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TILIVALLINE, A NEW PYRROLO[2, 1-*c*][1, 4] BENZODIAZEPINE METABOLITE FROM *KLEBSIELLA*[1]

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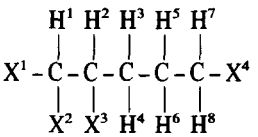
Abstract—From *Klebsiella pneumoniae* (+)(11S, 11aS) - 1,2,3,10,11,11a - hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5*H* - pyrrolo[2,1-*c*][1,4]benzodiazepin - 5 - one (**1**) has been isolated for which the name tilivalline is suggested. Structure elucidation and synthesis are reported.

In the course of our investigations of the secondary metabolites of *Klebsiella pneumoniae* var. *oxytoca*[2] a new structural type, (+)(11S, 11aS) - 1,2,3,10,11,11a - hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5*H* - pyrrolo[2,1-*c*][1,4] benzodiazepin - 5 - one (**1**) could be isolated for which the name tilivalline is suggested. Structure elucidation and synthesis will be reported here.

The elemental composition of **1** has been determined mass spectroscopically by exact mass measurement as $C_{20}H_{19}N_3O_2$. Characteristic features of the fragmentation pattern[3] are ions at *m/z* 89, 90, 117 and 130 typical for indole derivatives CH-monosubstituted in the heterocyclic part.[4] Treatment with D_2O indicates the presence of 3 exchangeable hydrogen atoms.

In the ^{1}H-NMR spectrum (Table 1) the following structural details can be recognized: (a) 2 broad signals at 9.1 and 10.5 ppm (1H each) which disappear upon addition of CD_3OD. The third exchangeable H (*v.* MS data) apparently gives a signal too broad to be recognized. (b) 8 protons in the aromatic region which—as demonstrated by Eu shift and partial decoupling experiments—comprise (i) a system of 3 vicinal H (7.5, br. d, 8 Hz; 6.6, t, 8 Hz; 7.0, br. d, 8 Hz) (ii) a system of 4 vicinal H (7.6, br. d, 8 Hz; 7.2, br. t, 8 Hz; 7.0, br. t, 8 Hz; 7.5, br. d, 8 Hz) apparently belonging to the indole benzene ring and (iii) a 1-H singlet (7.40 ppm) which suggests substitution of the indole ring at C-3 (3-methyl indole shows a signal at 7.00 ppm, 2-methyl indole at 6.14 ppm;[5] for other alkyl indoles similar differences in the chemical shifts of the α- and β-protons have been observed).[6] (c) 8 protons in the aliphatic region (which, as the ^{13}C-NMR spectrum, *vide infra*, shows the presence of 5 sp^3 carbon atoms only, have to be distributed between 3 CH_2 and 2 CH groups) belonging to the sequence **2** as shown by double resonance experiments. The 1H doublet (H^1) at 4.83 ppm couples only (9 Hz) with the 1H multiplet (H^2) at 4.30 ppm. The chemical shift of H^1 suggests for X^1 and X^2 either two heteroatoms or one heteroatom and sp^2-C carrying no H atom. Irradiation of the 4H multiplet centered at 1.80 ppm (2 CH_2) causes collapse of the H^2-multiplet to a sharp doublet (9 Hz) and of the 2H multiplet (1 CH_2) at 3.73 ppm to a broad singlet. The chemical shift (1.80 ppm) indicates that the 2 CH_2-groups making up the multiplet carry only aliphatic C-substituents which have to belong to the sequence **2** since (see ^{13}C-NMR data) no further sp^3 C-atoms are available. The position of the signals at 3.73 and 4.30 ppm is in agreement with X^3 and X^4 being heteroatoms.



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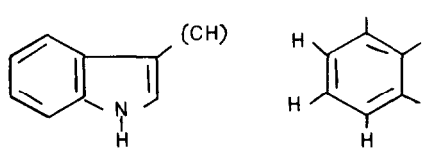
The ^{13}C-NMR spectrum contains signals for 2 CH_2 groups in the normal region (23.1 and 31.4 ppm), for CH_2X^4 at 48.6 ppm, and for the 2 CH-groups at 61.1 and 62.2 ppm. Further on, 15 signals for sp^2 C-atoms are observed (112–168 ppm), one of them (168.0 ppm) typical for a CO-group. Eight signals correspond to the indole ring (lack of a resonance between 97 and 103 ppm is in agreement[7,8] with substitution at C-3 as suggested by the ^{1}H-NMR spectrum), the remaining 6 can be attributed to a benzene ring. The carbonyl region of the IR spectrum shows a band at 1610 cm^{-1} (aromatic lactam or H-bonded aromatic carboxylic acid).

