Stereochemistry of 1,2,3-Trisubstituted Tetrahydro-β-carbolines

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Several 1,2,3-trisubstituted tetrahydro-β-carboline diastereoisomers have been synthesized and studied by ^1H and ^{13}C n.m.r. methods and CD spectroscopy. The relative configurations and predominant conformation have been established.

Recently, there has been considerable interest in probing the stereochemistry of 1,2,3-trisubstituted tetrahydro-β-carbolines, because of their importance in the synthesis of many pharmacologically active alkaloids. Many authors have attempted to develop a method for the rapid and reliable determination of the stereochemistry of such compounds, particularly by using ^{13}C n.m.r. spectroscopy.[1–3] Stereochemical considerations utilizing ^{13}C chemical shifts were, in many cases, based on the direct adoption of *X*-ray results, by assuming predominant conformations in solutions.[4] However, as the number of analogues investigated gradually increased, it became clear that while the 1,3-disubstituted derivatives could be analysed by exploiting the fact that the C-1 and C-3 carbons of the *cis* isomer resonate downfield of those of the *trans* isomer,[5,6] the extension of this method to 1,2,3-trisubstituted derivatives leads to ambiguities.[1,2] Recently Bailey and Hollinshead reported, on the basis of the ^{13}C n.m.r. investigation of 1,N(2)-benzyl,3-trisubstituted derivatives, that the carbon chemical-shift difference ($\delta_{NCcis} - \delta_{NCtrans} \approx 7$ ppm) provides a safe way of determining the relative configuration and stereostructure of 1,2,3-trisubstituted tetrahydro-β-carbolines.[3]

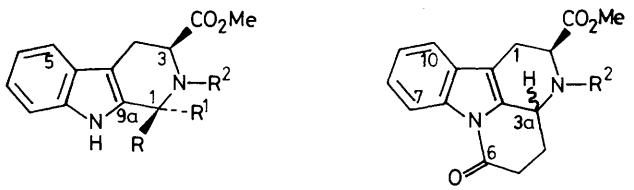
Results and Discussion

During the synthesis of different indole derivatives, we investigated analogous N(2)-benzyl and N(2)-methyl compounds. Our n.m.r. data revealed, that the above-mentioned statement does not hold in general, and the configurations and conformations of such compounds must be carefully investigated according to the actual substituents.

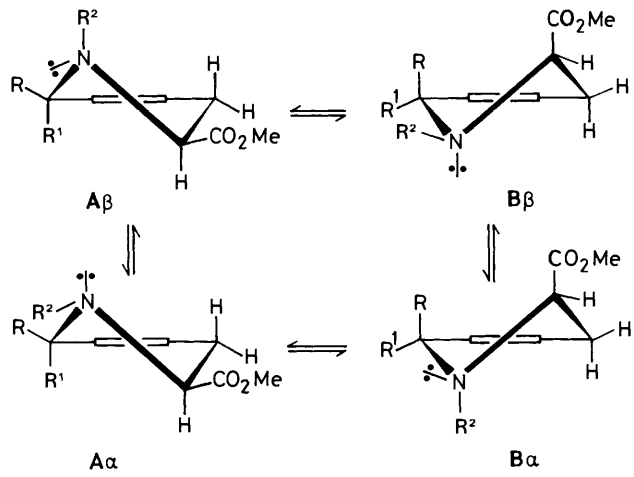
Derivatives (**1**)–(**4**) served as model compounds during our investigations. The *cis* or *trans* character of these compounds was proved by their unambiguous synthesis from (**5**)–(**8**); reactions which involved retention of configuration.

In 1,2,3-trisubstituted tetrahydro-β-carbolines, the tetrahydropyridine ring can exist in two half-chair conformations (**A** and **B**, Scheme), for which the activation energy of interconversion is small. Moreover, the small energy barrier for the inversions of the N(2) atom must also be taken into consideration. Although for half-chair conformations the equatorial position of the substituents is normally more favoured, this situation can be easily invalidated if steric interactions between the substituents and/or the other parts of the molecule are involved.

