts, dried and evaporated, were flash chromatographed (Et_2O-hexane, 60:40) to give piperidone **3** (oil, 1.17 g, 96%): IR (NaCl) 1703 (CO) cm^{-1}; ^1H NMR 2.49 (td, J = 11 and 4 Hz, 1H, 6-H_a), 2.51 (td, J = 11 and 4 Hz, 1H, 5-Ha), 2.60 (ddd, J = 11, 4 and 1 Hz, 1H, 3-He), 2.70-2.80 (m, 1H, 3-Ha), 2.78 (ddd, J = 11, 4 and 1 Hz, 1H, 5-He), 2.82 (dd, J = 11 and 4 Hz, 1H, 6-He), 2.90 and 3.10 (2 m, 1H each, NCH_2), 3.40 and 3.50 (2 m, 1H each, CH_2OBn), 4.40 (s, 2H, OCH_2Ph), 5.00 (t, J = 3 Hz, 1H, 2-H_e), 6.63 (s, 1H, In-3H), 7.20-7.50 (m, 11H, Ar-H), 7.79 (d, J =7 Hz, 2H, Ar-H), 8.12 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 38.8 (C-5), 44.4 (C-3), 47.6 (C-6), 51.5 (NCH_2), 58.5 (C-2), 68.9 (CH_2OBn), 72.9 (OCH_2Ph), 111.2 (In-C3), 114.9 (In-C7), 120.9 (In-C4), 123.7 (In-C5), 124.9 (In-C6), 126.2, 127.5, 128.3, 129.0, and 133.6 (Ar), 137.3 (In-C7a), 138.1 (In-C2), 139.4 (Ph-*ipso*), 141.2 (Ph'-*ipso*), 208.5 (C-4); MS (*m/z*, %): 488 (M^+, 1), 353 (5), 303 (13), 196 (17), 165 (16), 143 (17), 91 (100). Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 68.83; H, 5.78; N, 5.73; S, 6.56. Found: C, 68.49; H, 5.89; N, 5.39; S, 6.70.

1-(2-Benzyloxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Oximes (*Z*-13 and *E*-14). To a mixture of $NH_2OH.HCl$ (231 mg, 3.33 mmol) and K_2CO_3 (460 mg, 3.33 mmol) in dry DME (25 ml), a solution of piperidone **3** (812 mg, 1.66 mmol) in dry DME (50 ml) was added under N_2 atmosphere. The reaction mixture was stirred at 80°C for 1 h 30 min. The solvent was evaporated, and the residue, dissolved in aqueous K_2CO_3, was extracted with CH_2Cl_2. The organic extracts were washed with H_2O, dried, and evaporated to yield an oil which was flash chromatographed (CH_2Cl_2-MeOH, 99:1) to isolate oximes ***(Z)*-13** and ***(E)*-14** . **Oxime *Z*-13** (lower Rf, 260 mg, 31%): IR (NaCl) 3350-3250 (OH) cm^{-1}; ^1H NMR 2.30-2.48 (m, 2H, 3-H_a and 5-H_a), 2.55-2.63 (m, 3H, 3-H_e, 5-H_e, and 6-H_a), 2.70-2.80 (m, 1H, NCH_A), 3.15-3.20 (m, 2H, 6-H_e and NCH_B), 3.30-3.40 and 3.42-3.53 (2 m, 1H each, CH_2OBn), 4.40 (s, 2H, OCH_2Ph), 4.60 (t, J = 3 Hz, 2-H_e), 6.80 (s, 1H, In-3H), 7.20-7.50 (m, 11H, Ar-H), 7.75 (d, J = 7 Hz, 2H, Ar-H), 8.22 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 29.1 and 29.2 (C-3 and C-5), 49.6 (C-6), 52.2 (NCH_2), 57.5 (C-2), 68.8 (CH_2OBn), 72.9 (OCH_2Ph), 110.6 (In-C3), 115.1 (In-C7), 120.9 (In-C4), 123.8 (In-C5), 124.7 (In-C6), 126.3, 127.5, 128.3, and 129.0 (Ph), 129.2 (In-C3a), 133.6 (Ph), 137.3 (In-C7a), 138.5 (In-C2), 139.4 and 142.0 (Ph-*ipso*), 156.8 (C-4); MS *m/z* (%) 504 (M^+, 1), 382 (M^+ - OCH_2Ph, 58), 256 (33), 223 (32), 195 (59), 91 (100), 77 (43). Anal. Calcd for $C_{28}H_{29}N_3O_4S.1H_2O$: C, 64.47; H, 5.80; N, 8.06; S, 6.15. Found: C, 64.85; H, 5.66; N, 7.69; S, 5.85. **Oxime *E*-14** (higher Rf, 338 mg, 40%): ^1H NMR 2.38-2.50 (m, 3H, 3-H_a, 5-H_a, and 5-H_e), 2.55-2.72 (m, 3H, 3-H_e, 5-H_a, and NCH_A), 2.70 (dt, J = 12 and 3 Hz, 1H, 6-H_e), 3.07-3.17 (m, 1H, NCH_B), 3.30-3.40 and 3.40-3.50 (2 m, 1H each, CH_2OBn), 4.40 (s, 2H, OCH_2Ph), 4.58 (t, 1H, J = 3 Hz, 2-H_e), 6.80 (s, 1H, In-3H), 7.20-7.50 (m, 11H, Ar-H), 7.75 (d, J = 7 Hz, 2H, Ar-H), 8.22 (d, J = 7 Hz, 1H, In-7H), 8.31

(br s, 1H, NO*H*); ^{13}C NMR 23.6 (C-5), 36.7 (C-3), 48.8 (C-6), 52.7 (NCH_2), 58.5 (C-2), 68.7 (CH_2OBn), 72.9 (OCH_2Ph), 110.9 (In-C3), 115.1 (In-C7), 120.9 (In-C4), 123.7 (In-C5), 124.6 (In-C6), 126.3, 127.5, 128.3, and 129.2 (Ph), 129.3 (In-C3a), 133.8 (Ph), 137.3 (In-C7a), 138.2 (In-C2), 139.3 and 142.3 (Ph-*ipso*), 156.7 (C-4).

