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SYNTHESIS OF PENTACYCLIC RING SYSTEMS, INDOLO[2,3-*a*][1,2]-OXAZINO[5,6-*i*]QUINOLIZINE AND INDOLO[2,3-*a*]PYRANO[3,2-*i*]-QUINOLIZINE, AND THEIR APPLICATION FOR THE SYNTHESIS OF EBURNAMINE-VINCAMINE ALKALOIDS

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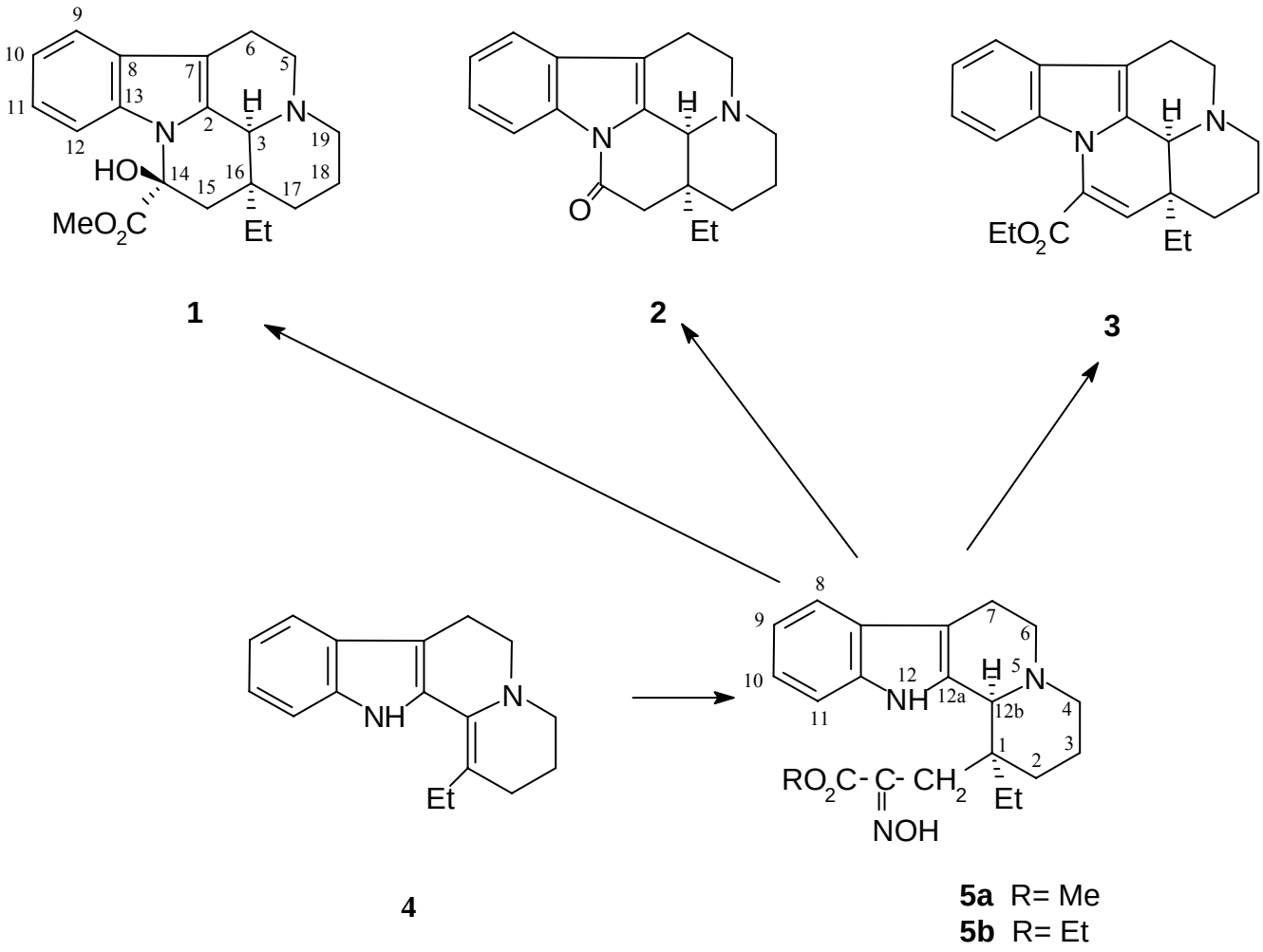
Abstract - 15a-Ethyl-14-carboxylic esters of the title pentacycles **(6)** and **(8)** were prepared *via* Wenkert's enamine **(4)**. Both compounds can be readily transformed into indoloquinolizinylpyruvate oxime esters **(5)**, key intermediates for the synthesis of vincamine alkaloids. The ring/chain equilibrium observed for compounds **(6)** and **(8)** was studied by UV and NMR spectroscopic methods.

