Sedum alkaloids. XI. Synthesis of sedinone and sedacrine by application of anodic oxidation

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α-Methoxycarbamate **12**, synthetic precursor of the 2,6-disubstituted alkaloids of *Sedum acre*, was obtained in high yield from 2-phenacylpiperidine **5**; the key step of the synthesis rests on the anodic methoxylation, which allows the functionalization of carbon 6. Nucleophilic substitution of the methoxy group by an acetonyl chain leads, after the required transformations, to sedinone **23**. Bromomethoxylation of the enecarbamate **19** followed by dehydrohalogenation and nucleophilic substitution of the methoxy group leads to sedacrine **33**. In both cases, the nucleophilic substitution of the methoxy group leads to a *cis* 2,6-disubstituted piperidine derivative.

Key words: synthesis, piperidine alkaloids, anodic methoxylation.

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L'α-méthoxycarbamate **12**, précurseur synthétique des alcaloïdes 2,6-disubstitués de *Sedum acre* a été obtenu avec un rendement élevé au départ de la 2-phénacylpipéridine **5**; l'étape clé de la synthèse est la méthoxylation anodique qui permet la fonctionnalisation du carbone 6. La substitution nucléophile du groupe méthoxy par une chaîne acétonyle conduit, après aménagement fonctionnel, à la sédinone **23**. La bromométhoxylation du ènecarbamate **19** suivie d'une déhydrohalogénation et de la substitution du groupe méthoxy permet d'accéder à la sédacrine **33**. Dans les deux cas, la substitution du groupe méthoxy conduit à un dérivé pipéridinique *cis* 2,6-disubstitué.

Mots clés : synthèse, alcaloïdes pipéridiniques, méthoxylation anodique.

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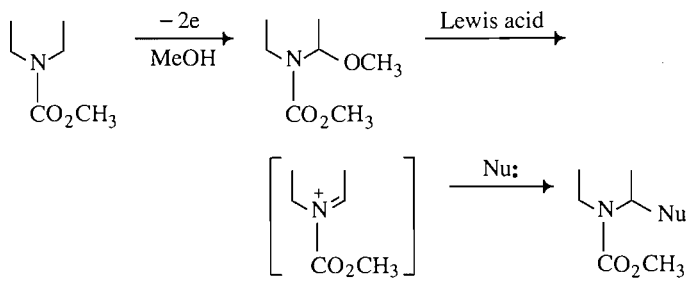
Introduction

Piperidine alkaloids constitute a large family of compounds, many of which exhibit a wide range of physiological activities. Because of this aspect, intense activity has been devoted to the isolation and structure determination of bases of this class and to the development of general routes for their synthesis (1). In this context, during the last few years, several methods were developed for the synthesis of 2,6-disubstituted piperidine alkaloids and especially for the bases isolated from *Solenopsis* species (2). Although electrochemical methoxylation emerged recently as a powerful method for the synthesis of piperidine derivatives (3, 4), no application to the synthesis of 2,6-disubstituted piperidine alkaloids has yet been recorded. Our interest in *Sedum* and related alkaloids prompted us to evaluate the potentiality of anodic methoxylation as a key step for the synthesis of members of this subgroup.

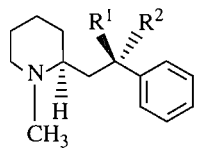
Anodic methoxylation allows the easy preparation of α-methoxyamides and α-methoxycarbamates. These compounds constitute interesting synthetic intermediates because of their facile conversion into the corresponding *N*-acyliminium ions, which have been shown to be versatile electrophiles. The combination of anodic methoxylation and nucleophilic substitution, e.g., with silyl enol ethers, appears to be a choice method for the introduction of a new C—C bond α to the nitrogen atom of cyclic amides and carbamates (Scheme 1).

The electrochemical preparation and the synthetic usefulness of α-methoxycarbamates were investigated by T. Shono in particular, who developed the syntheses of several alkaloids based on the sequence of Scheme 1. In the field of 2-alkylpiperidine alkaloids, application of this sequence leads, *inter alia*, to the synthesis of sedamine **1** and allosedamine **2** (5, 6).

