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MODELS OF FOLATE COFACTORS 20.[1] AN APPROACH TO DEETHYLEBURNAMONINE

AXEL R. STOIT[2] and UPENDRA K. PANDIT*

Organic Chemistry Laboratory, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

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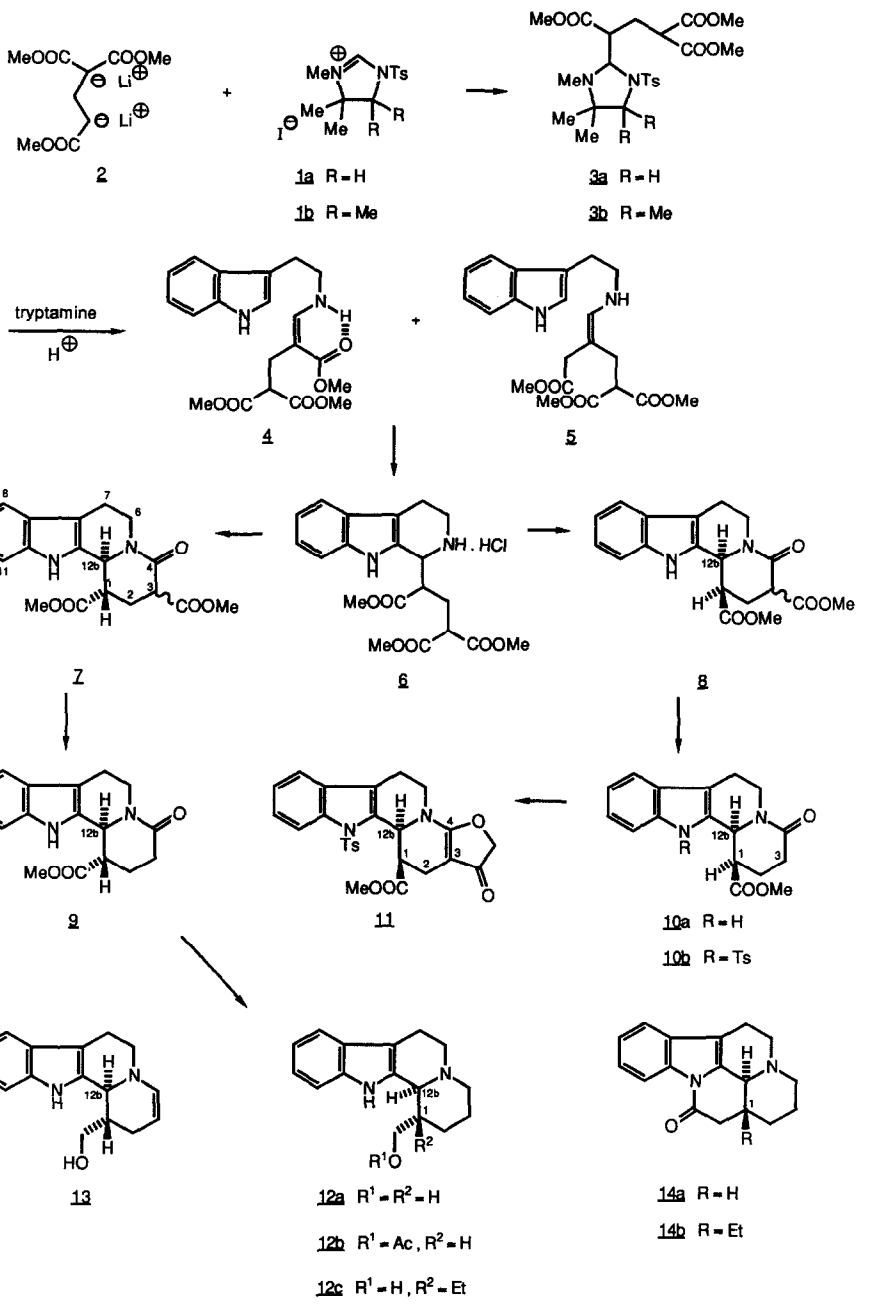
Abstract - The substituted 5,10-methylenetetrahydrofolate model (3a) derived from addition of the dianion of dimethyl 2-methoxycarbonylglutarate to 1,5,5-trimethyl-3-tosyl-1-imidazolidinium iodide (1) transfers a 7-carbon functionalized fragment to tryptamine to yield precursors of deethylepieburnamonine and deethyleburnamonine.