The 1-H and 3-H chemical shifts can be expected to show characteristic differences according to their equatorial or axial position. The measured chemical shifts (Table 1), however, reveal that 1-H resonances show such small differences in compounds (**1**)–(**4**), that its value cannot safely be used to derive



R	R^1	R^2	3a-H	R^2
(**1**) H	$[CH_2]_3OH$	Me	(**5**) α	H
(**2**) $[CH_2]_3OH$	H	Me	(**6**) β	H
(**3**) H	$[CH_2]_3OH$	CH_2Ph	(**7**) α	Me
(**4**) $[CH_2]_3OH$	H	CH_2Ph	(**8**) β	Me
(**9**) H	$[CH_2]_3OH$	H	(**11**) α	CH_2Ph
(**10**) $[CH_2]_3OH$	H	H	(**12**) β	CH_2Ph



Scheme.

stereochemical conclusions. Essentially the same can be said about 3-H, although its Δδ values are somewhat larger, and in the *cis* isomers δ3-H tends to be smaller. The vicinal couplings of 3-H, however, allow the assessment of the **A**:**B** conformational ratios. Table 2 shows the relevant coupling constants, calculated by the analysis of the corresponding ABX spin systems. For conformer **A**, the expected value for $^3J(3,4_{\beta,ax})$ is 10.9 Hz, as found in compounds (**5**) and (**7**), those characterized by a rigid **A** conformation. For **B**, the assessed value for $^3J(3,4_{\beta,eq})$ is *ca.* 1.7 Hz, by reference to the corresponding values found in (**6**) and (**8**), which are fixed in the **B** conformation. From these values the **A**:**B** ratios for compounds (**1**)–(**4**) can be calculated (Table

Table 1. Characteristic ^1H chemical shifts for compounds (**1**)–(**4**) ($CDCl_3$; Me_4Si).

Compound	OMe	3-H	4-H_β	4-H_α	1-H	1′-$H_{x,y}$[a]	2′-H_2	3′-H_2	NMe	$NCH_{x,y}$
(**1**)	3.72	3.96	3.11	3.05	3.99	1.94, 2.05	1.60–1.75	3.55–3.60	2.51	—
(**2**)	3.77	3.63	3.07	2.99	3.82	2.03, 2.17	1.54, 1.62	3.55–3.65	2.38	—
(**3**)	3.76	4.07	3.17	3.07	3.95	1.80, 1.87	1.50, 1.60	3.37, 3.45	—	3.61, 3.89
(**4**)	3.63	3.83	3.22[b]	2.99[b]	4.01	1.68, 1.88	*ca.* 1.76	3.54	—	3.92

[a] *x* denotes the more shielded geminal signal. [b] These assignments were supported by n.O.e. difference measurements (see Table 3).

Table 2. Characteristic ^1H–^1H coupling[a] and **A**:**B** conformation ratio for compounds (**1**)–(**4**) ($CDCl_3$).

Compound	(3,4$_\beta$)	(3,4$_\alpha$)	(4$_\beta$,4$_\alpha$)	(1,4$_\beta$)	(1,4$_\alpha$)	**A**:**B** (%)
(**1**)	8.0	5.3	16.0	1	1	68:32
(**2**)	10.9	4.3	15.4	2.3	1.5	100:0
(**3**)	9.2	5.2	15.9	1	1	82:18
(**4**)	4.9	6.6	15.9	1.6	1.2	35:65
	4.6[b]	5.7[b]	15.6[b]	1.5[b]	1.0[b]	32:68

[a] The given values resulted from the analysis of the corresponding ABX spin system. [b] Measured in CD_3OD.

2). As these ratios show, only compound (**2**) is conformationally homogeneous, achieving a 1,3-diequatorial arrangement. For the other *cis* compound (**4**) **A** has a significant contribution to the conformational equilibrium, which is in contrast with its predominant **B** conformation reported earlier.[4] Note, that for the *cis* compounds the contribution of the diaxial conformer increases within the NH–NMe–NBz series (0 ⟶ 65%) together with the increasing bulk of the N-substituent. In the case of the analogous *trans* (**3**), a predominance of the **A** conformation was assumed.[4] Our measurements show, however, that the contribution of **B** is quite large (18%). For compound (**1**), the percentage of **B** increases even further. This might be attributed to the decreased steric repulsion between NMe and the C-1 substituent, with respect to that of the much bulkier NBz substituent.

