Synthesis of Enantiopure Oxoindolo-quinolizines

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Received January 18th, 1999, respectively July 19th, 1999

Keywords: Antitumor agents, Nitrogen heterocycles, Synthesis design, Indoloquinolizines, Quinolizines

Abstract. Methyl (1*S*,3*S* and 1*R*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate (**3**) was hydrolyzed in the presence of sodium hydroxide to give (1*S*,3*S* and 1*R*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylic acid (**4**) which was reduced with $LiAlH_4$ to provide (1*S*,3*S*)- and (1*R*,3*S*)-1-(2,2-dimethoxyethyl)-3-hydroxymethyl-1,2,3,4-tetrahydrocarbolines (**10**) and then amidated in ammonia containing methanol to obtain (1*S*,3*S*)- and (1*R*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxamide (**14**). Acylation of (1*S*,3*S* and 1*R*,3*S*)-3, (1*S*,3*S* and 1*R*,3*S*)-4, (1*S*,3*S*)-10, (1*R*,3*S*)-10, (1*S*,3*S*)-14 and (1*R*,3*S*)-14 afforded the corresponding methyl (1*S*,3*S* and 1*R*,3*S*)-1-(2,2-dimethoxyethyl)- 2-(1,3-dioxobutyl)-1,2,3,4-tetrahydrocarbolines-3-carboxylate (**6**), (1*S*,3*S* and 1*R*,3*S*)-1-(2,2-dimethoxyethyl)-2-(1,3-dioxobutyl)-1,2,3,4-tetrahydrocarboline-3-carboxylic acid (**5**), (1*S*,3*S*)- and (1*R*,3*S*)-1-(2,2-dimethoxyethyl)-2-(1,3-dioxobutyl)-3-(1,3-dioxobutyl)oxymethyl-1,2,3,4-tetrahydrocarboline (**11**), (1*S*,3*S*)- and (1*R*,3*S*)-1-(2,2-dimethoxyethyl)-2-(1,3-dioxobutyl)-1,2,3,4-tetrahydrocarboline-3-carboxamide (**15**), respectively. After Aldol reaction, dehydration and dehydrogenation the desired (6*S*)-6-substituted 4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizines **8**, **9**, **12**, **13**, and **16** were obtained. Their anticancer activities *in vitro* were investigated.

Methyl (6*S*)-3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carboxylate (**8**) was obtained as a by-product in 1990 [1]. The bioassay revealed that this compound inhibited HL-60 leukemia cells *in vitro*. In order to find the dependence of the anticancer *in vitro* activity of (6*S*)-6-substituted 3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*] quinolizine on the substituents of 6-position (6*S*)-**8** was modified at the 6-position.

The Pictet–Spengler condensation of *L*-tryptophane methyl ester and 1,1,3,3-tetramethoxypropane provided methyl (1*S*,3*S* and 1*R*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate (**3**), a 2:1 mixture of stereoisomers (1*S*,3*S*)-**3** and (1*R*,3*S*)-**3** [2].

In the optimization of the Pictet–Spengler condensation the effect of the solvent and the reaction temperature on the yield and the ratio of (1*S*,3*S*)-**3** and (1*R*,3*S*)-**3** was observed. The results indicated that with hydrochloric acid as the catalyst both solvent and temperature had an effect on the yield but not on the ratio. In methanol at 45 °C the condensation afforded (1*S*,3*S* and 1*R*,3*S*)-**3** (2:1 mixture) in 95% yield (Tab. 1).

On refluxing (1*S*,3*S* and 1*R*,3*S*)-**3** and 2,2,6-trimethyl-1,3-dioxine-4-one in toluene or dimethylbenzene (1*S*,3*S* and 1*R*,3*S*)-**6** was obtained in poor yield only. Treating (1*S*,3*S* and 1*R*,3*S*)-**3** with diketene in acetone or ethyl acetate the yield was improved to 72% (Tab. 2).

Tab. 1 The effect of solvent and temperature on the yield and the ratio of (1*S*,3*S*)-**3** and (1*R*,3*S*)-**3**

solvent	temp. (°C)	yield (%)	(1*S*,3*S*)-**3**/ (1*R*,3*S*)-**3**
$CHCl_3$:MeOH(1:1)	25	86	2/1
$CHCl_3$:MeOH(1.4:1)	25	78	2/1
$CHCl_3$:MeOH(1:1)	37	88	2/1
$CHCl_3$:MeOH(1:1)	45	90	2/1
$CHCl_3$:MeOH(1:1)	60	30	2/1
THF	25	65	2/1
Acetone	25	76	2/1
MeOH	25	87	2/1
MeOH	37	91	2/1
MeOH	45	95	2/1
MeOH	60	35	2/1

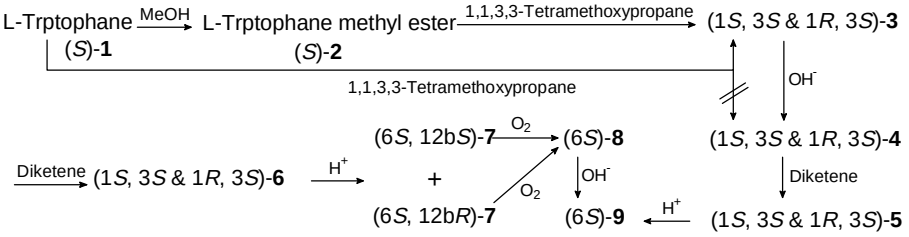
Tab. 2 Effect of acylating agent and temperature on the yield of (1*S*,3*S* and 1*R*,3*S*)-**6**

Acylating agent	solvent	Temp. (°C)	time (h)	yield (%)
2,2,6-trimethyl-1,3-dioxine-4-one	Toluene	Ref. (110)	0.75	14
2,2,6-trimethyl-1,3-dioxine-4-one	Xylene	Ref. (145)	0.75	11
Diketene	THF	25	10	20
Diketene	Acetone	25	10	72
Diketene	CH_3CO_2Et	25	48	69

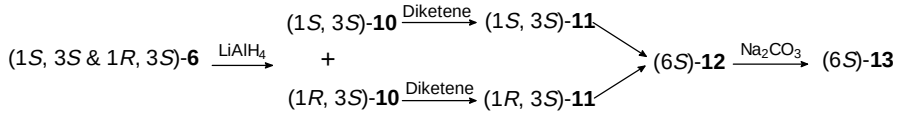
  1436-9966/99/3410X-677 $ 17.50 + .50/0

Synthesis of the cyclization product of (1*S*,3*S* and 1*R*,3*S*)-**6** depended significantly on the catalytic acid. When oxalic acid was used as the catalyst 51% of (6*S*, 12b*S*)- and 34% of (6*S*,12b*R*)-3-acetyl-1,4,6,7,12,12b-hexahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carboxylic acid methyl ester (**7**) were obtained, on the other hand, in the presence of hydrochloric acid (2 mol/l) (6*S*)-**8** (85%) was the main product and only 6% of (6*S*,12b*S*)-**7** were formed.

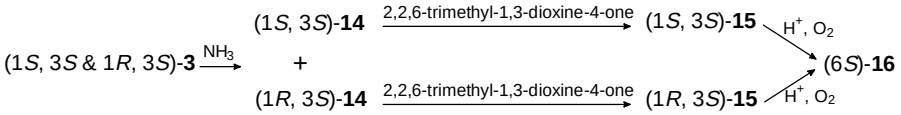
Hydrolysis of (1*S*,3*S* and 1*R*, 3*S*)-**3** in a mixture of methanol and chloroform (17:1) with sodium hydroxide as the catalyst provided (1*S*,3*S* and 1*R*,3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylic acid (**4**). After acylation and cyclization (6*S*)-3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carboxylic acid (**9**) was obtained. With the same reaction condition as that of the hydrolysis of (1*S*,3*S* and 1*R*,3*S*)-3 (6*S*)-**8** was converted into (6*S*)-**9** in lower



A: Synthesis of 6-methoxycarbonyl and 6-carboxyl-3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine

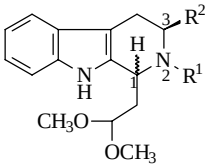


B: Synthesis of 6-hydroxymethyl and 6-(1,3-dioxobutyl) oxymethyl substituted 3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine

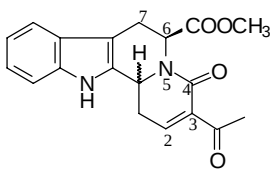


C: Synthesis of 3-acetyl-6-amido-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine

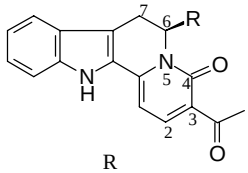
Wherein



	1-H	R^1	R^2
(1*S*, 3*S* and 1*R*, 3*S*)-**3**	H	H	$COOCH_3$
(1*S*, 3*S* and 1*R*, 3*S*)-**4**	H	H	COOH
(1*S*, 3*S* and 1*R*, 3*S*)-**5**	H	$COCH_2COCH_3$	COOH
(1*S*, 3*S* and 1*R*, 3*S*)-**6**	H	$COCH_2COCH_3$	$COOCH_3$
(1*S*, 3*S*)-**10**	H	H	CH_2OH
(1*R*, 3*S*)-**10**	H	H	CH_2OH
(1*S*, 3*S*)-**11**	H	$COCH_2COCH_3$	$CH_2OCOCH_2COCH_3$
(1*R*, 3*S*)-**11**	H	$COCH_2COCH_3$	$CH_2OCOCH_2COCH_3$
(1*S*, 3*S*)-**14**	H	H	$CONH_2$
(1*R*, 3*S*)-**14**	H	H	$CONH_2$
(1*S*, 3*S*)-**15**	H	$COCH_2COCH_3$	$CONH_2$
(1*R*, 3*S*)-**15**	H	$COCH_2COCH_3$	$CONH_2$



12b-H
(6*S*, 12b*S*)-**7**: H
(6*S*, 12b*R*)-**7**: H



R	
(6S)-**8**	$COOCH_3$
(6S)-**9**	COOH
(6S)-**12**	$CH_2OCOCH_2COCH_3$
(6S)-**13**	CH_2OH
(6S)-**16**	$CONH_2$

Scheme 1 The synthesis route for enantiopure oxoindolo-quinolizines
A: Synthesis of 6-methoxycarbonyl- and 6-carboxyl-3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine
B: Synthesis of 6-hydroxymethyl- and 6-(1,3-dioxobutyl)- oxymethyl-substituted 3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine; **C**: Synthesis of 3-acetyl-6-amido-4,6,7,12-tetrahydro-4-oxoindolo [2,3-*a*]quinolizine

yield only. The Pictet-Spenger condensation of *L*-tryptophane and 1,1,3,3-tetramethoxypropane failed to give (1*S*,3*S* and 1*R*,3*S*)-**4** either. The condensation and esterification took place simultaneously and (1*S*,3*S* and 1*R*,3*S*)-3 was the sole product (Scheme 1A).

With $LiAlH_4$ as the reducing agent the ester group of (1*S*,3*S* and 1*R*,3*S*)-3 can be smoothly converted into a hydroxymethyl group [3]. After acylation of the reduction products (1*S*,3*S*)- and (1*R*,3*S*)-1-(2,2-dimethoxyethyl)-3-hydroxymethyl-1,2,3,4-tetrahydrocarboline (**10**) the 1,3-dioxobutyl group was introduced into their 2 and 3 positions. The cyclization of (1*S*,3*S*)- and (1*R*, 3*S*)-1-(2,2-dimethoxyethyl)-2-(1,3-dioxobutyl)-3 (1,3-dioxobutyl)oxymethyl-1,2,3,4-tetrahydrocarboline (**11**) depended significantly on the catalytic acid. With oxalic acid as the catalyst no cyclization was observed. With hydrochloric acid (2 mol/l) instead of oxalic acid (6*S*)-6-(1,3-dioxobutyl)oxymethyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine (**12**) was formed, which was easily hydrolyzed to give (6*S*)-6-hydroxymethyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine (**13**) (Scheme 1B).

On ammonolysis [4] with ammonia in methanol (1*S*, 3*S* and 1*R*,3*S*)-**3** was converted into (1*S*,3*S*)- and (1*R*, 3*S*)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxamide (**14**), which were treated with 2,2,6-trimethyl-1,3-dioxine-4-one gave rise to (1*S*,3*S*)- and (1*R*,3*S*)-1-(2,2-dimethoxyethyl)-2-(1,3,-dioxobutyl)-1,2,3,4-tetrahydrocarboline-3-carboxamide (**15**), respectively. On cyclization both of them produced (6*S*)-3-acetyl-4,6,7,12,-tetrahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carboxamide (**16**) (Scheme 1C).

The inhibiting action of (6*S*)-**8**, (6*S*)-**9**, (6*S*)-12, (6*S*)-**13** and (6*S*)-**16** on HL-60 leukemia *in vitro* was recorded with the modified method of Denizot and Lang [5]. The data are listed in Table 3.

Tab. 3 Inhibiting action of 6-substituted 4-oxoindolo-[2,3-*a*]quinolizines to HL-60 on leukemia

Compound	inhibition ratio(%) at 10^{-7} mol/l	10^{-6} mol/l	10^{-5} mol/l
16	−13.92	−30.73	−56.64
9	−28.60	−10.22	9.41
13	−20.50	−0.11	8.60
12	−8.10	1.60	14.60
8	5.53	17.05	61.03

The results indicate that the substituents of 6-position have a significant effect on the *in vitro* anti-HL-60 activity. The ester group of 6-position may be necessary for antitumor activity of 6-substituted 4,6,7,12-tetrahydro-4-oxoindolo [2, 3-*a*]quinolizine *in vitro*.

The author Shiqi Peng wishes to thank the National Natural Science Foundation of China for financial support.

Experimental

All reactions were carried out under nitrogen (1 bar), except for the ammonolysis experiments. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300MHz with a VXR-300 instrument in deuteriochloroform with tetramethylsilane as internal standard. IR spectra were recorded with a Perkin-Elmer 983 instrument and mass spectra with a ZAB-MS (70 eV) spectrometer. Optical rotations were determined at 20 °C on Schmidt&Haensch Polartronic D instrument. Chromatography was performed with Qingdao silica gel H.

Methyl (1S,3S and 1R,3S)-1-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylate (**3**)

To a stirred solution of 436 mg (2 mmol) of *L*-tryptophane methyl ester (**2**) and 426 mg (2.6 mmol) of 1,1,3,3-tetramethoxypropane in 10 ml of chloroform/methanol (1:1), 80 mg of concentrated hydrochloric acid were added at room temperature to adjust the reaction mixture to pH 1. The solution was stirred at room temperature for 8 h, then TLC analysis (ethyl acetate) indicated complete disappearance of **2**. The reaction mixture was neutralized with 200 mg of sodium carbonate and filtered. Removing the solvent and purification by chromatography (ethyl acetate) provided 550 mg (86%) of **3**, as colourless syrup. The product consisted of a 2:1 mixture of stereoisomers (1*S*,3*S*)-**3** and (1*R*,3*S*)-**3** as determined by ^{1}H NMR spectroscopy. – IR ($CHCl_3$, mixture of stereoisomers): ν/cm^{-1} = 3440 and 3400 (NH), 3000 (C=CH), 2960 and 2840 (CH, CH_2 and CH_3), 1740 (C=O), 1600 and 1450 (aromatic C=C), 1320 and 1270 (C–O–C), 746 (1,2-disubstituted phenyl). – ^{1}H NMR of (1*S*, 3*S*)-**3**: δ/ppm = 1.95 (s, 1H, NH), 2.12 [t, J = 4 Hz, 1H, $(MeO)_2CH\underline{CH_2}$], 2.22 [t, J = 7 Hz, 1H, $(MeO)_2CH\underline{CH_2}$], 2.83 (m, J = 2 Hz, 1H, $\underline{CH_2}CHCO_2Me$), 3.12 (m, J = 2 Hz, 1H, $\underline{CH_2}CHCO_2Me$), 3.42 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.80 (dd, J = 1 Hz, J = 4 Hz, 1H, $NH\underline{CH}CO_2Me$), 3.92 (s, 3H, CO_2CH_3), 4.30 (m, J = 3 Hz, 1H, $\underline{CH}NHCHCO_2Me$), 4.65 (q, J = 3 Hz, 1H, acetal H), 7.13 (m, J = 7 Hz, 2H, aromatic H), 7.33 (d, J = 8 Hz, 1H, aromatic H), 7.48 (d, J = 7 Hz, 1H, aromatic H), 8.84 (s, 1H, pyrrole NH); (1*R*, 3*S*)-**3**: δ/ppm = 2.21 [t, J = 4 Hz, 1H, $(MeO)_2CH\underline{CH_2}$], 2.30 [t, J = 7 Hz, 1H, $(MeO)_2CH\underline{CH_2}$], 2.40 (s, 1H, NH), 2.95 (m, J = 2 Hz, 1H, $\underline{CH_2}CHCO_2Me$), 3.12 (m, J = 2 Hz, 1H, $\underline{CH_2}CHCO_2Me$), 3.36 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.75 (s, 3H, CO_2CH_3), 3.95 (dd, J = 7 Hz, J = 3 Hz, 1H, $NH\underline{CH}CO_2Me$), 4.36 (t, J = 7 Hz, 1H, $\underline{CH}NHCHCO_2Me$), 4.65 (t, J = 7 Hz, 1H, acetal H), 7.13 (m, J = 7 Hz, 2H, aromatic H), 7.33 (d, J = 8 Hz, 1H, aromatic H), 7.48 (d, J = 8 Hz, 1H, aromatic H), 8.50 (s, 1H, pyrrole NH). – MS (110 °C, mixture of stereoisomers): m/z (%) = 318 (34.8) [M^+], 286 (6.9) [$M^+ - CH_3OH$], 229 (100) [$M^+ - (MeO)_2CHCH_2$], 168 (91.3) [$M^+ - (MeO)_2CHCH_3 - HCO_2Me$], 75 (52.2) [$MeO^+$ CHOMe].