Interest in the synthesis of eburna and the related vinca alkaloids stems from their chemotherapeutic properties.[3] As a part of our current programme directed to the application of 5,10-methylenetetrahydrofolate models in synthetic studies,[4] we now report a convenient approach to the construction of the eburnamonine skeleton.

In line with the syntheses of other indoloquinolizidine derivatives via folate models,[5a-e] it was recognized that the desired model could be derived by the addition of glutarate anion to an imidazolidinium salt of type 1. Attempted addition of monoanions and dianions of dimethyl, diethyl and ditertiarybutyl glutarates to 1a, under a variety of conditions, led to complex mixtures from which no defined product could be isolated, though NMR spectra of the mixtures indicated the presence of the expected adducts. In contrast, when the dianion 2 was allowed to react with salts 1a and 1b, the corresponding imidazolidines 3a (85%) and 3b (76%) respectively, were obtained as diastereomeric mixtures.

With the availability of 3a,b, the stage was now set for the functionalized carbon-fragment transfer from the model to the desired substrate, namely, tryptamine. Application of the standard conditions for this reaction (CH_3CN, AcOH, reflux), resulted in the transfer of the seven carbon unit from 3a to yield a mixture (80%) of Z and E isomers 4 and 5, respectively, in a ratio of 3:2. However, the same conditions or replacement of acetic acid by trifluoroacetic acid left imidazolidine 3b unaffected.[6] This result can be rationalized in terms of the resistance to ring-opening of 3b -necessary for the transfer reaction[4]- due to influence of the gem-dimethyl substituents, the so called Thorpe-Ingold effect.[7a-c]

The mixture of 4 and 5 readily underwent a cyclization reaction leading to 6 (95%) under influence of HCl/benzene. It should be recognized that this step results in the generation of two asymmetric centres and thereby in the formation of diastereomers. Without separation, the mixture was subjected to treatment with triethylamine/acetic acid, whereupon, two diastereomeric pairs of lactams 7 and 8, corresponding to the first and second fraction from the column chromatographic separation, were obtained. The ratio of 3-α-COOMe/3-β-COOMe (3:2) in 7 could be evaluated by examining the ratio of the C(3)-H_{ax} (δ 3.43-3.51, m) to C(3)-H_{eq} (δ 3.60-3.73, m). The trans relationship between the C(12b)-H and the C(1)-H was deduced from the coupling pattern of the C(1)-H_{ax}. The signal for this proton (δ 3.22) consists of three sets of doublets $J_{12b,1ax}$ = 9.2, $J_{1ax,2ax}$ = 11.6, $J_{1ax,2eq}$ = 3.9. The second fraction 8 also contained the C(3)-epimers. A cis steric relation of C(12b)-H to C(1)-H

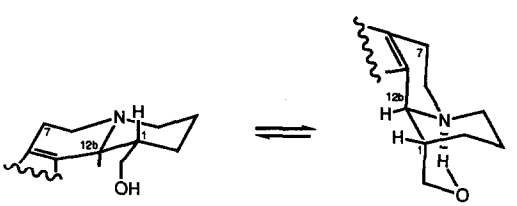

2
1a R = H
1b R = Me
3a R = H
3b R = Me
tryptamine
4
5
6
7
8
9
10a R = H
10b R = Ts
11
12a R¹ = R² = H
12b R¹ = Ac, R² = H
12c R¹ = H, R² = Et
13
14a R = H
14b R = Et

was attested by the broad doublet of C(12b)-H [δ 5.16, J = 4.1].

The removal of the C(3)-ester group in 7 or 8 was examined under a variety of reaction conditions. The standard conditions described in the literature[8a,b] (LiCl, DMSO/H_2O, 180°C) did not, in the case of 7 or 8, lead to decarbomethoxylation. In our hands, the best results [9 (56%), 10a (53%)] were obtained with $LiCl.3H_2O$ [9a,e] as the salt and a temperature of around 130°C (48 h). While the overall yield of 9 and 10a (∿ 30%), starting from the model (3a), is depressed due to the low yields of the decarbomethoxylation step, this still compares favourably with other approaches described for similar systems, in the literature.[10a,b] ^1H and ^{13}C NMR[11a-e] of 9 and 10a provide detailed information about the structures of these compounds (vide experimental). In an approach to construct the (fifth) ring E of the eburnamonine skeleton, compound 10a was first converted[12a,b] into the corresponding tosyl derivative 10b, and the latter alkylated with methyl bromoacetate. The product of this reaction was shown to be compound 11 (79%) instead of the expected C(1)-methoxycarbonylmethylene derivative. The structure of 11 follows from its spectral data. In particular, the bands in the IR spectrum at 1620 (w), 1586 (s) and 1574 (s) and the absence of any additional coupling above the AB pattern, as well as the magnitude of the coupling of the methylene group of the $-CO-CH_2-O$ moiety attest to structure 11. The most likely mechanism for the forming of 11 is initial acylation[13] at C(3), followed by enolization of the amide and subsequent intramolecular alkylation. It should be noted that whereas the α-protons of an ester are more acidic than that of an amide, the steric volume of the employed base (LDA) presumably favours a kinetically controlled deprotonation of the sterically accessible C-3 over that of C-1. However, in the absence of further information, it is not possible at this stage to exclude a mechanism in which the process is initiated by an amide O-alkylation and completed by C(3)-acylation of the intermediate enamine. Attempts to quench the reaction after the first step, at low temperatures, have proved unsuccessful.