The above conclusions were further supported by 1D- and 2D-n.O.e.[7,8] measurements, which also revealed some information about the stereo-position of the N(2)-substituent. The results of the 1D-n.O.e. difference experiments are listed in Table 3.

For compound (**1**), the intensity enhancement of 4-H_β upon the irradiation of NMe, together with the enhancement on the NMe when irradiating the 4-H protons proves the presence of the **A** β-conformer in the equilibrium. The saturation of NMe also results in a positive n.O.e. on 3-H, indicating that the **A** β-conformer cannot be predominant. The n.O.e. found on 3-H on saturation of 1′-H_x, is in accordance with the presence of conformation **A** in the equilibrium.

For compound (**3**), irradiation of 3-H gives an n.O.e. on 1′-H_2, which proves the presence of the **A** conformation, similarly as in the case of (**1**). The **A** β-conformation, again, cannot be exclusive, because of the positive enhancement found on 3-H when NCH_y is irradiated.

Since compound (**2**) can be considered as conformationally homogeneous (**A**) according to the relevant coupling constants, the n.O.e. results reveal direct information about the position of the NMe substituent. The saturation of NMe enhances 4-H_β, thus proving the presence of the **A** β-structure. The 1-H and 3-H signals also show positive enhancements in this experiment, which, on the other hand, shows the participation of the **A** α-conformation in the equilibrium. This finding is also corroborated by the n.O.e. found on the NMe when saturating 1-H. The n.O.e. caused on 3-H upon irradiation of 1-H accords with the *trans* diaxial disposition of 1-H and 3-H.

In compound (**4**), the n.O.e. results clearly indicate that in contrast with compound (**2**), in this case conformer **B** has a more pronounced contribution to the equilibrium. This can be concluded from the enhancements seen on 3-H and 4-H_α, when 4-H_β and NCH_2 are irradiated, respectively. The saturation of 1′-H_2 enhances the benzylic *ortho* proton signals, which indicates that the **B** α-conformation cannot be the only one present. Since, for this compound, the accomplishment of further 1D-n.O.e. measurements proved to be extremely difficult, due to the very closely spaced signals, we used the NOESY spectrum to obtain further stereochemical information. The NOESY crosspeak between 4-H_α and NCH_2 provides additional evidence on the presence of the **B** α-structure, while the connectivity from 4-H_β to NCH_2 proves the contribution of the **A** β-structure.

It is known, that the stereoselective interaction of the N lone electron pair and an antiperiplanar vicinal proton results in a diamagnetic shielding of the latter.[9] In such cases, salting out produces especially large paramagnetic shifts, which can in many cases provide useful stereochemical information.[10] However, the acid-sensitivity of our compounds did not allow the employment of this method. Owing to the same CHN electron pair interaction, the corresponding ^1J(C,H) value generally shows a characteristic decrease of *ca.* 5–10 Hz.[11] The measured values for compounds (**1**)–(**4**) (Table 4) show that their employment for stereochemical considerations in such conformationally inhomogeneous cases is practically useless.