5-Amino-1-(2-benzyloxyethyl)-4,4-diethoxy-2-[1-(phenylsulfonyl)-2-indolyl]piperidines (*cis*- and *trans*-15). To a mixture of oxime ***(Z)*-13** (160 mg, 0.32 mmol) and K_2CO_3 (88 mg, 0.64 mmol) in dry THF (3 ml), TsCl (61 mg, 0.32 mmol) was added, and the resulting mixture was stirred for 72 h at room temperature, under inert atmosphere. The crude was filtered through Celite® and the filtrate was evaporated to yield the corresponding ***(Z)*-tosyloxime** (209 mg), which was used without further purification. ***(Z)*-Tosyloxime:** ^{1}H NMR 2.45 (s, 3H, CH_3), 4.38 (s, 2H, OCH_2Ph), 4.65 (t, J = 3 Hz, 1H, 2-H_e), 6.61 (s, 1H, In-3H), 7.20-7.60 (m, 11H, Ar-H), 7.45 (d, J = 7 Hz, 2H, Tos-*o*), 7.75 (d, J = 7 Hz, 2H, Ar-H), 7. 88 (d, J = 7 Hz, 2H, Tos-*m*), 8.20 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 21.6 (CH_3), 28.9 (C-5), 31.2 (C-3), 49.2 (C-6), 51.8 (NCH_2), 56.9 (C-2), 68.6 (CH_2OBn), 72.8 (OCH_2Ph), 110.5 (In-C3), 115.1 (In-C7), 121.0 (In-C4), 123.8 (In-C5), 125.0 (In-C6), 126.0, 126.2, 126.3, 127.4, 127.5, 128.2, 128.7, 128.9, 129.1, 129.3, 129.5, 129.6, and 134.0 (Ph), 166.1 (C-4).

To potassium metal (40 mg, 1.03 matg) at 0°C and under inert atmosphere, dry EtOH (10 ml) was slowly added, and the mixture was stirred at 0°C until complete dissolution of the metal. Anhydrous $MgSO_4$ (350 mg) and a solution of the previously obtained *(Z)*-tosyloxime (340 mg, 0.52 mmol) in dry EtOH (10 ml) were added at 0°C. The mixture was allowed to reach room temperature, and was stirred for 1 h. The crude was filtered through Celite®, and the filtrate was evaporated to give an oil which was flash chromatographed (CH_2Cl_2-MeOH, 99:1) to isolate ***cis*-** and ***trans*-15. 5-Aminopiperidine *cis*-15** (Higher Rf, 120 mg, 40%): IR (NaCl) 3370 and 3280 (NH_2) cm^{-1}; ^{13}C NMR 15.3 and 15.5 (CH_3), 37.7 (C-3), 50.1 (C-5), 53.2 (NCH_2), 54.9 (C-6), 55.1 and 55.6 (OCH_2CH_3), 57.4 (C-2), 68.5 (CH_2OBn), 72.8 (OCH_2Ph), 100.5 (C-4), 109.9 (In-C3), 114.9 (In-C7), 120.8 (In-C4), 123.6 (In-C5), 124.3 (In-C6), 126.4, 127.3, 128.3, and 129.2 (Ph), 129.3 (In-C3a), 133.8 (Ph), 137.3 (In-C7a), 143.8 (Ar-*ipso*); MS *m/z* (%) 577 (M^+, 0.1), 532 (M^+ - OEt, 2), 486 (3), 419 (16), 410 (100), 381 (39), 328 (45), 282 (34), 91 (47). Anal. Calcd for $C_{32}H_{39}N_3O_5S$: C, 66.53; H, 6.80; N, 7.27. Found; C, 66.70; H, 6.63; N, 7.39. **5-Aminopiperidine *trans*-15** (Lower Rf, 33 mg, 11%): ^{13}C NMR 15.6 and 15.7 (CH_3), 39.0 (C-3), 53.5 (NCH_2), 53.6 (C-5), 56.1 and 57.8 (OCH_2CH_3), 57.1 (C-6), 57.3 (C-2), 68.3 (CH_2OBn), 72.8 (OCH_2Ph), 98.4 (C-4), 110.2 (In-C3), 115.0 (In-C7), 120.6 (In-C4), 123.7 (In-C5), 124.3 (In-C6), 126.4, 127.4, 128.2, 129.1, and 133.8 (Ph).

3-Amino-1-(2-benzyloxyethyl)-4,4-diethoxy-2-[(1-phenylsulfonyl)-2-indolyl]piperidines (*cis*-16 and *trans*-16). Operating as above, from oxime ***E*-14** (200 mg, 0.40 mmol), K_2CO_3 (110 mg, 0.80 mmol), and TsCl (76 mg, 0.40 mmol) in dry THF (4 ml), the corresponding ***(E)*-tosyloxime** (261 mg) was obtained, which was used without further purification. ***(E)*-Tosyloxime:** ^{1}H NMR 2.47 (s, 3H, CH_3), 4.37 (s, 2H, OCH_2Ph), 4.65 (t, J = 3 Hz, 1H, 2-H_e), 6.63 (s, 1H, In-3H), 7.15-7.55 (m, 11H, Ar-H), 7.40 (d, J = 7 Hz, 2H, Tos-*o*), 7.70 (d, J = 7 Hz, 2H, Ar-H), 7.90 (d, J = 7 Hz, 2H, Tos-*m*), 8.15 (d, J = 7 Hz, 1H, In-7H); ^{13}C NMR 21.5 (CH_3), 25.0 (C-5), 34.7 (C-3), 47.0 (C-6), 51.9 (NCH_2), 57.5 (C-2), 68.5 (CH_2OBn), 72.7 (OCH_2Ph), 110.9 (In-C3), 114.8 (In-C7), 120.8 (In-C4), 123,5 (In-C5), 124.8 (In-C6), 126.0, 127.3, 127.3, 128.1, 128.5, 128.7, 128.9, 129.1, 129.4, and 133.6 (Ph), 166.3 (C-4). Operating as for the preparation of aminopiperidines

15, from potassium (43 mg, 1.93 matg), anhydrous $MgSO_4$ (350 mg), and the previously prepared *(E)*-tosyloxime (359 mg, 0.55 mmol) in dry EtOH (10 ml), oxime ***cis*-16** (184 mg, 58%) was obtained, after flash chromatography (CH_2Cl_2-MeOH, 99:1). **3-Aminopiperidine *cis*-16**: IR (NaCl) 3380 and 3300 (NH_2) cm^{-1}; ^{13}C NMR 15.2 and 15.5 (CH_3), 27.3 (C-5), 50.6 (C-6), 53.0 (C-3), 54.0 and 55.3 (OCH_2CH_3), 54.8 (NCH_2), 60.8 (C-2), 68.8 (CH_2OBn), 72.7 (OCH_2Ph), 100.3 (C-4), 112.7 (In-C3), 115.1 (In-C7), 120.8 (In-C4), 123.6 (In-C5), 124.4 (In-C6), 126.7, 127.4, 128.3, 129.1, and 133.7 (Ph); MS *m/z* (%): 577 (M^+, 1), 532 (2), 437 (24), 436 (76), 410 (34), 291 (19), 279 (35), 130 (48), 91 (100). Anal. Calcd for $C_{32}H_{39}N_3O_5S$: C, 66.53; H, 6.80; N, 7.27. Found: C, 66.82; H, 6.56; N, 7.25.