Reduction of 9 with diisobutylaluminiumhydride[14] resulted in a mixture of 12a (40%) and 13 (28%). The last mentioned compound exhibits a strong enamine band at 1662 cm^{-1};[15a] its instability in air, [15a,b] did not, however, allow the determination of its NMR spectrum. In contrast to these results, reduction of 9 by lithium aluminiumhydride gave alcohol 12a in good yield (75%).

The stereochemistry of the quinolizidine ring in 12a is influenced by the nature and configuration of its substituents and can be determined by ^{13}C NMR spectrum.[11a-e] Based upon the linear relationship between the position of the conformational equilibrium and the ^{13}C chemical shifts for C(7) in trans- (21.8 ppm) and cis- (16.8 ppm)[16] quinolizidine systems, A and B, respectively, a value of 19.6 ppm for the alcohol (12a) implies an A/B ratio of 56/44. The relatively large contribution of conformation B can be understood in terms of intramolecular hydrogen-bonding of the hydroxyl proton



A B

with the lone pair electrons of the nitrogen. Such interactions have been observed by other workers.[17a-c] That both conformations are present is also supported by the chemical shift of C(12b)-H and the coupling constant between H(1) and H(12b). A broad doublet (J = 5.6) at δ 3.79 implies an average conformation between A and B possessing 1,2-diaxial and 1,2-diequatorial C(1)-C(12b) hydrogens. Acetylation of 12a[17a] led to 12b in which, as would be anticipated in line with the aforementioned reasoning, the quinolizidine ring assumes a trans configuration. This expresses itself in the emergence of Bohlmann bands[18,11a-e] (2810, 2760 and 2740 cm^{-1}) and a trans diaxial relationship

between the H(1) and H(12b) protons [H(12b) δ = 3,67, J = 8].

The synthesis of epi-eburnamonine (14b), starting from 12c, has been achieved in simple steps (OH → OMes → -CN → 14b).[19] In the light of these results, 12a constitutes a practical precursor of deethylepi-eburnamonine 14a. If 10a is subjected to the sequence of reactions described for 9, the synthesis of deethyleburnamonine should be achieved.

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EXPERIMENTAL

All mps are uncorrected. IR spectra were recorded on a Perkin Elmer 257 spectrometer. The absorptions are given in cm^{-1}. PMR spectra were run on a Bruker WM 250 instrument, using TMS as an internal standard. Mass spectra were obtained with a Varian Matt 711 spectrometer. Analyses were carried out at the microanalytical laboratory, Department of Physical Organic and Analytical Chemistry, Organic Chemistry Institute, TNO, Zeist, The Netherlands.

Methyl 2,4-dimethoxycarbonyl-4-[2-(1-tosyl-3,4,4-trimethyl)imidazolidinyl]butanoate (3a).
To a stirred solution of 10 mmol LDA in 150 ml THF was added 1090 mg (5 mmol) of ester 2, dissolved in 5 ml THF (-78°C, N_2). After an additional stirring for 25 min 1.97 g of 1a (5 mmol) was added to the reaction mixture. The reaction mixture was vigorously stirred for 1 h at -40°C and 2 h at 0°C. The resulting mixture was poured into a concentrated NH_4Cl solution and extracted with Et_2O. The organic layer was treated with brine, dried over Na_2SO_4 and concentrated. Chromatography on SiO_2 with EtOAc/hexane (1:5 → 1:1) gave 3a as a colourless oil.
3a: Yield 2.05 g (4.24 mmol, 85%). IR ($CHCl_3$): 1750 (s), 1731 (s), 1162 (s). NMR (250 MHz, C_6D_6, diastereomeric mixture (4:1)): 0.04 and 0.27 (1:4), 060 and 0.66 (1:4) (6H, 4xs, $NC(CH_3)_2$), 1.84 and 1.89 (6H, 2xs, NCH_3 and $TosCH_3$), 2.67-2.72 (1H, m, C_3H). 2.87-3.00 (2H, m, C_3H and CH_2NTos (1H), 2.89 ppm, d (J_{gem} = 10.7)), 3.10-3.30 (8H, m, $2xCOOCH_3$, C_4H en CH_2NTos (1H)), 3.56 and 3.60 (3H, 2xs, $COOCH_3$), 3.95-4.16 (1H, m, C_2H), 4.68 (d, J = 1.8) and 4.78 (d, J = 0.7); imidazolidine C_2H (1:4), 6.82 and 6.78 (2H, m, $TosC_3H$ and $TosC_5H$), 7.86 and 7.94 (2H, 2xd, J = 8.2, $TosC_2H$ and $TosC_6H$ (1:4). Found: M^+ (FD), 484. $C_{22}H_{32}N_2O_8S_1$ requires M^+, 484.

