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Asymmetric Synthesis of Indolo[2,3-*a*]quinolizidin-2-ones - Congeners to Yohimbine-Type Alkaloids

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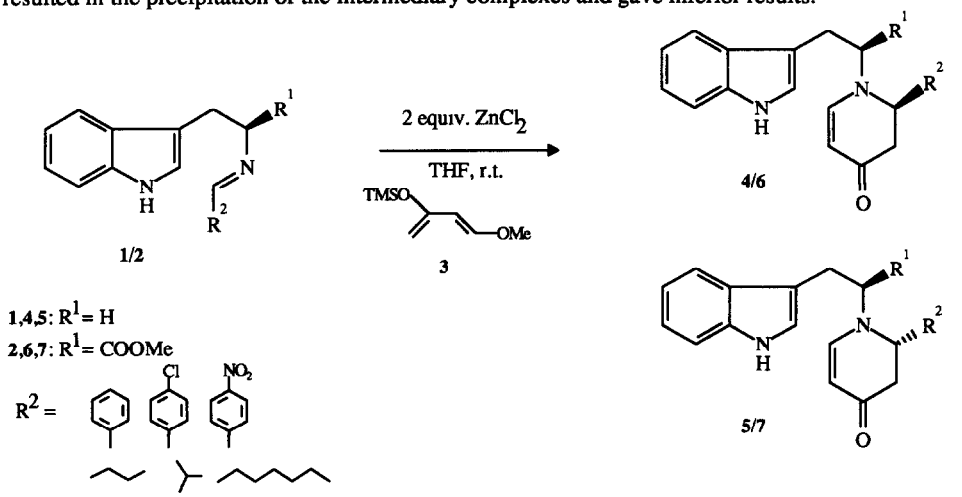
Abstract: Schiff bases derived from tryptophan methyl ester and tryptamine react with Danishefkys diene in the presence of $ZnCl_2$ to give enaminones which are subsequently transformed into indolo[2,3-*a*]quinolizidin-2-ones by acid-catalyzed cyclization. These tetracyclic aminoketones serve as viable intermediates in the construction of complex alkaloids, e. g. reserpine and deserpidine, and analogues thereof.

The construction of polycyclic indole alkaloids has attracted a widespread interest during the last decades and remains to be a challenge for the preparative chemist. In particular, the synthesis of pentacyclic indole derivatives related to yohimbine and reserpine, due to their potential pharmaceutical importance, has been the subject of intensive research efforts.[1] Consequently, several elegant routes leading to this class of natural products were developed. Among these, a particularly viable strategy consists in the synthesis and elaboration of intermediate indolo[2,3-*a*]quinolizidin-2-ones, which are accessible via several different routes,[2] but have, with one exception,[2k] only been obtained in racemic form. For instance, enaminones derived from tryptamine are viable precursors to these tetracyclic synthons.[2d,g] Conventionally, however, they are obtained from alkoxy-substituted pyridines and from pyridones in multistep procedures.[2d,3]
This paper describes a convenient access to substituted as well as unsubstituted enantiomerically homogeneous derivatives of these tetracyclic ketones and their conversion into congeners of naturally occurring alkaloids.
In previous studies we have demonstrated the potential of the Mannich-Michael reaction between amino acid ester imines and Danishefskys diene,[4] which delivers 2,3-didehydropiperidin-4-ones with high diastereoselectivity and good yields. As an extension to these studies we now report that the application of this methodology to the imines of tryptophan methyl ester and of tryptamine results directly in the formation of enaminones which are immediate precursors to the indolo[2,3-*a*]quinolizidin-2-one ring system.[5]

Synthesis of N-2-(3-Indolyl)ethyl-substituted Enaminones

In a first series of experiments, the 2-(3-indolyl)ethyl-substituted imines **1** were easily obtained in 80-95% yield from tryptamine and the respective aldehyde by treatment with $MgSO_4$ in ether/methylene dichloride (1:1 [v/v]). They were characterized by NMR spectral data and immediately reacted with Danishefskys diene **3** in the presence of 2 equivalents of $ZnCl_2$ at -20°C to 0°C in THF to give the enaminones **4/5** in yields of 40 to 79% (Scheme 1, Table 1). With 1 equivalent of this Lewis acid, the reactions were unexpectedly slow.

The use of alkylaluminum halides as promotors in CH_2Cl_2 at lower temperatures, i.e. conditions which proved to be the most advantageous with valine ester and isoleucine ester imines,[4] in the majority of the cases resulted in the precipitation of the intermediary complexes and gave inferior results.



Scheme 1

As can be seen in Table 1, the aromatic aldehydes deliver the desired enaminones **4/5** in considerably higher yields than the aliphatic carbonyl compounds.

If tryptophan methyl ester was used as the amine compound in this reaction sequence, the optically active vinylogous amides **6** and **7** were formed. To this end, the imines **2** were treated with 2 equivalents of $ZnCl_2$ in tetrahydrofuran at -20°C to 0°C, too, delivering the enaminones **6** and **7** in 45-73% yield after flash chromatography (Scheme 1, Table 2). As expected for ß-unbranched amino acid esters like tryptophan esters, the diastereomeric ratio observed for the Mannich-Michael reaction is substantially lower than e.g. for valine esters as chiral mediators and ranges from 2:1 for the aromatic up to 5:1 for the aliphatic derivatives. Again, for aromatic aldehydes the yields show the same tendency already observed for the tryptamine-derived imines. The absolute configuration of the major diastereomers **7** was determined for **7a** by NMR-

Table 1. Synthesis of the enaminones **4/5** and the indolo[2,3-*a*]quinolizidin-2-ones **8/9**.

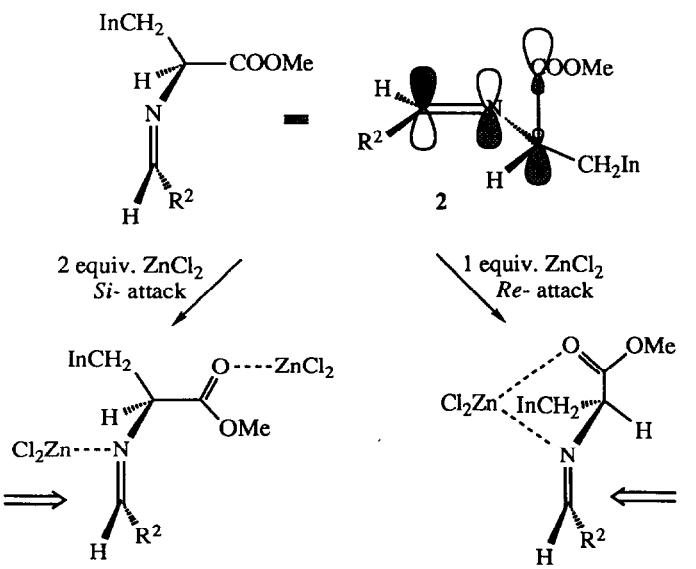
4/5	R	mp [°C]	yield [%]	**8/9**	R	mp [°C]	yield [%]	trans:cis (**8**:**9**)
a	nPr	156	49	**a**	nPr	178	85	80:20
b	iPr	136	41	**b**	iPr	172	63	82:18
c	nHept	144	40	**c**	nHept	oil	35	79:21
d	Ph	132	78	**d**	Ph	230	84	86:14
e	4-Cl-Ph	176	79	**e**	4-Cl-Ph	242	47	80:20
f	4-NO_2Ph	212	43	**f**	4-NO_2Ph	270	56	82:18

Table 2: Synthesis of the enaminones **6/7** and the indolo[2,3-*a*]quinolizidin-2-ones **10/11**.

6/7	R	$[\alpha]_D$[a)] [°]	mp [°C]	yield [%]	7:6	10/11	R	$[\alpha]_D$[a)] [°]	mp [°C]	yield [%]	trans:cis (10:11)
a	nPr	-230.5	oil	55	83:17	**a**	nPr	92.7	192	62	88:12
b	iPr	-153.4	oil	55	85:15	**b**	iPr	117.2	oil	68	94:6
c	C_9H_{18}	-121.8	oil	45	82:18	**c**	C_9H_{18}	94.3	oil	35	95:5
d	Ph	67.4	151	68	70:30	**d**	Ph	24.1	220	61	>95:5
e	4-Cl-Ph	85.6	179	73	66:34	**e**	4-Cl-Ph	41.9	250	56	>95:5
f	4-NO_2-Ph	73.2	198	46	66:34	**f**	4-NO_2-Ph	28.3	245	55	>95:5

a) c= 1, CH_2Cl_2.

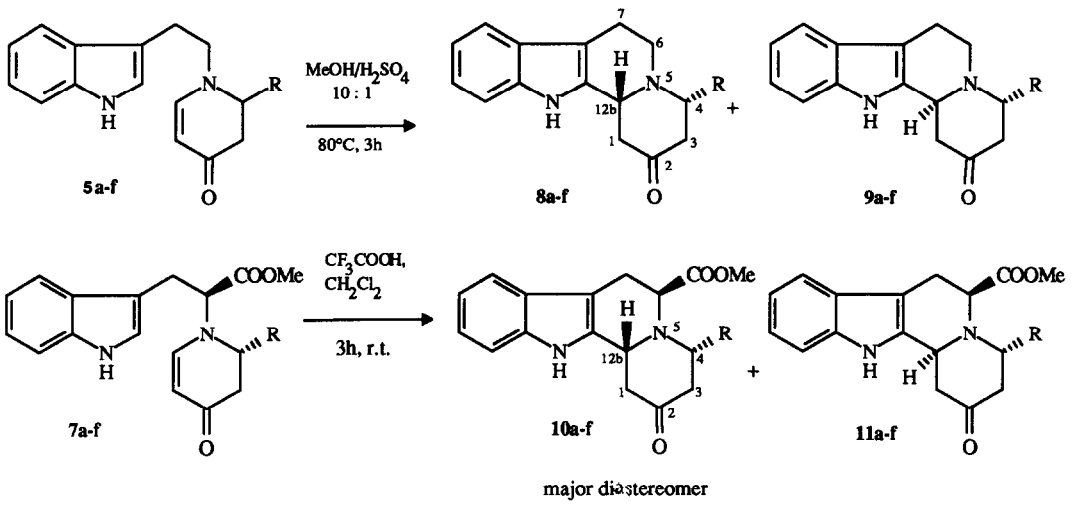
techniques after cyclization to the indolo[2,3-*a*]quinolizidinones (vide infra). It should be noted that the sense of the asymmetric induction in this transformation is opposite to the results obtained in the reactions of valine and isoleucine esters with the diene **3** in the presence of 1 equivalent of $ZnCl_2$.[4)] It was postulated that under these conditions a cis-configured imine complex is formed in which the Zn^{2+}-cation is chelated by the imine nitrogen and the ester carbonyl group [4)] In the presence of 2 equivalents of $ZnCl_2$, however, both the C=O- and the C=N group are complexed by a separate metal cation (Scheme 2). In the resulting intermediate the α-C-COOR bond, in analogy to the Felkin-Anh model[6)] for nucleophilic attack on carbonyl groups, is oriented perpendicular to the imine double bond, thus creating a parallel orientation of the σ* orbital of the α-C-COOR-bond and the π*- orbital of the C=N bond. The silylenol ether present in **3** then attacks **2** preferably from the *Si*-side and the isomers **7** are formed in excess. This hypothesis is confirmed by the observation, that the application of two equivalents of $ZnCl_2$ in the case of isoleucine ester imines does reverse the sense of the stereoselection, too.[4b)]