INTRODUCTION

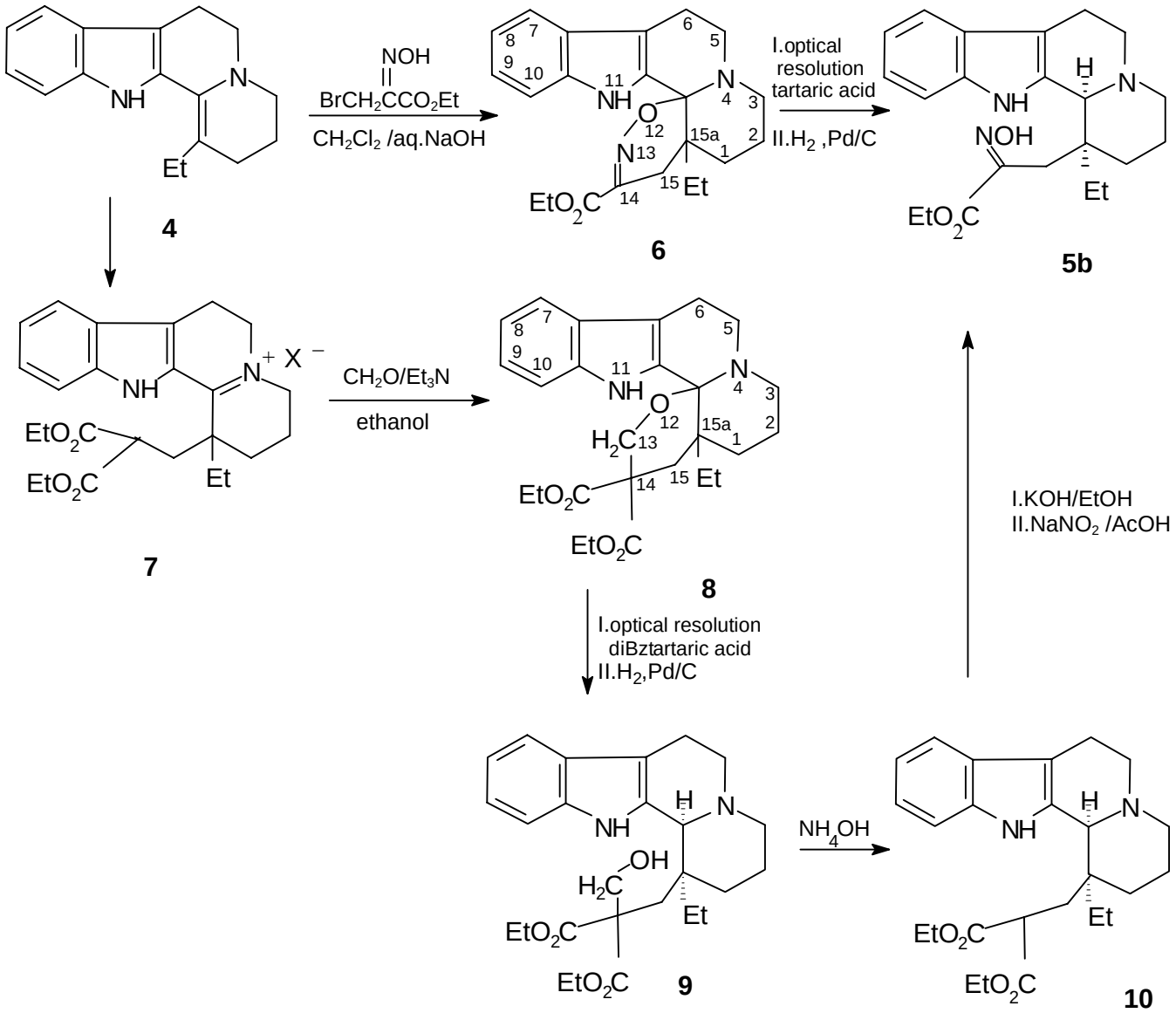
(+)-Vincamine **(1)**, (-)-eburnamonine **(2)** and (+)-ethyl apovincaminate **(3)** exhibit valuable cerebrovascular and cerebroprotective activities.[1-4] The results of continued efforts directed toward the synthesis of eburnamine-vincamine alkaloids were reviewed in recent years.[5,6] Since then, several new approaches have been published.[7-9] A new synthesis, reported from our laboratory,[10,11] uses an alkylation route *via* the Wenkert's enamine, one of the main synthetic entries into the eburnamine-vincamine group.[5] Key intermediates of this approach are indoloquinolizinylpyruvate oxime esters **(5)** (Scheme 1).[10,12]The present report describes new and advantageous routes to these versatile intermediates. An obvious way from **4** to **5** would be direct alkylation with alkyl bromopyruvate oxime, followed by stereoselective reduction.[13] Rossey and Wenkert[14] alkylated enamine **(4)** with methyl bromopyruvate dinitrophenylhydrazone in the presence of triethylamine to obtain the corresponding indoloquinolizinium bromide.



Scheme 1

RESULTS AND DISCUSSION

No reaction product was observed under the above-mentioned reaction conditions with ethyl bromopyruvate oxime. However, by the simultaneous addition of ethyl bromopyruvate oxime and aqueous sodium hydroxide solutions to **4** under phase transfer conditions, alkylation could be achieved such that the intermediate indoloquinolizinium compound was found to undergo cyclization to **6**.[15] The racemic compound **(6)** was separated into 15a*R* and 15a*S* enantiomers by resolution with (+)-tartaric acid. The stereoselective reduction of (15a*S*)-**6** led to (1S,12b*S*)-**5b** oxime ester (Scheme 2). By following another variant of the enamine **(4)** alkylation route,[12] diethyl hexahydroindoloquinolizinium-dicarboxylate **(7)**was allowed to react with formaldehyde in the presence of triethylamine. The structure of the product was confirmed as diethyl 15a-ethylindolopyranoquinolizine dicarboxylate **(8)** by its spectroscopic data.[16] The resolution of **8** with(-)-dibenzoyltartaric acid, followed by stereoselective reduction, furnished (-)-diethoxycarbonyl-hydroxymethyl-ethyl-octahydroindoloquinolizine **(9)** which was converted into the

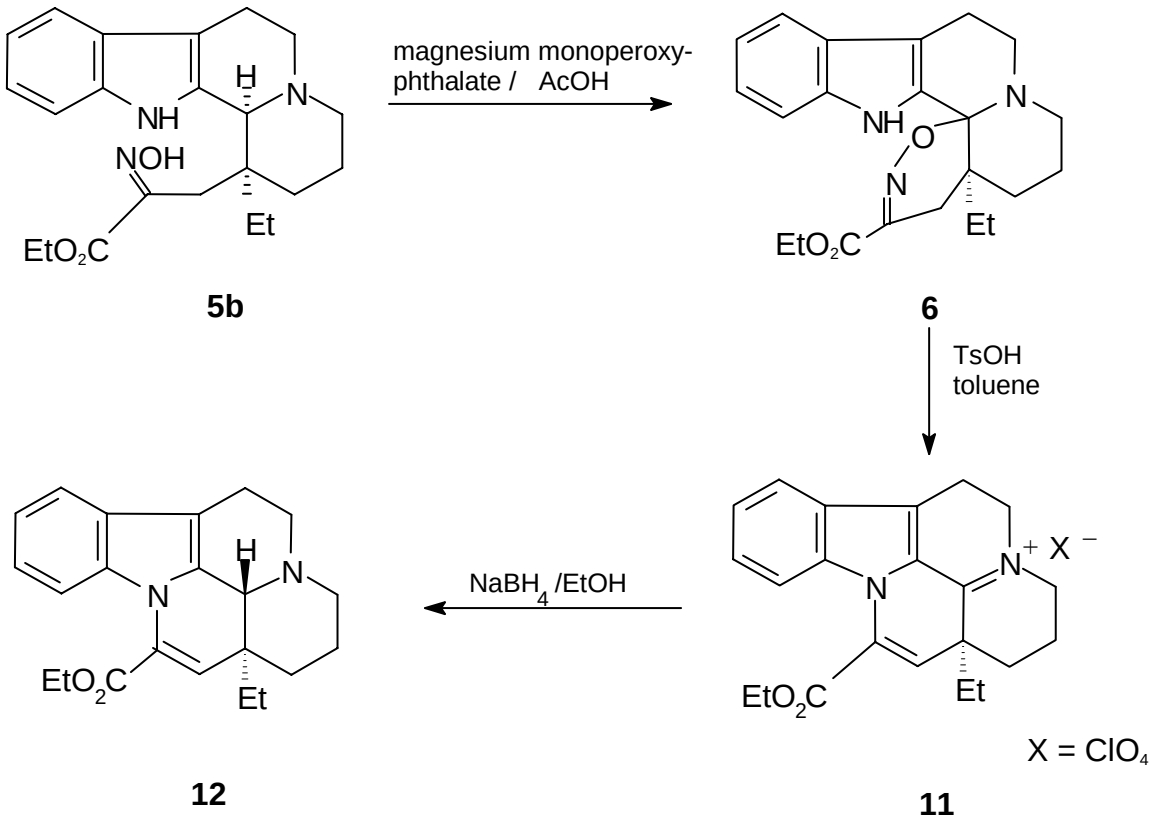


Scheme 2

corresponding diester **(10)** by means of aqueous ammonium hydroxide. The transformation of indoloquinolizinyl diester **(10)** into ethyl indoloquinolizinyl-pyruvate oxime **(5b)** was carried out without isolation of the intermediate monoester (Scheme 2).