Methyl 2,4-dimethoxycarbonyl-4-[2-(1-tosyl-3,4,5,5-pentamethyl)imidazolidinyl]butanoate (3b).
Procedure was identical with that for 3a (1b was used instead of 1a). After chromatography (SiO_2/EtOAc) 3b was recrystallized from Et_2O (6°C, 24 h).
3b: Yield 1.95 g (3.81 mmol, 76%). White crystals (diastereomeric mixture), m.p. 170-185°C. IR ($CHCl_3$): 1752 (s), 1731 (s), 1368 (s), 1162 (s). NMR (250 MHz, $CDCl_3$, diastereomeric mixture) (5:1), chemical shifts of major diastereomer are given): 0.35 and 0.85 (6H, 2xs, $CH_3NC(CH_3)_2$), 1.15 and 1.26 (6H, 2xs, $TosNC(CH_3)_2$), 2.38 (3H, s, NCH_3), 2.32-2.43 (4H, m, $TosCH_3$ and C_3H), 2.53-2.65 (1H, m, C_3H), 3.01 (1H, dd, J = 2.8, J = 10.0, C_4H), 3.71 and 3.73 (9H, 2xs, $3xCOOCH_3$), 3.83 (1H, dd, J = 4.8, J = 10.7, C_2H), ($J_{2,3a}$ = 10.7, $J_{2,3b}$ = 4.8, $J_{4,3a}$ = 10.0, $J_{4,3b}$ = 2.8 and $J_{4,2'}$ = 0), 4.53 (1H, s, $C_2'H$), 7.24 and 7.77 (4H, 2xd, J = 8.1, TosArH). Found, C, 56.03; H, 7.26; N, 5.42; S, 6.16. Calc for $C_{24}H_{36}N_2S_1O_8$: C, 56.27; N, 7.08; N, 5.47; S, 6.26.

(Z and E) methyl 2,4-dimethoxycarbonyl-5-(tryptaminyl)-4-pentenoate (4 and 5).
A mixture of 3a (1.45 g, 3 mmol), 960 mg (6 mmol) tryptamine was stirred in CH_3CN (30 ml) and CH_3COOH (3 ml) under nitrogen (80°C, 4 h). After removal of the solvent, the residue was chromatographed on SiO_2 using EtOAc/hexane (1:2). The enamine ester 4, 5 was obtained as a light yellow oil.
4, 5: Yield 930 mg (2.4 mmol, 80%). IR ($CHCl_3$): 3480 (m), 3400 (w), 3340 (w), 1750 (s), 1729 (s), 1674 (s), 1640 (s), 1610 (s). NMR (250 MHz, C_6D_6, 4, 5 = 3:2): 2.56 and 2.61 (2H, 2xt, J = 6.7, CH_2CH_2NH (Z and E isomer)), 2.82-2.95 (2H, m, CH_2CH_2NH (Z and E)), 2.99 and 3.03 (2H, 2xd, J = 6.7, C_3H (Z and E isomer)), 3.22 (2/5x6H, s, $C_2(COOCH_3)_2$ (E)), 3.27 (3/5x6H, s, $C_2(COOCH_3)_2$ (Z)), 3.45 (3/5x3H, s, $COOCH_3$ (Z)), 3.53 (2/5x3H, s, $COOCH_3$ (E)), 4.04 (3/5H, t, J = 6.7, C_2H (Z)), 4.14 (2/5H, t. J = 6.7, C_2H (E)), 5.1-5.2 (2/5H, bs, enamine NH (E)), 6.51 (3/5H, bd, J = 12.7, C_5H (Z)), 6.87-6.97 (1H, bs, indol NH), 7.02-7.43 (m, C_6H_6 and indol ArH), 7.50 (2/5, d, J = 13.9, C_5H (E)), 8.1-8.2 (3/5H, bs, enamine NH (Z)). Found: M^+, 388.1613. $C_{20}H_{24}N_2O_6$ requires M^+, 388.1634. MS (70 eV, m/e (%): 388(42), 357(11), 258(44), 226(71), 157(92), 144(56), 143(47), 130(100).