Scheme 2

Cyclization of the Enaminones to Indolo[2,3-*a*]quinolizidin-2-ones

Treatment of the vinylogous amides **5** with dilute sulfuric acid in aqueous methanol at 80°C[3a] resulted in a cyclization reaction in which the indolo[2,3-*a*]quinolizidinones **8** and **9** were formed in moderate to high yield and with a trans/cis ratio of 4-5:1 (Scheme 3, Table 1). All attempts to induce the cyclization by treatment with Lewis acids like BF_3·Et_2O and $EtAlCl_2$ were unsuccessful. The trans isomers **8** and the cis isomers **9** were readily separated by flash chromatography. The relative configuration of the predominating trans-quinolizidinones **8** was ascertained by NMR- and IR spectroscopy. Thus, the IR spectra showed characteristic Bohlmann bands[7] at ν= 2700- 2850 cm^{-1} and a strong NOE signal enhancement was detected between the respective 4-H, 6-H_a and 12b-H.



Scheme 3

Similarly, the vinylogous amide **7a** was subjected to the acid catalyzed cyclization, but to our surprise failed to undergo this reaction under the same conditions. However, if trifluoroacetic acid was employed, the ring closure of the enaminones **7a-f** to the tetracyclic nitrogen bases **10** and **11** occurred smoothly already at room temperature (Table 2, Scheme 3). Alternatively, trifluoroacetic acid anhydride could be used as the initiating electrophile with comparable results. Remarkably, under these mild conditions the products are formed with higher selectivities and less byproducts. In particular, with the enaminones of aromatic aldehydes only one stereoisomer could be detected. The absolute configuration of the predominating diastereomers **10** was again ascertained by means of NOE-difference spectra (see Figure 1). Thus, NOE signal enhancements were observed between the respective 12b-H and 4-H and also the 6-H proved to be in the vicinity of the substituent "R". However, in neither case could an NOE effect be detected between 6-H and 4-H or 6-H and 12b-H. In addition, the trans-quinolizidin-2-ones **10** showed Bohlmann bands in the IR spectra. The preferred formation of the trans-fused systems under the reaction conditions is in accordance with the expectations for the outcome of a ring closure under thermodynamic control,[8] i. e. it represents the high

stability of the trans-arrangement of the substituents at C-6 and C-12b of ring C and a reduction of an $A^{1,2}$ strain in the isomers **10** as compared to the cis isomers **11**.

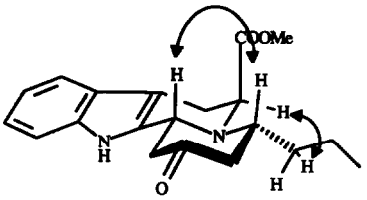
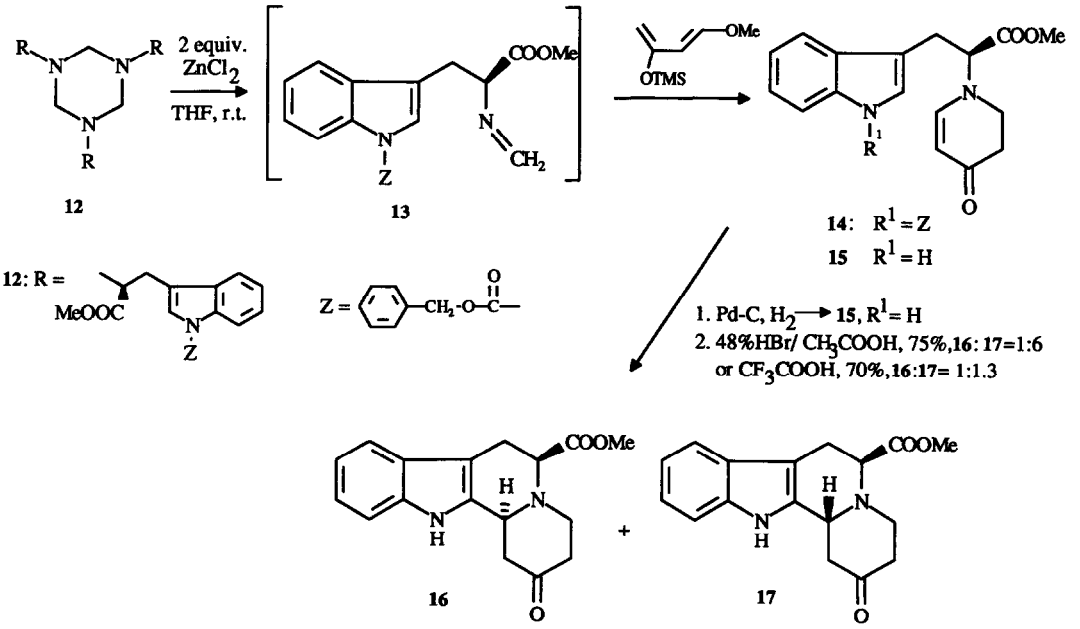


Figure 1: NOE-signal enhancements detected for **10a**

Synthesis of Congeners to Naturally Occurring Indole Alkaloids

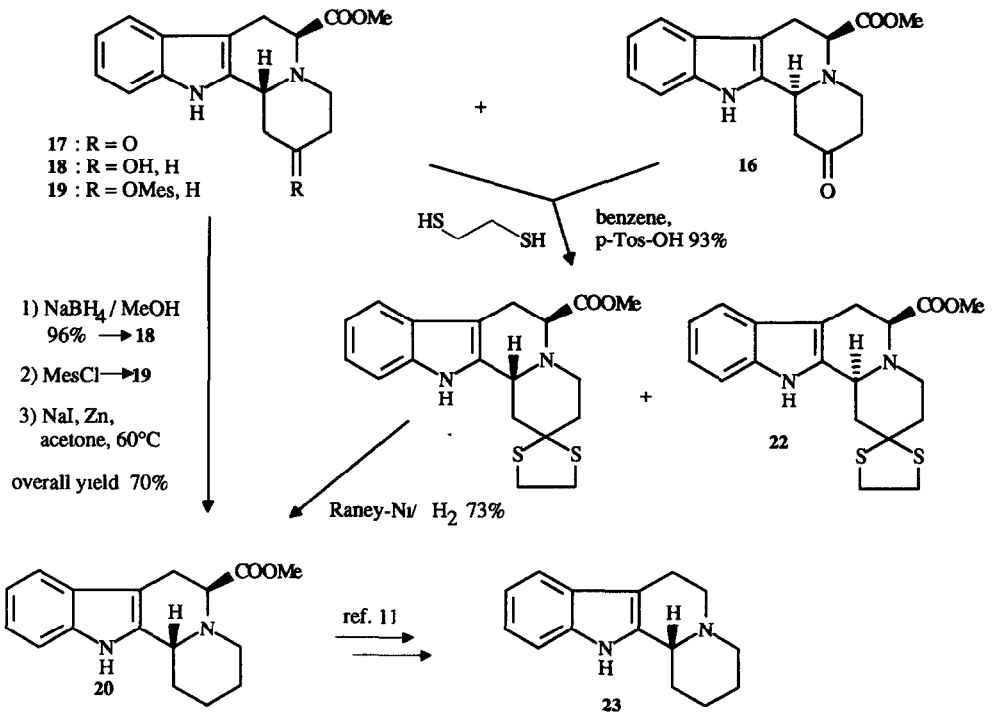
The tetracyclic ketones **10** and **11** may be of interest as precursors of analogues to naturally occurring alkaloids. However, the substitutent at C-4 does not find an analogy in a specific natural product. For the construction of alkaloids the enaminone **15** bearing no further substituent at C-4 has to be built up as an intermediate (Scheme 4).



Scheme 4

To this end, the formaldimine **13** was generated *in situ* from the hexahydrotriazine **12** by treatment with $ZnCl_2$ and immediately reacted with Danishefskys diene to deliver the desired enaminone **14** in satisfactory yield (Scheme 4). The triazine **12** which is readily available from N^{ind}-Z-protected tryptophan methyl ester and formaldehyde[9] has to be addressed as a trimer of the monomeric aldimine **13**. To overcome problems in both the formation of the triazines and the subsequent tandem Mannich-Michael reaction, the indole nitrogen