Only once **3-aminopiperidine *trans*-16** was detected: ^1H NMR (from 9 mg of a 1:1 mixture of *cis* and *trans* isomers) 1.00 and 1.28 (2 t, J = 7 Hz, 3H each, CH_3), 1.75-1.95 (m, 5-H_a and NCH_A), 2.00 (dt, J = 11 Hz, 1H, 5-H_e), 2.50 (t, J = 11 Hz, 1H, 6-H_a), 2.51-2.70 (m, NCH_B), 3.05 (d, J = 11 Hz, 1H, 3-H_a), 3.15 (dt, J = 11 and 4 Hz, 6-H_e), 3.30-3.65 (m, CH_2OBn and OCH_2CH_3), 4.30 (d, J = 11 Hz, 1H, 2-H_a), 4.33 (s, 2H, OCH_2Ph), 6.72 (s, 1H, In-3H), 7.20-7.50 (m, Ar-H), 7.81 (d, J = 7 Hz, 2H, Ar-H), 8.28 (d, J = 7 Hz, 1H, In-7H).

3-Amino-1-(2-benzyloxyethyl)-4,4-diethoxy-2-(2-indolyl)piperidine (17). A solution of amine **16** (170 mg, 0.29 mmol) in 10% aqueous NaOH (7 ml) and EtOH (15 ml) was refluxed for 5 h. The solvent was evaporated, and the aqueous residue was extracted with CH_2Cl_2. The organic extracts were washed with H_2O, dried, and evaporated to give an oil which was flash chromatographed (CH_2Cl_2-MeOH, 99:1) to yield amine **17** (50 mg, 39%): IR (NaCl) 3400-3200 (In-NH and NH_2) cm^{-1}; ^1H NMR 1.15 and 1.25 (2 t, J = 7 Hz, 3H each, CH_3), 1.70-1.80 (br s, 2H, NH_2), 1.84 (br d, J = 13 Hz, 1H, 5-H_e), 1.97 (td, J = 13 and 4 Hz, 1H, 5-H_a), 2.15-2.20 (m, 1H, NCH_A), 2.35 (td, J = 13 and 4 Hz, 1H, 6-H_a), 2.74-2.84 (m, 1H, NCH_B), 3.00 (br d, J = 13 Hz, 1H, 6-H_e), 3.05 (d, J = 1 Hz, 1H, 3-H_e), 3.30-3.60 (m, 6H, OCH_2CH_3 and CH_2OBn), 3.90 (d, J = 1Hz, 1H, 2-H_a), 4.45 (s, 2H, OCH_2Ph), 6.35 (s, 1H, In-3H), 7.05 (t, J = 7 Hz, 1H, In-5H), 7.10 (t, J = 7 Hz, 1H, In-6H), 7.20-7.45 (m, 6H, In-7H and Ar-H), 7.50 (d, J = 7 Hz, 1H, In-4H), 10.15 (br s, 1H, In-NH); ^{13}C NMR 15.3 and 15.5 (CH_3), 28.1 (C-5), 50.1 (C-6), 53.7 and 54.8 (OCH_2CH_3), 55.3 (NCH_2), 55.8 (C-3), 61.3 (C-2), 68.5 (CH_2OBn), 73.0 (OCH_2Ph), 100.2 (C-4), 101.8 (In-C3), 111.2 (In-C7), 119.2 (In-C4), 119.9 (In-C5), 121.1 (In-C6), 127.6 (Ph-*p*), 127.9 (Ph-*o*), 128.2 (Ph-*m*), 135.9 (In-C7a), 138.0 (In-C2), 138.8 (Ph-*ipso*); MS *m/z* (%) 437 (M^+, 4), 392 (12), 346 (42), 329 (33), 280 (39), 270 (85), 271 (40), 214 (28), 158 (28), 158 (78), 130 (85), 91 (100). Anal. Calcd for $C_{26}H_{35}N_3O_3$: C, 71.37; H, 8.06; N, 9.60. Found: C, 71.59; H, 8.43; N, 9.52.

3-Amino-1-(2-benzyloxyethyl)-4,4-diethoxy-2-(2-indolyl)piperidine Methyl Carbamate (18). A suspension of NaH (60% in oil, 4 mg, 0.11 mmol) was washed twice with dry hexane, and once with dry THF under inert atmosphere, and cooled at 0°C before addition of a solution of amine **17** (40 mg, 0.09 mmol) in dry THF (10 ml). After 15 min, methyl chloroformate (10 µl, 0.11 mmol) was added, and the reaction was stirred at 0°C for 3 h. The crude was poured on iced H_2O, the solvent was evaporated, and the aqueous residue was extracted with CH_2Cl_2. The organic extracts, dried and evaporated, yielded carbamate **18** (44 mg, quantitative), which was used without further purification. IR (NaCl) 3350 and 3160 (NH), 1728 (CO) cm^{-1}; ^1H NMR 1.15 and 1.20 (2 t, J = 7 Hz, 3H each, CH_3), 1.75 (td, J = 11 and 3 Hz, 1H, 5-H_a), 2.00 (m, 1H, NCH_A), 2.15 (br d, J = 11 Hz, 1H, 5-H_e), 2.35 (td, J = 11 and 2 Hz, 1H, 6-H_a), 2.80 (m, 1H, NCH_B),

2.95 (br d, J = 11 Hz, 1H, 6-H_e), 3.10 (s, 1H, 3-H_e), 3.30* and 3.35 (2s, OCH_3), 3.40-3.63 (m, 6H, OCH_2CH_3 and CH_2OBn), 4.00 (d, J_{AB} = 3 Hz, 1H, OCH_APh), 4.12 (s, 1H, 2-H_a), 4.50 (d, J_{AB} = 3 Hz, 1H, OCH_BPh), 5.35* and 5.49 (2 d, J = 10 Hz, OCONH), 6.40 and 6.65* (2s, In-3H), 6.75* and 7.00 (2m, In-5H), 7.20-7.50 (m, 8H, Ar-H), 8.95* and 9.00 (2 br s, In-NH); ^{13}C NMR 15.2 and 15.3 (OCH_2CH_3), 28.7 (C-5), 49.4 (C-6), 51.9 (OCH_3), 53.5 (NCH_2), 55.3 and 55.8 (OCH_2CH_3), 56.4 (C-3), 61.7 (C-2), 68.4 (CH_2OBn), 73.4 (OCH_2Ph), 98.7 (C-4), 101.6 (In-C3), 110.6 (In-C7), 119.1 (In-C4), 120.2 (In-C5), 121.0 (In-C6), 127.9 (In-C3a), 128.0 (Ph-*o*), 128.3 (Ph-*p*), 128.6 (Ph-*m*), 136.1 (In-C7a), 137.2 (Ph-*ipso*), 138.0 (In-C2), 156.3 (CO).