$C_{17}H_{22}N_2O_4$ Calcd.: 318.1580
Found 318.1580 (MS, high solution).

(1S,3S and 1R,3S)-1-(2,2-Dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxylic acid (**4**)

a) At room temperature to a stirred solution of 300 mg (0.94 mmol) of **3** and 15 ml of methanol 0.9 ml of aqueous NaOH (2 mol/l) were added. The reaction mixture (pH 12) was stirred

at room temperature for 15 h, then TLC analysis ($CHCl_3$: MeOH, 20 : 1) indicated complete disappearance of **3**. The reaction mixture was acidified with 0.9 ml of acetic acid and filtered. The filtrate was evaporated, and the residue was purified by chromatography ($CHCl_3$: MeOH : HAc, 100 : 20 : 1) to give 250 mg (87%) of **4**, as colorless needles, which consisted of a 2 : 1 mixture of stereoisomers (1*S*,3*S*)-**4** and (1*R*, 3*S*)-**4** as determined by ^{1}H NMR spectroscopy. –*m.p.* 182–183 °C. – IR (KBr, mixture of stereoisomers): ν/cm^{-1} = 3395 (NH), 2800–3200 (COOH), 2936 and 2833 (CH, CH_2 and CH_3), 1710 (C=O), 1628 and 1451 (aromatic C=C), 1389 and 1222 (C–O–C), 740 (1,2-disubstituted phenyl). – ^{1}H NMR of (1*S*, 3*S*)-**4** (D_2O): δ/ppm = 2.25 [m, 2H, $(MeO)_2CH\underline{CH_2}$], 2.61 (dd, *J* = 7.5 Hz, *J* = 8.3 Hz, 1H, $\underline{CH_2}CHCOOH$), 2.98 (dd, *J* = 8.4 Hz, *J* = 8.0 Hz, 1H, $\underline{CH_2}CHCOOH$), 3.40 (dd, *J* = 5.4 Hz, *J* = 6.0 Hz, 1H, NH–$\underline{CH}COOH$), 3.47 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.95 (dd, *J* = 6.1 Hz, *J* = 5.6 Hz, 1H, $\underline{CH}NHCHCOOH$), 4.74 (m, 1H, acetal H), 7.05 (t, *J* = 17.8 Hz, 1H, aromatic H), 7.15 (t, *J* = 18.2 Hz, 1H, aromatic H), 7.35 (d, *J* = 7.5 Hz, 1H, aromatic H), 7.45 (d, *J* = 7.6 Hz, 1H, aromatic H); (1*R*, 3*S*)-**4**: δ/ppm = 2.24 [m, 2H, $(MeO)_2CH\underline{CH_2}$], 2.64 [dd, *J* = 7.2 Hz, *J* = 8.2 Hz, 1H, $\underline{CH_2}CHCOOH$], 3.06 (dd, *J* = 8.0 Hz, *J* = 8.3 Hz, 1H, $\underline{CH_2}CHCOOH$], 3.45 (dd, *J* = 5.0 Hz, *J* = 6.3 Hz, 1H, $NH\underline{CH}COOH$), 3.45 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 4.01 (t, *J* = 7.1 Hz, 1H, $\underline{CH}NHCHCOOH$), 4.76 (m, 1H, acetal H), 7.06 (t, *J* = 17.8 Hz, 1H, aromatic H), 7.14 (t, *J* = 18.1 Hz, 1H, aromatic H), 7.36 (d, *J* = 7.5 Hz, 1H, aromatic H), 7.44 (d, *J* = 7.6 Hz, 1H, aromatic H). – MS (ESI, mixture of stereoisomers): *m/z* = 327 $[M+Na]^+$.

$C_{16}H_{20}N_2O_4$	Calcd.:	C 63.14	H 6.62 N 9.20
(304.14)	Found:	C 62.96	H 6.63 N 8.99.

b) A solution (pH 1) of 200 mg (0.93 mmol) of *L*-tryptophane (**1**), 5 ml of acetone, 0.17 ml (1.03 mmol) of 1,1,3,3-tetramethoxypropane and 0.15 ml of concentrated hydrochloric acid was stirred at room temperature for 48 h, then TLC ($CHCl_3$: MeOH, 15 : 1) indicated complete disappearance of **1**. The reaction mixture was evaporated to remove the solvent. The residue was purified by chromatography ($CHCl_3$: MeOH, 20 : 1) and 222 mg (75%) of (1*S*,3*S* and 1*R*,3*S*)-**3** was obtained exclusively.

(6S)-3-Acetyl-4, 6,7,12-tetrahydro-4-oxoindolo [2,3-a]quinolizine-6-carboxylic acid (**9**)

a) 200 mg (0.66 mmol) of **4** were dissolved in 25 ml of acetone and cooled in an ice bath. To this cold solution 0.08 ml (0.94 mmol) of diketene and 0.05 ml of triethylamine were added dropwise. The reaction mixture was stirred at room temperature for 24 h then TLC analysis indicated complete disappearance of **4**. The mixture was cooled in ice bath, and 0.04 ml of distilled water were added. The solution was stirred at room temperature for 0.5 h. The produced (1*S*,3*S* and 1*R*, 3*S*)-**5** was treated with 0.1 ml of hydrochloric acid (2 mol/l) without further separation and purification. The reaction mixture was stirred at room temperature for another 4 h. To the solution excess of sodium carbonate was added. The resulting suspension was filtered. The filtrate was evaporated, and the residue was purified by chromatography ($CHCl_3$: MeOH : HAc, 100 : 20 : 1) to provide 174 mg (82%) of (6*S*)-**9**, as yellow powder.

b) 200 mg (0.60 mmol) of (6*S*)-**8** were dissolved in 10 ml of methanol and to the solution 0.6 ml of aqueous solution of NaOH (2 mol/l) were added. The reaction mixture was stirred at room temperature for 24 h and acidified with acetic acid. After filtration, evaporation and chromatography ($CHCl_3$: MeOH : HAc, 100 : 20 : 1) 60 mg (32%) of (6*S*)-**9** were obtained, and 120 mg (60%) of (6*S*)-**8** were recovered. – (6*S*)-**9**; *m.p.* 204–205 °C. $[\alpha]_D$ = 28.5° (c = 2, H_2O). – IR (KBr): ν/cm^{-1} = 3392 (NH), 2800 ~ 3400 (COOH), 2922 (CH, CH_2 and CH_3), 1690 (C=O), 1606, 1546, 1497 and 1430 (aromatic C=C), 745 (1,2-di-substituted phenyl). – ^{1}H NMR: δ/ppm = 2.41 (s, 3H, $COCH_3$), 3.01 (dd, *J* = 7.2 Hz, *J* = 7.4 Hz, 1H, $\underline{CH_2}CHCOOH$), 3.66 (d, *J* = 17.1 Hz, 1H, $\underline{CH_2}CH$ COOH), 5.59 (d, *J* = 7.2 Hz, 1H, $CH_2\underline{CH}COOH$), 6.58 (d, *J* = 8.0 Hz, 1H, N–C=$\underline{CH}$–CH=C), 7.01 (t, *J* = 14.8 Hz, 1H, aromatic H), 7.16 (t, *J* = 15.4 Hz, 1H, aromatic H), 7.26 (t, *J* = 17.0 Hz, 1H, aromatic H), 7.99 (d, *J* = 7.9 Hz, 1H, aromatic H), 8.01 (d, *J* = 8.0 Hz, 1H, N–C=CH–$\underline{CH}$=C). – MS (ESI): *m/z* = 345 $[M + Na]^+$.