Methyl 2,4-dimethoxycarbonyl-4-[1-(1,2,3,4-tetrahydro-β-carbolinyl)]butanoate.HCl salt (6).
The enamine ester, as a mixture of 4 and 5 1.1 g (2.84 mmol) was dissolved in a saturated HCl/benzene solution (20 ml) (20°C, 10 min). After evaporation of the solvent and recrystallization from Et_2O the product could be obtained as white crystals.
6: Yield 1145 mg (2.7 mmol, 95%). m.p. depending on the composition of the diastereomeric mixture. IR ($CHCl_3$): 3480-3340 (m), 2800-2400 (m), 1752 (s), 1734 (s), 1575 (w). NMR (250 MHz, $CDCl_3$/NaOD/D_2O, diastereomeric mixture): 1.99-2.25 (2H, m, C_3H), 2.65-3.85 (15H, m, $3xCOOCH_3$, $C_3'H$ (2x), $C_4'H$ (2x), C_2H and C_4H), 4.35 (1H, bs, $C_1'H$), 6.95-7.24 (2H, m, $C_6'H$ and $C_7'H$), 7.30 and 7.45 (2H, 2xd. J = 7.4, $C_5'H$ and $C_8'H$). Found: M^+ (free base), 388.1628. $C_{20}H_{24}N_2O_6$ requires M^+, 388.1634.

1,3-Dimethyloxycarbonyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-4-ones (7 and 8).
A mixture of 975 mg of the β-carboline.HCl salt 6, 25 ml benzene, 4 ml CH_3COOH and 1 ml triethylamine was refluxed under nitrogen (80°C, 20 h). The resulting mixture was poured into a saturated

$NaHCO_3$ soln, extracted with $CHCl_3$, washed with brine and dried over Na_2SO_4. Chromatography on SiO_2 using EtOAc/CH_2Cl_2 (2:5) gave 7 as white amorphous material after treatment with EtOAc/hexane (1:4). The second fraction 8 was obtained after eluting with EtOAc/CH_2Cl_2 2:5, which was obtained as white amorphous material. Yield 7 + 8 (1:1); 615 mg (1.73 mmol, 75%). Unreacted starting material 6 was obtained after eluting with MeOH. Yield 6; 85 mg (0.22 mmol, 10%, free base).

7: IR ($CHCl_3$): 3450 (m), 1736 (s), 1730 (s), 1642 (s), 1438 (s). NMR (250 MHz, $CDCl_3$, COSY, (A = 3-β-$COOCH_3$, B = 3-α-$COOCH_3$)): 2.19-2.31 (2/5H, m, C_2H_{ax} (A)), 2.43-2.63 (1H, m, $C_2H_{eq,ax}$ (B) and C_2H_{eq} (A)), 2.72-2.95 (3x3/5H, m, $C_7H_{eq,ax}$ (A+B)), C_6H_{ax} (A+B) and C_1H_{ax} (B)), 3.22 (2/5H, ddd, J = 3.9, J = 9.2, J = 11.6, C_1H_{ax} (A)), ($J_{12b,1ax}$ = 9.2, $J_{1ax,2ax}$ = 11.6, $J_{1ax,2eq}$ = 3.9), 3.43-3.51 (3/5H, m, C_3H_{ax} (B)), 3.60-3.73 (2/5H, m, C_3H_{eq} (A)), 3.68 and 3.77 (3H, 2xs, $C_3(COOCH_3)$ (A+B), 3.89 and 3.90 (3H, 2xs, $C_1(COOCH_3)$ (A+B)), 5.05-5.19 (2H, m, $C_{12b}H$ (A+B) and C_6H_{eq} (A+B)), 7.05-7.21 (2H, m, C_9H and $C_{10}H$), 7.30 (1H, d, J = 7.1, $C_{11}H$), 7.47 (1H, d, J = 7.4, C_8H), 8.49 (1H, bs, NH).