Treatment of **1** with CH_2N_2 results in N-methylation of the indole-NH (**3**) (shift of the mass of M^+ and those of the indole fragments, *vide supra*, by 14 u). Reaction with Ac_2O/pyridine at 20° yields a diacetate (**4**), at 60° a triacetate (**5**). In the IR spectrum of **4** two additional CO bands can be found at 1775 (phenolic OAc) and 1665 cm^{-1} (amide). Partial saponification of **4** with HCl/dioxan yields **6** in agreement with the presence of one OAc-group. Since all exchangeable H (*vide supra*) can be acetylated the amide in **1** has to be tertiary. In the ^{1}H-NMR spectrum of **4** only the signal at 4.83 in **1** is shifted significantly to 6.33 ppm, hence X^1 in **2** has to be NH. The unusual position of the acetyl signals in **4** (0.92 and 1.72 ppm) shows the strong influence of an aromatic ring current. From the data obtained so far the following structural elements of **1** can be deduced (Scheme 1):

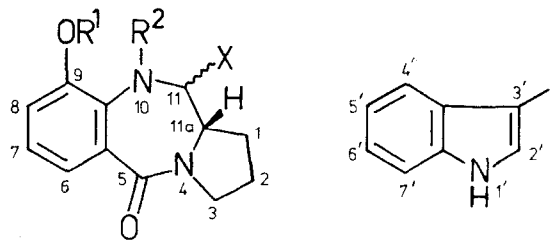


Scheme 1.

Table 1. ^{1}H-NMR data of 1,2,3,10,11,11a - hexahydro - 5*H* - pyrrolo[2,1-c][1,4]benzodiazepine derivatives

compound	C - atom 3	2	1	11a	11 (⇀H)	11 (⇢H)	solvent
1	3.88 m	1.66 m	1.66 m	4.43 m		4.92 d;9	pyridine-d_5
	3.73 m	1.80 m	1.80 m	4.30 m		4.83 d;9	acetone-d_6
4$^+$	3.67 m	2.05 m	2.05 m	4.00 m		6.33 d;12	CD_2Cl_2
8^{++}	3.90 m	1.63 m	1.63 m	4.40 m		4.90 d;9	pyridine-d_5
1'	3.41 + 3.79 m	0.87 + 1.28 m	1.92 m	4.32 m	5.30 d;3		pyridine-d_5
8'$^{+++}$	3.40 + 3.80 m	0.87 + 1.25 m	1.91 m	4.28 m	5.30 d;2		pyridine-d_5
15	3.75 m	1.57 m	1.57 + 1.97 m	3.75 m	3.52 d;13.5; 1	3.13 dd;13.5;9	pyridine-d_5

$^+$ acetate: 0.92; s and 1.72; s. $^{++}$ OCH_3: 3.50. $^{+++}$ OCH_3: 3.07



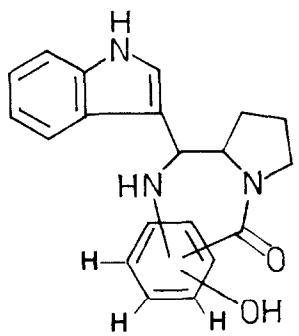
1: $R^1 = R^2 = H$, X = 3'-indolyl, C-11: 

1': $R^1 = R^2 = H$, X = 3'-indolyl, C-11: 

3: $R^1 = R^2 = H$, X = N-methyl-3'-indolyl, C-11: as in **1**
4: $R^1 = R^2$ = Ac, X = 3'-indolyl, C-11: as in **1**
5: $R^1 = R^2$ = Ac, X = N-acetyl-3'-indolyl, C-11: as in **1**
6: $R^1 = H$, R^2 = Ac, X = 3'-indolyl, C-11: as in **1**
8: $R^1 = CH_3$, $R^2 = H$, X = 3'-indolyl, C-11: as in **1**
8': $R^1 = CH_3$, $R^2 = H$, X = 3'-indolyl, C-11: as in **1'**
15: $R^1 = R^2 = R^3 = H$, X = H

Since the indole moiety has to carry a CH-substituent *only* (*vide supra*) (Ar) has to be the benzene ring (NH is Ar- and not aliphatically substituted since in **4** only *one* ^{1}H-NMR signal has been shifted). As X^3 and X^4 are heteroatoms (*vide supra*) they have to be the N of the tertiary amide; hence for X^2 there remains the indole ring. The structural elements can, therefore, be combined as follows (**7**).