The easy separation of crystalline pentacyclic intermediates **(6)** and **(8)** and their (15a*S*)-enantiomers after resolution, as well as the increased stereoselectivity of the catalytic hydrogenation are the main advantages of the above-outlined routes. Since the transesterification of **5b** into **5a**[12] and further transformation into eburnamonine **(2)** as well as vincamine **(1)** and apovincamine was already described,[10,12] these routes construct new formal syntheses of eburnamine-vincamine alkaloids possessing a *cis C*/*D* ring junction.

The *trans* isomers of eburnamine-vincamine alkaloids proved to be useful starting materials for other biologically active compounds.[11] Recently, Costa *et al*.[9e] presented a potential advanced intermediate for the enantioselective synthesis of (3*R*,16*S*)-**1**. In order to prepare *trans* compounds we treated ethyl

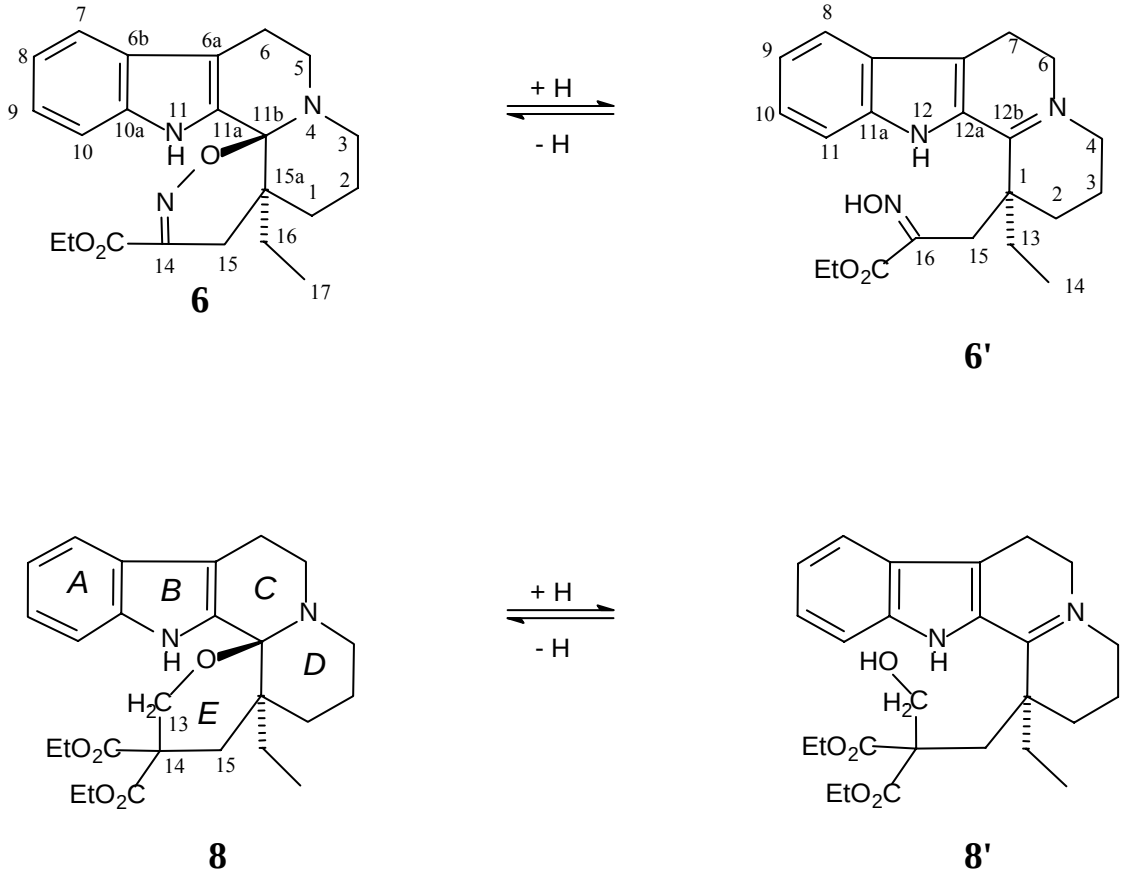


Scheme 3

indolooxazinoquinolizine carboxylate **(15a*S*-6)** with *p*-toluenesulfonic acid in toluene. The so obtained ethyl 3,4-dehydroapovincaminate **(11)** was separated as a perchlorate salt. Reduction with sodium tetrahydroborate furnished *trans*-ethyl (3*R*-16*S*)-apovincaminate **(12)** (Scheme 3). The oxime ester **(5b)**, derived from indolopyranoquinolizine **(8)**, was oxidized with magnesium monoperoxyphthalate in acetic acid. In contrast to expectation the isolated product was not the N^5-oxide, but indolooxazinoquinolizine **(6)**. The above-noted reactions provide a chemical connection between the two pentacyclic ring systems **(6)** and **(8)** and an entry into the *trans* series (Scheme 3). The formation of the oxacycles is reversible and in acidic solutions ring *E* reopens with addition of a proton to give **6'** and **8'** (Scheme 4). The pH-dependent UV/VIS spectra and ^{13}C NMR data of **6** $\rightleftharpoons$ **6'** and **8** $\rightleftharpoons$ **8'** support this finding (see below). The observed ring-chain equilibrium is related to pseudobase formation, as has been interpreted under extended terms by Bunting.[17] In this process the pseudobase is formed by addition of a hydroxy or alkoxide anion to a heterocyclic cation to give a neutral covalent adduct base. In the case of **6'** and **8'** a heterocyclic cation, bearing a hydroxymethyl or a hydroxylamino group, transforms under basic conditions into a neutral species by loss of a proton, forming new intramolecular C-O bond in **6** and **8**.