$C_{18}H_{14}N_2O_4$	Calcd.:	C 67.08	H 4.38 N 8.69
(322.10)	Found:	C 66.95	H 4.55 N 8.53.

Methyl (1S,3S and 1R,3S)-1-(2,2-dimethoxyethyl)-2-(1,3-dioxobutyl)-1,2,3,4 -tetrahydrocarboline-3-carboxylate (**6**)

a) The solution of 276 mg (0.87 mmol) of **3** in 4 ml of toluene was mixed with 0.158 ml (1.04 mmol) of 2,2,6-trimethyl-1,3-dioxine-4-one. The reaction mixture was refluxed for 45 min., then TLC analysis ($CHCl_3$: MeOH, 20 : 1) indicated complete disappearance of **3**. After removal of the solvent and purification of the residue by chromatography ($CHCl_3$: MeOH, 30 : 1) 50 mg (14%) of 6 were obtained.

b) Using procedure *a*) with xylene instead of toluene 40 mg (11%) of **6** were obtained.

c) The solution of 276 mg (0.87 mmol) of **3**, 4 ml of THF and 0.01 ml of triethylamine was mixed with 0.2 ml (2.4 mmol) of diketene. The reaction mixture was stirred at room temperature for 10 h, then TLC analysis ($CHCl_3$: MeOH, 20 : 1) indicated complete disappearance of **3**. After removal of the solvent and purification of the residue by chromatography ($CHCl_3$: MeOH, 30 : 1) 76 mg (20%) of 6 were obtained.

d) Using procedure *c*) with ethyl acetate instead of THF 255 mg (69%) of **6** were obtained.

e) Using procedure *c*) with acetone instead of THF 269 mg (72%) of **6** were obtained. – IR ($CHCl_3$): ν/cm^{-1} = 3410 (NH), 3000, 2940 and 2850 (CH, CH_2 and CH_3), 1715 (ester C=O), 1650 (C=O), 1590, 1450 and 1400 (aromatic C=C), 1350 (C–O–C), 740 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.01–2.40 [m, 7H, $COCH_3$, $(MeO)_2CH\underline{CH_2}CH$ and $\underline{CH_2}CHCO_2Me$], 3.40–3.82 (m, 11H, $\underline{CH_3}OCH$ OCH_3, CO_2CH_3 and $COCH_2CO$), 4.62–6.11 (m, 3H, $CH_2\underline{CH}\underline{C}O_2Me$, $N\underline{CH}CH_2\underline{CH}$ $(OCH_3)_2$], 7.10 (m, *J* = 7.0 Hz, 2H, aromatic H), 7.32 (d, *J* = 8.0 Hz, 1H, aromatic H), 7.48 (d, *J* = 7.0 Hz, 1H, aromatic H), 9.06–9.23 (m, 1H, pyrrole NH). – MS (105 °C): *m/z* (%) = 402 (8.4) $[M^+]$, 370 (25.0) $[M^+ – MeOH]$, 327 (3.0), $[M^+ – CH(OCH_3)_2]$, 317 (5.0) $[M^+ – COCH_2COCH_3]$, 312 (7) $[M^+ – CH_3CH(OCH_3)_2]$, 285 (62.0) $[M^+ – COCH_2COCH_3$-MeOH], 228 (25) $[M^+ – COCH_2COCH_3$-CO_2Me +2H], 168 (100) $[M^+ – CH_3CH(OCH_3)_2$-$COCH_2COCH_3$-CO_2Me].

$C_{21}H_{26}N_2O_6$ Calcd.: 402.1791
Found: 402.1790 (MS, high resolution).

Methyl (6S,12bR)- and (6S,12bS)-3-acetyl-1,4,6,7,12,12b-hexahydro-4-oxoindolo [2,3-a] quinolizine-6-carboxylate (**7**)

a) The suspension of 300 mg (0.75 mmol) of **6**, 10 ml of acetone and 60 mg of oxalic acid was stirred at room temperature for 100 h, then TLC analysis indicated complete disappearance of **6**. The reaction mixture was neutralized with excess of $NaHCO_3$ to adjust the solution to pH 8. After filtration and evaporation the residue was separated by chromatography ($CHCl_3$:MeOH, 200:1) to give 130 mg (51%) of (6*S*,12b*S*,)-**7** and 86 mg (34%) of (6*S*,12b*R*,)-**7**. (6*S*,12b*S*)-**7**; *m.p.* 225 °C (dec.). $[\alpha]_D$ = 44.7° (c = 2, $CHCl_3$). – IR (KBr): ν/cm^{-1} = 3339 (NH), 2949 and 2840 (CH, CH_2 and CH_3), 1723 (ester C=O), 1646 (C=O), 1480 and 1417 (aromatic C=C), 746 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.01 (s, 3H, $COCH_3$), 3.11 (ddd, *J* = 10.0 Hz, *J* = 3.0 Hz, *J* = 1.0 Hz, 1H, $\underline{CH_2}$CH=C), 3.40–3.59 (m, 3H, $\underline{CH_2}$CH=C and $\underline{CH_2}$CHCO$_2$Me), 3.86 (s, 3H, CO_2CH_3), 4.01 (dd, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H, $CH_2\underline{CH}$ CO_2Me), 5.66 (dd, *J* = 10.0 Hz, *J* = 5.0 Hz, 1H, N$\underline{CH}$ CH_2CH=C), 7.21 (m, *J* = 7.0 Hz, 2H, aromatic H), 7.41 (d, *J* = 8.0 Hz, 1H, aromatic H), 7.54 (d, *J* = 7.0 Hz, 1H, aromatic H), 7.66 (s, 1H, $CH_2\underline{CH}$=C), 7.90 (s, 1H, pyrrole NH). – MS (150 °C): *m/z* (%) = 338 (87) [M$^+$], 320 (28) [M$^+$ – H_2O], 295 (9), [M$^+$ – $COCH_3$], 277 (100) [M$^+$ – H_2O–$COCH_3$], 259 (50) [M$^+$ – CO_2Me–H_2O–2H], 253 (58) [M$^+$ – $COCH_2COCH_3$]. (6*S*, 12b*R*)-**7**; *m.p.* 153–154 °C. $[\alpha]_D$ = 8.4° (c = 2, $CHCl_3$). – IR (KBr): ν/cm^{-1} = 3288 (NH), 2927 and 2829 (CH, CH_2 and CH_3), 1725 (ester C=O), 1627 (C=O), 1450 and 1430 (aromatic C=C), 743 (1,2-di-substituted phenyl). – ^{1}H NMR: δ/ppm = 2.46 (s, 3H, $COCH_3$), 2.92 (dt, *J* = 15.0 Hz, *J* = 3.0 Hz, *J* = 1.0 Hz, 1H, $\underline{CH_2}$CH=C), 3.09(ddd, *J* = 8.0 Hz, *J* = 4.0 Hz, *J* = 2.0 Hz, 1H, $\underline{CH_2}$CH=C), 3.62 (s, 3H, CO_2CH_3), 3.63 (m, *J* = 3.0 Hz, 1H, $\underline{CH_2}$CH CO_2Me), 3.91 (d, *J* = 3.0 Hz, 1H, $\underline{CH_2}$CHCO$_2$Me), 5.10 (d, *J* = 12.0 Hz, 1H, N$\underline{CH}$ CH_2CH=C), 5.40 (dd, *J* = 4.0 Hz, *J* = 2.0 Hz, 1H, $CH_2\underline{CH}$ CO_2Me), 7.19 (s, 1H, NCHCH$_2\underline{CH}$=C), 7.20 (m, *J* = 6.0 Hz, 2H, aromatic H), 7.36 (d, *J* = 7.0 Hz, 1H, aromatic H), 7.50 (d, *J* = 7.0 Hz, 1H, aromatic H), 8.19 (s, 1H, pyrrole NH). – MS (150 °C): *m/z* (%) = 338 (89) [M$^+$], 320 (28) [M$^+$ – H_2O], 295 (9), [M$^+$ – $COCH_3$], 277 (100) [M$^+$ – H_2O-$COCH_3$], 259 (49) [M$^+$ – CO_2Me-H_2O-2H], 253 (59) [M$^+$ – $COCH_2$ $COCH_3$].