The ^{13}C chemical shifts for compounds (**1**)–(**4**) and (**9**)–(**10**) are collected in Table 4. Both *cis* and *trans* isomers were distinguished on the basis of different α, β, and γ SCS values caused by axial or equatorial substituents.[12] By comparing the C-4 chemical shifts for compounds (**1**) and (**3**) with those of model compound (**9**), the observed upfield shifts (−4.4 and −4.0 ppm) show the presence of mainly axially oriented NMe and NBz groups. Compounds (**2**) and (**10**) both exist in the **A** conformation, therefore the comparison of their C-4 chemical shifts allows an approximate assessment of the $\mathbf{A}_\alpha$:$\mathbf{A}_\beta$ ratio. The upfield shift caused by the NMe group is only −1.8 ppm, in contrast with the γ Me SCS value (*ca.* −4 ppm) found for similar half-chair conformations.[13] This suggests that the ratio of the **A** α- and β-conformations is *ca.* 1:1. The 5.1 ppm upfield shift of C-4 in (**4**) compared with that of (**10**) is caused not only by the γ-*gauche* effect, but also partly by the presence of **B** conformers which contribute to the extent of *ca.* −2 ppm, so that the appearance of conformers with equatorial NBz can be concluded. In our case the NCH_2 carbon shifts differ only by 3.9 ppm for the *trans*-(**3**) and *cis*-(**4**) compounds. Moreover, for the NMe derivatives the *cis* isomer is the one which shows the smaller NMe chemical shift. The method of determination of relative configurations suggested by Bailey and Hollinshead thus cannot be generalized for other substituents. The reason for this might be the fact that the conformational equilibrium is obviously rather sensitive to the characteristics of the actual substituents.

For optically active tetrahydro-β-carbolines the stereochemical features can be conveniently investigated by CD. Compounds (**1**)–(**4**) were synthesized from L-tryptophan such that the absolute configuration at C-α was preserved, thus (**1**)

Table 3. Results of n.O.e. measurements for compounds (**1**)–(**4**).

Compound	Proton irradiated	n.O.e. observed (%) 3-H	4-H_β	4-H_α	1-H	1′-$H_{x,y}$	NMe	NCH_2	*ortho* (benzene)	7-H	NH
(**1**)	NMe	2	2		8			—	—		
	4-H_2	6					2	—	—	3	
	1′-H_x	7.5			3	H_y:3					2
(**2**)	NMe	5	3		6			—	—		
	1-H	3				4.5	4.5	—	—		
	1′-H_x				4	H_y:6		—	—		2
	1′-H_y				2	H_x:8	4	—	—		2
(**3**)	NCH_x	7			12		—	H_y:26.5	6		
	1-H					H_y:4	—	H_x:4			
	3-H			5		10	—				
(**4**)	NCH_2			1	1	1	—		11		
	1-H					1.5	—		2.5		1
	3-H			4			—		4		
	4-H_β	2.5		8			—		0.5	0.5	
	1′-H_2				4		—	2	1.5		2.5

Table 4. Characteristic ^{13}C chemical shifts and ^1J(C,H) coupling constants for compounds (**1**)–(**4**), (**9**), and (**10**), referenced to internal Mc_4Si.

	δ(*J*/Hz) *trans-* (**1**)	*cis-* (**2**)	*trans-* (**3**)	*cis-* (**4**)	*trans-* (**9**)	*cis-* (**10**)
C-1	58.2 (135)	60.0 (136)	55.5 (139)	57.8 (134)	50.5	52.6
C-3	59.6 (135)	64.6 (140)	56.7 (137)	59.3 (138)	52.5	56.3
C-4	20.7	23.3	21.1	20.6	25.1	25.7
C-5	106.5	107.1	107.0	106.4	107.0	107.7
C-9a	133.9	132.7	134.7	133.8	135.3	134.9
C-1′	32.2	28.5	30.9	30.6	33.0	31.9
C-2′	29.9	29.3	28.7	29.3	29.7	28.5
NCH_2			53.6	57.5		
NCH_3	38.4	37.1				

Table 5. CD spectra of compounds (**1**)–(**4**) in acetonitrile solution.