8: IR($CHCl_3$): 3460 (m), 1740 (s), 1735 (s), 1642 (s), 1460 (m), 1438 (s). NMR (200 MHz, $CDCl_3$, (chemical shifts of major diastereomer): 2.25-3.05 (5H, m, C_6H_{ax}, $C_7H_{eq,ax}$ and $C_2H_{eq,ax}$), 3.56-3.86 (8H, m, $C_{(1,3)}OOCH$ at 3.56 and 3.77, 3.68 and 3.71 and further C_1H and C_3H), 4.94-5.05 (1H, m, C_6H_{eq}), 5.16 (1H, bd, J = 4.1, $C_{12b}H$), 7.06-7.39 (3H, m, C_9H, $C_{10}H$ and $C_{11}H$), 7.47 (1H, d, J = 7.5, C_8H), 8.19 (1H, bs, NH). Found: M+, 356.1330. $C_{19}H_{20}N_2O_5$ requires M+, 356.1372.

1-Methoxycarbonyl-1,2,3,4,6,12,12b-octahydroindolo[2,3-a]quinolizine-4-ones (9, 10a).
A mixture of 7 (500 mg, 1.4 mmol) and 2 eq LiI.$3H_2O$ (526 mg) was stirred in 15 ml dry DMSO (132°C, 36 h). After cooling, the resulting mixture was poured into brine, extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Chromatography on SiO_2 with CH_2Cl_2/EtOAc/hexane (3:2:1) gave 9, which was recrystallized from EtOAc to give white crystals.
10a was prepared from 8 in an identical manner. Recrystallization from MeOH gave 10a as white crystals.

9: Yield 233 mg (0.78 mmol, 56%). m.p. 187-188°C. IR ($CHCl_3$): 3450 (m), 3500-3300 (w), 1725 (s), 1635 (s). NMR (250 MHz, $CDCl_3$, COSY and dR): 2.08 (1H, ddd, J = 5.2, J = 12.2, J = 14.5, C_2H_{ax}), (J_{2gem} = 14.5, $J_{2ax,3ax}$ = , $J_{2ax,1ax}$ = 12.2, $J_{2ax,3eq}$ = 5.2), 2.20-2.28 (1H, m, C_2H_{eq}), 2.43 (1H, ddd, J = 5.7, J = 12.2, J = 17.7, C_3H_{ax}), (J_{3gem} = 17.7, $J_{3ax,2eq}$ = 5.7), 2.63 (1H, ddd, J = 3.0, J = 5.2, J = 17.7, C_3H_{eq}), ($J_{3eq,2eq}$ = 3.0), 2.69-2.92 (4H, m, C_1H_{ax} C_6H_{ax} and $C_7H_{eq,ax}$), 3.89 (3H, s, $COOCH_3$), 5.09-5.14 (2H, m, C_6H_{eq} and $C_{12b}H$ (J = 8.8)), 7.06-7.20 (2H, m, C_9H and $C_{10}H$), 7.31 (1H, d, J = 7.9, $C_{11}H$), 7.48 (1H, d, J = 7.7, C_8H), 8.42 (1H, bs, $N_{12}H$). ^{13}C NMR (50.32 MHz, DMSO-d_6, ^{13}C-^1H): 41.57 (C_1), 21.61 (C_2), 29.86 (C_3), 167.94 (C_4), 40.76 (C_6), 20.50 (C_7), 109.12 (C_{7a}), 126.61 (C_{7b}), 117.69 (C_8), 118.83 (C_9), 121.27 (C_{10}), 111.55 (C_{11}), 136.00 (C_{11a}), 133.12 (C_{12a}), 55.11 (C_{12b}), 52.54 (OCH_3), 172.87 (ester C=O).
10a: Yield 220 mg (53%). m.p. 251-253°C. IR ($CHCl_3$): 3465 (w), 1730 (s), 1632 (s). NMR (250 MHz, $CDCl_3$): 2.03-2.18 (2H, m, $C_2H_{eq,ax}$), 2.52-2.59 (2H, m, $C_3H_{eq,ax}$), 2.68-2.75 (1H, m, C_6H_{ax}), 2.86-2.99 (2H, m, $C_7H_{eq,ax}$), 3.35 (1H, q, J = 4.4, J = 7.6, C_1H_{eq}), ($J_{1eq,ax}$ = $J_{1eq,12b}$ = 4.4 and $J_{1eq,2eq}$ = 7.6), 3.61 (3H, s, $COOCH_3$), 4.99-5.06 (1H, m, C_6H_{eq}), 5.11 (1H, bd, J = 4.4, $C_{12b}H$), 7.06-7.19 (2H, m, C_9H and $C_{10}H$), 7.31 (1H, d, J = 7.7, $C_{11}H$), 7.48 (1H, d, J = 7.5, C_8H), 8.30 (1H, bs, $N_{12}H$). ^{13}C NMR (50.32 MHz, DMSO-d_6): 41.24 (C_1), 21.82 (C_2), 28.88 (C_3), 167.82 (C_4), 38.97 (C_6), 20.37 (C_7), 108.42 (C_{7a}), 126.30 (C_{7b}), 117.67 (C_8), 118.21 (C_9), 120.84 (C_{10}), 111.11 (C_{11}), 136.22 (C_{11a}), 132.04 (C_{12a}), 54.12 (C_{12b}), 51.33 (OCH_3), 171.04 (ester C=O). MS (70 eV, m/e, (%)): 298(100), 297(12), 242(21), 170(22), 169(22), 157(50), 143(43), 130(13). Found: M+, 298.1302. $C_{17}H_{18}N_2O_3$ requires M+, 298.1317.