b) Using procedure *a*) with 0.3 ml of hydrochloric acid (2 mol/l) instead of 60 mg of oxalic acid after10 h 218 mg (85%) of (6*S*)-**8** were obtained directly and no (6*S*,12b*R*)-**7** or (6*S*,12b*S*)-**7** was found.

Methyl (6S)-3-acetyl-4,6,7,12-tetrahydro-4-oxoindolo [2,3-a]quinolizine-6-carboxylate (**8**)

a) The solution of 200 mg (0.59 mmol) of (6*S*, 12b*S*)-**7**, 15 ml of acetone and 0.02 ml of hydrochloric acid (2 mol/l) was stirred at room temperature for 10 h, then TLC analysis indicated complete disappearance of (6*S*, 12b*S*)-**7**. To the reaction mixture sodium carbonate was added to adjust the solution to pH 8. After filtration and evaporation the residue was purified by chromatography ($CHCl_3$:MeOH, 50:1) to give 170 mg (86%) of (6*S*)-**8**, as yellow needles.

b) Using procedure *a*) with (6*S*,12b*R*)-**7** instead of (6*S*,12b*S*)-**7** after 4 h. 175 mg (88%) of (6*S*)-**8** were obtained; *m.p.* 210 °C (dec.). $[\alpha]_D$ = 33.2° (c = 2, $CHCl_3$). – IR (KBr): ν/cm^{-1} = 3302 (NH), 2951, 2921 and 2850 (CH, CH_2 and CH_3), 1733 (ester C=O), 1661 (C=O), 1589, 1567, 1540 and 1430 (aromatic C=C), 1355 and 1325(C–O–C), 750 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.08 (s, 3H, $COCH_3$), 3.34 (dd, *J* = 10.0 Hz, *J* = 7.0 Hz, 1H, $\underline{CH_2}$CHCO$_2$ Me), 3.66 (s, 3H, CO_2CH_3), 3.78 (dt, *J* = 15.0 Hz, *J* = 2.0 Hz, 2H, $\underline{CH_2}$CHCO$_2$Me), 6.25 (dd, *J* = 7.0 Hz, *J* = 1 Hz, 1H, NC=$\underline{CH}$–CH=C), 6.52 (d, *J* = 7.0 Hz, 1H, NC=CH–$\underline{CH}$=C), 7.18 (dt, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H, aromatic H), 7.32 (d, *J* = 8.0 Hz, 1H, aromatic H), 7.38 (d, *J* = 8.0 Hz, 1H, aromatic H), 7.64 (d, *J* = 8.0 Hz, 1H, aromatic H), 8.82 (s, 1H, pyrrole NH). – MS (170 °C): *m/z* (%) = 336 (67) [M$^+$], 320 (34) [M$^+$ – H_2O + 2H], 261 (50) [M$^+$ – $COCH_3$-MeOH], 259 (48) [M$^+$ – CO_2Me-H_2O], 234 (26) [M$^+$ – CO_2Me-$COCH_2$], 227 (100) [M$^+$ – $CO_2C(COCH_3)CHCH$], 204 (58) [M$^+$–(2-methylpyrrole)-H].

(1R,3S)- and (1S,3S)-1-(2,2-Dimethoxyethyl)-3-hydroxymethyl-1,2,3,4-tetrahydrocarboline (**10**)

The suspension of 10 ml of THF and 240 mg (6.32 mmol) of $LiAlH_4$ was stirred at 40 °C. After 1 h the solution of 2.0 g (6.28 mmol) of **3** in 20 ml of THF was added. The reaction mixture was stirred at 40 °C for another 3 h, then TLC analysis indicated complete disappearance of **3**. After filtration and evaporation the residue was separated by chromatography (ethyl acetate: methanol, 5:1) to give 0.99 g (54%) of (1*S*, 3*S*)-**10** and 0.56 g (31%) of (1*R*,3*S*)-**10**, as colorless needles. (1*S*, 3*S*)-**10**; *m.p.* 170–171 °C. $[\alpha]_D$ = –45.3° (c = 1.4, MeOH). – IR (KBr): ν/cm^{-1} = 3380 (NH), 3300 (OH), 2918 and 2827 (CH, CH_2 and CH_3), 1619, 1488 and 1427 (aromatic C=C), 1365, 1318 and 1224 (C–O–C), 760 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.15 [t, *J* = 6.0 Hz, 2H, $(MeO)_2$ $CH\underline{CH_2}$], 2.20 (s, 1H, NH), 2.36 (s, 1H, OH), 2.70 (dd, *J* = 5.4 Hz, *J* = 7.8 Hz, 1H, $\underline{CH_2}CH_2CH_2OH$), 3.15 (d, *J* = 6.0 Hz, 1H, $\underline{CH_2}CHCH_2OH$), 3.40 (m, *J* = 6.0 Hz, 2H, $\underline{CH_2}$OH), 3.45 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.86 (dd, *J* = 6.0 Hz, *J* = 5.4 Hz, 1H, $CH_2\underline{CH}CH_2OH$), 4.21 (m, *J* = 2.0 Hz, NH$\underline{CH}$ $CH_2CH(OCH_3)_2$), 4.66 [dd, *J* = 6.0 Hz, *J* = 2.0 Hz, 1H, $CH_2\underline{CH}(OCH_3)_2$], 7.10 (m, *J* = 7.0 Hz, 1H, aromatic H), 7.15 (t, *J* = 7.0 Hz, 1H, aromatic H), 7.30 (d, *J* = 7.0 Hz, 1H, aromatic H), 7.46 (d, J = 7.0 Hz, 1H, aromatic H), 8.83 (s, 1H, pyrrole NH). – MS (110 °C): *m/z* (%) = 290 (24.5) [M$^+$], 272 (2.0) [M$^+$ – H_2O], 259 (13.6), [M$^+$ – CH_2OH], 201 (85.0) [M$^+$ – $CH_2CH(OCH_3)_2$], 182 (18.4) [M$^+$ – $CH_2CH(OCH_3)_2$-H_2O-H], 169 (93.2) [M$^+$ – $CH_2CH(OCH_3)_2$-CH_2OH-H], 75 (100) [$^+CH(OCH_3)_2$].

$C_{16}H_{22}N_2O_3$ (290.16) Calcd.: C 66.19 H 7.64 N 9.65
Found: C 65.99 H 7.66 N 9.40.