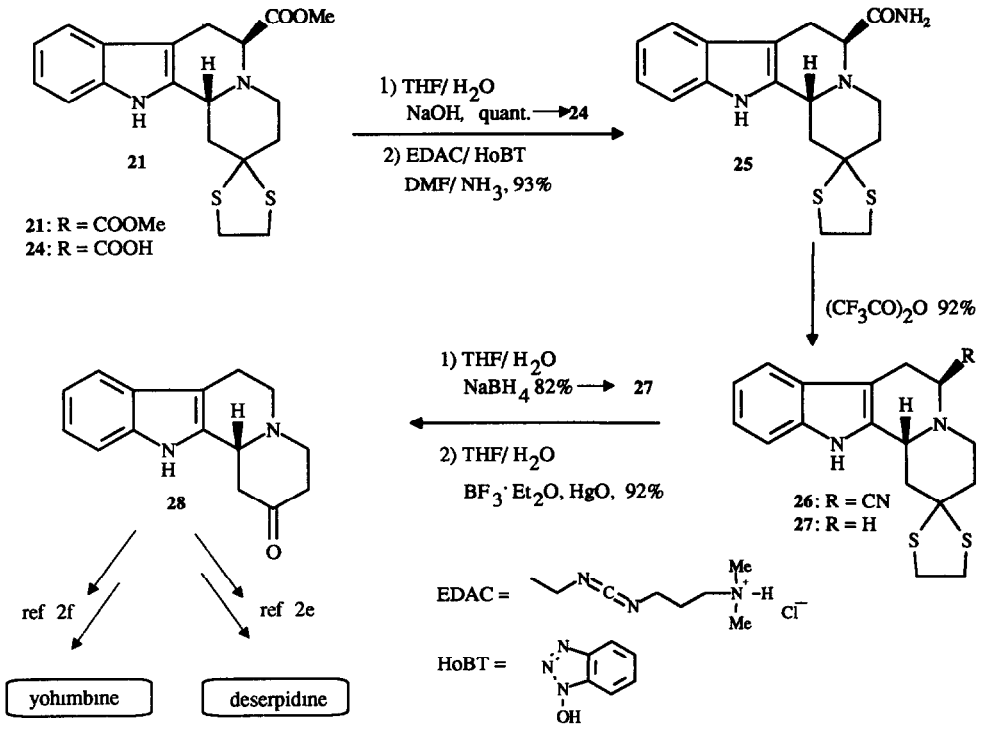
had to be protected as a benzyl urethane.[10] However, in the presence of this electron-withdrawing blocking function, the cyclization to the tetracyclic ketones could not be initiated. Only after hydrogenolytic removal of the urethane moiety (**14** ->**15**) did treatment with acid give the desired products **16** and **17**. Whereas after treatment with trifluoroacetic acid nearly equal amounts of the trans- and the cis-isomer were found (**16**:**17**= 1:1.3), the cyclization using a solution of 48% HBr in acetic acid induced the preferred formation of the trans-isomer **17** (trans:cis = 6-7:1) in 75% combined yield. The role of the nature of the acid has not been investigated in detail. Nevertheless, it appears that also in the presence of the stronger acid HBr initially the cis and the trans quinolizidinones may be formed with a lower selectivity and that they subsequently are rapidly converted to the mixture which represents the relative thermodynamical stabilities of the products.



Scheme 5

The indolo[2,3-*a*]quinolizidin-2-ones can advantageously be applied as precursors to complex alkaloids. To demonstrate this, in a first approach, the ketone **17** was converted to the tetracyclic amino acid ester **20** which has already been transformed to the naturally occurring, yet unnamed nitrogen base[11] **23** (Scheme 5). To effect the required deoxygenation of the keto function, the carbonyl group was first reduced to the alcohol **18**, which was not further characterized but in a one-pot-procedure immediately converted to the mesylate **19**. This compound was treated with NaI/Zn in acetone to deliver the amine **20** in 70% overall yield. Alternatively, the mixture of the ketones **16** and **17** may be converted to the thioacetals **21** and **22**. A prior separation of **16** and **17** is not indicated, since during the thioketalization step partial epimerization at C-12b is observed, and since **21** and **22** are easily separated by flash chromatography at this stage. Whereas

the desulfurization of **22** surprisingly only lead to unidentified decomposition products, the trans-thioketal **21** was converted smoothly to the ester **20** upon treatment with Raney nickel and hydrogen.



Scheme 6

The specific rotation observed for **20** ($[\alpha]_D^{23} = 97°$(c= 1.0, MeOH)) is in perfect agreement with literature data (ref. [11]:$[\alpha]_D^{23} = 97°$ (c= 1.0, MeOH)). It thereby proves the absolute configuration of **17** and demonstrates that the tandem Mannich-Michael reaction of the tryptophan methyl ester-derived imines with the Danishefsky diene proceeds without noticeable racemization.

In a second approach, which is more important in the light of a general applicability of indolo[2,3-*a*]quinolizidin-2-ones, the methoxycarbonyl group was removed from the tetracyclic framework present in **17**, leaving the 2-keto group intact, since this carbonyl function may be used as a handle for the attachment of further substituents and/or rings. To this end, the ester **21** was saponified to the carboxylic acid **24** (Scheme 6). Subsequent treatment of **24** with $POCl_3$ and $NaBH_4$ as described by Rappoport et al.[11] resulted in the total decomposition of the starting material. However, the application of Yamadas method[12] for decarboxylation was successful. It consists in the transformation of the amino acid into an α-amino nitrile and its treatment with $NaBH_4$, i.e. the use of a retro-Strecker reaction followed by the reduction of the iminium species generated thereby. Thus, the carboxylic acid **24** was converted to the amide **25** using a water

soluble carbodiimide and N-hydroxybenzotriazole (HoBt)[13] as activating reagents (Scheme 6). All attempts to synthesize the amide **25** from the ester directly either by treatment with NH_3/ MeOH or by using a procedure developed by Weinreb et al.[14] were not successful. The amide **25** was subsequently dehydrated to the nitrile **26** by employing trifluoracetic acid anhydride in the presence of pyridine.[15] Heating of the resulting compound **26** in THF/pyridine and a fourfold excess of $NaBH_4$, resulted in the removal of the former amino acid carboxyl group (->**27**). Finally, the dithiane protecting group of **27** was cleaved by treating the thioketal with 2 equiv. of $BF_3{\cdot}Et_2O$ and HgO in aqueous THF to deliver the indolo[2,3-*a*]quionlizidin-2-one **28** in optically active form. Its enantiomeric purity was determined to be ca. 75-80% by HPLC using a chiral stationary phase (ChiraDex, Merck AG, Darmstadt, Germany; see the Experimental Part). Since **21** had been obtained in enantiomerically pure form (vide supra; Scheme 5), most probably the partial racemization occurred during the regeneration of the keto group from the dithiane, e. g. by acid-catalyzed ring-opening/ring closure. The racemic ketone *rac*-**28** has previously been used for the construction of yohimbine by Kametani et al.[2f], for the synthesis of deserpidine, the des-methoxy-analogue of reserpine, by Szantay et al.[2e] and, recently, for the construction of various yohimbine isomers by Kuehne et al.[2h] Therefore, the first synthesis of optically active **28** described here, constitutes a formal total synthesis of these natural products in nonracemic form.

In conclusion, the method presented in this paper makes indolo[2,3-*a*]quinolizidin-2-ones, which are congeners to naturally occurring complex indole alkaloids and analogues thereof, available by a straightforward procedure. Since numerous derivatives of the employed silyloxy dienes are accessible, various tetracyclic nitrogen bases with related structures may be constructed in this manner, too. Work along these lines is in progress.

EXPERIMENTAL

General materials and methods were already described.[4] All specific rotations were measured at 23°C.

General Procedure for the Preparation of the Imines **1** and **2**

To a solution of 1 mmol of the amino acid ester or of tryptamine in 50 ml of CH_2Cl_2/diethyl ether 3:1 (v/v), 1 mmol of the respective aldehyde was added. The solution was stirred until water separated, and after addition of $MgSO_4$ stirring was continued for another 15 min. Filtration and washing of the residue with CH_2Cl_2 followed by evaporation of the solvent *in vacuo* afforded the imines as yellowish oils, which in the cases of aromatic aldehydes frequently crystallize. The Schiff bases were directly used in the tandem Mannich-Michael reaction without further purification or characterization.

General Procedure for the Preparation of the 2,3 Didehydro-piperidin-4-ones **4**/**5** and **7**

To a solution of 1 mmol of the respective imine in 50 ml of THF was added 2 ml of a 1M solution of $ZnCl_2$ in THF/CH_2Cl_2 (1:1 [v/v]). After addition of 0.25 ml (1.3 mmol) of 1-methoxy-3-trimethylsilyloxy-butadiene **3** the reaction mixture was kept at room temperature overnight. It was poured on saturated solution of $NaHCO_3$, and the aqueous phase was carefully extracted twice with 70 ml of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$. After filtration, 1 g of silica gel was added and the solvent was removed *in vacuo*. The remaining silica gel, onto which the reaction mixture had been absorbed by this

procedure, was then used for flash chromatography with petroleum ether/acetone mixtures (2-1:1, [v/v]) to deliver the desired products as yellow crystals .
According to this protocol the following compounds were prepared. For yields, diatereomer ratios and physical data see Tables 1, 2, 3 and 4
N-[2-(Indol-3-yl)ethyl]-2,3- didehydro-4-oxo-6-n-propyl piperidine (**5a**)
N-[2-(Indol-3-yl)ethyl]-2,3- didehydro-4-oxo-6-iso-propyl piperidine (**5b**)
N-[2-(Indol-3-yl)ethyl]-2,3- didehydro-4-oxo-6-n-heptyl piperidine (**5c**)
N-[2-(Indol-3-yl)ethyl]-2,3- didehydro-4-oxo-6-phenyl piperidine (**5d**)
N-[2-(Indol-3-yl)ethyl]-2,3- didehydro-4-oxo-6-[p-chlorphenyl] piperidine (**5e**)
N-[2-(Indol-3-yl)ethyl]-2,3- didehydro-4-oxo-6-[p-nitrophenyl] piperidine (**5f**)

5a	$C_{18}H_{22}N_2O$ (282.4)	Calcd: C: 76.84	H: 7.52	N: 9.96	
		Found: C: 76.50	H: 7.53	N: 9.60	
5b	$C_{18}H_{22}N_2O$ (282.4)	Calcd: C: 76.84	H: 7.52	N: 9.96	
		Found: C: 76.54	H: 7.57	N: 9.45	
5c	$C_{22}H_{30}N_2O$ (338.5)	Calcd: C: 78.30	H: 8.66	N: 8.30	
		Found: C: 77.96	H: 8.70	N: 8.26	
5d	$C_{21}H_{20}N_2O$ (338.5)	Calcd: C: 79.97	H: 6.07	N: 8.88	
		Found: C: 79.57	H: 6.53	N: 9.09	
5e	$C_{21}H_{19}N_2OCl$ (350.9)	Calcd: C: 71.89	H: 5.46	N: 7.98	Cl: 10.10
		Found: C: 71.74	H: 5.31	N: 8.06	Cl: 10.20
5f	$C_{21}H_{19}N_3O_3$ (361.4)	Calcd: C: 69.79	H: 5.30	N: 11.60	
		Found: C: 69.82	H: 5.52	N: 10.93	