12-(2-Benzyloxyethyl)-9,9-diethoxy-7-oxo-7,8,8a,9,10,11,12,12a-octahydropyrido[2',3':5,6]pyrimidino-[3,4-*a*]indole (19). A solution of carbamate **18** (45 mg, 0.09 mmol) in dry THF (8 ml) was slowly added, under inert atmosphere and at 0°C, on previously washed NaH (see above, 4 mg, 0.11 mmol). The reaction mixture was stirred for 3 h. The crude was poured on iced H_2O, the solvent was evaporated, and the aqueous residue was extracted with CH_2Cl_2. The organic extracts, dried and evaporated, gave an oil which was flash chromatographed (Et_2O) to yield tetracycle **19** (37 mg, 99%). IR (NaCl) 3200 (NH), 1700 (CO) cm^{-1}; ^1H 1.20 and 1.25 (2 t, J = 7 Hz, 3H each, CH_3), 1.92-2.04 (m, 2H, NCH_A and 10-H_a), 2.47-2.60 (m, 2H, 10-H_e and 11-H_e), 2.87-2.98 (m, 2H, NCH_B and 11-H_a), 3.24-3.34 (m, 1H, OCH_2CH_3), 3.40-3.55 (m, 5H, OCH_2CH_3 and CH_2OBn), 3.73 (br s, 1H, 8a-H), 3.82 (br s, 1H, 12a-H), 4.35 (s, 2H, OCH_2Ph), 5.40 (s, 1H, NH), 6.50 (s, 1H, 1-H), 7.20-7.30 (m, 7H, Ar-H), 7.50 (d, J = 7 Hz, 1H, 2-H), 8.35 (d, J = 7 Hz, 1H, 5-H); ^{13}C NMR 15.1 and 15.2 (CH_3), 28.9 (C-10), 48.3 (C-11), 52.0 (NCH_2), 54.1 (C-12a), 54.4 (C-8a), 55.4 and 55.6 (OCH_2CH_3), 68.2 (CH_2OBn), 73.0 (OCH_2Ph), 98.0 (C-9), 107.4 (C-1), 115.2 (C-5), 120.4 (C-2), 122.6 (C-3), 124.3 (C-4), 127.5 (Ph-*o*), 127.6 (Ph-*p*), 128.3 (Ph-*m*), 134.2, 135.5, 138.2, 150.7 (C-7); MS *m/z* (%) 463 (M^+, 1), 342 (12), 296 (6), 255 (10), 184 (27), 158 (88), 130 (78), 117 (37), 91 (29), 84 (100). Anal. Calcd for $C_{27}H_{33}N_3O_4$: C, 69.96; H, 7.18; N, 9.06. Found: C, 70.02, H, 7.09; N, 9.23.

12-(2-Benzyloxyethyl)-9,9-diethoxy-8-metil-7-oxo-7,8,8a,9,10,11,12,12a-octahydropyrido[2',3':5,6]piri-midino[3,4-*a*]indole (20). A solution of tetracycle **19** (43 mg, 0.09 mmol) in dry THF (3 ml) was slowly added, under inert atmosphere and at 0°C, on previously washed NaH (see above, 5 mg, 0.11 mmol). The reaction mixture was stirred for 15 min. CH_3I (7 µl, 0.11 ml) was added, the reaction mixture was allowed to reach room temperature, and stirred for 2 h. The crude was poured on iced H_2O, the solvent was evaporated, and the aqueous residue was extracted with CH_2Cl_2. The organic extracts, dried and evaporated, gave an oil which was flash chromatographed (Et_2O) to yield tetracycle **20** (44 mg, 99%). IR (NaCl) 1691 (CO) cm^{-1}; ^1H NMR 0.95 and 1.15 (2 t, J = 7 Hz, 3H each, CH_3), 1.80-1.90 (m, 2H, 10-H_a and NCH_A), 2.75 (dt, J = 11 and 4 Hz, 1H, 11-H_e), 3.10-3.30 (m, 4H, 11-H_a, NCH_B, and CH_2OBn), 3.25 (s, 3H, NCH_3), 3.40 (q, J = 7 Hz, 2H, OCH_2CH_3), 3.65 (m, 3H, 12a-H and OCH_2CH_3), 4.55 (s, 2H, OCH_2Ph), 4.60 (br s, 1H, 8a-H), 6.40 (s, 1H, 1-H), 7.10 (t, J = 7 Hz, 1H, 3-H), 7.15 (t, J = 7 Hz, 1H, 4-H), 7.20-7.40 (m, 5H, Ph-H), 7.45 (d, J = 7 Hz, 1H, 2-H), 8.33 (d, J = 7 Hz, 1H, 5-H); ^{13}C NMR 14.6 and 15.4 (CH_3), 29.6 (C-10), 38.0 (br s, NCH_3), 44.0 (br s, C-11), 53.8 (NCH_2), 56.1 (C-12a), 57.0 (C-8a), 57.3 and 62.0 (br s, OCH_2CH_3), 69.8 (CH_2OBn), 73.2 (OCH_2Ph), 99.0 (C-9), 105.0 (br s, C-1), 114.8 (C-5), 119.6 (C-2), 121.8 (C-3), 123.1 (C-4), 127.6 (Ph-*o*), 127.7 (Ph-*p*), 128.4 (Ph-*m*), 135.6, 138.1, 151.4 (C-7); MS *m/z* (%) 477 (M^+, 1), 402 (1), 310 (1), 199

* Two carbamate rotamers are observed in a 1:4 proportion. The asterisk indicates signals corresponding to the minor rotamer.

(52), 198 (22), 117 (30), 91 (21), 84 (33). Anal. Calcd for $C_{28}H_{35}N_3O_4$: C, 70.41; H, 7.39; N, 8.80. Found: C, 70.34; H, 7.25; N, 8.50.