Compd.	$c/10^{-4}$ mol dm^{-3}	λ/nm (Δε)
(**1**)	18.4	295 (−0.30), 286 (−0.18), 265 (−0.82), 234 (−3.32), 217 (+8.3)
(**2**)	4.85	294 (+1.05), 286 (+1.18), 279 (+1.23), 274 (+1.29), 232 (+7.60), 211 (−10.5)
(**3**)	6.46	290 (+0.96), 280 (+1.25), 275 (+1.22), 266 (+0.84), 259 (+0.43), 249 sh (+0.12), 236 (−1.2)
(**4**)	4.88	294 (+0.75), 281 (+0.55), 271 (+0.39), 249 (−1.12), 233 (+6.8), 210 (−7.2)

and (**3**) are (1*R*,3*S*)-, and (**2**) and (**4**) (1*S*,3*S*)-diastereomers, respectively. For compound (**2**) existing in conformation **A**, one would expect [14] three positive Cotton effects around 295–290 (α-band), 290–260 (p-band), and 233 nm, as well as a negative Cotton effect around 215 nm. These latter two CD bands are stronger than the others and can be associated with the β,β′-transitions of the benzene chromophore. Their shapes are similar to that of a typical CD couplet [15] although they have, of course, a completely different origin. The CD spectrum of (**2**) is of exactly the same shape and magnitude as that of the reference compound yohimbane, thus proving that under the conditions of this measurement (very dilute solution in acetonitrile) the same conformation must prevail. The common issue of n.m.r. and CD studies is that (**1**) in solution can adopt two conformations; their ratios differ somewhat, but not too drastically. The CD spectrum of (**1**) (in acetonitrile, Table 5) fits to an approximate 1:2 mixture of **A** and **B**. One must, of course, take into account that the concentrations, for experimental reasons, differ appreciably for these two types of measurement. In concentrated solutions of (**4**) (in $CDCl_3$ or CD_3OD) the **A**:**B** ratio has been determined as 1:2, however, the CD spectrum is typical for that conformation with both these substituents in the quasiequatorial position. From the $\Delta\varepsilon_{max}$ values within the first CD band one can deduce that this conformation is by far the predominant one. An additional (negative) CD at 250 nm (−0.8) can be taken as an indication that some MO interactions also exist between the indole and the benzyl system. Unfortunately no *X*-ray structure of (**4**) is available, but in the comparable case of methyl *cis*-2-benzyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-yl propionate all three substituents (on C-1, C-3, and the N-atom) are in axial positions.[4] Thus, depending on the immediate environment of such a molecule only other molecules of some type tightly packed in the crystal; non-rigid clusters of such molecules in concentrated solution; only solvent molecules in the very dilute solution; either one or the other extreme conformation of the heteroring is the preferred one.

From the n.m.r. spectra of (**3**) follows that, in contrast with the other isomer, the benzylic protons show markedly different chemical shifts, thus indicating the presence of one preferred conformation around the N–CH_2Ph bond. The ratio of the two ring conformations **A**:**B** was determined from n.m.r. as *ca.* 4:1. This must then also be the most preferred conformation in dilute solution, as is born out by the positive CD at *ca.* 292 nm ($\Delta\varepsilon = +0.8$). At shorter wavelength the shape of the CD curve deviates, however, appreciably from that of the other investigated compounds, as well as from that of the model yohimbanes,[14] proving that the benzyl chromophore interacts strongly with the indole π-system. The results of our investigations shows clearly that the conformation of such an indole derivative may not only depend on the characteristics of the substituents but also on the concentration.

Experimental

I.r. spectra were measured with a Spectromom 2000 spectro-

photometer. The ^1H and ^{13}C n.m.r. spectra were recorded on a Bruker AM-400 spectrometer at room temperature. In the 1D measurements 32K data points were used for the FID. The ^{13}C assignments were supported by 2D carbon–proton correlated measurements where 1K × 1K data matrices were transformed. N.O.e. difference and 2D correlated experiments were recorded by using the Bruker software package. For homonuclear n.O.e. experiments a delay time of 4.5 s was applied. The n.m.r. spectra prove that compounds investigated contain < 1% impurities. CD spectra were recorded with a Jobin-Yvon-ISA Dichrographe Mark III connected on-line to a PDP-8e computer. All melting points are uncorrected.