X-RAY STUDY OF COMPOUNDS 6 AND 8

The recrystallization of compounds **(6)** and **(8)** from acetone provided single crystals suitable for X-Ray



Scheme 4

crystallographic analysis. ORTEP[18] diagrams with atomic numbering are depicted in Figures 1 and 2. The molecules form hydrogen bonded dimers. The ethoxycarbonyl moieties in both **6** and **8** exhibit positional disorder (site occupation factors: 0.70(1):0.30(1) for both molecules of **6** and 0.55(3):0.45(3) for **8**). The crystals of **6** and **8** are similarly monoclinic with space groups $P2_1/c$ and $P2_1/n$, respectively, but in the asymmetric unit of **6** there are two (symmetry independent) molecules. In both molecules **(6)** and **(8)** the planar indole moiety (rings A and B) is fused to a quinolizine group forming together a plane slightly bent at the outer piperidine ring (*D*) of chair shape. Since the C=C double bond is shared with the indole group, the first piperidine ring (*C*) is flexible. In both molecules of **6** the conformation of ring *C*, as shown by the puckering parameters (Q=0.509, 0.492 Å, θ=52.3, 54.3°, φ=167.7, 164.0°), is transitional between the envelope, half chair and skew forms, while in **8** it assumes a half chair shape (Q=0.500 Å, θ=49.6°, φ=144.8°). In both compounds **6** and **8** a six-membered heteroring is closed by the oxygen atom on C11b with *cis*-junction. In accordance with the double bond formed by the ring nitrogen N13 with C14 (the latter is substituted with an ethoxycarbonyl moiety) both oxazine rings in the symmetry independent molecules of **6** exhibit a half chair conformation (Q=0.454, 0.447 Å, θ=127.8, 129.7°, φ=83.3, 82.2°). In contrast, in **8** the tetrahydropyrane ring assumes a chair conformation, while C14 bears two ethoxycarbonyl groups, one of which shows a slight rotational disorder around the O-CH_2CH_3 bond.

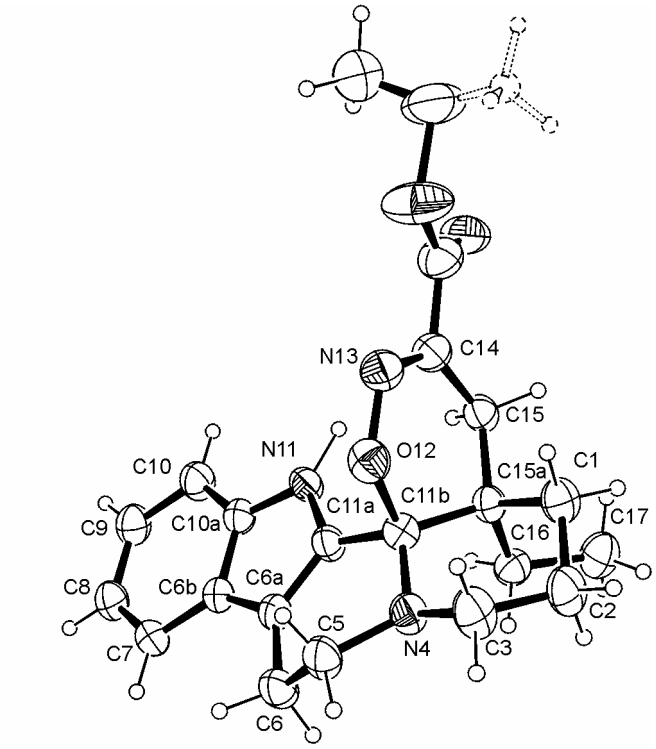


Figure 1 The molecular diagram of molecule 1 of compound **(6)** with the numbering of atoms. Atomic displacement ellipsoids represent 40% probabilities. Hydrogen atoms linked to the $CO_2CH_2CH_3$ sidechain are omitted for clarity.

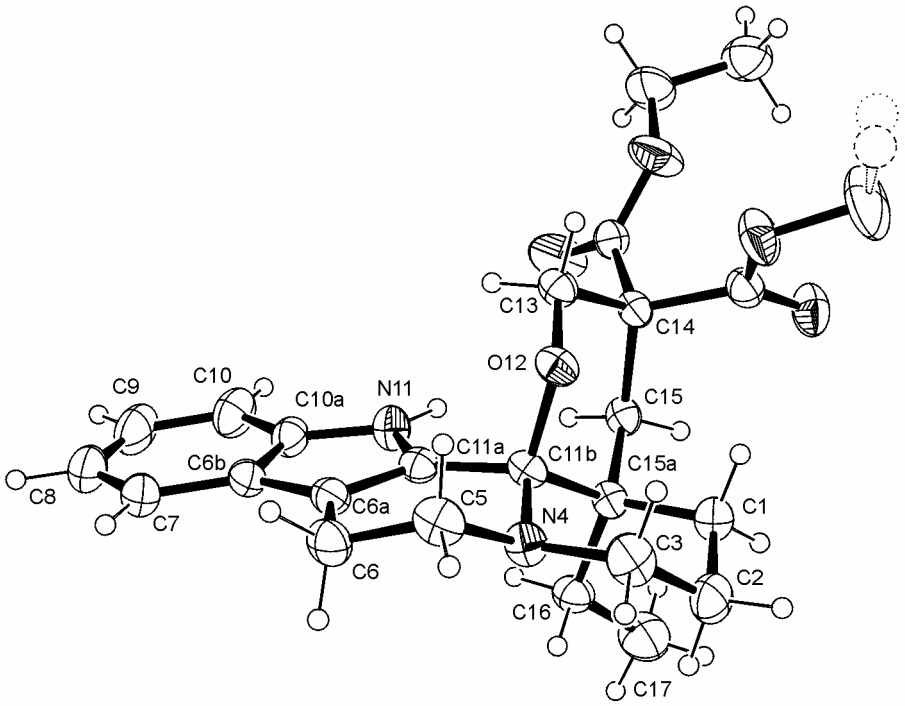


Figure 2 The molecular diagram of **8** with the numbering of atoms. Atomic displacement ellipsoids represent 40% probabilities.

Similarly, in both molecules of **6** the terminal methyl groups pertaining to the ethoxycarbonyl moiety exhibit positional disorder.

UV/VIS AND NMR INVESTIGATION OF THE 6 ⇌ 6' AND 8 ⇌ 8' EQUILIBRIA

For UV analysis, qualitative UV/VIS spectra were recorded starting from 0.02 % solutions of **6** and **8** in

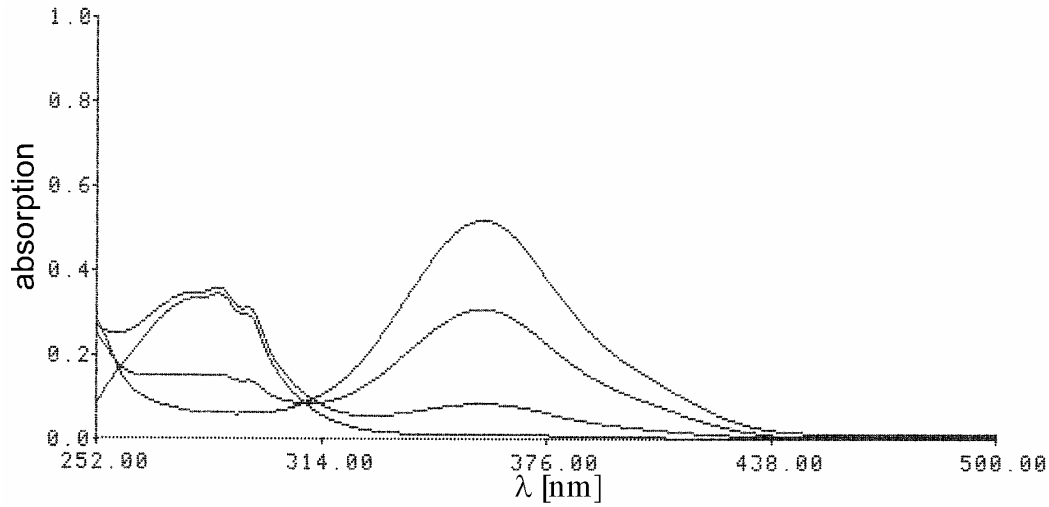


Figure 3 The pH-dependent qualitative absorption change of uv/vis spectra of compound **(6)**. The concentration of acetic acid was increased from 0 to 0.01%.