Debenzylation of compound 20 with $Me_2S/BF_3.Et_2O$ (21 and 22). To a solution of tetracycle **20** (50 mg, 0.10 mmol) in dry CH_2Cl_2 (5 ml), freshly distilled $BF_3.Et_2O$ (0.16 ml, 1.13 mmol), and Me_2S (0.14 ml, 3.14 mmol) were added consequently. The reaction mixture was heated at 30°C for 18 h, poured on diluted NH_4OH (pH>7), and the layers separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts, dried and evaporated, yielded an oil which was flash chromatographed (CH_2Cl_2-MeOH, 97:3) to isolate compounds **21** and **22**. **Ketone 21** (lower Rf, 5 mg, 18%): IR (NaCl) 3500-3300 (OH), 1723 (NCON), 1693 (CO) cm^{-1}; ^1H NMR 2.23 (dt, J = 13 and 2 Hz, 1H, 10-H_e), 2.63 (td, J = 13 and 7 Hz, 1H, 10-H_a), 3.12 (s, 3H, NCH_3), 3.15 (dt, J = 13 and 2 Hz, 1H, 11-H_e), 3.20 (t, J = 5 Hz, 2H, NCH_2), 3.42 (td, J = 13 and 2 Hz, 1H, 11-H_a), 3.75 (t, J = 5 Hz, 2H, CH_2OH), 4.12 (d, J = 6 Hz, 1H, 8a-H), 4.91 (d, J = 6 Hz, 1H, 12a-H), 6.40 (s, 1H, 1-H), 7.15 (t, J = 7 Hz, 1H, 3-H), 7.20 (t, J = 7 Hz, 1H, 4-H), 7.40 (d, J = 7 Hz, 1H, 2-H), 8.30 (d, J = 7 Hz, 1H, 5-H); ^{13}C NMR 36.0 (NCH_3), 38.9 (C-10), 47.1 (C-11), 55.8 (NCH_2), 59.8 (CH_2OH), 61.1 (C-12a), 66.2 (C-8a), 103.8 (C-1), 115.8 (C-5), 120.0 (C-2), 122.8 (C-3), 124.6 (C-4), 128.7(C-12b), 132.4 (C-5a), 135.8 (C-1a), 150.8 (C-3), 203.0 (C-9); MS *m/z* (%) 313 (M^+, 25), 283 (15), 282 (28), 253 (16), 211 (100), 198 (79), 155 (20), 129 (11), 84 (57). Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.17; H, 6.07; N, 13.41. Found: C, 65.43; H, 5.89; N, 13.21. **Enol ether 22** (higher Rf, 10 mg, 28%): IR (NaCl) 3500-3300 (OH), 1688 (CO and C=C) cm^{-1}; ^1H NMR 1.26 (t, J = 7 Hz, 3H, CH_3), 3.17 (m, 2H, NCH_2), 3.25 (dd, J = 5 and 1 Hz, 1H, 11-H), 3.30 (s, 3H, NCH_3), 3.56-3.70 (2 m, 4H, CH_2OH, OCH_2CH_3, and 11-H), 4.25 (br s, 1H, 8a-H), 4.45 (br s, 1H, 12a-H), 4.58 (br d, J = 5 Hz, 1H, 10-H), 6.51 (s, 1H, 1-H), 7.20 (t, J = 7 Hz, 1H, 3-H), 7.30 (t, J = 7 Hz, 1H, 4-H), 7.50 (d, J = 7 Hz, 1H, 2-H), 8.35 (d, J = 7 Hz, 1H, 5-H); ^{13}C NMR 14.4 (CH_3), 38.0 (NCH_3), 44.7 (C-11), 55.9 (C-8a), 56.7 (OCH_2CH_3), 57.1 (C-12a), 58.7 (NCH_2), 62.6 (CH_2OH), 93.8 (C-10), 103.7 (C-1), 115.5 (C-5), 120.0 (C-2), 122.5 (C-3), 123.9 (C-4); MS *m/z* (%) 341 (M^+, 41), 313 (55), 312 (100), 282 (21), 281 (35), 253 (29), 252 (32), 251 (12), 200 (21), 199 (39), 155 (8), 112 (18). Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 73.88; H, 6.79; N, 12.30. Found: C, 73.60; H, 6.58; N, 12.29.

5-Amino-4,4-diethoxy-1-(2-hydroxyehyl)-2-[1-(phenylsulfonyl)-2-indolyl]piperidine (23). Operating as for the preparation of compounds **21** and **22**, from amine ***cis*-15** (95 mg, 0.16 mmol), $BF_3.Et_2O$ (0.24 ml, 1.97 mmol), and Me_2S (0.21 ml, 4.93 mmol), in dry CH_2Cl_2 (5 ml), aminoalcohol **23** (32 mg, 40%) was obtained, after flash chromatography (CH_2Cl_2-MeOH, 95:5). IR (NaCl) 3500-3100 (OH and NH_2) cm^{-1}; ^1H NMR 1.15 and 1.25 (2 t, J = 7 Hz, 3H each, CH_3), 1.82 (br t, J = 12 Hz, 1H, 3-H_a), 2.02 (br d, J = 12 Hz, 1H, 3-H_e), 2.50-2.60 (m, 1H, NCH_A), 2.55 (d, J = 12 Hz, 1H, 6-H_a), 2.80-2.90 (br s, 2H, NH_2), 3.08 (s, 1H, 5-H_e), 3.12 (d, J = 12 Hz, 1H, 6-H_e), 3.25 (m, 1H, NCH_B), 3.40-3.70 (m, 2H, CH_2OH), 3.60-3.80 (m, 4H, OCH_2CH_3), 4.26 (dd, J = 12 and 3 Hz, 1H, 2-H_a), 6.85 (s, 1H, In-3H), 7.25 (t, J = 7 Hz, 1H, In-5H), 7.30 (t, J = 7 Hz, 1H, In-6H), 7.40 (m, 4H, Ar-H), 7.77 (d, J = 7 Hz, 2H, Ar-H), 8.29 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 15.2 and 15.4 (CH_3), 37.7 (C-3), 49.9 (C-6), 53.8 (NCH_2), 54.8 (C-5), 55.0 and 55.5 (OCH_2CH_3), 56.9 (C-2), 58.7 (CH_2OH), 99.2 (C-4), 110.3 (In-C3), 114.9 (In-C7), 120.9 (In-C4), 123.7 (In-C5), 124.5 (In-C6), 126.4 (Ph-*o*), 129.2 (Ph-*m*), 129.4 (In-C3a), 133.8 (Ph-*p*), 136.9 (In-C7a), 139.4 (Ar-*ipso*), 142.9 (In-C2); MS *m/z* (%) 487 (M^+, 1), 456 (5), 410 (100), 381 (40), 328 (67), 282 (51), 215 (70), 130 (68), 102 (53), 77 (97). Anal. Calcd for $C_{25}H_{33}N_3O_5S$: C, 61.58; H, 6.82; N, 8.62. Found: C, 61.59; H, 6.90; N, 8.60.