1-Methoxycarbonyl-N_{12}-tosyl-1,2,3,4,6,7-hexahydro-12b(H)-indolo[2,3-a]quinolizine-4-on (10b).
To a suspension of 0.4 mmol NaH in dry THF (15 ml) was added 101 mg (0.338 mmol) of quinolizine 10a. After being stirred for 30 min under nitrogen (0°C), 66.7 mg (0.35 mmol) tosyl chloride was added. The resulting mixture was stirred for 32 h (20°C). After addition of a saturated NH_4Cl soln, the mixture was extracted with Et_2O, washed with brine and dried over Na_2SO_4. Chromatography on SiO_2 with EtOAc and recrystallization from Et_2O gave 10b as white crystals.
10b: Yield 129 mg (0.285 mmol, 84%). m.p. 100-203°C. IR ($CHCl_3$): 1735 (s), 1635 (s), 1438 (m), 1370 (s), 1170 (s). NMR (250 MHz, $CDCl_3$): 2.22-2.27 (5H, m, $TosCH_3$ and $C_2H_{eq,ax}$), 2.59-2.68 (5H, m, $C_3H_{eq,ax}$, $C_7H_{eq,ax}$ and C_6H_{ax}), 3.27 (3H, s, $COOCH_3$), 4.01 (1H, dd, J = 3.8, J = 8.4, C_1H_{eq}), ($J_{1eq,12b}$ = $J_{2eq,3ax}$ = 3.8, $J_{2eq,3eq}$ = 8.4), 5.00-5.07 (1H, m, C_6H_{eq}), 5.32 (1H, bd, J = 3.8, $C_{12b}H$), 7.07 and 7.43 (4H, 2xd, J = 8.3, AB system TosArH), 7.18-7.33 (3H, m, C_8H, C_9H and $C_{10}H$), 8.08 (1H, d, J = 8.0, $C_{11}H$). Found: M+, 452.1430. $C_{24}H_{24}N_2O_5S_1$ requires M+, 452.1406.

Furanone derivative (11).
To a stirred solution of 0.22 mmol LDA in 15 ml THF (-78°C, nitrogen) was added 100 mg (0.22 mol) of 10b, dissolved in 5 ml THF. Stirring was continued for 15 min. After this to the mixture was added 33.85 mg (0.02 ml) methyl bromoacetate and stirring was continued for another 30 min at -78°C and 2 h at 20°C. The resulting mixture was treated with a saturated NH_4Cl soln. The organic phase was separated and washed with brine, dried over Na_2SO_4 and concentrated. Chromatography on SiO_2 with EtOAc/MeOH (9:1) and crystallization from EtOAc/hexane gave 11 as white crystals.
11: Yield 86 mg (0.175 mmol, 79%). m.p. 142-144°C (Dec). IR ($CHCl_3$): 1735 (m), 1620 (w), 1586 (s), 1574 (s), 1511 (m), 1372 (m), 1170 (s). NMR (250 MHz, $CDCl_3$, COSY and dR): 2.27 (3H, s, $TosCH_3$), 2.64-2.94 (4H, m, $C_7H_{eq,ax}$ and $C_2H_{eq,ax}$, 2.72 (dd, J = 6.5, J = 15.8) and 2.91 (dd, J = 1.4, J = 15.8)), 3.08 (1H, dt, J = 3.4, J = 12.0, C_6H_{ax}), 3.30 (3H, s, $COOCH_3$), 4.03-4.06 (1H, m, C_1H_{eq}), 4.47 (1H, dd, J = 3.4, J = 12.0, C_6H_{eq}), 4.51 and 4.54 (2H, 2xd, J = 15.1, AB system $COCH_2O$), 5.24 (1H, bs, $C_{12b}H$), 7.09 and 7.46 (4H, 2xd, J = 8.3, AB system TosArH), 7.20-7.35 (3H, m, C_8H, C_9H and $C_{10}H$), 8.10 (1H, d, J = 8.4, $C_{11}H$). Found: M+, 492.1370. $C_{26}H_{24}N_2O_6S_1$ requires M+, 492.1355. MS (70 eV, m/e (%)): 492 (76), 461 (5), 433 (8), 337 (100), 277 (24), 199 (40).