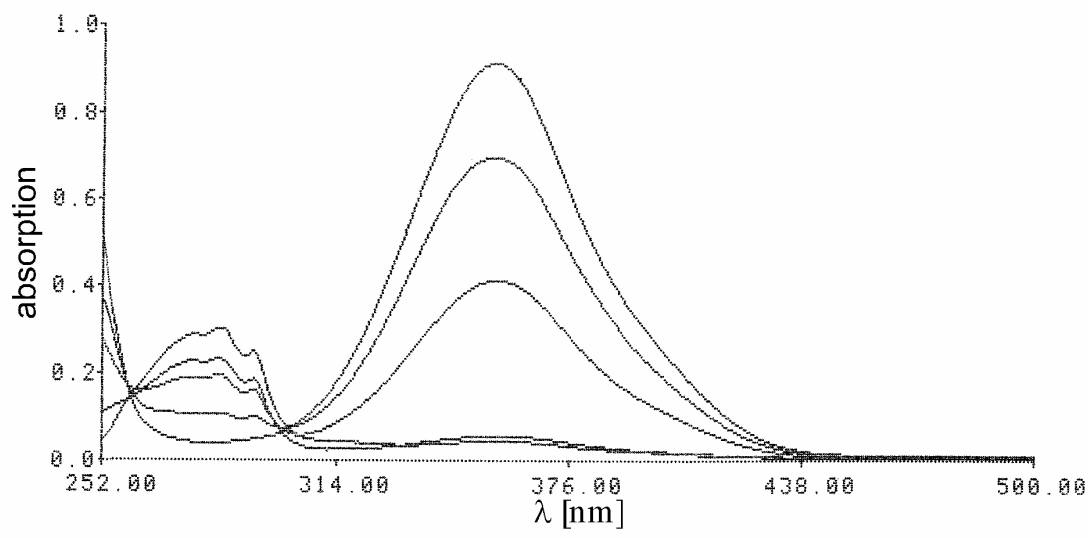


Figure 4 The pH-dependent qualitative absorption change of uv/vis spectra of compound **(8)**. The concentration of acetic acid was increased from 0 to 0.1%.

ethanol. In order to shift the equilibrium toward the ring-opened quinolizinium ions **6'** and **8'**, the

concentration of acetic acid was increased from 0 to 0.01 % and 0.1 %, respectively. The pH-dependent change of the spectrum is reflected by a hyperchromic shift of the maximum at λ=288 nm to 360 nm (Figures 3 and 4). The presence of the ring/chain equilibrium was independently verified by NMR measurements: starting from DMSO-d_6 solutions of **6** and **8**, deuterated TFA was added in increasing amounts,whereby a gradual shift towards **6'** and **8'** was observed in a process that is slow on the chemical shift timescale. With TFA being in excess, the equilibrium could be shifted entirely toward **6'** and **8'**. The structures of **6'** and **8'** could be conveniently and unambiguously verified by their characteristic ^{13}C NMR data (Table 2), as discussed earlier in relation to some close analogues.[19]

EXPERIMENTAL

Melting points were determined with a Büchi 510 apparatus and are uncorrected. The $[\alpha]_D$ observed using a Perkin Elmer 243B polarimeter. The UV/VIS spectra were recorded on a Perkin Elmer Lambda 15 uv/vis spectrophotometer. The NMR studies were performed on a Varian INOVA-500 (^1H: 500 MHz) or an INOVA-300 (^1H: 300 MHz, compounds **(6')** and **(8')**) instrument in DMSO-d_6 solution at 30 ^oC(δ_{TMS}=0.00 ppm). Assignments, unless indicated otherwise, were corroborated by the concerted use of two-dimensional ^1H-^1H (gradient-selected double-quantum-filtered COSY) and ^1H-^{13}C correlation experiments (HSQC, HMBC) as well as NOE experiments. NMR data are given in Tables 1 and 2.

FAB MS spectra were recorded in glycerol matrix on a Finnigan MAT 95SQ instrument equipped with a caesium ion gun. Ei MS spectra were recorder on a VG Trio-2 spectrometer using 70 eV electron energy and a direct insertion probe (250 ^oC). IR measurements were carried out on a PERKIN-ELMER 1000 spectrophotometer in KBr pellets (resolution 4 cm^{-1}).

Intensity data were collected on an Enraf-Nonius CAD4 diffractometer at room temperature. The structures were determined by direct methods[20] and were refined by anisotropic full matrix least-squares[21] for the non-hydrogen atoms. Hydrogen atomic coordinates were calculated from assumed geometries. The methyl groups were refined as a rotating rigid group. No absorption corrections were applied. Crystal data, data collection and least-squares parameters are summarized in Table 3, Neutral atomic scattering factors and anomalous scattering factors were taken from ref.[22]

Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} and facilitated by UV detection.

(±)-Ethyl 15a-ethyl-2,3,6,11,15,15a-hexahydro-1*H*,5*H*-indolo[2,3-*a*][1,2]oxazino[5,6-*i*]quinolizine-14-carboxylate (6): To a solution of **4** (10 g, 40 mmol) in CH_2Cl_2 (15 mL) benzyltriethyl ammonium chloride (1 g, 4.4 mmol) was added, then solutions of ethyl bromopyruvate oxime (13.6 g, 60 mmol)