N-((*S*)-2-Carboxymethyl-2-[indol-3-yl] ethyl)-(6*S*)-2,3-didehydro-4-oxo-6-n-propyl piperidine (**7a**)
N-((*S*)-2-Carboxymethyl-2-[indol-3-yl] ethyl)-(6*S*)-2,3-didehydro-4-oxo-6-i-propyl piperidine (**7b**)
N-((*S*)-2-Carboxymethyl-2-[indol-3-yl] ethyl)-(6*S*)-2,3-didehydro-4-oxo-6-n-nonyl piperidine (**7c**)
N-((*S*)-2-Carboxymethyl-2-[indol-3-yl] ethyl)-(6*R*)-2,3-didehydro-4-oxo-6-phenyl piperidine (**7d**)
N-((*S*)-2-Carboxymethyl-2-[indol-3-yl] ethyl)-(6*R*)-2,3-didehydro-4-oxo-6-[p-chlorophenyl] piperidine (**7e**)
N-((*S*)-2-Carboxymethyl-2-[indol-3-yl] ethyl)-(6*R*)-2,3-didehydro-4-oxo-6-[p-nitrophenyl] piperidine (**7f**)

7a	$C_{20}H_{24}N_2O_3$ (340.4)	Calcd: C: 70.57	H: 7.11	N: 8.23	
		Found: C: 70.82	H: 7.40	N: 8.43	
7b	$C_{20}H_{24}N_2O_3$ (340.4)	Calcd: C: 70.57	H: 7.11	N: 8.23	
		Found: C: 70.71	H: 7.00	N: 8.60	
7c	$C_{26}H_{36}N_2O_3$ (424.5)	Calcd: C: 73.65	H: 8.55	N: 6.60	
		Found: C: 73.39	H: 8.83	N: 6.54	
7d	$C_{23}H_{22}O_3N_2$ (374.4)	Calcd: C: 73.78	H: 5.92	N: 7.48	
		Found: C: 73.85	H: 6.06	N: 7.52	
7e	$C_{23}H_{21}O_3N_2Cl$ (408.9)	Calcd: C: 67.56	H: 5.18	N: 6.85	Cl: 8.67
		Found: C: 67.90	H: 5.53	N: 7.12	Cl: 8.96
7f	$C_{23}H_{21}O_5N_3$ (419.4)	Calcd: C: 65.86	H: 5.05	N: 10.02	
		Found: C: 65.30	H: 5.12	N: 9.93	

General Procedure for the Cyclization of N-[2-(Indol-3-yl)ethyl]-2,3-didehydro-piperidin-2-ones **8** and **9**.
To a solution of 1 mmol of the N-[2-(Indol-3-yl)ethyl]-2,3-didehydro-piperidin-2-one in 20 ml of methanol 5 ml of a 10% solution of H_2SO_4 in water were added and the reaction mixture was heated to reflux until tlc monitoring indicated that the conversion was complete (ca. 2h). The methanol was removed *in vacuo*, the residue taken up in 10 ml of water and the pH was adjusted to 12. The mixture was extracted twice with 70

Table 3: ^{1}H- and ^{13}C-NMR data of the racemic enaminones **5a-f** (δ [ppm], multiplicity, J [Hz]).

5	N-H	In 4-H	IIn 7-	In 6-H	In 5-H	In 2-H	2-H	3-H	7-H_a	7-H_b	6-H	8-H_a	8-H_b	5-H_a	5-H_b	R
a	9.3, s	7.5, d, 7.8	7.3, d, 8.1	7.1, m	7.1, m	7.0, s	6.7, d, 7.4	4.8, d	3.5, m	3.5, m	3.3, m	3.0, m	3.0, m	2.6, m	2.2, m	1.3, m, $2CH_2$; 0.8, CH_3
b	9.0, s	7.5, d, 7.8	7.3, d, 8.1	7.2, d	7.1, d	6.9, s	6.7, d, 7.2	4.8, d	3.5, m	3.5, m	3.1, m	3.0, m	3.0, m	2.6, m	2.3, m	2.2, m, β–H; 0.8,CH_3
c	8.9, s	7.5, d, 7.8	7.4, d, 8.1	7.2, d	7.1, d	7.0, s	6.7, d, 7.2	4.8, d	3.5, m	3.5, m	3.3, m	3.0, m	3.0, m	2.6, m	2.2, m	1.6, m, 2H; 1.2, m 10H; 0.8, m CH_3
d	10.9, s	7.3, m	7.3, m	7.1, t	6.9, t	7.2, s	7.3, m	4.6, d, 7.6	3.2, m	3.2, m	4.8, m	2.9, m	2.9, m	2.7, dd, 7, 16.2	2.2, dd 6.7	7.3, m, 5H, Ph
e	10.9, s	7.4, m	7.4, m	7.0, t	6.9, t	7.2, s	7.4, m	4.6, d, 7.5	3.6, m	3.2, m	4.8, dd, 6.4, 6.6	2.9, m	2.9, m	2.7, dd, 6.6, 16	2.3, dd 6.7	7.3, m, 4H, Ph
f	10.9, s	7.35, d,7.6	7.4, m	7.0, t	6.9, t	7.3, s	7.4, d, 7.7	4.7, d, 7.6	3.6, m	3.3, m	5.0, m	3.0, m	3.0, m	2.6, dd, 4.7, 16	2.3, dd 6.7	8.2, d, 8.0, 7.5, Ph

5	C=O	C-2	InC-7a	InC-3a	InC-2	InC-5	InC-4	InC-6	InC-7	InC-3	C-3	C-6	C-7	C-5	C-8	R
a	190.6	157.7	136.5	126.7	122.9	121.9	119.2	118.9	111.6	111.0	95.9	56.4	54.4	39.1	31.1	26.3, 18.7, 13.8
b	191.2	153.4	136.2	126.6	123.1	122.0	119.4	118.0	111.7	111.0	96.3	67.1	55.4	36.4	28.8	26.4, 19.6, 18.1
c	190.6	152.7	136.5	126.7	123.1	122.1	119.4	118.1	111.6	111.3	96.1	56.7	54.5	39.3	31.7	29.4, 29.1, 29.0, 26.4, 25.6, 22.6, 14.1
d	188.0	154.2	136.2	126.9	123.3	120.9	118.2	118.1	111.4	110.5	96.5	59.3	53.6	43.2	24.7	139.1 (C-ipso), 128.7, 127.5
e	187.8	154.2	136.2	126.9	123.3	121.0	118.2	118.1	111.4	110.5	96.6	58.6	53.7	43.0	24.7	147.1(CCl),138.1 (C-ipso), 128.7, 128.5
f	187.3	154.1	136.2	126.9	123.4	121.0	118.2	118.1	111.4	110.4	96.6	58.6	54.0	42.0	24.7	147 (CNO_2), 138.7 (C-ipso),128.0, 123.7

Table 4: ^{1}H- and ^{13}C-NMR data of the enantiomerically pure enaminones **7a-f** (δ [ppm], multiplicity, J [Hz]).

7	N-H	In 4-H	In 7-H	In 6-H	In 5-H	In 2-H	2-H	3-H	7-H	OCH_3	6-H	8-H_a	8-H_b	5-H_a	5-H_b	R
a	8.7, s	7.55, d, 7.8	7.35, d, 8.0	7.2, m	7.2, m	7.0, s	7.2, m	5.0, d, 7.6	4.2, m	3.7, s	3.4, m	3.5, dd, 15.1	3.2, dd	2.7, dd, 7.8, 16	2.2, dd 5.2	1.4, m; 1.05, m, $2CH_2$, 0.6, CH_3
b	8.9, s	7.55, d, 7.9	7.35, d, 8.1	7.2, m	7.2, m	7.0, s	7.27, d, 7.6	5.0, d	4.2, dd 7.7, 7.8	3.7, s	3.4, m	3.5, dd, 7.5,15.2	3.4, m	2.6, dd, 8, 15.6	2.3, dd 3.2	1.8, m, β–H; 0.76, 0.55, CH_3
c	8.7, s	7.36, d, 8.1	7.2, m	7.2, m	7.1, m	6.9, d 2.3	7.55, d, 7.8	4.8, dd 0.4, 8	4.2, dd 6.2, 8.7	3.7, s	3.2, m	3.5, dd 6.6,15.4	3.1, dd 7.1	2.7, dd 6.9, 16	2.2, dd 6.4	1.5-0.9, m, 19H
d	8.7, s	7.3, m	7.3, m	7.1, m	6.9, m	7.2, s	7.5, m	5.2, dd 7.9, 7	4.0, m	3.7, s	4.6, dd 6.2, 12	3.4, dd, 7.6,13.6	3.1, dd 11.2	2.7, dd, 8, 16.2	1.9, dd 5.6	7.5-7.2, m, 5H, Ph
e	8.8, s	7.4, m	7.4, m	7.0, m	6.5, m	7.2, s	7.5, m	5.2, d 7.9,	3.9, m	3.7, s	4.6, dd, 7.9, 9.9	3.4, dd 7.6, 14	3.1, dd 10.6	2.6, dd, 6, 15.8	2.4, dd 7.2	7.5-7.1, m, 4H, Ph
f	10.9, s	7.4, d, 7.6	7.4, m	7.0, m	6.9, m	7.3, s	7.4, m	4.9, m	4.2, m	3.6, s	4.6, dd 5.9, 9.4	3.4, m	3.3, m	2.6, dd, 7.8, 14	2.3, dd 8.9	8.2, d, 8.0, 7.5, Ph

7	C-4	C=O	C-2	InC7a	InC3a	InC-2	InC-5	InC-4	InC-6	InC-7	C-8a	C-3	C-7	C-6	OCH_3	C-5	C-8	R
a	191.3	171.4	149.0	136.2	126.7	123.0	122.3	119.7	117.9	111.6	109.4	98.2	64.6	58.1	52.4	39.2	31.4	26.7, 18.7, 13.8
b	191.7	171.6	149.1	136.3	126.7	123.6	122.3	119.2	117.9	111.5	109.4	98.2	64.5	63.7	52.4	35.6	26.3	29.3, 19.1, 16.3
c	191.2	171.6	148.7	136.3	126.7	123.3	122.3	119.7	117.8	111.6	109.4	98.4	64.5	58.3	52.5	39.1	31.7	29.9, 29.7, 29.6, 29.3, 29.1, 25.6, 22.6, 14.1
d	190.6	171.3	151.1	136.1	126.4	123.3	122.1	119.4	118.1	111.3	109.6	100. 7	64.4	63.1	52.4	39.1	31.1	137.9 (C-ipso),128.8, 128.3 127.5 (Ph)
e	191.0	171.1	151.0	136.2	126.8	123.3	122.3	119.6	118.0	111.4	109.5	100. 8	63.7	63.0	52.4	44.1	26.7	136.3 (CCl),134.1(C-ipso),128.7,128.5(Ph)
f	188.1	170.9	151.4	136.2	126.7	124.4	123.0	120.9	118.3	111.4	108.5	98.4	63.8	59.6	52.2	42.4	25.4	147.0 (CNO_2), 146.0 (C-ipso),127.6, 126.7

ml of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and the product mixture was absorbed onto silica gel and purified by flash chromatography with petroleum ether/ acetone (4-5:1 [v/v]). According to this protocol the following compounds were prepared. For yields, diastereomer ratios and physical data see Tables 1 and 5