(1*R*,3*S*)-**10**; *m.p.* 156–157 °C. $[\alpha]_D$ = –38.5° (c = 1.5, MeOH). – IR (KBr): ν/cm^{-1} = 3390 (NH), 3325 (OH), 2917 and 2826 (CH, CH_2 and CH_3), 1620, 1452 and 1427 (aromatic C=C), 1358, 1319 and 1224 (C–O–C), 753 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.13 (t, *J* = 5.8 Hz, 2H, $(MeO)_2$ $CH\underline{CH_2}$), 2.24 (s, 1H, NH), 2.32 (s, 1H, OH), 2.52 (dd, *J* = 9.0 Hz, *J* = 6.0 Hz, 1H, $\underline{CH_2}CHCH_2OH$), 2.80 (dd, *J* = 12.0 Hz, *J* = 4.0 Hz, 1H, $\underline{CH_2}CHCH_2OH$), 3.30 (m, *J* = 5.6Hz, 2H, $\underline{CH_2}$OH), 3.33 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.85 (dd,

J = 8.0 Hz, *J* = 2.0 Hz, 1H, $CH_2\underline{CH}CH_2OH$), 4.30 (t, *J* = 7.0 Hz, 1H, $NH\underline{CH}CH_2CH(OCH_3)_2$), 4.63 [t, *J* = 5.0 Hz, 1H, $\underline{CH}(OCH_3)_2$], 7.12 (m, *J* = 7.0 Hz, 2H, aromatic H), 7.35 (d, *J* = 8.0 Hz, 1H, aromatic H), 7.44 (d, *J* = 8.0 Hz, 1H, aromatic H), 8.45 (s, 1H, pyrrole NH). – MS (90 °C): *m/z* (%) = 290 [M^+], 272 (1.4) [$M^+ - H_2O$], 259 (4.7), [$M^+ - CH_2OH$], 201 (33.8) [$M^+ - CH_2CH(OCH_3)_2$], 182 (6.8) [$M^+ - CH_2CH(OCH_3)_2$-H_2O-H], 169 (29.7) [$M^+ - CH_2CH(OCH_3)_2$-CH_2OH-H], 75 (100) [$^+CH(OCH_3)_2$].

$C_{16}H_{22}N_2O_3$	Calcd.:	C 66.19	H 7.64 N 9.65
(290.16)	Found:	C 66.25	H 7.60 N 9.60.

(1S,3S)- and (1R,3S)-1-(2,2-Dimethoxyethyl)-2-(1,3-dioxobutyl)-3-(1,3-dioxobutyl)oxymethyl-1, 2, 3, 4-tetrahydrocarboline (**11**)

a) To the solution of 500 mg (1.73 mmol) of (1*S*,3*S*)-**10** in 10 ml of acetone were added 0.45 ml (5.20 mmol) of diketene and 0.2 ml of triethylamine at 0 °C. The reaction mixture was stirred at room temperature for 24 h, then TLC analysis indicated complete disappearance of (1*S*, 3*S*)-**10**. The reaction mixture was quenched with 0.1 ml of water at 0 °C for 2 h. The resultant solution was extracted with $CHCl_3$ (3 × 10 ml). The organic phases were combined and dried on Na_2SO_4. After filtration and evaporation the residue was purified by chromatography ($CHCl_3$:MeOH, 100:1) to give 570 mg (72%) of (1*S*,3*S*)-**11**, as colorless syrup. $[\alpha]_D$ = –51.5° (c = 2, CH_3Cl). – IR (KBr): ν/cm^{-1} = 3374 (NH), 2932 and 2831 (CH, CH_2 and CH_3), 1739 (ester, C=O), 1712 (ketone C=O), 1631 (amide C=O), 1600, 1500 and 1450 (aromatic C=C), 1357, 1318 and 1234 (C–O–C), 740 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.07–2.25 [m, 2H, $\underline{CH_2}CH(OCH_3)_2$], 2.23–2.30 (m, 6H, 2×$COCH_3$), 3.05–3.39 (m, 2H, $\underline{CH_2}CH\,CH_2CO_2$), 3.41~3.69 [m, 12H, $CH(O\underline{CH_3})_2$, $CH_3CO\underline{CH_2}CO$, $\underline{CH_2}O\,CO\underline{CH_2}COCH_3$], 4.13–4.55 (m, 2H, $CH_2\underline{CH}N\underline{CH}\,CH_2$), 4.96[m, 1H, $CH_2\underline{CH}(OCH_3)_2$], 7.11 (t, *J* = 7.0 Hz, 1H, aromatic H), 7.17 (d, *J* = 7.5 Hz, 1H, aromatic H), 7.36 (d, *J* = 8.0 Hz, 1H, aromatic H), 7.49 (d, *J* = 7.0 Hz, 1H, aromatic H), 8.55–8.80 (m, 1H, pyrrole NH). – MS (ESI): *m/z* = 481 [M+Na]$^+$.

$C_{24}H_{30}N_2O_7$	Calcd.:	C 62.87	H 6.59 N 6.11
(458.21)	Found:	C 62.69	H 6.49 N 5.99.

b) Using procedure *a*) with (1*R*,3*S*)-**10** instead of (1*S*,3*S*)-**10** 600 mg (76%) of (1*R*,3*S*)-**11** were obtained, as colorless syrup. $[\alpha]_D$ = 46.7° (c = 2, $CHCl_3$). – IR (KBr): ν/cm^{-1} = 3382 (NH), 2928 and 2833 (CH, CH_2 and CH_3), 1742 (ester, C=O), 1713 (ketone C=O), 1634 (amide C=O), 1600, 1461 and 1423 (aromatic C=C), 1358, 1314 and 1235 (C–O–C), 745 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 1.96 – 2.30 (m, 2H, $\underline{CH_2}CH\,(OCH_3)_2$), 2.24–2.30 (m, 6H, 2×$COCH_3$), 2.88–3.49 (m, 2H, $\underline{CH_2}CHCH_2OCO$), 3.40–4.12 [m, 12H, $CH(O\underline{CH_3})_2$, $CH_3CO\underline{CH_2}CO$, $\underline{CH_2}OCO\underline{CH_2}COCH_3$], 4.47–5.42 (m, 2H, $CH_2\underline{CH}N\underline{CH}CH_2$), 5.42[m, 1H, $CH_2\underline{CH}(OCH_3)_2$], 7.08 (t, *J* = 7.5 Hz, 1H, aromatic H), 7.16 (d, *J* = 8.0 Hz, 1H, aromatic H), 7.31 (d, *J* = 7.5 Hz, 1H, aromatic H), 7.43 (d, *J* = 8.0 Hz, 1H, aromatic H), 8.80–9.10 (m, 1H, pyrrole NH). – MS (ESI): *m/z* = 481 [M + Na]$^+$.

$C_{24}H_{30}N_2O_7$	Calcd.:	C 62.87	H 6.59 N 6.11
(458.21)	Found:	C 62.78	H 6.48 N 5.90.

(6S)-3-Acetyl-6-(1,3-dioxobutyl)oxymethyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-a]quinolizine (**12**)

The solution of 300 mg (0.67 mmol) of (1*S*,3*S*)-**11** or (1*R*, 3*S*)-**11** in 20 ml of acetone was treated with 0.5 ml of hydrochloric acid (2 mol/l). The reaction mixture was stirred at room temperature for 12 h, then TLC analysis indicated complete disappearance of (1*S*,3*S*)-**11** or (1*R*,3*S*)-**11**. The solution was neutralized with Na_2CO_3 adjusting to pH 8. After filtration and evaporation the residue was purified by chromatography ($CHCl_3$:MeOH, 100:1) to give 210 mg (83%) of (6*S*)-**12**, as yellow syrup. $[\alpha]_D$ = 57.1° (c = 2, $CHCl_3$). – IR (KBr): ν/cm^{-1} = 3398 (NH), 2968 and 2920 (CH, CH_2 and CH_3), 1742 (ester, C=O), 1713 (ketone C=O), 1651 (amide C=O), 1586, 1541 and 1495 and 1423 (aromatic C=C), 740 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.15–2.42 (m, 3H, $COCH_2CO\underline{CH_3}$), 2.71 (s, 3H, C=C–$COCH_3$), 3.24–3.40 (m, 2H, $\underline{CH_2}CHNCO$), 3.80 (m, 2H, $CO\underline{CH_2}COCH_3$), 4.20 (q, *J* = 17.0 Hz, 1H, $\underline{CH_2}CHNCO$), 4.29 (q, *J* = 18.1 Hz, 1H, $\underline{CH_2}CHNCO$), 5.88 (d, *J* = 6.8 Hz, 1H, $CH_2\underline{CH}NCO$), 6.44 (d, *J* = 4.6 Hz, 1H, N–C=$\underline{CH}$–CH=C–$COCH_3$), 7.17 (m, 1H, aromatic H), 7.20 (m, 1H, aromatic H), 7.33 (d, *J* = 8.3 Hz, 1H, aromatic H), 7.60 (d, *J* = 7.7 Hz, 1H, aromatic H), 8.35 (s, 1H, N–C=CH–$\underline{CH}$=C–$COCH_3$), 8.50 (s, 1H, pyrrole NH). – MS (ESI): *m/z* = 415 [M + Na]$^+$.