Table 1 **^{1}H NMR Assignments***

Proton	Compd **6**	Compd **8**	**Proton**	Compd **9**	Compd **10**	Compd **6'**	Compd **8'**
1	1.18 m 1.57 m	1.30-1.41 m 1.52-1.64 m	**2**	1.41-1.61 m	1.40-1.55 m	~ 1.92 m	~ 1.93 m
2	1.42 m 1.70 m	1.30-141 m 1.52-1.64 m	**3**	1.40 m 1.98 m	1.40-1.55 m 1.71 m	~ 1.96 m	~ 1.96 m
3	2.70-2.77 m 3.07 m	2.59 m 2.87 m	**4**	2.24 m 2.92 m	2.29 m 2.91-2.98 m	3.90 - ~ 4.15 m	~ 3.87 m
	-	-		-	-	-	-
5	2.86 dd (11.7,5.4) 3.34 td (11.7,4.0)	2.65 m 3.32 m	**6**	2.40 m 2.95 m	2.42 m 2.91-2.98 m	3.90 - ~ 4.15 m	~ 4.00 m
6	2.63 m 2.70-2.77 m	2.54 m 2.75 m	**7**	2.54 m 2.78 m	2.52 m 2.74 m	3.24 m	3.22 m
7	7.43 d (7.8)	7.42 d (7.8)	**8**	7.35 d (7.8)	7.33 d (7.8)	7.75 d(8.4)	7.74 d (8.4)
8	6.99 m	6.99 m	**9**	6.94 m	6.93 m	7.22 m	7.63 m
9	7.09 m	7.11 m	**10**	7.01 m	7.01 m	7.46 m	7.46 m
10	7.41 d (8.1)	7.46 d (8.3)	**11**	7.47 d (8.3)	7.45 d (8.2)	7.65 d(8.4)	7.21 d (8.4)
11	9.23 s	9.86 s	**12**	9.57 s	9.75 s	11.64 s	11.8 s
11b	-	-	**12b**	3.24 s	3.28 s	-	-
16	0.80 m 1.88 m	1.13 br m 1.82 m	**13**	1.44 m 2.08 m	1.40-1.55 m 1.87 m	1.96 m 2.39 m	2.19 q (6.9)
17	0.68 t (8.0)	0.74 t (7.6)	**14**	1.03-1.08 m	1.02 t (7.5)	0.84 t (7.2)	0.98 t (6.9)
15	2.58 d (20.1) 2.81 d (20.1)	2.58 br m 2.80 br m	**15**	1.55 d (15.5) 2.73 d (15.5)	1.78 dd (15.0, 6.1) 2.34 dd (15.0, 6.1)	3.26 d (13.8) 3.41 d (13.8)	2.77 d (16.1) 3.04 d (16.1)
14	-	-	**16**	-	3.24 t (6.1)	-	-
13	-	3.80 d (12.5) 4.41 br d	**17**	3.80 dd (10.5, 4.7) 3.93 dd (10.5, 4.7)	-	-	3.70 d (11.0) 3.79 d (11.0)
OH	-	-	**OH**	4.79 t (4.7)	-	-	
CH_3 CH_2O	1.28 t (7.1)	1.19 t (7.1)	**CH_3**CH_2O	1.03-1.08 m	1.09 t (7.1)	1.19 t (6.9)	1.06 t (7.0)
CH_3**CH_2**O	4.20-4.30 m	4.18 m	CH_3**CH_2**O	3.94-4.04 m	3.91-4.05 m	~ 4.16 m	~ 4.08 m
CH'$_3$ CH_2O	-	1.24 t (7.1)	**CH'$_3$**CH_2O	1.03-1.08 m	1.03 t (7.1)	-	1.15 t (7.0)
CH_3**CH'$_2$**O	-	4.24 m	CH_3**CH'$_2$**O	3.94-4.04 m	3.91-4.05 m	-	~ 4.08 m

*Coupling constants (Hz) are given in parentheses.

in CH_2Cl_2 (25 mL) and sodium hydroxide (2.8 g, 70 mmol) in water (26 mL) were dropped simultaneously under -5 ^oC. The reaction mixture was stirred for 30 min, the organic layer was separated, washed with water (100 mL), dried on anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was crystallized from EtOH (20 mL) to obtain 11.1 g (73 %) of **6**, mp 202-204 ^oC; MS (EI) *m/z* %: 381(23) M^+; 364(7); 352(8); 308(37); 251(63); 237(100). IR (cm^{-1}): 3341 (NH); 1721 (C=O); 1695 (C=N); 1285(N-O-C); 1232 (C-O-C); 767, 740 (Ar); 2962; 2937; 1588; 1466; 1374; 1168; 1020. *Anal*. Calcd for $C_{22}H_{27}N_3O_3$: C,69.26; H,7.13; N,11.01. Found: C,68.97; H,7.19; N,10.96.

Resolution of 6: To a solution of **6** (10 g, 26 mmol) in a mixture of CH_2Cl_2 (66 mL) and EtOH (33 mL), (+)-tartaric acid (3.9 g, 26 mmol) was added, and the mixture was stirred for 2 h, then filtered and washed

Table 2 ^{13}**C NMR Assignments (DMSO-d$_6$)**

Carbon	Compd **6**	Compd **8**	**Carbon**	Compd **9**	Compd **10**	Compd **6'**	Compd **8'**
15a	33.2	37.1	**1**	39.7	38.9	44.6	44.1
1	29.1	28.1	**2**	31.6	31.9	29.0	26.3
2	20.5	20.8	**3**	21.6	21.5	18.7	17.8
3	48.5	49.4	**4**	57.9	56.3	55.2[a]	54.9
5	48.0	46.5	**6**	53.8	53.5	55.0[a]	54.3
6	21.4	21.0, br	**7**	21.6	21.7	19.2	18.9
6a	112.8	112.2	**7a**	110.4	110.4	123.8[b]	123.7[c]
6b	125.1	125.5	**7b**	126.1	126.1	126.8[b]	125.8[c]
7	118.1	118.0	**8**	116.9	117.0	122.0	121.9
8	118.8	118.7	**9**	118.2	118.2	122.2	121.9
9	121.9	121.7	**10**	120.3	120.4	129.2	128.9
10	112.0	111.9	**11**	111.7	111.7	114.3	114.0
10a	136.7	135.9	**11a**	136.5	136.6	141.4	141.0
11	-	-	**12**	-	-	-	-
11a	131.5	132.2	**12a**	133.0	132.6	125.8[b]	125.8[c]
11b	94.2	89.2	**12b**	67.2	66.2	171.7	172.1[d]
16	25.0	25.3	**13**	28.5	29.6	33.3	31.2
17	6.5	6.7	**14**	8.6	8.2	8.6	8.1
15	31.7	35.9, br	**15**	31.1	31.3	34.4	37.7
14	146.1	51.8	**16**	56.6	46.7	148.8	59.0
13	-	63.6, br	**17**	63.0	-	-	64.5
CH$_3$CH$_2$O	14.0	13.7	**C**H$_3$CH$_2$O	13.5	13.6	14.2	13.8
CH$_3$**C**H$_2$O	60.9	61.4	CH$_3$**C**H$_2$O	60.3	60.7	62.2	61.9
CO$_2$Et	163.4	169.8	**C**O$_2$Et	170.5	169.5	165.2	170.6[c]
CH'$_3$CH$_2$O	-	13.7	**CH'**$_3$CH$_2$O	13.5	13.7	-	13.9
CH$_3$**CH'**$_2$O	-	61.7	CH$_3$**CH'**$_2$O	60.3	60.8	-	62.1
C'O$_2$Et	-	170.4	**C'**O$_2$Et	170.5	169.9	-	170.8[c]

[a,b,c,d] Interchangeable assignments

with CH_2Cl_2 (10 mL) to give 4.8 g of (15a*S*)-**6** tartarate,which was recrystallized from ethanol, mp 140-143 ^oC $[\alpha]_D$= +256^o (c=1, DMF). The tartarate crystals were dissolved in water (100 mL) and the pH was adjusted to 9 with 25% NH_4OH solution. The separated crystals were filtered and washed with water to yield 3.4 g (34 %) of (15a*S*)-**6**, mp 135- 137 ^oC (acetone), $[\alpha]_D$= +486^o (c=1, $CHCl_3$). The mother liquor of the resolution was allowed to stand overnight to give 4.3 g f (15a*R*)-**6** tartarate, mp 139-141 ^oC