1-Hydroxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (12a).
To a stirred solution of 200 mg (0.67 mmol) of 9 in 20 ml dry THF was added 140 mg (3.7 mmol) $LiAlH_4$. After stirring for 5 h at 0°C under nitrogen, the reaction mixture was diluted with a 10%

KOH soln. The organic phase was separated, washed with a $NaHCO_3$ soln and dried over Na_2SO_4. Evaporation of the solvent and recrystallization from MeOH gave 12a as white crystals.
12a: Yield 128 mg (0.5 mmol, 75%). m.p. 244-245°C (dec). IR (KBr): 3500-3200 (m), 3220 (s), 2810 (m), 2790 (m), 2760 (m), 2740 (m), 1080 (s). NMR (250 MHz, DMSO-d_6, COSY and dR): 1.40-1.65 (4H, m, C_3H (2x) and C_2H (2x)), 2.07-2.09 (1H, m, C_1H), 2.40-2.60 (m, DMSO, C_4H and C_7H), 2.79-2.82 (3H, m, C_6H , C_7H and C_4H), 3.10-3.20 (1H, m, C_6H), 3.70 (2H, bm, CH_2OH), 3.79 (1H, bd, J = 5.6, $C_{12b}H$), 4.99 (1H, bs, OH), 6.90-7.20 (2H, m, C_9H and $C_{10}H$), 7.31-7.38 (2H, m, C_8H and $C_{11}H$), 10.61 (1H, bs, NH). ^{13}C NMR (50.32 MHz, DMSO-d_6): 38.91 (C_1), 25.96 (C_2), 22.02 (C_3), 50.56 and 50.82 (C_4, C_6), 19.60 (C_7), 106.72 (C_{7a}), 126.86 (C_{7b}), 117.24 (C_8), 118.15 (C_9), 120.17 (C_{10}), 111.18 (C_{11}), 135.78 (C_{11a}), 134.92 (C_{12a}), 58.23 (C_{12b}), 62.92 (CH_2OH). Found: M^+, 256.1565. $C_{16}H_{20}N_2O_1$ requires M^+, 256.1575.

1-Acetoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (12b).
A mixture of 120 mg (0.47 mmol) of 12a, 2 ml acetic anhydride and 3 ml pyridine was stirred under nitrogen for 72 h (20°C). The resulting mixture was diluted with a saturated $NaHCO_3$ soln, extracted with Et_2O, washed with a $NaHCO_3$ soln and dried over Na_2SO_4. The residue upon work-up was chromatographed on SiO_2 with EtOAc and recrystallized from EtOH to give 12b as white crystals.
12b: Yield 103 mg (0.34 mmol, 74%). m.p. 130°C. IR ($CHCl_3$): 3470 (m), 3350 (m), 2810 (m), 2760 (m), 2740 (m), 1728 (s). NMR (200 MHz, $CDCl_3$, COSY): 1.56-1.84 (4H, m, $C_2H_{eq,ax}$ and $C_3H_{eq,ax}$), 2.07-2.17 (1H, m, C_1H_{ax}), 2.17 (3H, s, $COCH_3$), 2.61-3.26 (6H, m, $C_4H_{eq,ax}$, $C_6H_{eq,ax}$ and $C_7H_{eq,ac}$), 3.67 (1H, bd, J = 8.0, C_{12bH}), 4.32 and 4.60 (2H, 2xdd, resp. J = 4.2, J = 11.7 and J = 4.6, J = 11.7, CH_2OH, 7.05-7.19 (2H, m, C_9H and $C_{10}H$), 7.35 (1H, d, J = 7.1, $C_{11}H$), 7.49 (1H, d, J = 7.1, C_8H), 8.68 (1H, bs, NH). Found: M^+, 298.1667. $C_{18}H_{22}N_2O_2$ requires M^+, 298.1681.

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* To whom enquiries should be addressed.
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