Synthesis of 2β-*Methoxycarbonyl*-3-*methyl*-1,2,3,3aα,4,5-*hexahydrocanthin*-6-*one* (**7**), 1β-(3-*Hydroxypropyl*)-3β-*methoxycarbonyl*-2-*methyl*-1,2,3,4-*tetrahydro*-2-*carboline* (**2**), 3-*Benzyl*-2β-*methoxycarbonyl*-1,2,3,3aα,4,5-*hexahydrocanthin*-6-*one* (**11**) *and* 2-*Benzyl*-1β-(3-*hydroxypropyl*)-3β-*methoxycarbonyl*-1,2,3,4-*tetrahydro*-2-*carboline* (**4**).—(**7**): 2β-Methoxycarbonyl-1,2,3,3aα,4,5-hexahydrocanthin-6-one (**5**)[16] (1.50 g, 5.3 mmol) formic acid (99%, 3 cm^3), and formalin (30%, 4 cm^3) were stirred at 90 °C for 1 h. The mixture was poured into ice, made alkaline with 5% aqueous Na_2CO_3 to pH 8, and extracted with CH_2Cl_2 (80 cm^3). The combined organic layer was dried ($MgSO_4$) and evaporated. The resulting oil was crystallized from MeOH to yield (**7**) (1.2 g, 76%), m.p. 154–156 °C, $[\alpha]_{546}^{20} = -132°$ (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 720 and 1 685 cm^{-1} (C=O); *m/z* 298 (33%) and 239 (100). $\delta_H(CDCl_3)$ 3.02 (1-H_β), 2.95 (1-H_α), 3.62 (2-H), 3.67 (3a-H), and 2.39 (NMe); δ_C 23.5 (C-1), 65.1 (C-2), 57.4 (C-3a), 26.6 (C-4), 33.0 (C-5), and 36.8 (NMe).

(**2**): Compound (**7**) (1.90 g, 6.4 mmol) was dissolved in a mixture of CH_2Cl_2 (25 cm^3) and MeOH (25 cm^3), and $NaBH_4$ (0.7 g, 18.4 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 3 h. The solution was evaporated *in vacuo* and the residue was treated with water (100 cm^3) and extracted with CH_2Cl_2 (70 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting oil was crystallized from Et_2O to yield (**2**) (1.4 g, 72.6%), m.p. 136–138 °C, $[\alpha]_{546}^{20} = -107°$ (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 745 cm^{-1} (C=O); *m/z* 302 (8%) and 243 (100).

(**11**): Compound (**5**)[16] (2.20 g, 7.73 mmol), dissolved in dimethylformamide (40 cm^3), $NaHCO_3$ (2 g, 23 mmol) and benzyl bromide (1.1 cm^3, 9 mmol) were stirred under reflux for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was treated with water (80 cm^3) and extracted with CH_2Cl_2 (100 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting oil was crystallized from MeOH to give (**11**) (2.30 g, 79.5%), m.p. 164–165 °C, $[\alpha]_{546}^{20} = -18°$ (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 740 and 1 700 cm^{-1} (C=O); *m/z* 374 (19%) and 315 (100); $\delta_H(CDCl_3)$ 3.14 (1-H_β), 3.00 (1-H_α), 4.00 (2-H), 4.13 (3a-H), and 3.90 (NCH_2Ph); δ_C 22.9 (C-1), 62.8 (C-2), 56.4 (C-3a), 27.8 (C-4), 32.5 (C-5), and 53.2 (NCH_2Ph).

(**4**): (**11**) (2.40 g, 6.4 mmol) was dissolved in a mixture of CH_2Cl_2 (30 cm^3) and MeOH (30 cm^3), and $NaBH_4$ (0.7 g, 18.4 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 3.5 h. The solution was evaporated *in vacuo* and the residue was treated with water (120 cm^3) and extracted with CH_2Cl_2 (100 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting oil was crystallized from MeOH to give (**4**) (1.75 g, 72.4%), m.p. 127–129 °C, $[\alpha]_{546}^{20} = -49°$ (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 725 cm^{-1} (C=O); *m/z* 378 (5%) and 319 (100).