1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-4-n-propyl quinolizine (**8a**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-4-i-propyl quinolizine (**8b**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-4-n-heptyl quinolizine (**8c**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-4-phenyl quinolizine (**8d**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-4-(p-chlorophenyl) quinolizine (**8e**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-4-(p-nitrophenyl) quinolizine (**8f**)

8a	$C_{18}H_{22}N_2O$ (282.4)	Calcd: C: 76.84	H: 7.52	N: 9.96	
		Found: C: 76.54	H: 7.63	N: 9.99	
8b	$C_{18}H_{22}N_2O$ (282.3)	Calcd: C: 76.84	H: 7.52	N: 9.96	
		Found: C: 76.82	H: 7.48	N: 9.89	
8c	$C_{22}H_{30}N_2O$ (338.5)	Calcd: C: 78.30	H: 8.66	N: 8.30	
		Found: C: 78.24	H: 8.73	N: 8.41	
8d	$C_{21}H_{20}N_2O$ (316.4)	Calcd: C: 79.72	H: 6.37	N: 8.85	
		Found: C: 79.25	H: 6.25	N: 9.06	
8e	$C_{21}H_{20}N_2OCl$ (350.8)	Calcd: C: 72.89	H: 5.46	N: 8.01	Cl: 10.10
		Found: C: 72.48	H: 5.44	N: 8.39	Cl: 10.20
8f	$C_{21}H_{19}N_3O_3$ (361.4)	Calcd: C: 69.79	H: 5.30	N: 11.60	
		Found: C: 69.54	H: 5.38	N: 11.21	

General Procedure for the Cyclization of Optically Active N-[2-(Indol-3-yl)ethyl]-2,3-didehydro-piperidin-2-ones **10**

A solution of 3 mmol of the enantiomerically pure enaminone **7** in a mixture of 2 ml of CH_2Cl_2 and 10 ml of trifluoroacetic acid was stirred at room temperature until tlc-monitoring indicated complete conversion (2-3h). The solvent was removed in vacuo and the residue taken up in 10 ml of water. The pH was adjusted to 12 and the products were isolated as described for **8**.

According to this protocol the following compounds were prepared. For yields, diastereomer ratios and physical data see Tables 2 and 6
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(4*R*,6*S*,12b*R*)-6-carboxymethyl-4-n-propyl quinolizine (**10a**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(4*R*,6*S*,12b*R*)-6-carboxymethyl-4-i-propyl quinolizine (**10b**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(4*R*,6*S*,12b*R*)-6-carboxymethyl-4-n-nonyl quinolizine (**10c**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(4*S*,6*S*,12b*R*)-6-carboxymethyl-4-phenyl quinolizine (**10d**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(4*R*,6*S*,12b*R*)-6-carboxymethyl-4-[p-chlorophenyl] quinolizine (**10e**)
1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(4*R*,6*S*,12b*R*)-6-carboxymethyl-4-[p-nitrophenyl] quinolizine (**10f**)

10a	$C_{18}H_{22}N_2O$ (282.4)	Calcd: C: 76.84	H: 7.52	N: 9.96
		Found: C: 76.81	H: 7.64	N: 9.87

10b	$C_{18}H_{22}N_2O$ (282.4)	Calcd: C: 76.84	H: 7.52	N: 9.96	
		Found: C: 76.82	H: 7.48	N: 9.89	
10c	$C_{26}H_{36}N_2O_3$ (424.5)	Calcd: C: 73.65	H: 8.55	N: 6.60	
		Found: C: 73.41	H: 8.70	N: 6.42	
10d	$C_{23}H_{22}O_3N_2$ (374.4)	Calcd: C: 73.78	H: 5.92	N: 7.48	
		Found: C: 73.77	H: 5.99	N: 7.48	
10e	$C_{23}H_{21}O_3N_2Cl$ (408.9)	Calcd: C: 67.56	H: 5.18	N: 6.85	Cl: 8.67
		Found: C: 67.23	H: 5.30	N: 6.57	Cl: 8.80
10f	$C_{23}H_{21}O_5N_3$ (419.4)	Calcd: C: 65.86	H: 5.05	N: 10.02	
		Found: C: 65.29	H: 5.35	N: 9.63	

General Procedure for the Synthesis of the Unsubstituted Indolo[2,3-*a*]quinolizidin-2-one **14**

A solution of 10 mmol of the N-benzyloxycarbonyl protected tryptophan methylester in 70 ml of CH_2Cl_2 was stirred vigorously and a solution of 10 mmol of formaldehyde in 20 ml of water were added. After 1h the reaction mixture was poured into a speration funnel and the organic phase was collected, dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the resulting hexahydrotriazine was immediately used in the Mannich-Michael reaction applying the conditions described above.

N-((*S*)-1-Carboxymethyl-2-[(N´-carbobenzoxy)indol-3-yllethyl)-4-oxo-2,3-didehydro-piperidine (**14**)

$[\alpha]_D^{23}$= -149.3° (c= 1.0, CH_2Cl_2). - 400-MHz-^{1}H-NMR ($CDCl_3$): δ = 8.2 (s, 1H, In 2-H), 7.5-7.2 (m, 9H, In 4-H, In 5-H, In 6-H, In 7-H, Ph), 6.9 (d, J = 7.7 Hz, 1H, NC<u>H</u>=C), 5.4 (s, 2H, OCH_2Ph), 4.9 (d, J = 7.7 Hz, 1H, 3-H), 4.2 (dd, J_1 = 5.5 Hz, J_2 = 4.3 Hz, 1H, CH_{2a}), 3.7 (s, 3H, OCH_3), 3.6-3.3 (m, 3H, 6-$H_{a,b}$, CH_{2b}), 3.1 (dd, J_1 = 5.1 Hz, J_2 = 10.0 Hz, 1H, CH_{2b}), 2.4-2.2 (m, 2H, 5-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR ($CDCl_3$): δ = 191.4 (C-4), 170.0 (COOMe), 150.2 (C-2), 135.2 (In C-7a), 134.6 (C-ipso), 129.3 (Ph), 128.5, 128.3, 128.1 (3C, Ph), 124.9 (In C-3a), 123.5 (In C-2), 122.9 (In C-5), 118.1 (In C-4), 115.5 (In C-3), 115.3 (In C-6), 99.8 (In C-2), 68.5 (OCH_2Ph), 65.8 (C-α), 52.4 (OCH_3), 45.3 (C-5), 35.4 (C-6), 25.5 (In CH_2). - $C_{25}H_{24}N_2O_4$ (416.4), Calcd: C: 72.10, H: 5.81, N: 7.21. - Found: C: 72.50, H: 5.70, N: 7.48 %.

N-((*S*)-1-Carboxymethyl-2-[indol-3-yllethyl)-4-oxo-2,3-didehydro-piperidine (**15**)

To solution of 5.7 g of compound **14** in 250 ml of methanol 200 mg of palladium on charcoal were added and was stirred under of hydrogen 1 atm for 12 h. The desired compound was isolated as a yellow oil in quantitative yield by filtration through a Celite pad and evaporation of the methanol.

$[\alpha]_D^{23}$= -164.0° (c= 1.9, CH_2Cl_2); yellow oil. - 400-MHz-^{1}H-NMR: δ = 8.7 (s, 1H, N-H), 7.5 (d, J = 7.8 Hz, 1H, In 4-H), 7.4 (d, J = 8.2 Hz, 1H, In 7-H), 7.2 (m, 2H, In 5-H, In 6-H), 7.0 (d, J = 2.3 Hz, 1H, In 2-H), 6.9 (d, J = 7.6 Hz, 1H, 2-H), 4.9 (d, J =8.0 Hz, 1H, 3-H), 4.2 (dd, J_1 = 5.3 Hz, J_2 = 4.9 Hz, 1H, α-H), 3.7 (s, 3H, OCH_3), 3.5-3.3 (m, 3H, 6-$H_{a,b}$, In CH_2), 3.2 (dd, J_1 = 6.8 Hz, J_2 = 10.4 Hz, 1H, In CH_2), 2.5-2.2 (m, 2H, 5-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR: δ = 191.4 (C-4), 170.0 (C=O), 153.3 (C-2), 136.5 (In C-4), 126.7 (In C-3a), 123.5 (In C-7a), 122.6 (In C-5), 119.3 (In C-6), 117.8 (In C-7b), 117.3 (In C-2), 99.8 (C-3), 66.9 (C-α), 52.6 (OCH_3), 45.6 (C-5), 35.6 (C-6), 26.3 (In C-8). - $C_{17}H_{18}N_2O_3$ (298.2), Calcd:
C: 68.44, H: 6.08, N: 9.39. - Found: C: 67.99, H: 5.99, N: 9.48%.

1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(6*S*, 12b*S*)-6-carboxymethyl-quinolizine (**17**)

To a solution of 900 mg (3.0 mmol) of the 2,3-didehydropiperidin-4-one **15** in 3 ml of CH_2Cl_2 10 ml of a solution of HBr (33%) in acetic acid was added. The color of the mixture turned a deep red or black. After two min the acid was removed *in vacuo*. The residue was taken up in a mixture of 5 ml of methanol and was

Table 5: ^{1}H- and ^{13}C-NMR data of the racemic indolo[2,3-*a*]quinolizidinones **8a-f** (δ [ppm], multiplicity, J [Hz]).