From the three possible combinations: NH, CO, OH; NH, OH, CO; and OH, NH, CO the first one can be excluded since by increment calculations the triplet of the central aromatic H would be expected at lowest field (in **1** it actually occurs at highest field, see above). From the other two the sequence OH, NH, CO is more likely since (a) a *m*-position of NH and CO would yield a highly strained *trans*-cyclo-octene system, and (b) 3-



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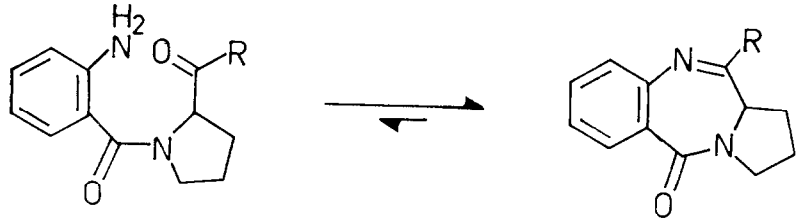
hydroxy anthranilic acid could be isolated from the same culture medium.[2] Thus, structure **1** (so far no stereochemistry) can be suggested for a new metabolite.

Pyrrolo[2,1-*c*][1,4]benzodiazepines can be obtained synthetically by spontaneous cyclization[9,10] of N - (2 - aminobenzoyl) - pyrrole - 2 - ketones (Scheme 2):



Scheme 2.

Starting the synthesis from L-proline would settle one of the two asymmetric centres (11a) of **1**. Introduction of the indole ring should be possible by treatment of the protected proline acid chloride with indole Grignard reagent which induces condensation at C-3 of the indole ring.[11-13]

Protection of the amino and hydroxyl functions has to be done in a way that neither the acid-labile indole ring is attacked during the removal nor does the proline part suffer alkali-induced racemization. Introduction of the aromatic nitrogen as a NO_2 group which can be reduced prior to cyclization, and a benzyl (hydrogenolytic cleavage) or methyl ether (cleavage with $(CH_3)_3SiI$) for the aromatic OH have, therefore, been chosen.

The synthesis of **1**/**1'** and **8**/**8'** is summarized in Scheme 3. Benzyloxycarbonyl protected L-proline (**9**) was treated with $[(CH_3)_2N{=}CHCl]^+Cl^-$ to give the acid chloride **10** without affecting the centre of chirality.[14] Since basic reaction conditions cannot be avoided during the Grignard reaction racemization of the ketone **11** occurred to a certain degree: synthetic **1** could be obtained with 77% optical purity only. Both, condensation (after hydrogenolytical removal of the benzyloxycarbonyl group) of **12** with the imidazolide of 3-benzyloxy- or 3-methoxy-2-nitrobenzoic acid, resp., and the reduction of **13** and **14** (hydrogenolysis of the benzyl ether in the case of **14**, reduction of the nitro group with concomitant cyclization by condensation of the newly created amino group with the keto group, and hydrogenation of the resulting Schiff base were complicated by the low solubility of **12** and **13**/**14**, resp. ($\sim$ 1 mg/ml). Reduction of the Schiff bases yields two stereoisomers (**1**/**1'** and **8**/**8'**) the relative amount of which depends upon the phenol ether group: While roughly equal amounts of **8** and **8'** were obtained, in the case of the benzyl ether, however, the wrong (11R) isomer **1'** was formed predominantly (92%). While the benzyl group was removed readily during the hydrogenation step all attempts to cleave the methoxy group in **8**/**8'** with $(CH_3)_3SiI$ were unsuccessful. Synthetic and natural **1** proved to be identical with all respects (m.p., IR, UV, NMR, MS, chromatographic behavior).

The intermediates in the synthesis of **1** and **8** have been characterized by their mass (see Experimental) and NMR spectra (Table 2). The most important question whether the indole ring has actually been substituted in 3-position could be settled readily. The chemical shifts of the α- and β-protons, resp., in 3- and 2-acyl indoles not only differ by about 1 ppm but they are also strongly influenced by the solvent.[5] Indoles with an RCO-group at C-3 give a signal for the α-proton at $\sim$ 8.2 ppm, while the β-proton in the corresponding 2-substituted indole gives a signal at $\sim$ 7.2 ppm when DMSO-d_6 is used as solvent.