Synthesis of 2β-*Methoxycarbonyl*-3-*methyl*-1,2,3,3aβ,4,5-*hexahydrocanthin*-6-*one* (**8**), 1α-(3-*Hydroxypropyl*)-3β-*methoxycarbonyl*-2-*methyl*-1,2,3,4-*tetrahydro*-β-*carboline* (**1**), 3-*Benzyl*-2β-*methoxycarbonyl*-1,2,3,3aβ,4,5-*hexahydrocanthin*-6-*one* (**12**), *and* 2-*Benzyl*-1α-(3-*hydroxypropyl*)-3β-*methoxycarbonyl*-1,2,3,4-*tetrahydro*-β-*carboline* (**3**).—(**8**): 2β-Methoxycarbonyl-1,2,3,3aβ,4,5-hexahydrocanthin-6-one (**6**)[16] (1.50 g, 5.3 mmol) formic acid (99%, 3 cm^3), and formalin (30%, 4 cm^3) were stirred at 90 °C for 1 h. The warm mixture was poured onto ice, made alkaline with 5% aqueous Na_2CO_3 to pH 8, and extracted with CH_2Cl_2 (90 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting oil was crystallized from MeOH to yield (**8**) (1.25 g, 79%), m.p. 127–131 °C, $[\alpha]_{546}^{20}$ +65° (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 720 and 1 700 cm^{-1} (C=O); *m/z* 298 (88%) and 239 (100); $\delta_H(CDCl_3)$ 3.09 (1-H_β), 312 (1-H_α), 312 (1-H_α), 3.95 (2-H), 4.27 (3-H), and 2.69 (NMe); δ_C 24.0 (C-1), 61.8 (C-2), 52.2 (C-3a), 27.7 (C-4), 33.1 (C-5) and 39.7 (NMe).

(**1**): Compound (**8**) (2.06 g, 6.7 mmol) was dissolved in a mixture of CH_2Cl_2 (30 cm^3) and MeOH (30 cm^3), and NaBH4 (0.7 g, 18.4 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 3 h. The solution was evaporated *in vacuo* and the residue was treated with water (100 cm^3) and extracted with CH_2Cl_2 (80 cm^3). The combined organic layers were dried ($MgSO_4$), and evaporated. The resulting oil was crystallized from Et_2O to give (**1**) (1.50 g, 74.3%), m.p. 124–125 °C, $[\alpha]_{546}^{20} = +62°$ (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 730 cm^{-1} (C=O); *m/z* 302 (16%) and 243 (100).

(**12**): Compound (**6**)[16] (2.20 g, 7.73 mmol), dissolved in dimethylformamide (40 cm^3), $NaHCO_3$ (2 g, 23 mmol) and benzyl bromide (1.1 cm^3, 9 mmol) were stirred under reflux for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was treated with water (90 cm^3) and extracted with CH_2Cl_2 (120 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting oil was crystallized from MeOH to yield (**12**) (1.85 g, 64%), m.p. 165–166 °C, $[\alpha]_{546}^{20} = -47°$ (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 740 and 1 700 cm^{-1} (C=O); *m/z* 374 (43%) and 283 (100); $\delta_H(CDCl_3)$ 3.10 (1-H_β), 3.01 (1-H_α), 3.91 (2-H), 4.55 (3a-H), and 3.98 and 4.26 (^2J 14.4 Hz, NCH_2Ph); δ_C 24.1 (C-1), 57.7 (C-2), 51.5 (C-3a), 28.4 (C-4), 33.1 (C-5), and 54.9 (NCH_2Ph).

(**3**): Compound (**12**) (2.30 g, 6.1 mmol) was dissolved in a mixture of CH_2Cl_2 (30 cm^3) and MeOH (30 cm^3), and then $NaBH_4$ (0.7 g, 18.4 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 3 h. The solution was evaporated *in vacuo* and the residue was treated with water (110 cm^3) and extracted with CH_2Cl_2 (80 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated. The resulting oil was crystallized from Et_2O to yield (**3**) (1.95 g, 84.7%), m.p. 163–164 °C, $[\alpha]_{546}^{20} = +55°$ (*c* 1, CH_2Cl_2); ν_{max}(KBr) 1 700 cm^{-1} (C=O); *m/z* 378 (11%) and 319 (100).

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