We pointed out, in a preceding communication, that all the 2,6-disubstituted alkaloids isolated from *Sedum acre* contain a (−)-sedamine moiety (7). This feature allows their synthesis to be based on the alkylation at C-6 of a common 2-substituted piperidine derivative. In this respect, the anodic methoxylation process seemed promising because it was observed that the least



SCHEME 1



1 $R^1 = H, R^2 = OH$
2 $R^1 = OH, R^2 = H$

substituted α-carbon atom of *N*-acylpiperidines is oxidized specifically (5); a rationalization of this observation has been offered (8).

Results and discussion

We wish to report here the synthesis of the alkaloids sedinone **23** and sedacrine **33** via the precursor **12** using anodic methoxylation methodology.

Preparation of the precursor 12

2-Phenacylpiperidine **5** was obtained (70% overall yield) by the method we described earlier (9) via hydrogenolysis (H_2, Pd/C) of the isoxazoline **4** resulting from the cycloaddition between the nitrone **3** and phenylacetylene (Scheme 2). Acylation of the nitrogen atom of **5** with methyl chloroformate under

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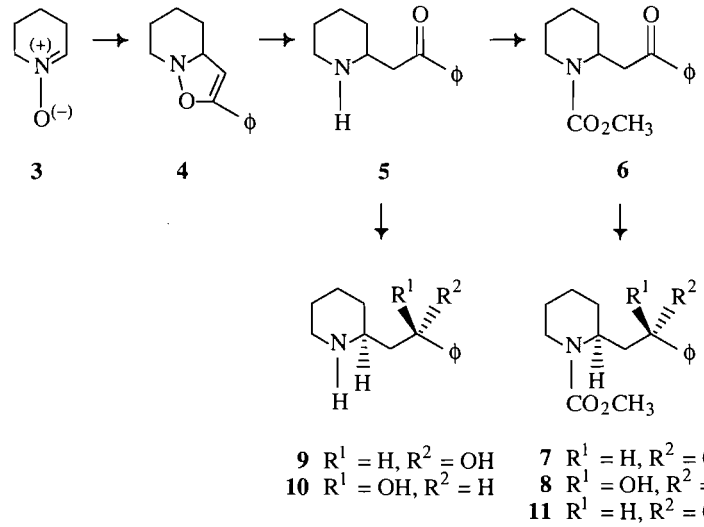
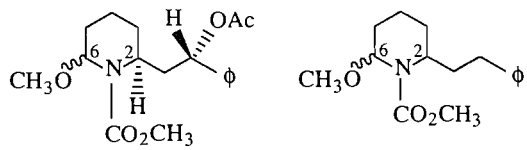


SCHEME 2

Schotten–Baumann conditions yielded quantitatively the carbamate **6**. The same compound had previously been obtained in comparable yield through the sequence anodic methoxylation – nucleophilic substitution (6). Reduction of the keto group of **6** with $NaBH_4$ in MeOH furnished a 70:30 mixture of the diastereoisomeric alcohols **7** and **8**. However, a 98:2 mixture of **7** and **8** was obtained when the reduction was performed with lithium tri-*tert*-butoxyaluminium hydride in THF. Under the same conditions, 2-phenacylpiperidine **5** was transformed into a 35:65 mixture of **9** and **10**. The high selectivity observed for the reduction of the ketone function of the carbamate **6** with $Li(tBuO)_3AlH$ is worthy of note because the sequence described above constitutes a simple and efficient route for the synthesis of sedamine-type derivatives. Thus, norsedamine **9** and sedamine **1** were obtained by basic ethanolysis and by $LiAlH_4$ reduction of **7** respectively. Another efficient stereoselective synthesis of sedamine-type derivatives was described recently (10). On the other hand, it had been established previously that allosedamine-type derivatives are accessible in high yield and with a high stereoselectivity via cycloaddition between nitrone **3**, or derivatives of **3**, and styrene (11).