Cyclisation of alcohol 23 with K^{t}BuO (24 and 25). To a solution of aminoalcohol **23** (32 mg, 0.07 mmol) in dry THF (3 ml), cooled at 0°C and under inert atmosphere, recently sublimated K^{t}BuO (19 mg, 0.17 mmol) was added. After stirring at 0°C for 30 min, the crude reaction mixture was poured on aqueous NH_4Cl and extracted with Et_2O. The organic extracts, dried and evaporated, yielded an oil which was flash chromatographed (CH_2Cl_2-MeOH, 95:5) to isolate compounds **24** and **25**. **3-Aminoindoloquinolizidine 24** (lower Rf, 5 mg, 23%): IR (NaCl) 3200 (In-NH and NH_2), 2800-2750 (Bohlman) cm^{-1}; ^{1}H NMR 1.20 and 1.22 (2 t, J = 7 Hz, 3H each, CH_3), 1.30 (br s, 2H, NH_2), 1.80 (t, J = 12 Hz, 1H, 1-H$_a$), 2.21 (br d, J = 12 Hz, 1H, 1-H$_e$), 2.64 (br dd, J = 14 and 4 Hz, 1H, 7-H$_e$), 2.72 (br t, J = 14 Hz, 1H, 7-H$_a$), 2.82 (dd, J = 12 and 2 Hz, 1H, 4-H$_a$), 2.93 (dd, J = 12 and 2 Hz, 1H, 4-H$_e$), 2.93-3.02 (m, 2H, 6-H$_a$ and 6-H$_e$), 3.07 (t, J = 2 Hz, 1H, 3-H$_e$), 3.45 (br d, J = 12 Hz, 1H, 12b-H), 3.50-3.65 (m, 4H, OCH_2CH$_3$), 7.05 (t, J = 7 Hz, 1H, 9-H), 7.10 (t, J = 7 Hz, 1H, 10-H), 7.25 (d, J = 7 Hz, 1H, 11-H), 7.45 (d, J = 7 Hz, 1H, 8-H), 8.00 (br s, 1H, In-NH); MS *m/z* (%) 329 (M$^+$, 18), 282 (20), 254 (54), 239 (24), 238 (71), 184 (50), 171 (42), 170 (100), 169 (83), 149 (27). Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.43; H, 8.59; N, 12.71. **11-Amino-7,8,9,10,11,12,13,13a-octahydropyrido[1',2':1,2]pyrazino[4,3-*a*]indole** (**25**, higher Rf, 6 mg, 27%): ^{1}H NMR 1.25 (t, J = 7 Hz, 6H, CH_3), 1.85 (t, J = 12 Hz, 1H, 13-H$_a$), 1.90-2,10 (br s, 2H, NH_2), 2.45 (d, J = 12 Hz, 1H, 13-H$_e$), 2.75-2.80 (m, 2H, 7-H), 2.95 (dd, J = 12 and 3 Hz, 1H, 10-H$_a$), 3.05 (br s, 1H, 11-H$_e$), 3.05-3.15 (m, 1H, 8-H$_e$), 3.40 (br d, J = 12 Hz, 1H, 10-H$_e$), 3.50-3.65 (m, 4H, OCH_2CH$_3$), 4.02 (td, J = 12 and 4 Hz, 1H, 8-H$_a$), 4.15 (dd, J = 12 and 4 Hz, 1H, 13a-H), 6.20 (s, 1H, 1-H), 7.05 (t, J = 7 Hz, 1H, 3-H), 7.15 (t, J = 7 Hz, 1H, 4-H), 7.25 (d, J = 7 Hz, 1H, 5-H), 7.55 (d, J = 7 Hz, 1H, 2-H).

3-Amino-4,4-diethoxy-1-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]piperidine (26). Operating as for the preparation of compounds **21** and **22,** from piperidine **16** (121 mg, 0.21 mmol), Me_2S (0.27 ml, 6.28 mmol), $BF_3.Et_2O$ (0.31 ml, 2.51 mmol), in dry CH_2Cl_2 (8 ml), aminoalcohol **26** (41 mg, 40%) was obtained, after flash chromatography (CH_2Cl_2-MeOH, 95:5): IR (NaCl) 3500-3100 (OH and NH) cm^{-1}; ^{1}H NMR 1.15 and 1.35 (2 t, J = 7 Hz, 3H each, CH_3), 1.65 (br t, J = 12 Hz, 1H, 5-H$_a$), 1.62 (br d, J = 12 Hz, 1H, 5-H$_e$), 1.95 (td, J = 12 and 3 Hz, 1H, 6-H$_a$), 2.10-2.20 (m, 1H, NCH$_A$), 2.60-2.70 (m, 1H, NCH$_B$), 3.00 (s, 1H, 3-H), 3.30-3.40, 3.40-3.55, and 3.55-3.70 (3 m, 6H, OCH_2CH$_3$ and CH_2OH), 4.67 (d, J = 1Hz, 1H, 2-H$_a$), 6.95 (s, 1H, In-3H), 7.25-7.55 (m, 6H, Ar-H), 7.80 (d, J = 7 Hz, 2H, Ar-H), 8.32 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 15.2 and 15.4 (CH_3), 27.4 (C-5), 52.9 (C-3), 54.9 (C-6), 55.0 (NCH_2), 55.2 and 55.3 (OCH_2CH_3), 58.6 (CH_2OH), 60.3 (C-2), 99.9 (C-4), 113.2 (In-C3), 115.0 (In-C7), 121.0 (In-C4), 123.7 (In-C5), 124.6 (In-C6), 126.6 (Ph-*o*), 129.1 (Ph-*m*), 133.8 (Ph-*p*), 136.9 (In-C7a), 138.9 (Ph-*ipso*); MS *m/z* (%) 487 (M$^+$, 1), 456 (1), 410 (21), 396 (9), 332 (46), 329 (43), 254 (20), 201(78), 189 (72), 157 (85), 130 (100), 84 (51). Anal. Calcd for $C_{25}H_{33}N_3O_5S$: C, 61.58; H, 6.82; N, 8.62. Found: C, 61.39; H, 6.53; N, 8.41.

Treatment of alcohol 26 with K^{t}BuO (8 and 27). Operating as for the preparation of compounds **24** and **25**, from piperidine **26** (98 mg, 0.20 mmol) and recently sublimated K^{t}BuO (90 mg, 0.81 mmol), in THF (6 ml), compounds **8** and **27** were isolated after flash chromatography (CH_2Cl_2-MeOH, 97:3). **1-Aminoindolo[2,3-*a*]quinolizidine 8** (lower Rf, 7 mg, 8%): IR (NaCl) 3250-3300 (NH_2), 2750-2800 (Bohlman) cm^{-1}; ^{1}H NMR 1.20 and 1.25 (2 t, J = 7 Hz, 3H each, CH_3), 1.70-1.80 (br s, 2H, NH_2), 1.98-2.00 (m, 1H, 3-H$_e$), 2.48 (td, J = 12 and 5 Hz, 1H, 3-H$_a$), 2.61 (td, J = 12 and 5 Hz, 1H, 7-H$_a$), 2.70 (dm, J = 12 Hz, 1H, 6-H$_e$), 2.82 (dt, J = 12