8	N-H,	8-H,	11-H	10-H	9-H	12b-H	1-H_a	1-H_b	6-H_a	6-H_b	4-H	7-H_a	7-H_b	3-H_a	3-H_b	R
a	8.2, s	7.5, d, 7.6	7.3, d, 7.7	7.2, m	7.2, m	3.9, dd 1.0,9.5	2.8,	2.9, dd	3.2, dd	2.8, m	2.7, m	2.6, m	2.6, m	2.4, m	2.4, m	1.8, m; 1.6, $2CH_2$, 1.0, t, CH_3
b	10.8, s	7.5, d, 7.8	7.3, d, 8.0	7.0, t, 7.3	6.9, t	4.0, m	2.7, m	2.7, m	3.2, dd 6.4,16	2.7, m	2.5, m	2.6, m	2.55,m	2.3, m	2.3, m	2.1, m; 0.92, 0.87, $2CH_3$
c	10.7, s	7.5, d, 7.8	7.25, d, 8.0	7.1, t, 7.3	6.9, t	4.2, m	2.8, m	2.8, m	3.2, dd 6.8,15	2.8, m	2.5, m	2.73,m	2.63,m	2.3, m	2.3, m	1.2, m, 10H; 0.8, t CH_3
d	10.8, s	7.3, d, 8.0	7.3, d	7.0, dd, 7.2	6.9, dd	3.9, d, 11.9	3.1, d, 13.9	2.7, m	2.9, dd 3.4, 11	2.7, m	3.7, dd 7.0, 12	2.7, m	2.5, m	2.4, m	2.2,	7.4, m, 5H, Ph
e	10.8, s	7.35, d, 7.6	7.2, d	7.0, t, 5.9	6.9, t	3.9, d, 11.0	3.1, m	2.6, m	2.9, m	2.6, m	3.8, dd, 6.7, 12	2.6, m	2.6, m	2.4, m	2.2, m	7.4, m, 4H, Ph
f	10.8, s	7.4, d, 7.8	7.3, d, 7.3	7.0, d, 7.3	6.9, t	3.9, m	3.1, d, 14.0	2.7, m	2.8, m	2.6, m	3.9, m	2.6, m	2.5, m	2.5, m	2.3, m	8.3, d, 8.0; 7.4, 4H, Ph

8	C-2	C-11a	C-12a	C-8a	C-9	C-8	C-10	C-11	C-7a	C-12b	C-4	C-6	C-1	C-3	C-7	R
a	208.6	136.2	134.0	126.9	121.6	119.3	118.0	111.0	108.5	62.0	58.4	45.3	45.0	36.1	22.1	18.3, 13.8, 11.8
b	208.2	135.9	135.4	126.3	120.5	119.3	117.5	110.9	106.5	66.2	56.8	44.2	41.0	40.0	29.0	21.3, 19.8, 17.8
c	208.2	136.4	135.9	126.5	120.5	119.3	117.5	111.2	106.5	66.2	56.8	44.5	41.0	41.0	31.0	29.4, 29.1, 29.0, 26.4, 25.6, 22.5, 14.0
d	206.0	136.1	134.3	126.3	120.6	118.4	117.5	111.0	107.0	67.2	58.3	49.8	48.1	45.0	21.5	142.9 (C-ipso) 128.8, 127.5, 127.1
e	205.8	136.1	134.3	126.3	120.6	118.4	117.5	111.1	107.0	66.0	58.1	49.4	48.0	44.9	21.5	141.9 (C-ipso),129.1, 128.2, 127.6, 126.5
f	205.4	136.1	134.3	124.0	120.7	118.5	117.6	111.0	106.9	65.9	57.9	48.9	48.1	44.8	21.5	150.7 (C-ipso),146.8, 128.4, 126.3

Table 6: ^{1}H- and ^{13}C-NMR data of the enantiomerically pure indolo[2,3-*a*]quinolizidin-2-ones **10a-f** (δ [ppm], multiplicity, J [Hz]).

10	12-H	8-H	11-H	10-H	9-H	12b-H	6-H	OCH_3	4-H	7-H_a	7-H_b	1-H_a	1-H_b	3-H_a	3-H_b	R
a	8.2, s	7.5, d, 7.6	7.3, d, 6.9	7.1, m	7.1, m	4.7, d, 8.4	4.3, d, 4.9	3.6, s	3.4, m	3.3, d 8.4	3.1, dd 4.8,8.6	2.8, dd 1.3, 14	2.5, dd 8.4	2.4, m	2.4, m	1.6, m; 1.4, $2CH_2$; 1.0, t, CH_3
b	8.2, s	7.5, d, 7.6	7.3, d, 6.9	7.1, m	7.1, m	4.75, d 11.6	4.2, d, 4.9	3.8, s	3.35, m	3.35, m	3.2, dd 4.8,8.6	2.85, d 14.5	2.5, m	2.5, m	2.5, m	2.1, m; 0.9, $2CH_3$
c	7.9, s	7.47, d, 7.8	7.3, d, 8.1	7.1, m	7.1, m	4.67, d 11.6	4.3, dd 1.3,6.0	3.5, s	3.43, m	3.4, dd 0.2,3.7	3.3, dd 10	2.8, dd 3, 6.3	2.5, m	2.5, m	2.5, m	1.3, m, 16H; 0.8, t, CH_3
d	10.9, s	7.3, m	7.3, m	7.0, m	6.9, m	4.7, d, 11.6	4.4, dd 3.6, 11	3.5, s	3.7, d, 5.1	3.1, m	2.7, m	3.1, m	2.7, m	2.5, m	2.4, m	7.4, m, 5H, Ph
e	8.0, s	7.4, m	7.3, m	7.0, m	6.9, m	4.8, d, 11.6	4.6, dd 4.1,11	3.5, s	3.8, m	3.2, d, 15.4	2.9, m	3.0, dd 2.1, 7.6	2.7, m	2.7, m	2.7, m	7.4, m, 4H, Ph
f	8.3, s	7.4, m	7.3, m	7.0, m	6.9, m	4.9, d, 11.9	4.8, dd 5.4, 9	3.5, s	3.7, m	3.1, dd 2.1,5.9	2.7, m	3.2, d, 15.4	3.0, d	2.7, m	2.7, m	7.6, 7.5, 4H, Ph

10	C-2	C=O	C-11a	C-12a	C-8a	C-9	C-8	C-10	C-11	C-7a	C-12b	C-6	C-4	OMe	C-1	C-3	C-7	R
a	209.0	173.3	136.5	133.5	126.8	121.9	119.5	118.1	111.0	106.3	58.2	55.3	53.0	51.5	47.9	46.8	36.1	25.3, 17.8, 14.8
b	209.0	173.3	136.7	133.3	126.6	121.8	119.4	118.1	111.0	106.3	62.9	55.5	52.3	51.4	47.4	40.8	29.1	25.3, 19.8, 14.8
c	208.5	173.3	136.4	133.4	126.7	121.8	119.4	118.1	110.9	106.3	58.2	55.3	51.9	51.5	47.9	46.8	33.8	31.8, 29.9, 29.7, 29.3, 25.4, 24.3, 22.6, 14.9
d	206.4	172.4	136.3	134.0	126.2	121.0	118.6	117.7	111.1	104.6	64.0	56.0	53.0	51.3	50.0	46.9	24.6	141.5 (C-ipso) 129.1, 128.1, 127.4
e	206.3	172.8	136.5	134.0	126.8	122.0	119.6	118.2	111.0	106.9	63.9	56.3	53.2	51.4	50.6	47.7	25.0	139.8 (C-ipso),132.9, 129.5, 129.3, 128.9
f	205.7	172.5	136.5	132.6	126.7	122.1	118.2	117.6	111.1	106.9	63.8	56.7	53.0	51.6	50.1	47.5	24.9	148.8 (C-ipso),147.9, 128.4, 124.3

added to a mixture of $NaHCO_3$/ CH_2Cl_2. The compound **16** was extracted with 40 ml of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel using petroleum ether/ethyl acetate (5:1 [v/v]) yielded 670 mg (75%) of the two diastereomers **16** and **17** in a ratio of 1:6.

If the reaction is run on a bigger scale (>5 g) one should take care of a good mixing (increasing amount of CH_2Cl_2), the reaction time should be prolonged to 15 min (controlled by tlc) and removal of the acetic acid should not be performed to dryness, otherwise the resulting hydrobromide can hardly be dissolved in methanol.

1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(6*S*,12b*S*)-6-carboxymethyl-quinolizine (**16**)

$[\alpha]_D^{23}$= 115.2° (c= 0.8, MeOH); mp.:190°C. - 400-MHz-^{1}H-NMR :δ = 10.8 (s, 1H, 12-H), 7.4 (d, J = 7.8 Hz, 1H, 8-H), 7.3 (d, J = 8.0 Hz, 1H, 11-H), 7.0 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H, 10-H), 6.9 (dd, J_2 = 0.8 Hz, J_2 = 8.0 Hz, 1H, 9-H), 4.5 (d, J = 10.9 Hz, 1H, 12b-H), 4.1 (dd, J_1= 4.1 Hz, J_2= 3.8 Hz, 1H, 6-H), 3.5 (s, 3H, OCH_3), 3.2 (m, 2H, 7-H), 3.1 (m, 2H, 1-$H_{a,b}$), 2.9 (dd, J_1= 11.3 Hz, J_2= 3.5 Hz, 1H, 4-H_a), 2.6 (dd, J = 3.8 Hz, 1H, 4-H_b), 2.4 (dd, J_1=12.9 Hz, J_2=12.8 Hz, 1H, 3-H_a), 2.3 (d, J = 14.0 Hz, 1H, 3-H_b). - 100.6-MHz-^{13}C-NMR : δ = 207.5 (C-2), 172.8 (C=O), 136.1 (C-11a), 134.1 (C-12a), 126.2 (C-8a), 120.8 (C-10), 118.7 (C-9), 117.8 (C-8), 111.0 (C-11), 103.8 (C-7a), 59.8 (C-12b), 52.6 (C-6), 51.1 (OCH_3), 46.8 (C-1), 41.1 (C-3), 40.1 (C-4), 24.1 (C-7). - $C_{17}H_{18}N_2O_3$ (298.2), Calcd: C: 68.44, H: 6.08, N: 9.39. - Found: C: 68.43, H: 6.32, N: 9.53%.