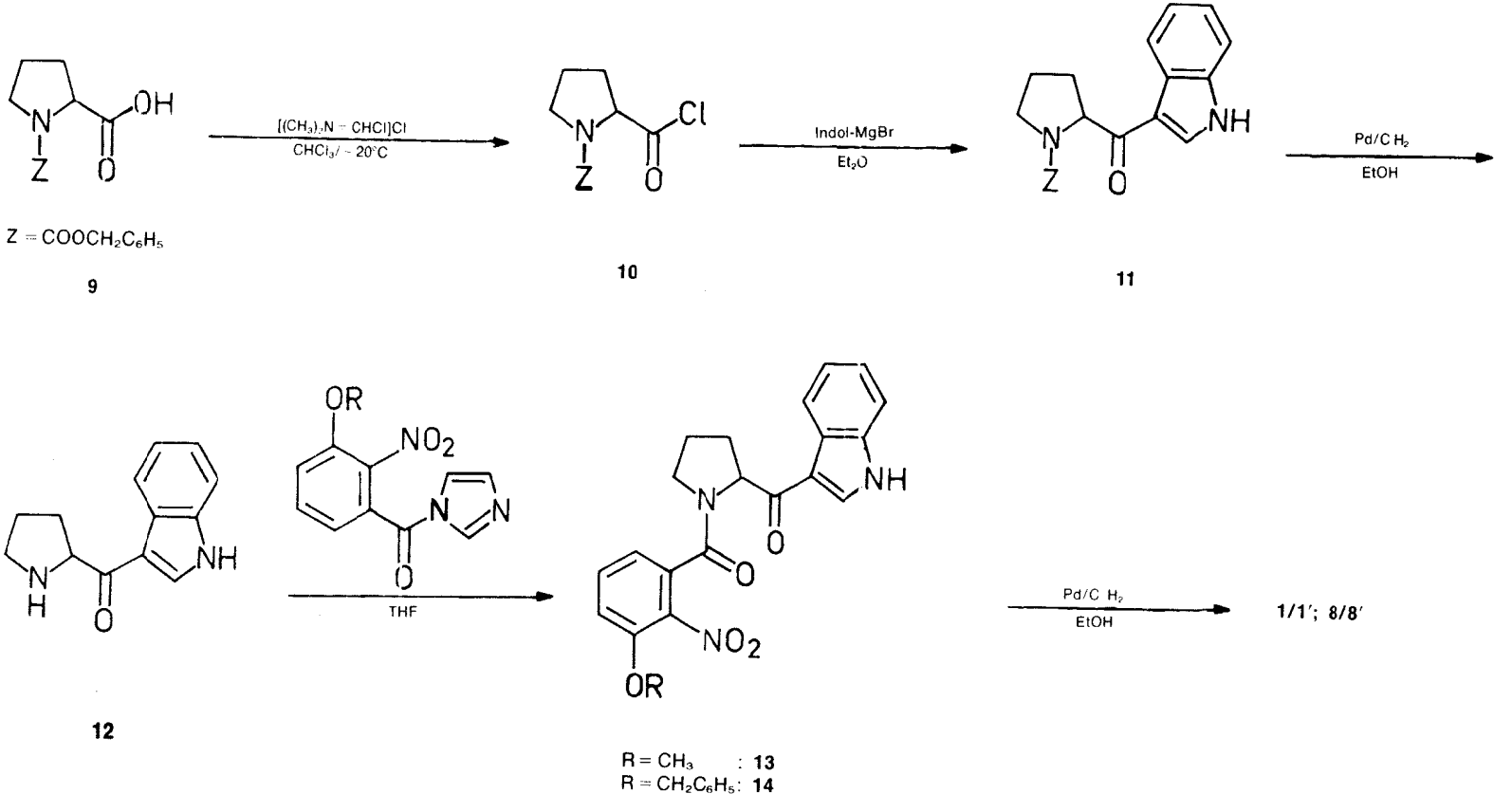
By changing to the less polar $CDCl_3$ the α-proton is shifted by $\sim$ 0.4 ppm to higher field, while the β-proton is hardly influenced (< 0.1 ppm). Now, the ketone **11** exhibits in CD_2Cl_2 a doublet (which collapses to a singlet upon addition of D_2O) at 7.92 ppm, in DMSO-d_6, however, at 8.49 ppm ($\Delta = 0.57$ ppm) in accordance with the behavior expected for an α-proton. For the further interpretations of the NMR-spectra see Table 2. They are complicated since due to the restricted rotation of the amide group two conformers can be observed for **11**, **13** and **14**, which results in the duplication of several signals disappearing only at elevated temperatures.