and 3 Hz, 1H, 7-H_e), 2.84-3.00 (m, 2H, 4-H_a and 6-H_a), 3.02 (br dd, J = 12 and 5 Hz, 1H, 4-H_e), 3.30 (br s, J = 5 Hz, 1H, 1-H_e), 3.50-3.60 (m, 4H, OCH_2CH_3), 3.74 (br s, 1H, 12b-H), 7.05 (t, J = 7 Hz, 1H, 9-H), 7.10 (t, J = 7 Hz, 1H, 10-H), 7.25 (d, J = 7 Hz, 1H, 11-H), 7.45 (d, J = 7 Hz, 1H, 8-H), 8.00 (br s, 1N, In-NH); MS *m/z* (%) 329 (M^+, 38), 284 (83), 254 (56), 234 (94), 184 (76), 169 (92), 171 (100), 156 (42), 126 (40). Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.54; H, 8.12; N, 12.37. **13-Amino-7,8,9,10,11,12,13,13a-octahydropyrido[1',2':1,2]pyrazino[4,3-*a*]indole** (**27**, higher Rf, 25 mg, 25%): IR (NaCl) 3450-3350 (NH_2) cm^{-1}; ^1H NMR 1.22 and 1.26 (2 t, J = 7 Hz, 3H each, CH_3), 1.60 (br s, 2H, NH_2), 1.90 (br d, J = 12 Hz, 1H , 11-H_e), 2.02 (td J = 12 and 5 Hz, 1H, 11-H_a), 2.46 (td, J = 12 and 3 Hz, 1H, 7-H_a), 2.77 (td, J = 12 and 4 Hz, 1H, 10-H_a), 2.84-2.93 (m, H, 10-H_e), 3.12 (dd, J = 12 and 4 Hz, 1H, 8-H_e), 3.47 (br s, 1H, 13-H_e), 3.50-3.65 (m, 4H, OCH_2CH_3), 3.78 (br s, 1H, 13a-H), 4.00-4.20 (m, 2H, 8-H_a and 7-H_e), 6.26 (br s, 1H, 1-H), 7.08 (t, J = 7 Hz, 1H, 3-H), 7.11 (t, J = 7 Hz, 1H, 4-H), 7.26 (d, J = 7 Hz, 1H, 5-H), 7.55 (d, J = 7 Hz, 1H, 2-H); MS *m/z* (%) 329 (M^+, 29), 284 (100), 270 (17), 255 (48), 238 (77), 171 (91), 156 (24), 114 (24). Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.33; H, 8.50; N, 12.54.

Indolo[2,3-*a*]quinolizidin-2-one Oxime (29).[20] Operating as for the preparation of oximes **13** and **14**, from quinolizidone **28**[10] (490 mg, 2.04 mmols), $NH_2OH.HCl$ (284 mg, 4.08 mmol), and K_2CO_3 (564 mg, 4.08 mmol), in dry DME (30 ml), heating at 60°C for 3 h, oximes ***(Z)*-29** and ***(E)*-29** were isolated after flash chromatography (CH_2Cl_2-MeOH, 97:3). **Oxime *(E)*-29** (higher Rf, 234 mg, 45%): IR (KBr) 3289 (OH) cm^{-1}; ^1H NMR ($CDCl_3$ + drops of CD_3OD) 2.20-2.30 (ddd, J = 13, 12 and 6 Hz, 1H, 3-H_a), 2.35 (dd, J = 13 and 11 Hz, 1H, 1-H_a), 2.52 (td, J = 12 and 2 Hz, 1H, 7-H_a), 2.70 (td, J = 12 and 4 Hz, 1H, 4-H_a), 2.81 (br d, J = 13 Hz, 1H, 7-H_e), 2.92 (dt, J = 13 and 2 Hz, 1H, 1-H_e), 2.95-3.12 (m, 1H, 6-H_a), 3.16-3.24 (m, 2H, 3-H_e and 6-H_e), 3.34-3.38 (br d, J = 12 Hz, 1H, 4-H_e), 3.44 (dd, J = 11 and 2 Hz, 1H, 12b-H_a), 7.07 (t, J = 7 Hz, 1H, 9-H), 7.09 (t, J = 7 Hz, 1H, 10-H), 7.37 (d, J = 7 Hz, 1H, 11-H), 7.48 (d, J = 7 Hz, 1H, 8-H); ^{13}C NMR ($CDCl_3$ + drops of CD_3OD) 21.1 (C-7), 24.0 (C-3), 34.8 (C-1), 52.2 (C-6), 53.3 (C-4), 59.4 (C-12b), 107.1 (In-C7b), 110.8 (C-11), 117.7 (C-8), 118.8 (C-9), 121.0 (C-10), 126.5 (C-7a), 133.1 (C-12a), 136.2 (C-11a), 156.3 (C-2); MS *m/z* (%) 256 (M^++1, 73), 239 (23), 238 (75), 209 (18), 197 (39), 182 (23), 170 (28), 169 (100), 168 (32), 156 (22), 153 (22). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.53; H, 6.70; N, 16.35. **Oxime *(Z)*-29** (lower Rf, 250 mg, 48%): IR (KBr) 3300-3280 (OH) cm^{-1}; ^1H NMR ($CDCl_3$ + drops of CD_3OD) 2.08 (dd, J = 13 and 12 Hz, 1H, 1-H_a), 2.44 (br d, J = 12 Hz, 1H, 1-H_e), 2.48-2.58 (m, 1H, 3-H_a), 2.60 (m, 1H, 7-H_a), 2.70 (td, J = 11 and 4 Hz, 1H, 4-H_a), 2.80 (br d, J = 13 Hz, 1H, 7-H_e), 2.95-3.10 (m, 1H, 6-H_a), 3.15-3.24 (m,. 2H, 3-H_e and 6-H_e), 3.42 (br d, J = 12 Hz, 1H, 4-H_e), 3.79 (dm, J = 12 Hz, 1H, 12b-H_a), 7.08 (br t, J = 7 Hz, 1H, 9-H), 7.14 (br t, J = 7 Hz, 1H, 10-H), 7.34 (br d, J = 7 Hz, 1H, 11-H), 7.47 (br d, J = 7 Hz, 8-H), 9.25 (br s, 1H, In-NH); ^{13}C NMR ($CDCl_3$ + drops of CD_3OD) 21.3 (C-7), 28.2 (C-3), 31.0 (C-1), 52.5 (C-6), 54.6 (C-4), 58.2 (C-12b), 107.6 (In-C7b), 110.9 (C-11), 117.9 (C-8), 119.0 (C-9), 121.3 (C-10), 126.7 (C-7a), 135.5 (C-11a), 156.2 (C-2). Anal. Calcd for $C_{15}H_{17}N_3O.1/2\ H_2O$: C, 68.15; H, 6.86; N, 15.89. Found: C, 67.70; H, 6.61; N, 15.62.

Neber rearrangement on oxime 29 to give 24, 8, and 31. Operating as for the preparation of compounds **15** and **16**, from a 1:1 mixture of oximes **29** (250 mg, 0.98 mmol), TsCl (186 mg, 0.98 mmol), and K_2CO_3 (270 mg, 1.96 mmol) in dry THF (10 ml), a 1:1 mixture of the corresponding tosyloximes (400 mg, quantitative)