1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(6*S*,12b*R*)-6-carboxymethyl-quinolizine (**17**

$[\alpha]_D^{23}$= -59.2° (c= 0.9, MeOH). - 400-MHz-^{1}H-NMR :δ = 10.8 (s, 1H, 12-H), 7.4 (d, J = 7.6 Hz, 1H, 8-H), 7.3 (d, J = 8.0 Hz, 1H, 11-H), 7.0 (t, J_1 = 7.3 Hz, J_2 = 7.6 Hz, 1H, 10-H), 6.9 (t, J_1 = 7.3 Hz, J_2 = 8.0 Hz, 1H, 9-H), 3.96 (d, J = 8.3 Hz, 1H, 12b-H), 3.7 (s, 3H, OCH_3), 3.5 (dd, J_1= 6.6 Hz, J_2= 8.6 Hz, 1H, 6-H), 3.0 (m, 2H, 7-$H_{a,b}$), 2.9 (m, 2H, 1-$H_{a,b}$), 2.6 -2.4 (m, 4H, 3-$H_{a,b}$, 4-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR : δ = 206.8 (C-2), 172.8 (C=O), 136.0 (C-11a), 133.1 (C-12a), 126.0 (C-8a), 120.9 (C-10), 118.5 (C-9), 117.6 (C-8), 111.0 (C-11), 104.5 (C-7a), 63.4 (C-12b), 57.6 (C-6), 51.1 (OCH_3), 48.0 (C-1), 44.5 (C-3), 40.7 (C-4), 25.0 (C-7). - $C_{17}H_{18}N_2O_3$ (298.2), Calcd: C: 68.44, H: 6.08, N: 9.39. - Found: C: 68.13, H: 6.00, N: 9.23%.

1,2,3,4,6,7,12,12b-Octahydro-2-(1,3-dithiolan-2-yl)-indolo[2,3-*a*]-(6*S*,12b*R*)-6-carboxymethylquinolizine (**21**) and 1,2,3,4,6,7,12,12b-Octahydro-2-(1,3-dithiolan-2-yl)-indolo[2,3-*a*]-(6*S*,12b*S*)-6-carboxymethyl-quinolizine (**22**)

To a suspension of 3.2 g (10.7 mmol) of the ketone **17** in 100 ml of benzene, 4.2 g (2 equiv.) of toluene-sulfonic acid hydrate and 1 ml (1.1 equiv.) of ethanedithiol were added. The reaction mixture was heated to reflux in a Dean-Stark apparatus until the expected amount of water had separated (15-20 min), and an oily mass, insoluble in benzene, had precipitated at the bottom of the flask. The reaction mixture was diluted with 100 ml of CH_2Cl_2 and the organic phases were extracted with 2x 50 ml of a sat. solution of Na_2CO_3. The diastereomeric thioketals **21** and **22** were obtained in 93% combined yield in a ratio of 3.5:1. They can easily be separated by flash chromatography using petroleum ether/ ethyl acetate 4:1 (v/v).

21: $[\alpha]_D^{23}$= 54.9° (c= 0.5, CH_3OH); mp.: 190°C. - 400-MHz-^{1}H-NMR ($CDCl_3$):δ = 7.78 (s, 1H, 12-H), 7.4 (d, J = 7.5 Hz, 1H, 8-H), 7.25 (d, J = 6.8 Hz, 1H, 11-H), 7.09 (m, 2H, 9-H, 10-H), 4.45 (dd, J_1 = 1.8 Hz, J_2 = 11.2 Hz, 1H, 12b-H), 3.8 (dd, J_1= 1.9 Hz, J_2= 6.3 Hz, 1H, 6-H), 3.6 (s, 3H, OCH_3), 3.3 (s, 5H, 1-H_a, S-CH_2CH_2-S), 3.2 (dd, J_1 = 4.1 Hz, J_2 = 6.3 Hz, 1H, 7-H_a), 3.16 (m, 1H, 7-H_b), 2.9 (m, 1H, 1-H_b), 2.4 (ddd, J_1= 2.5 Hz, J_2= 4.8 Hz, J_3 = 10.2, 1H, 4-H_a), 2.6 (ddd, J_1 = 4.8 Hz, J_2 = 8.4 Hz, J_3 = 12.9 Hz, 1H, 4-H_b),

2.0 (m, 2H, 3-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR ($CDCl_3$):δ = 172.9 (C=O), 136.2 (C-11a), 133.8 (C-12a), 127.1 (C-8a), 121.8 (C-10), 119.4 (C-9), 118.0 (C-8), 110.7 (C-11), 105.8 (C-7a), 66.3 (C-2), 61.0 (C-12b), 53.1 (OCH_3), 52.0 (C-4), 51.1 (C-6), 47.9 (C-1), 42.9 (C-3), 39.1 (S-CH_2), 38.0 (S-CH_2), 24.9 (C-7). - $C_{19}H_{22}N_2O_2S_2$ (374.5), Calcd: C: 60.93, H: 5.92, N: 7.48. - Found: C: 61.13, H: 6.00, N: 7.53%.

(**22**): $[\alpha]_D^{23}$= -70.3° (c= 0.22, CH_3OH). - 400-MHz-^{1}H-NMR ($CDCl_3$):δ = 7.8 (s, 1H, 12-H), 7.4 (d, J = 7.6 Hz, 1H, 8-H), 7.3 (d, J = 7.8 Hz, 1H, 11-H), 7.0 (t, J_1 = 7.3 Hz, J_2 = 7.6 Hz, 1H, 10-H), 6.9 (t, J_1 = 7.3 Hz, J_2 = 8.0 Hz, 1H, 9-H), 3.96 (d, J = 8.3 Hz, 1H, 12b-H), 3.7 (s, 3H, OCH_3), 3.5 (dd, J_1= 6.6 Hz, J_2= 8.6 Hz, 1H, 6-H), 3.3 (s, 4H, S-CH_2CH_2-S), 3.0 (m, 2H, 7-$H_{a,b}$), 2.9 (m, 2H, 1-$H_{a,b}$), 2.6 -2.4 (m, 4H, 3-$H_{a,b}$, 4-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR ($CDCl_3$):δ = 172.8 (C=O), 136.6 (C-11a), 133.1 (C-12a), 126.0 (C-8a), 120.9 (C-10), 118.5 (C-9), 117.6 (C-8), 111.0 (C-11), 104.5 (C-7a), 63.4 (C-12b), 57.6 (C-6), 51.7 (C-4), 51.1 (OCH_3), 48.0 (C-1), 44.5 (C-3), 25.0 (C-7).-

1,2,3,4,6,7,12,12b-Octahydro-indolo[2,3-*a*]-(6*S*,12b*R*)-6-carboxymethyl-quinolizine (**20**)

Method A: To a solution of 500 mg (1.68 mmol) of the thioketal **21** in 50 ml of methanol 2 g of freshly prepared Raney-nickel were added and the reaction mixture was stirred under a hydrogen atmosphere for 12h at room temperature. Filtration through a Celite pad and removal of the solvent afforded the crude product. Chromatography using petroleum ether/ethyl acetate (4:1 [v/v]) delivered 347 mg (73%) of the desired compound **20**.

Method B: To a solution of 510 mg (1.7 mmol) of the ketone **17** in 20 ml of methanol were added 85 mg (2.2 mmol) of $NaBH_4$. The reaction mixture was kept for 30 min at ambient temperature and then 5 ml water were added. The methanol was removed *in vacuo* and the remaining aqueous phase was extracted twice with 50 ml of CH_2Cl_2. 490 mg (96%) of the crude alcohol **18** were isolated after drying with $MgSO_4$ and removal of the solvent. This compound was directly converted into the deoxygenated product **20** without characterization.

To this end a solution of 450 mg (1.5 mmol) of the alcohol **18** in 20 ml of CH_2Cl_2 190 mg (1.1 equiv.) of pyridine and 0.12 ml (1eq.) mesylchloride in 40 ml of CH_2Cl_2 were added. After 2h the reaction mixture was poured on water and extracted twice with 50 ml of CH_2Cl_2. The combined organic phase was dried with $MgSO_4$ and the solvent was evaporated. The residue was taken up in acetone and treated with an excess of NaI and zink powder at 60°C. Filtration through a Celite pad and flash chromatography with petroleum ether/ ethylacetate (4:1 [v/v]) delivered 350 mg of the title compound **20** (70% overall yield).

$[\alpha]_D^{23}$= 97° (c= 1.0, MeOH) ref. [11]:$[\alpha]_D^{23}$= 97° (c= 1.0, MeOH). - 200-MHz-^{1}H-NMR($CDCl_3$): δ =7.7 (s, 1H, 12-H), 7.45 (d, J = 6.3 Hz, 1H, 8-H), 7.3 (d, J = 5.8 Hz, 1H, 11-H), 7.0 (m, 1H, 9-H, 10-H), 4.28 (d, J = 8.5 Hz, 1H, 12b-H), 3.8 (dd, J_1= 1.6 Hz, J_2= 6.5 Hz, 1H, 6-H), 3.5 (s, 3H, OCH_3), 3.3 -2.9 (m, 4H, 1-$H_{a,b}$,7-$H_{a,b}$), 3.1 (m, 2H, 1-$H_{a,b}$), 2.9 (dd, J_1= 11.3 Hz, J_2= 3.5 Hz, 1H, 4-H_a), 2.6 (dd, J = 3.8 Hz, 1H, 4-H_b), 2.4 (dd, J_1=12.9 Hz,J_2=12.8 Hz, 1H, 3-H_a), 2.3 (d, J = 14.0 Hz, 1H, 3-H_b). - 50.3-MHz-^{13}C-NMR : δ = 173.2 (C=O), 136.1 (C-11a), 135.1 (C-12a), 127.2 (C-8a), 121.2 (C-10), 119.2 (C-9), 117.9 (C-8), 110.6 (C-11), 105.2 (C-7a), 61.5 (C-12b), 53.7 (C-6), 53.08 (C-4), 51.1 (OCH_3), 31.8 (C-1), 26.1, 24.8, 24.1.

1,2,3,4,6,7,12,12b-Octahydro-2-(1,3-dithiolan-2-yl)-indolo[2,3-*a*]-(6*S*,12b*R*)-6-carboxy-quinolizine (**24**)

To a solution of 2 g (5.3 mmol) of the ester **21** in 40 ml THF, 420 mg (2 equiv.) of NaOH in 5 ml H_2O were added and the mixture was heated to 40°C until all starting material has been consumed (tlc control, ca 3h). The solvent was evaporated *in vacuo* and the remaining solid was taken up in 30 ml of water. Upon portionwise addition of diluted HCl (0.1 N) the zwitterionic amino acid precipitated from the solution. Five

subsequent crops were collected to give the carboxylic acid **24** in an overall yield of 1.87 g (98%), which was used without purification in the following reaction.