The NMR spectra of the diastereomers **1**/**1'** and **8**/**8'** show characteristic differences (see Table 1), viz. a coupling constant for the protons at C-11 and C-11a of 2–3 Hz and of 9 Hz, resp. By considering Dreiding models it can be shown that independent of the conformation of the 7-membered ring the dieder angle of $H^{11}\cdots C\text{–}C\blacktriangleleft H^{11a}$ in **15** is always significantly bigger ($\geq 140°$) than that of $H^{11}\blacktriangleright C\text{–}C\blacktriangleleft H^{11a}$ ($\leq 90°$). This is of importance in so far as in **1**/**1'** and **8**/**8'** the indolyl group should be oriented preferentially in an equatorial position and hence the diastereomers would most likely have different conformations. According to the Karplus–Conroy correlation the small coupling constant should correspond to the cisoid hydrogens ($H^{11}\blacktriangleright C\text{–}C\blacktriangleleft H^{11a}$, (**1'**, **8'**) and the large one to the transoid (natural) orientation ($H^{11}\cdots C\text{–}C\blacktriangleleft H^{11a}$) (**1**, **8**). Since both natural and synthetic **1** are dextrarotatory they do possess the same absolute configuration; **1** is, therefore, (+) (11S, 11aS) - 1,2,3,10,11,11a - hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5*H* - pyrrolo[2,1-c][1,4]benzodiazepin - 5 - one.

From pyrrolo[2,1-*c*][1,4]benzodiazepine a series of potent antibiotics (anthramycine,[15,16] sibiromycine,[17-19] tomamycine,[20,21] neothramycine[22]) is derived which have been isolated from various lower fungi. They are all substituted in the pyrrolidine ring and carry at C-11 a carbonyl or a hydroxyl group or are (by elimination of the latter) Schiff bases. Thus, tilivalline is the first representative of a new class of pyrrolobenzodiazepine derivatives and the first compound containing the pyrrolobenzodiazepine ring system isolated from a bacterium.

EXPERIMENTAL

^{1}H-NMR: Varian EM-390 (TMS, δ-values). ^{13}C-NMR: Varian CFT-20 (CD_3COCD_3 as internal standard). Mass spectra: Varian MAT 731 (exact mass measurements), Varian CH7A (direct), Finnigan 3200 with data system 6100 (direct). IR: Perkin-Elmer 720. UV: Beckmann 25. Optical rotation: Perkin-Elmer Polarimeter 241. M.ps: Kofler (uncorrected). Column chromatography:

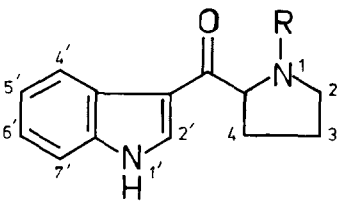

OH
N
Z
O
[(CH3)2N = CHCl]Cl
CHCl3/ - 20°C
Cl
Indol-MgBr
Et2O
NH
Pd/C H2
EtOH
Z = COOCH2C6H5
9
10
11
12
OR
NO2
N
THF
R = CH3 : 13
R = CH2C6H5: 14
1/1'; 8/8'

Scheme 3.

Table 2. ^{1}H-NMR data of 2-pyrrolidenyl-3'-indolyl ketones

Substance	Conditions	NH	H-2'+	H-4'	H-5'-7'	H-2	H-3/H-4	H-5	OCH_2Ar OCH_3	CH_2ArH	H-5''	H-4''+6''
11	CD_2Cl_2	9.70 m	7.92 d3	8.46 m	7.15-7.60 m	5.03-5.20 m	1.8 - 2.5 m	3.70 m	5.08§ s 5.25§§ s	7.18§ s 7.50§§ s		
	$(CD_3)_2SO$ RT	11.57 br.s	8.49 m	8.27 m	7.57 m 7.27 m	5.25 m	2.36 m 1.90 m	3.56 t	4.89§ s 5.10§§ s	7.11§ s 7.42§§ s		
	$(CD_3)_2SO$ 100°		8.27 m	8.23 m	7.50 1H m 7.20 2H m	5.17 dd8.1;3.6	2.37 m 1.93 m	3.55 t6.6	5.00 s	7.20		
12	$(CD_3)_2SO$	++	8.46 s	8.26 m	7.55 1H m 7.25 2H m	4.50 t	2.25 m 1.73 m	2.85 m 3.04 m				
13	$(CD_3)_2SO$	11.50§ 11.57§§	8.35§ 8.62§§ d2	8.25 dd	7.15-7.65 m	5.15§ m 5.48§§ m 5.33 m(110°C)	2.4 m 1.97 m	3.50 m	3.86§ s 3.95§§ s 3.90 s(110°C)		7.73 t7.5	7.15-7.65 m 6.80§ (=H-4'')
14	$(CD_3)_2SO$	11.47§ 11.53§§	8.60 d2	8.27 m	7.18-7.62 m	5.20-5.58 m	2.4 m 1.93 m	3.67 m	5.25§ s 5.34§§ s 5.3 br.s(80°)	7.47	7.67 t8	7.18-7.62 m 6.80§ (=H-4'')