$C_{22}H_{20}N_2O_5$	Calcd.:	C 67.34	H 5.14 N 7.14
(392.14)	Found:	C 67.20	H 5.06 N 7.04.

(6S)-3-Acetyl-6-hydroxymethyl-4,6,7,12-tetrahydro-4-oxoindolo [2,3-a] quinolizine (**13**)

The suspension of 200 mg (0.5 mmol) of **12**, 15 ml of methanol and excess of Na_2CO_3 was stirred at room temperature for 8 h, then TLC indicated complete disappearance of **12**. After filtration and evaporation the residue was purified by chromatography ($CHCl_3$:MeOH, 30:1) to give 160 mg (90%) of **13**, as yellow needles; *m.p.* 201–202 °C. $[\alpha]_D$ = 22.2° (c = 1, MeOH). – IR (KBr): ν/cm^{-1} = 3440 (OH), 3303 (NH), 2944 and 2840 (CH, CH_2 and CH_3), 1711 (ketone C=O), 1649 (amide C=O), 1604, 1582, 1492 and 1427 (aromatic C=C), 745 (1,2-disubstituted phenyl). – ^{1}H NMR (acetone-d_6): δ/ppm = 2.60 (s, 3H, $COCH_3$), 3.14 (d, *J* = 6.8 Hz, 2H, $\underline{CH_2}CHNCO$), 3.45 (t, *J* = 9.4 Hz, 1H, $\underline{CH_2}OH$), 3.47 (t, *J* = 10.2 Hz, 1H, $\underline{CH_2}OH$), 3.54 (dd, *J* = 6.7 Hz, J = 6.0 Hz, 1H, OH), 5.56 (m, 1H, $CH_2\underline{CH}NCO$), 6.79 (d, *J* = 7.7 Hz, 1H, C=$\underline{CH}$–CH=C–CO), 7.11 (m, 1H, aromatic H), 7.27 (m, 1H, aromatic H), 7.45 (d, *J* = 8.4 Hz, 1H, aromatic H), 7.66 (d, *J* = 8.0 Hz, 1H, aromatic H), 8.08 (d, *J* = 7.8 Hz, 1H, C=CH–$\underline{CH}$=C–CO), 8.56 (s, 1H, pyrrole NH). – MS (ESI): *m/z* = 331 [M + Na]$^+$.

$C_{18}H_{16}N_2O_3$	Calcd.:	C 70.12	H 5.23 N 9.09
(308.12)	Found:	C 69.99	H 5.15 N 8.98.

(1S,3S)- and (1R,3S)-1-(-2,2-Dimethoxyethyl)-1,2,3,4-tetrahydrocarboline-3-carboxamide (**14**)

The solution of 2.00 g (9.17 mmol) of **3**, 2 ml of chloroform and 30 ml of methanol saturated with ammonia was stirred at room temperature for 10 days. Then TLC analysis indicated complete disappearance of **3**. After removal of the solvent the residue was separated by chromatography ($CHCl_3$:MeOH, 20:1) to give 1.18 g (62%) of (1*S*,3*S*)-**14** and 0.59 g (31%) of (1*R*,3*S*)-**14**, as yellow powder.

(1*S*, 3*S*)-**14**; *m.p.* 155 °C. $[\alpha]_D = -47.50°$ (c = 0.89, MeOH). –IR (KBr): ν/cm^{-1} = 3457, 3315 and 3220 (NH), 2931 and 2831 (CH, CH_2 and CH_3), 1662 (C=O), 1616, 1563, 1459 and 1420 (aromatic C=O), 1320 and 1285 (C–O–C), 745 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 1.82 (s, 1H, NH), 2.08 (m, *J* = 14.2 Hz, *J* = 7.2 Hz, 1H, $(MeO)_2CH\underline{CH_2}$), 2.10 (m, *J* = 14.2 Hz, *J* = 7.2 Hz, *J* = 2.7 Hz, 1H, $(MeO)_2CH\underline{CH_2}$), 2.79 (ddd, *J* = 16.3 Hz, *J* = 11.2 Hz, *J* = 1.9 Hz, 1H, $\underline{CH_2}CHCONH_2$), 3.24 (dd, *J* = 4.5 Hz, *J* = 1.9 Hz, 1H, $\underline{CH_2}CHCONH_2$), 3.44 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.65 (dd, *J* = 11.7 Hz, *J* = 4.6 Hz, 1H, $CH_2\underline{CH}CONH_2$), 4.32 (t, *J* = 7.3 Hz, 1H, $\underline{CH}NHCHCONH_2$), 4.67 [dd, *J* = 7.2 Hz, *J* = 2.7 Hz, 1H, $(MeO)_2\underline{CH}$], 5.67 (s, 1H, NH_2), 6.98 (s, 1H, NH_2), 7.09 (t, *J* = 7.5 Hz, 1H, aromatic H), 7.16 (t, *J* = 7.5 Hz, 1H, aromatic H), 7.32 (d, *J* = 7.8 Hz, 1H, aromatic H), 7.50 (d, *J* = 7.5 Hz, 1H, aromatic H), 8.75 (s, 1H, pyrrole NH). – MS (135 °C): *m/z* (%) = 303 (10.5) [M^+], 271 (15.6) [M^+ – MeOH], 240 (14.7) [M^+ – MeOH–OCH_3], 227 (30.5) [M^+ – MeOH-$CONH_2$], 214 (37.6) [M^+–$(MeO)_2CHCH_2$], 169 (100) [M^+–$(MeO)_2CHCH_2$–$HCONH_2$], 75 (56.0) [$(MeO)_2CH]^+$.

$C_{16}H_{21}N_3O_3$	Calcd.:	C 63.35	H 6.98	N 13.85
(303.16)	Found:	C 63.25	H 6.94	N 13.80.

(1*R*,3*S*)-**14**; *m.p.* 194–195 °C. $[\alpha]_D = -34.8°$ (c = 1.12, MeOH). – IR (KBr): ν/cm^{-1} = 3461, 3294 and 3246 (NH), 2926 and 2833 (CH, CH_2 and CH_3), 1670 (C=O), 1572 and 1434 (aromatic C=C), 1315 and 1280 (C–O–C), 751 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 1.81 (s, 1H, NH), 2.11 [dd, *J* = 5.6 Hz, *J* = 6.7 Hz, 2H, $(MeO)_2CH\underline{CH_2}$], 2.83 (dd, *J* = 9.8 Hz, *J* = 16.1 Hz, 1H, $\underline{CH_2}CHCONH_2$), 3.27 (dd, *J* = 4.9 Hz, *J* = 16.1 Hz, 1H, $\underline{CH_2}CHCONH_2$), 3.38 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.74 (dd, *J* = 4.9, *J* = 9.8 Hz, 1H, $CH_2\underline{CH}CONH_2$), 4.27 (t, *J* = 6.8 Hz, 1H, $(MeO)_2CHCH_2\underline{CH}$), 4.69 (t, *J* = 5.7 Hz, 1H, $(MeO)_2\underline{CH}$), 5.61 (s, 1H, $CONH_2$), 6.98 (s, 1H, $CONH_2$), 7.10 (t, *J* = 7.7 Hz, 1H, aromatic H), 7.17 (t, *J* = 6.6 Hz, 1H, aromatic H), 7.31 (d, *J* = 7.8 Hz, 1H, aromatic H), 7.51 (d, *J* = 7.8 Hz, 1H, aromatic H), 8.27 (s, 1H, pyrrole NH). – MS (110 °C): *m/z* (%) = 303 (27.2) [M^+], 271 (14.7) [M^+ – MeOH], 259 (37.0) [M^+ – $CONH_2$], 227 (19.1) [M^+ – MeOH–$CONH_2$], 214 (24.0) [M^+ – $(MeO)_2CHCH_2$], 169 (100) [M^+ – $(MeO)_2CHCH_2$–$HCONH_2$], 75 (12.1) [$MeOCHOMe^+$].

$C_{16}H_{21}N_3O_3$	Calcd.:	C 63.35	H 6.98	N 13.85
(303.16)	Found:	C 63.41	H 6.85	N 13.90.