was obtained, which was used without further purification. **Tosyloximes** (from a 1.5:1 mixture of *E:Z*-tosyloximes obtained once): ^{1}H NMR 2.43 and 2.44* (2 s, 3H each, Tos-CH_3), 3.33 (br d, J = 12 Hz, 1H, 12b-H$_a$), 3.65* (br d, J = 12 Hz, 1H, 12b-H$_a$'), 7.00-7.70 (m, In-H), 7.35 and 7.37* (2 d, J = 7 Hz, 2Heach, Tos-*o*), 7.89 and 7.90* (2 d, J = 7 Hz, 2H each, Tos-*m*), 8.10 and 8.25* (2 br s, In-NH); ^{13}C NMR 21.4* and 21.6 (Tos-*C*H$_3$), 21.6* and 21.7 (C-7), 26.5 and 30.7* (C-3), 30.9* and 35.3 (C-1), 52.0* and 51.8 (C-6), 52.9 and 53.9* (C-4), 57.4* and 58.5 (C-12b), 111.1and 111.2* (C-11), 118.0* and 118.1(C-8), 119.3* and 119.5 (C-9), 121.6* and 122.7 (C-10), 165.5* and 165.8 (C-2). From the above tosyloximes (400 mg, 0.98 mmol), potassium (115 mg, 2.94 matg), and $MgSO_4$ (400 mg) in dry EtOH (20 ml), an oil was obtained, which was flash chromatographed (CH_2Cl_2-MeOH, 98:2) to isolate compounds **24** (lower Rf, 26 mg, 8%), **8** (intermediate Rf, 103 mg, 32%), and **31** (higher Rf, 35 mg, 11%). ***trans*-1-Amino-2,2-diethoxyindolo[2,3-*a*]quinolizidine (31)**: IR (NaCl) 3200 (In-NH and NH_2), 2800-2750 (Bohlman) cm^{-1}; ^{1}H NMR 1.20 and 1.25 (2 t, J = 7 Hz, 3H each, CH_3), 1.80 (br s, 2H, NH_2), 1.95-2.20 (m, 1H, 3-H$_e$) , 2.55 (td, J = 12 and 5 Hz, 1H, 3-H$_a$), 2.68 (td, J = 12 and 5 Hz, 1H, 7-H$_a$), 2.72 (br s, 1H, ,7-H$_e$), 2.77 (td, J = 12 and 4 Hz, 1H, 6-H$_a$), 2.87 (dt, J = 12 and 5 Hz, 1H, 4-H$_e$), 2.94 (d, J = 10 Hz, 1H, 1-H$_a$), 3.00 (dm, J = 12 Hz, 1H, 6-H$_e$), 3.06-3.15 (m, 1H, 4-H$_a$), 3.30 (d, J = 10 Hz, 1H, 12b-H$_a$), 3.50-3.70 (m, 4H, OCH_2CH$_3$), 7.05 (t, J = 7 Hz, 1H, 9-H), 7.10 (t, J = 7 Hz, 1H, 10-H), 7.30 (d, J = 7 Hz, 1H, 11-H), 7.50 (d, J = 7 Hz, 1H, 8-H); MS *m/z* (%) 329 (M$^+$, 38), 284 (83), 238 (94, (171 (100).

1-Amino-2,2-diethoxyindolo[2,3-*a*]quinolizidine Methyl Carbamate (32). Operating as for the preparation of carbamate **18**, from aminoquinolizidine **8** (70 mg, 0.21 mmol), K_2CO_3 (75 mg), and methyl chloroformate (0.02 ml, 0.255 mmol) in dry acetone (3 ml), at room temperature, carbamate **32** (81 mg, 99%) was obtained. IR (KBr) 3422 and 3320 (In-NH and OCONH), 1696 (CO) cm^{-1}; ^{1}H NMR 1.16 and 1.24 (2 t, J = 7 Hz, 3H each, CH_3), 1.76 and 1.88** (td, J = 14 and 5 Hz, and br s, 1H, 3-H$_a$), 2.00 (dt, J = 14 and 2 Hz, 1H, 3-H$_e$), 2.46 (td, J = 12 and 2 Hz, 1H, 7-H$_a$), 2.61 (td, J = 12 and 4 Hz, 1H, 6-H$_a$), 2.70 (br d, J =14 Hz, 1H, 4-H$_e$), 2.84 (br d, J = 12 Hz, 1H, 6-H$_e$), 2.91 (br t, J = 14 Hz, 1H, 4-H$_a$), 3.06 (dd, J = 11 and 5 Hz, 1H, 1-H$_e$), 3.43 (s, 3H, OCH_3), 3.50-3.60 and 3.60-3.70 (2 m, 3H and 1H, OCH_2CH$_3$), 3.80 (br s, 1H, 12b-H$_a$), 4.35** and 5.60 (2 d, J = 11 Hz, 1H, CONH), 7.05 (t, J = 7 Hz, 1H, 9-H), 7.10 (t, J = 7 Hz, 1H, 10-H), 7.28 (d, J = 7 Hz, 1H, 11-H), 7.42 (d, J = 7 Hz, 1H, 8-H), 8.22 (br s, 1H, In-NH); ^{13}C NMR 15.2 (CH_3), 21.3 (C-7), 29.1 (C-3), 51.5 (C-1), 51.6 (C-6), 52.8 (C-4), 52.1 (NCH_3), 55.5 and 56.0 (OCH_2CH$_3$), 60.5 (C-12b), 99.1 (C-2), 110.0 (C-7b), 111.2 (C-11), 117.7 (C-8), 119.4 (C-9), 121.3 (C-10), 127.1 (C-7a), 132.2 (C-11a), 136.3 (C-12a), 157.4 (C=O); MS *m/z* (%) 387 (M$^+$, 13), 342 (38), 312 (31), 296 (30), 268 (30), 267 (100), 239 (28), 197 (20), 184 (28), 169 (36). Anal. Calcd for $C_{21}H_{28}N_3O_4$: C, 65.27; H, 7.30; N, 10.87. Found: C, 65.32; H, 7.45; N, 10.51.

17-Azaeburna derivative (33). Operating as for the preparation of tetracycle **19**, from carbamate **32** (83 mg, 0.21 mmol), NaH (10 mg, 0.25 mmol, 60% in oil), in dry THF (6 ml), 17-azaeburna derivative **33** (46 mg, 60%) was obtained, after flash chromatography (CH_2Cl_2-MeOH, 93:7). IR (NaCl) 3300 (NH), 1702 (CO) cm^{-1}; MS *m/z* (%) 355 (M$^+$, 21), 326 (4), 239 (40), 197 (100), 158 (35), 130 (18), 84 (28). Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.32; H, 7.48; N, 11.26.

* The asterisk indicates the signals of the minor isomer (*Z*).

** The double asterisk indicates signals splitted due to rotamers.

17-Azaeburna derivative (2). Operating as for the preparation of compound **20**, from compound **33** (25 mg, 0.07 mmol), NaH (6 mg, 0.14 mmol, 60% in oil), and CH_3I (5 μl, 0.08 mmol) in dry THF (3 ml), compound **2** (26 mg, 99%) was obtained, after flash chromatography (CH_2Cl_2-MeOH, 93:7). IR (NaCl) 1687 (CO) cm^{-1}; MS *m/z* (%) 369 (M^+, 11), 253 (25), 212 (16), 211 (100), 158 (33), 130 (13), 84 (17). Anal. Calcd for $C_{21}H_{27}N_3O_3$: C, 68.27; H, 7.34; N, 11.37. Found: C, 68.39; H, 7.51; N, 11.20.

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