+ At lowest field due to the deshielding effect of the carbonyl group. ++ Both NH signals cannot be detected. §§§ Signals marked by the same symbol (§, §§) belong to the same conformer (§ to §§ at 25° ~ 1:4)



11: R = $COOCH_2C_6H_5$
12: R = H
13: R = $COC_6H_3(2\text{-}NO_2)(3\text{-}OCH_3)$
14: R = $COC_6H_3(2\text{-}NO_2)(3\text{-}OCH_2C_6H_5)$

Silicagel 60, Merck, 0.04–0.06 mm. Tlc: Silicagel plates F 254/366, Woelm. Hplc: Polygosil 60-D10 and 60-D10 RP-8 (reversed phase), Macherey & Nagel.

Isolation of **1**. 360 l of the culture medium[2] of *Klebsiella pneumoniae* var. *oxytoca* were extracted with ethyl acetate and the concentrated organic phase was treated with 5% aquous HCl. To the aquous phase Na_2CO_3 was added till a pH of 8.5 was reached. The ethyl acetate extract of the alkaline solution was chromatographed ($CHCl_3$ with increasing—up to 50%—amounts of CH_3OH). The main fraction was redissolved in ethyl acetate and treated with an 0.6% aquous solution of H_3BO_3 to remove 2,3-butanediol (the main metabolite of *Klebsiella*). The residue after evaporation of the organic phase was chromatographed again ($CHCl_3/CH_3OH$, 10:1) and finally purified by reversed phase hplc (CH_3OH/H_2O, 2:1). Yield: 48 mg **1** m.p. 168°. $[\alpha]_D^{25}$ (CH_3OH) = + 126.8°, $[\alpha]_{578}^{25}$ = + 131.3°. ^{1}H-NMR: see Table 1. ^{13}C-NMR: 168.0, 146.1, 137.9, 136.0, 126.4, 124.3, 123.3, 122.6, 121.1, 120.0, 120.0, 117.7, 117.2, 116.0, 112.6, 62.2, 61.1, 48.6, 31.4, 23.1, UV(CH_3OH): 219 (4.46), 239 (sh), 255 (sh), 278 (sh), 288 (sh), 232 (3.47). Mass spectrum: see Ref. 1. Mol. weight (mass spectroscopically) 333,1469 (Calc. for $C_{20}H_{19}N_3O_2$ 333.1477).

(11*S*, 11*aS*) - 1,2,3,10,11,11*a* - *Hexahydro* - 9 - *hydroxy* - 11 - [3' - (1' - *methyl*) - *indolyl*] - 5*H* - *pyrrolo*[2,1-*c*][1,4]*benzodiazepin* - 5 - *one* (**3**). To a CH_3OH solution of **1** an ether solution of CH_2N_2 was added till the yellow color remained. After 15 min the solvent was distilled off and the residue purified by tlc ($CHCl_3/CH_3OH$ 8:1). Mol. weight (mass spectroscopically): 347.

(11*S*, 11*aS*) - 9 - *Acetoxy* - 10 - *acetyl* - 1,2,3,10,11,11*a* - *hexahydro* - 11 - (3' - *indolyl*) - 5*H* - *pyrrolo*[2,1-*c*][1,4]*benzodiazepin* - 5 - *one* (**4**) and (11*S*, 11*aS*) - 9 - *Acetoxy* - 1', 10 - *diacetyl* - 1,2,3,10,11,11*a* - *hexahydro* - 11 - (3' - *indolyl*) - 5*H* -

pyrrolo[2,1-*c*][1,4]*benzodiazepin* - 5 - *one* (**5**). 14 mg **1** were treated at room temp with 3 ml of a mixture of pyridine/Ac_2O (2:1) for 16 hr. After addition of H_2O the solvents were removed *in vacuo*. Column chromatography ($CHCl_3/CH_3OH$ 12:1) yielded 2 mg **5** (mol. weight (mass spectroscopically) 459; MS *v.*[1]) and 12 mg **4** (mol. weight (mass spectroscopically) 417; MS *v.*,[1] NMR: *v.* Table 1, IR *v.* text). Reaction at 60° yields predominantly **5**.