Table 3 **Crystal data and structure refinement**

	6	**8**		**6**	**8**
Empirical formula	$C_{22}H_{27}N_4O_2$	$C_{26}H_{34}N_2O_5$	Index ranges		
Formula weight	379.48	454.55	*h*	-14 - 13	- 13 – 14
Temperature, K	293(2)		*k*	0 - 39	0 - 9
Radiation and wavelength, Å	Cu-*K*α, λ = 1.54180	Mo-*K*α, λ = 0.71069	*l*	0 - 15	-27 - 0
Crystal system	monoclinic		Reflections collected	6570	3673
Space group	$P2_1/c$	*P2/n*	Independent reflections	6570	3673
Unit cell dimensions			Reflections />2σ(*I*)	3136	2058
a, Å	11.769(2)	12.411(5)	Refinement method	full-matrix least-squares on F^2	
b, Å	31.373(5)	8.229(5)	Data / restraints / parameters	6570 / 4 / 514	3673 / 2 / 312
c, Å	12.633(4)	24.070(5)	Goodness-of-fit on F^2	0.810	0.837
β,°	110.90(3)	101.04(2)	Final *R* indices [*I*>2σ(*I*)]		
Volume, $Å^3$	4357.6(17)	2412.8(18)	*R*1	0.0634	0.0400
Z	8	4	*wR*2	0.1547	0.982
Density (calculated), Mg/m^3	1.151	1.251	*R* indices (all data)		
μ, mm^{-1}	0.605	0.087	*R*1	0.1182	0.0964
F(000)	1624	976	*wR*2	0.1653	0.1123
Crystal colour	colourless		Max. and mean shift/esd	0.074, 0.002	0.005, 0.000
Crystal size. mm	0.18 x 0.16 x 0.12	0.50 x 0.25 x 0.10	Extincion coefficient		0.0085(10)
θ range for data collection, °	4.02 - 75.01	2.62 - 23.97	Largest diff. peak and hole, e $Å^{-3}$	0.482 and -0.226	0.197 and -0.250

(EtOH), $[\alpha]_D$= -228° (c=1, DMF). The basewas separated from the tartarate as described above to afford 3 g (30%) of (15a*R*)-**6**, mp 130-133 °C (acetone), $[\alpha]_D$=-488° (c=1, $CHCl_3$).

Ethyl (1*S*,12b*S*)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-(2'-hydroxyimino)-propionate (5b) from (15a*S*)-6 tartarate: (15a*S*)-**6** tartarate (5.31 g, 10 mmol) was dissolved in a mixture of water (60 mL) and EtOH (124 mL) and hydrogenated over 10 % palladium on activated carbon (0.2 g) at 40 °C. The reaction mixture was filtered and acidified with concd HCl (2 mL). The separated crystals were isolated by filtration to yield 3.44 g (82 %) of **5b** HCl, mp 257-260 °C, $[\alpha]_D$ = -61° (c=1, DMF). **5b** HCl and **5b**, deliberated from the HCl salt were identical with the authentic samples.[12]

(±)-Diethyl-15a-ethyl-2,3,6,11,15,15a-hexahydro-1*H*,5*H*-indolo[2,3-*a*]pyrano[3,2-*i*]quinolizine-14,14-(13*H*)-dicarboxylate (8): A mixture of **7** (X=Cl) (55.3 g, 120 mmol), EtOH (160 mL), paraformaldehyde

(4.8 g, 160 mmol) and triethylamine (14.2 g, 19.5 mL, 140 mmol) was stirred for 50 min at 50 ^{o}C. After cooling to 10 ^{o}C, water (130 mL) was added. The separated crystals were filtered, washed with water (2x30 mL) and EtOH (30 mL) to yield 48.6 g (85 %) of (±)- **8**, mp 153-154 ^{o}C (acetone); MS (EI) *m/z* %: 454(0.2)M^{+}; 425 (0.1); 252(39); 237(100); 127(53). 99(57). IR (cm^{-1}): 3448 (N-H); 1731, 1718 (C=O); 1261, 1224 (C-O-C); 748 (Ar); 2924; 1471; 1147; 1079; 981; 886; 514. *Anal*. Calcd for $C_{26}H_{34}N_2O_5$: C,68.69; H,7.52; N,6.15. Found: C,68.42; H,7.55; N,6.37.

Resolution of 8: To racemic diester (±)-**8** (18.2 g, 40 mmol) in EtOH (180 mL) and CH_2Cl_2 (10 mL) dibenzoyl-*L*-tartaric acid monohydrate (15.0 g, 40 mmol) was added. The reaction mixture was stirred for 2 h at rt, filtered and washed with EtOH (2x15 mL) to afford 17.4 g (53%) of (15a*R*)-**8** dibenzoyl-*L*-tartarate, mp 139-141^{o}C (ethanol), $[\alpha]_D$= -72.5^{o} (c=1, DMF). The filtrate was evaporated *in vacuo*. The residue was quenched with 5 % sodium carbonate (50 mL). The separated crystals were filtered and washed with water (2x10 mL) to give 8.37g (46 %), of (15a*S*)-**8**, mp 133-136 ^{o}C (recrystallization from acetone), $[\alpha]_D$= +95.8^{o} (c=1, CH_2Cl_2).

(1*S*-12b*S*)1-(2',2'-Diethoxycarbonyl-2'-hydroxymethyl-ethyl)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine(1*S*,12b*S*-9): The solution of (+)-**8** (30 g, 66 mmol) in DMF (60 mL) was hydrogenated over 10 % palladium on activated carbon (0.3 g) for 2 h. After filtration of the catalyst water (100 mL) was added and the solution was extracted with $CHCl_3$ (3x50 mL). The combined extracts were washed with water (2x40 mL) dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was crystallized twice from EtOH/petroleum ether to yield 19.5 g (65 %) of **9,** mp 215-218 ^{o}C, $[\alpha]_D$= -28,9^{o} (c=1, DMF); MS (EI) *m/z* %: 456(0.1) M^{+}; 426(6); 381(5);267(100);237(4); 197(12); 169(17). IR (cm^{-1}): 3562, 3513 (O-H); 3379 (N-H); 1716 (C=O); 1275, 1209 (C-O-C); 1041 (CH_2-OH); 739 (Ar); 2977; 1662; 1469; 1447; 1155; 1069; 879; 820. *Anal*. Calcd for $C_{26}H_{36}N_2O_5$: C,68.39; H,7.94; N,6.13. Found: C,68.04; H,8.17; N,6.11.