1,2,3,4,6,7,12,12b-Octahydro-2-(1,3-dithiolan-2-yl)-indolo[2,3-*a*]-(6*S*,12b*R*)-6-carboxamido-quinolizine (**25**)

To a suspension of 1.8 g of the acid **24** (5 mmol) in 20 ml of anhydrous DMF 957 mg of N-(dimethylaminopropyl)-N´-ethylcarbodiimide hydrochloride (DEAC) and 670 mg (5.1 mmol) N-hydroxybenzotriazole was added. Stirring was continued until all solid components were dissolved (30 min) and then 1 ml of an aqueous solution of NH_3 was injected via syringe. The reaction was stirred for another 5h, the DMF was removed by distillation and the precipitate was extracted by repeated treatment with water/ CH_2Cl_2 (5ml/50ml). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated. Flash chromatography of the residue using petroleum ether/ acetone 1:1 (v/v) delivered 1.65 g (92%) of the pure amide **25**. - $[\alpha]_D^{23}$= -5.9° (c= 1.0, CH_3OH); mp.: 180°C. - 400-MHz-^{1}H-NMR (DMSO-d_6):δ = 9.9 (s, 1H, 12-H), 7.05 (d, J = 7.2 Hz, 1H, 8-H), 6.95 (d, J = 8.0 Hz, 1H, 11-H), 6.7-6.6 (m, 2H, 9-H, 10-H), 6.0 (s, 1H, NH_2), 5.7 (s, 1H, NH_2), 3.89 (d, J = 9.3 Hz, 1H, 12b-H), 3.38(s, 4H, S-CH_2CH_2-S), 3.0 (d, J = 4.7 Hz, 1H, 6-H), 2.87 (m, 1H, 7-H_a), 2.79-2.4 (m, 3H, 7-H_b, 1-$H_{a,b}$), 2.5 (m, 1H, 4-H_a), 2.0 (m, 1H, 4-H_b), 1,7 (m, 2H, 3-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR (DMSO-d_6):δ = 172.8 (C=O), 135.7 (C-11a), 133.8 (C-12a), 125.9 (C-8a), 123.7 (C-10), 120.1 (C-9), 117.6 (C-8), 110.0 (C-11), 103.3 (C-7a), 65.5 (C-2), 60.7 (C-12b), 52.6 (C-6), 50.1 (C-1), 45.6 (C-3), 41.1 (C-4), 37.3 (S-CH_2, 2C) 23.7 (C-7).- $C_{18}H_{21}N_3OS_2$ (359.3), Calcd: C: 60.14, H: 5.89, N: 11.69. - Found: C: 59.93, H: 5.80, N: 11.63%.

1,2,3,4,6,7,12,12b-Octahydro-2-(1,3-dithiolan-2-yl)-indolo[2,3-*a*]-(6*S*,12b*R*)-6-cyano-quinolizine (**26**)

The amide **25** (1.4 g, 3.88 mmol) was suspensed in 70 ml of CH_2Cl_2 and after addition of 0.7 ml (2.2 equiv.) of pyridine the solution was cooled to 0°C. Upon addition of trifluoroacetic acid anhydride with a syringe, the light yellow color of the reaction mixture turned red. After gradually warming to room temperature within 2h the reaction mixture was poured on water and extracted twice with 50 ml of CH_2Cl_2/ sat. solution of $NaHCO_3$. The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated *in vacuo* (bath temperature < 30°C). The nitrile **26** (1.3 g; 97%) was precipitated from CH_2Cl_2/petroleum ether. - $[\alpha]_D^{23}$= 107.6° (c= 0.21, $CHCl_3$); mp.: 210°C. - 400-MHz-^{1}H-NMR (DMSO-d_6):δ = 10.1 (s, 1H, 12-H), 7.2 (d, J = 7.2 Hz, 1H, 8-H), 7.0 (d, J = 8.0 Hz, 1H, 11-H), 6.8 (dd, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H, 10-H), 6.7 (dd, J_1 = 1.1 Hz, J_2 = 8.0 Hz, 1H, 9-H), 3.8 (d, J = 4.8 Hz, 1H, 12b-H), 3.5 (dd, J_1 = 1.5 Hz, J_2 = 11.2 Hz, 1H, 6-H), 3.1 (s, 4H, S-CH_2CH_2-S), 2.98 (dd, J_1 = 1.5 Hz, J_2 = 7 Hz, 1H, 7-H_a), 2.7-2.5 (m, 5H, 7-H_b, 1-$H_{a,b}$, 4-H_a), 2.0 (m, 1H, 4-H_b), 1,7 (m, 2H, 3-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR (DMSO-d_6):δ = 136.8 (C-11a), 133.4 (C-12a), 125.9 (C-8a), 120.7 (C-10), 118.1 (C-9), 116.9 (C-8), 116.1 (C≡N), 110.0 (C-11), 102.5 (C-7a), 64.9 (C-2), 54.4 (C-12b), 52.0 (C-6), 51.1 (C-1), 45.0 (C-3), 41.1 (C-4), 37.3 (S-CH_2, 2C) 25.7 (C-7). - $C_{18}H_{19}N_3S_2$ (341.5), Calcd: C: 63.31, H: 5.61, N: 12.30. - Found: C: 63.35, H. 5.37, N: 12.10%.

1,2,3,4,6,7,12,12b-Octahydro-2-(1,3-dithiolan-2-yl)-indolo[2,3-*a*]-(12b*R*)-quinolizine (**27**)

To a suspension of 600 mg (1.7 mmol) of the nitrile **26** in 80 ml of THF. 30 ml of ethanol and 5 ml of pyridine were added. The resulting mixture was heated to 60°C and 1.2 g (31.6 mmol) of $NaBH_4$ were added in four portions during 12h. For work up the solvents were evaporated, the reaction mixture was taken up in CH_2Cl_2 and the solution was extracted with water. The organic layer was separated and dried with $MgSO_4$ and the solvent removed *in vacuo*. Flash chromatography of the residue with petroleum ether/ ethyl acetate

3:1 (v/v) afforded 470 mg (85%) of the desired compound **27**. - $[\alpha]_D^{23}$= 54.1° (c= 0.8, $CHCl_3$); mp.: 162°C. - 400-MHz-^{1}H-NMR ($CDCl_3$):δ = 7.75 (s, 1H, 12-H), 7.46 (d, J = 7.4 Hz, 1H, 8-H), 7.0 (d, J = 7.7 Hz, 1H, 11-H), 7.0 (m, 2H, 9-H, 10-H), 3.47 (dd, J_1 = 4.8 Hz, J_2 = 11.3 Hz, 1H, 12b-H), 3.3 (s, 4H, S-CH_2CH_2-S), 3.0 (m, 3H, 7-$H_{a,b}$, 1-H_a), 2.7 (m, 3H, 1-H_b, 6-$H_{a,b}$), 2.0 (m, 1H, 4-H_a), 2.4 (ddd, J_1 = 2.4 Hz, J_2 = 7.9 Hz, J_3 = 15.6 Hz, 1H, 4-H_b), 2,3 (m, 2H, 3-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR ($CDCl_3$):δ = 136.0 (C-11a), 133.7 (C-12a), 126.4 (C-8a), 121.4 (C-10), 119.4 (C-9), 118.1 (C-8), 110.7 (C-11), 108.4 (C-7a), 66.9 (C-2), 59.1 (C-12b), 54.6 (C-6), 52.4 (C-1), 46.2 (C-3), 42.3 (C-4), 39.2, 37.3 (S-CH_2), 25.7 (C-7). - $C_{17}H_{20}N_2S_2$ (316.5), Calcd: C: 64.52, H: 6.37, N: 8.85. - Found: C: 64.70, H: 6.31, N: 8.56%.

1,2,3,4,6,7,12,12b-Octahydro-2-oxoindolo[2,3-*a*]-(12b*R*)-quinolizine (**28**)

To a solution of 500 mg (1.6 mmol) of the thioketal **27** in 10 ml of THF, 0.5 ml of water, 680 mg (2 equiv.) of yellow HgO and 0.48 ml of BF_3·Et_2O were added. After 14h the solvent was decanted and the residue was carefully washed with THF. The solvent was removed *in vacuo* and the residue was taken up in 50 ml of CH_2Cl_2. The solution was extracted with sat. aqueous $NaHCO_3$, dried with $MgSO_4$ and the solvent was removed *in vacuo*. Flash chromatography of the residue with petroleum ether/actone (2:1 [v/v]) delivered 350 mg (92%) of the ketone **28**. - $[\alpha]_D^{23}$= 44.5° (c= 1.1, CH_2Cl_2). The enantiomeric purity of **28** was determined by analytical HPLC using a LiChroCart 250-4 ChiraDex column (Merck AG, Darmstadt, Germany) and methanol/10mM NaH_2PO_4 (pH 7) 40:60 (v/v) as eluent. As reference a racemic sample of **28** was used which had been obtained from tryptamine according to the route outlined in Scheme 4. Base line separation of the enantiomers could not be achieved but the ratio of the enantiomers could be estimated to be ca. 3-4:1. - 400-MHz-^{1}H-NMR ($CDCl_3$):δ = 7.99 (s, 1H, 12-H), 7.5 (d, J = 7.6 Hz, 1H, 8-H), 7.0 (d, J = 7.7 Hz, 1H, 11-H), 7.0 (m, 2H, 9-H, 10-H), 3.61 (dd, J_1 = 2.1 Hz, J_2 = 9.7 Hz, 1H, 12b-H), 3.3 (m, 1H, 7-H_a), 3.2 (m, 1H, 7-H_b), 3.0 (m, 1H, 1-H_a), 2.8 (m, 7H, 1-$H_{a,b}$, 3-$H_{a,b}$, 4-H_a, 6-$H_{a,b}$). - 100.6-MHz-^{13}C-NMR ($CDCl_3$):δ = 207.3 (C-2), 136.2 (C-11a), 133.0 (C-12a), 126.9 (C-8a), 121.9 (C-10), 119.4 (C-9), 118.6 (C-8), 110.2 (C-11), 108.4 (C-7a), 58.5 (C-12b), 54.2 (C-6), 5.9 (C-1), 45.7 (C-3), 41.6 (C-4), 21.7 (C-7).

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