(11*S*, 11*aS*) - 10 - *Acetyl* - 1,2,3,10,11,11*a* - *Hexahydro* - 9 - *hydroxy* - 11 - (3' - *indolyl*) - 5*H* - *pyrrolo*[2,1-*c*][1,4]*benzodiazepin* - 5 - *one* (**6**). 1 mg **4** was treated with 0.5 ml 18% HCl and 0.5 ml dioxane at 60° for 4 hr. Dilution with H_2O, extraction with $CHCl_3$ and purification by tlc ($CHCl_3/CH_3OH$ 8:1) yielded **6**. Mol. weight (mass spectroscopically) 375 MS *v.*[1]

(2*S*) - *N* - *Benzyloxycarbonyl* - 2 - *pyrrolidinyl* - 3' - *indolyl* - *ketone* (**11**). 6.35 g (0.05 mole) $[CHCl{=}N(CH_3)_2]^+Cl^-$[23] in 30 ml abs. $CHCl_3$ were reacted with a $CHCl_3$ soln of 12.5 g (0.05 mole) of (S) - N - benzyloxycarbonylprolin (**9**). After 15 min the solvent was removed and 100 ml abs. ether were added. This ether soln was added dropwise at 0° under vigorous stirring to a soln of indole Grignard (21.8 g = 0.2 mole C_2H_5Br, 4.8 g = 0.2 mole Mg, 11.7 g = 0.1 mole indole in 1 l ether). A precipitate was formed immediately. The stirring was continued for 1.5 hr. The reaction product was hydrolysed by addition of 250 ml conc. NH_4Cl soln, the precipitate was filtered off and recrystallized from C_2H_5OH. Yield 9.8 g (53%), m.p. 203°. $[\alpha]_D^{25}$ (CH_3OH) = −102.7°, $[\alpha]_{578}^{25}$ = −107.2°. UV (CH_3OH) 211 (4.44), 242 (4.12), 258 (sh), 299 (4.12). NMR: s. Table 2. MS: *m/z* 348 (7): M^+, 204 (21): [M - indolylcarbonyl]$^+$, 160(31): $[204-CO_2]^+$, 144 (31): [indolylcarbonyl]$^+$ 91(100): $C_7H_7^+$. IR: 1670, 1640 (sh) cm^{-1} (CO).

(2*S*) - 2 - *Pyrrolidinyl* - 3' - *indolyl* - *ketone* (**12**). 8.5 g (24 mmole) **11** in 300 ml hot C_2H_5OH were added to a suspension of 0.1 g Pd–C (10%) in 50 ml C_2H_5OH prehydrogenated for 2 hr. Hydrogenation for 2 hr, removal of the catalyst, evaporation to dryness and recrystallization from C_2H_5OH yielded 5.0 g (95%) (**12**). m.p. 168°. $[\alpha]_D^{25}$ = −82.6°, $[\alpha]_{578}^{25}$ = −87.0°. UV (CH_3OH): 207 (4.41), 237 (4.12), 258 (3.96), 299 (4.10). NMR: *v.* Table 2. MS: *m/z* 214 (2): M^+, 144 (14): [indolylcarbonyl]$^+$, 70 (100): [M − indolylcarbonyl]$^+$. IR: 1630 cm^{-1} (CO).