(1S,3S)- and (1R,3S)-1-(2,2-Dimethoxyethyl)-2-(1,3-dioxobutyl)-1,2,3,4-tetrahydrocarboline-3-carboxamide (**15**)

a) The solution of 100 mg (0.33 mmol) of (1*S*, 3*S*)-**14** in 5 ml of acetone was treated at 0 °C with 0.04 ml (0.47 mmol) of diketene and 0.02 ml of triethylamine. The reaction mixture was stirred at room temperature for 48 h, then TLC indicated complete disappearance of (1*S*, 3*S*)-**14**. To this solution 0.02 ml of distilled water were added at 0 °C and stirred for another 0.5 h. After removal of the solvent the residue was diluted with 20 ml of $CHCl_3$ and washed with water (3× 2 ml). The organic phase was evaporated and the residue was purified by chromatography to give 95 mg (73%) of (1*S*, 3*S*)-**15**, as yellow powder; *m.p.* 146–147 °C. $[\alpha]_D = 37.3°$ (c = 2, $CHCl_3$). – IR (KBr): ν/cm^{-1} = 3322 (NH), 2932 and 2832 (CH, CH_2 and CH_3), 1678 (Ketone C=O), 1630 (amide C=O), 1429 (aromatic C=C), 1310 and 1120 (C–O–C), 745 (1,2-disubstituted phenyl). – ^{1}H NMR: δ/ppm = 2.02–2.28 (m, 2H, $(CH_3O)_2CH\underline{CH_2}$), 2.32–2.34 (m, 3H, $\underline{CH_3}COCH_2CO$), 2.85–3.02 (m, 1H, $\underline{CH_2}CHCONH_2$), 3.39 (s, 3H, OCH_3), 3.40–3.60 (m, 1H, $\underline{CH_2}CHCONH_2$], 3.45 (m, 1H, $CH_3CO\underline{CH_2}CO$), 3.47 (m, 1H, $CH_3CO\underline{CH_2}CO$), 3.55 (s, 3H, OCH_3), 3.80–3.89 (m, 1H, $CH_2\underline{CH}CONH_2$), 4.43–4.84 (m, 1H, $N\underline{CH}CH_2CH(OCH_3)_2$), 5.21–5.53 [m, 1H, $CH_2\underline{CH}(OCH_3)_2$], 5.29–5.76 (m, 1H, $CONH_2$), 6.21–6.70 (m, 1H, $CONH_2$), 7.09 (m, 1H, aromatic H), 7.15 (m, 1H, aromatic H), 7.31 (m, 1H, aromatic H), 7.50 (m, 1H, aromatic H), 8.76–8.96 (m, 1H, pyrrole NH). – MS (ESI): *m/z* (%) = 410 [M + Na]$^+$.

$C_{20}H_{25}N_3O_5$	Calcd.:	C 62.00	H 6.50	N 10.85
(387.18)	Found:	C 61.89	H 6.39	N 10.70.

b) Using procedure *a*) with (1*R*,3*S*)-**14** instead of (1*S*,3*S*)-**14** after 24 h 105 mg (82%) of (1*R*,3*S*)-**15** were obtained, as yellow powder; *m.p.* 152–153 °C. $[\alpha]_D = -12.7°$ (c = 2, $CHCl_3$). – IR (KBr): ν/cm^{-1} = 3320 (NH), 2922 and 2820 (CH, CH_2 and CH_3), 1675 (ketone C=O), 1640 (amide C=O), 1401 (aromatic C=C), 1327 and 1121 (C–O–C). – ^{1}H NMR: δ/ppm = 2.15–2.28 [m, 2H, $(CH_3O)_2CH\underline{CH_2}$], 2.28(m, 3H, $\underline{CH_3}CO$ CH_2CO), 2.40–2.56 (m, 2H, $\underline{CH_2}CHCONH_2$), 2.56–2.71 (m, 2H, $CH_3CO\underline{CH_2}CO$), 3.41 (s, 6H, $(OCH_3)_2$, 3.48–3.86 (m, 1H, $CH_2\underline{CH}CONH_2$), 4.39–4.69 (m, 1H, $(CH_3O)_2$ $CHCH_2$ $\underline{CH}N$), 5.05–5.74 (m, 1H, $(CH_3O)_2\underline{CH}CH_2$, 5.61–5.87 (m, 1H, $CONH_2$), 6.20–6.67 (m, 1H, $CONH_2$), 7.11 (m, 1H, aromatic H), 7.15 (m, 1H, aromatic H), 7.25 (m, 1H, aromatic H), 7.50 (m, 1H, aromatic H), 8.13–8.56 (m, 1H, pyrrole NH). – MS (ESI): *m/z* (%) = 410 [M + Na]$^+$.

$C_{20}H_{25}N_3O_5$	Calcd.:	C 62.00	H 6.50	N 10.85
(387.18)	Found:	C 61.96	H 6.40	N 10.65.

c) The suspension of 100 mg (0.33 mmol) of (1*S*,3*S*)-**14**, 15 ml of toluene and 60 mg (0.4 mmol) of **2**, 2,6-trimethyl-1, 3-dioxine-4-one was stirred at 100 °C for 4 h, then TLC indicated complete disappearance of (1*S*,3*S*)-**14**. After removal of the solvent the residue was purified by chromatography (ethyl acetate) to give 100 mg (78%) of (1*S*,3*S*)-**15**, as yellow powder.

d) Using procedure *c*) with (1*R*,3*S*)-**14** instead of (1*S*,3*S*)-**14** after 1 h 115 mg (90%) of (1*R*,3*S*)-**15** were obtained, as yellow powder.

(6S)-3-Acetyl-4,6,7,12-tetrahydro-4-oxoindolo[2,3-a]quinolizine-6-carboxamide (**16**)

a) The solution of 100 mg (0.26 mmol) of (1*S*,3*S*)-**15**, 5 ml of acetone and 0.02 ml of hydrochloric acid (2 mol/l) was stirred at room temperature for 1 h, then TLC indicated complete disappearance of (1*S*,3*S*)-**15**. The reaction mixture was neutralized with excess of Na_2CO_3 to adjust to pH 8. After filtration and evaporation, the residue was purified by chromatography ($CHCl_3$:MeOH, 20:1) to give 70 mg (85%) of **16**, as yellow powder.

b) Using procedure *a*) with (1*R*,3*S*)-**15** instead of (1*S*,3*S*)-**15** after 0.5 h 75 mg (91%) of **16** were obtained, as yellow powder; *m.p.* 190–191°C. $[\alpha]_D = 34.2°$ (c = 0.9, MeOH). – IR (KBr): ν/cm^{-1} = 3430, 3300 and 3219 (NH), 2914, 2902 and 2844 (CH, CH_2 and CH_3), 1710 (ketone C=O), 1678 and 1660 (amide C=O), 1583, 1546 and 1427 (aromatic C=C), 746 (1,2-disubstituted phenyl). – ^{1}H NMR (acetone-d_6): δ/ppm = 2.60 (s, 3H, $COCH_3$), 3.80 (m, 1H, $\underline{CH_2}CH$

$CONH_2$), 3.91 (m, 1H, $\underline{CH_2}CHCONH_2$), 5.75 (d, J = 6.4 Hz, 1H, $CH_2\underline{CH}CONH_2$), 6.10 (s, 1H, $CONH_2$), 6.20 (s, 1H, $CONH_2$), 6.86 (d, J = 5.4 Hz, 1H, NC=$\underline{CH}$CH=C), 7.11 (t, J = 14.0 Hz, 1H, aromatic H), 7.25 (t, J = 13.8 Hz, 1H, aromatic H), 7.46 (d, J = 7.6 Hz, 1H, aromatic H), 7.61 (d, J = 7.5 Hz, 1H, aromatic H), 8.17 (d, J = 7.9 Hz, 1H, NC=CH $\underline{CH}$=C), 8.42 (s, 1H, pyrrole NH). – MS (ESI): *m/z* (%) = 344 $[M + Na]^+$.

$C_{18}H_{15}N_3O_3$	Calcd.:	C 67.28	H 4.70	N 13.07
(321.34)	Found:	C 67.16	H 4.67	N 12.95.

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