(1*S*,12b*S*)-1-(2',2'-Diethoxycarbonylethyl)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine(1*S*,12b*S*-10): A solution of (+)-**8** (30 g, 66 mmol) in DMF (60 mL) was hydrogenated over 10 % palladium on activated carbon (0.6 g) for 2 h. After filtration, 25% NH_4OH solution (12 mL) was added and the mixture was stirred for 30 min. EtOH (10 mL) then water (150 mL) was added. Thecrystals were separated, washed with water, then suspended in a mixture of EtOH/water 2:1 (110 mL) to yield 24.3 g (86 %) of (1*S*,12b*S*)-**10**, mp 85-87 ^{o}C (recrystallization from EtOH/water), $[\alpha]_D$= -96.6^{o} (c=1, DMF); MS (EI) *m/z* %: 426(12) M^{+}; 425(12); 381(9); 267(100); 237(6); 197(13); 169(22). IR (cm^{-1}): 3367 (N-H); 2818, 2766 (N-CH_2); 1751, 1735, 1715 (C=O); 1321, 1296 (C-O-C); 743 (Ar); 2940;1656;1463;

1367; 1219; 1136; 855; 668; 437. *Anal*. Calcd for $C_{25}H_{34}N_2O_4$: C,70.22; H,8.01; N,6.55. Found: C,69.56; H,8.11; N,6.61.

Preparation of (1*S*,12b*S*)-5b from (1*S*,12b*S*)-10: To (1*S*,12b*S*)-**10** (42.6 g, 100 mmol) in EtOH (100 mL) a solution of potassium hydroxide (7 g, 125 mmol) in water (30 mL) was added and stirred for 2 h at 25-30 ^oC. The pH was adjusted to 7 with AcOH and the solution was evaporated *in vacuo*. The residue was dissolved in AcOH (90 mL). A solution of sodium nitrite (11 g, 159 mmol) in water was added at 10 ^oC and stirred for 2 h at 10-15 ^oC, then a mixture of concd HCl (36 mL) and water (72 mL) was added to give 36.8 g (88 % yield) of **5b** hydrochloride, mp 258-261^oC, (lit.,[12] mp 248^o), $[\alpha]_D$= -61^o (c=1, DMF). Aquoeus NH_4OH 25 % solution (61.5 mL) was added to give a solution. After 30 min stirring water (120 mL) was added, the mixture was stirred for 1 h, then filtered and washed with 20 % EtOH/water (2x20 mL) to yield 28.8 g (75 %) of (1*S*,12b*S*)-**5b**, mp 172-173 ^oC, $[\alpha]_D$= -61^o (c=1, DMF). (lit.,[12] mp 172-173 ^oC, $[\alpha]_D^{25}$ = -59^o).

Preparation of (15a*S*)-6 from (1*S*,12b*S*)-5b: To (1*S*,12b*S*)-**5b** (5.15 g, 13.4 mmol) in AcOH (15 mL) magnesium monoperoxyphthalate hexahydrate (6 g, 85 %, 10.3 mmol) was added in five portions at 20^{o}C. The reaction mixture was stirred for 2 h at 27-28 ^oC. A solution of sodium pyrosulfite (1.6 g) in water (15 mL) then 25 % NH_4OH solution (43 mL) were added and the solution was extracted with CH_2Cl_2 (3x15 mL). The combined extracts were dried ($MgSO_4$) and L-tartaric acid (2 g, 13.3 mol) was added. The mixture was stirred for 4 h to afford (15aS)-**6** L-tartarate, 6.25 g (88 %), mp 138-141 ^oC (EtOH), $[\alpha]_D$= +242.5^o, (c=1, DMF). (15a*S*)-**6** base, mp 128-130 ^oC (acetone), $[\alpha]_D$: + 476^o (c=1, $CHCl_3$).

(16*S*)-3,4-Didehydro-14-ethoxycarbonyl-eburnameninium perchlorate ((16*S*)-11, X=ClO_4^-): A mixture of *p*-toluenesulfonic acid hydrate (5.0 g, 26 mmol) (1*S*)-**5** (2.6 g, 6.8 mmol), toluene (40 mL) and EtOH (5 ml) was stirred and distilled until the temperature of the overhead rose to 108 ^oC. The reaction mixture was refluxed for 8 h. The solvent was evaporated *in vacuo* and the residue was dissolved in EtOH (12 mL). Addition of 70 % perchloric acid (1 mL), followed by water (3 mL) yielded yellow crystals of **11** (X=ClO_4^-), 1.54 g (50 % yield), mp 190-193 ^oC (recrystallization from ethanol/water), $[\alpha]_D$= -64.3^o (c=1, DMF); ^1H NMR (DMSO-d_6): 0.67 (t, 3H, J=7.6Hz, H_3-21); 1.33 (t, 3H, J=7.1Hz, $OCH_2C\mathbf{H}_3$); 1.88 (m, 2H, H_2-20); 1.96 (m, 1H, H_x-17); 2.07 (m, 1H, H_x-18); 2.13 (m, 1H, H_y-17); 2.42 (m, 1H, H_y-18); 3.26 (m, 1H, H_x-6); 3.46 (m, 1H, H_y-6); 3.75 (m, 1H, H_x-19); 4.00 (m, 1H, H_y-19); 4.03-4.14 (m, 2H, H_2-5); 4.41 (q, 2H, J=7.1Hz, $OC\mathbf{H}_2CH_3$); 6.45 (s, 1H, H-15); 7.32 (m, 1H, H-10); 7.49-7.55 (m, 2H, H-11,12); 7.84 (d, 1H, J=8.1Hz, H-9). ^{13}C NMR (DMSO-d_6): 7.9 (C-21); 13.8 ($OCH_2\mathbf{C}H_3$); 16.8 (C-18); 18.9 (C-

6);24.1 (C-17); 32.1 (C-20); 40.3 (C-16); 50.5 (C-19); 52.4 (C-5); 62.3 (O**C**H_2CH_3); 115.1 (C-12); 122.4 (C-9); 122.7 (C-10); 123.2, 125.3 (C-7,C-8); 124.2 (C-15); 125.5 (C-2); 127.1 (C-14); 128.7 (C-11); 137.5 (C-13); 161.1 (**C**OOEt); 166.4 (C-3). MS (FAB) *m/z* %: 349 (100) cation; 321(24); 320(41); 277(42). IR (cm^{-1}): 1743 (C=O); 1645 (C=C); 1263 (C-O-C); 1089 (ClO_4^-); 767, 758 (Ar); 2974;1574;1474; 1328; 1151; 1017; 623. *Anal.* Calcd for $C_{22}H_{25}N_2O_6Cl$: C, 58,86; H,5,61; N,6,23. Found: C,58,92; H,5,69; N,6,29.

Ethyl (3*R*, 16*S*)- apovincaminate (12): To a solution of **11** (X=ClO_4^-) (1.54 g, 3.42 mmol) in EtOH (7 mL), sodium tetrahydroborate (0.17 g, 4.5 mmol) was added. After stirring for 30 min, 2 % aqueous sodium hydroxide solution (40 mL) was added. The resulting crystals were filtered to yield 1.06 g (88 %) of **12**, mp 122-124^o (EtOH), $[\alpha]_D$= -144 ^{o}C (c=1, $CHCl_3$), identical with an authentic sample.[11]

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