(2*S*) - *N* - (3 - *Benzyloxy* - 2 - *nitrobenzoyl*) - 2 - *pyrrolidinyl* - 3' - *indolyl* - *ketone* (**14**). 1.09 g (4 mmole) 3 - benzyloxy - 2 - nitrobenzoic acid[24] in 25 ml abs. THF and 0.64 g (4 mmole) carbonyldiimidazole were stirred for 1 hr. After addition of 0.86 g (4 mmole) **12** stirring was continued for 16 hr. The precipitate was filtered off and recrystallized from C_2H_5OH: 580 mg (31%) **14** m.p. 222°. $[\alpha]_D^{25}$ = −214.8°, $[\alpha]_{578}^{25}$ = −227.4°. UV (CH_3OH) 205 (4.73), 240 (4.26), 257 (4.09), 298 (4.18). NMR: *v.* Table 2. MS: *m/z* 469 (0.03): M^+, 325 (2): [M − indolylcarbonyl]$^+$, 256 (11): $(C_7H_7O)(NO_2)C_6H_3CO^+$, 144 (55): [indolylcarbonyl]$^+$, 91 (100): $C_7H_7^+$. IR 1635 cm^{-1} (CO).

(11*S*, 11*aS*) - *and* (11*R*, 11*aS*) - 1,2,3,10,11,11*a* - *Hexahydro* - 9 - *hydroxy* - 11 - (3' - *indolyl*) - 5*H* - *pyrrolo*[2,1-*c*][1,4]*benzodiazepin* - 5 - *one* (**1** + **1'**). 235 mg (0.5 mmole) **14** in 500 ml hot C_2H_5OH were added to a suspension of 50 mg Pd–C (10%) in 100 ml C_2H_5OH prehydrogenated for 2 hr. After hydrogenation for 4 hr the catalyst was filtered off and the solution evaporated to dryness. Yield: 163 mg (98%) of **1** + **1'**. Separation by hplc (hexane/isopropanol 3:1) and recrystallization from CH_3OH yielded 92% **1'** and 8% **1**. **1**: $[\alpha]_D^{25}$ = +98.1°, $[\alpha]_{578}^{25}$ = +101.3° (77% optical purity). In all other respects synthetic and natural **1** proved to be identical. **1'**: m.p. 252°. $[\alpha]_D^{25}$ = +431.7°, $[\alpha]_{578}^{25}$ = +455.6° (opt. purity should also be 77% only). UV (CH_3OH): 221 (4.45), 255 (sh), 278 (sh), 287 (3.55), 355 (3.31). NMR: *v.* Table 1. MS: *v.*[1] IR: 1620 cm^{-1} (CO).

(2*S*) - *N* - (3 - *Methoxy* - 2 - *nitrobenzoyl*) - 2 - *pyrrolidinyl* - 3' - *indolylketone* (**13**). 3.94 g (20 mmole) 2 - Methoxy - 3 - nitrobenzoic acid[25] reacted as described for **14** yielded 2.59 g (33%) **13** m.p. 278°. $[\alpha]_D^{25}$ = −255.5°, $[\alpha]_{578}^{25}$ = −270.1°. UV: 207 (4.72), 238 (4.28), 255 (4.12), 297 (4.23). NMR: *v.* Table 2, MS: *m/z* 393 (0.5): M^+, 249 (8): [M − indolylcarbonyl]$^+$, 180 (100): $(CH_3O)(NO_2)C_6H_3CO^+$, 144 (100): [indolylcarbonyl]$^+$. IR: 1665, 1610 cm^{-1} (CO).

(11*S*, 11*aS*) - *and* (11*R*, 11*aS*) - 1,2,3,10,11,11*a*, - *Hexahydro* - 11 - (3' - *indolyl*) - 9 - *methoxy* - 5*H* - *pyrrolo*[2,1-*c*][1,4]*benzodiazepin* - 5 - *one* **8** + **8'**). 393 mg (1 mmole) **13** when reacted as described for **1** + **1'** yielded 333 mg (96%) **8** + **8'**. Separation by hplc (hexane/isopropanole 5:1) gave **8** and **8'** in a ratio of 48:52.

8: m.p. 130°, $[\alpha]_D^{25}$ = +64.1°, $[\alpha]_{578}^{25}$ = +67.1° (optical purity probably as for synthetic **1**). UV (CH_3OH): 216 (4.51), 236 (sh), 255 (sh), 280 (sh), 288 (sh), 300 (sh). NMR: *v.* Table 1. MS: *v.*[1] mol. weight (mass spectroscopically) 347. IR: 1615 cm^{-1} (CO).

8': m.p. 141, $[\alpha]_D^{25}$ = +319.7°, $[\alpha]_{578}^{25}$ = +337.5° (optical purity probably as for **1'**). UV (CH_3OH): 223 (4.61), 255 (sh), 280 (sh), 290 (sh), 334 (3.51). NMR: *v.* Table 1. MS: *v.*[1] mol. weight (mass spectroscopically) 347. IR: 1615 cm^{-1} (CO).

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