Acetylation of the alcohol **7** yielded quantitatively **11**, which was submitted to anodic oxidation.

All anodic oxidations performed in this study were carried out at room temperature in methanol containing Et_4NOTs as a supporting electrolyte, in an undivided cell equipped with two vitreous carbon electrodes; a constant potential of 8.00 V was applied. After 8 F/mol of electricity was passed, the oxidation of the acetyl derivative **11** was complete and yielded quantitatively the 6-methoxylated compound **12**. In agreement with structure **12**, the ^{13}C nmr spectrum showed the presence of only 4 methylene groups. In the ^1H nmr spectrum ($CDCl_3$; 250 MHz) of **12**, H-2 and H-6 appeared as broad signals centered at 4.28 and 5.40 ppm respectively; a broadening of signals, due to the "slow" rotation around the N—CO_2CH_3 bond, is observed for all the compounds of this series. The broad signals at 3.28 and 3.72 ppm are attributed to the methoxy group at C-6 and to the N—CO_2CH_3 group, respectively, by comparison with the spectrum of the trideutero derivative obtained after anodic methoxylation of **11** in CD_3OD. When the ^1H nmr spectrum of **12** was recorded at 57°C, sharp signals were observed for the three methyl groups; there was no indication of the presence of another isomer. The configuration at C-6 was, however, not established.



12 **13**

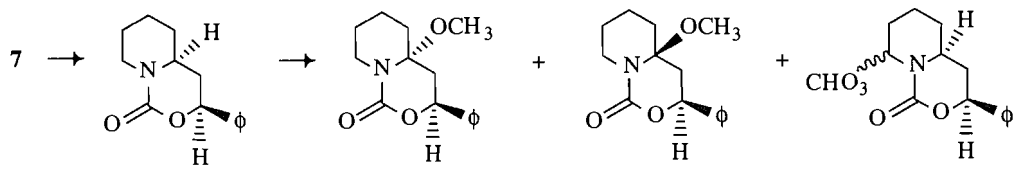
In the same experimental conditions, oxidation of the ketone **6** in methanol furnished regiospecifically the α-methoxycarbamate **13** in 96% yield. On the other hand, anodic methoxylation of the bicyclic derivative **14** (Scheme 3), obtained by transesterification from **7**, gave a mixture of isomers **15**, **16**, and **17** in a 1:1:1 ratio. In this case, the lack of regioselectivity can be ascribed to the strain induced in the less substituted iminium intermediate by the presence of the lactam cycle.

Synthesis of sedinone 23

The replacement of the methoxy group of **12** by an acetonyl side chain was carried out by treatment of **12** with 2-trimethylsilyloxypropene **20** in CH_2Cl_2 in the presence of $TiCl_4$, as a Lewis acid (Scheme 4). After column chromatography only one isomer, the 2,6-disubstituted derivative **18**, was isolated in 70% yield, along with the enecarbamate **19** (10% yield), which results from the elimination of methanol from **12**.

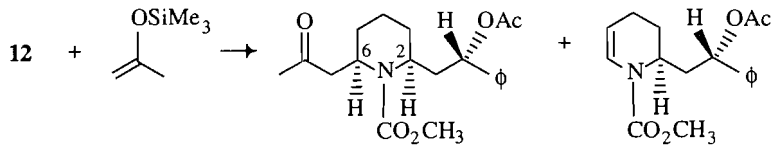
The *cis* configuration of **18** was not established at this stage but rests on the isolation of sedinone **23** as the major isomer after the steps described below (Scheme 5).

Protection of the keto group of **18** with ethylene glycol yielded quantitatively the dioxolane **21** whose carbomethoxyl and acetyl groups were reduced with $LiAlH_4$ to give the *N*-methyl derivative **22** (82% yield). Deprotection of **22** was carried out in boiling 0.1 N aqueous hydrochloric acid; a 90:10 mixture of sedinone **23** and 6-episedinone **24** was isolated (96% yield). The acetal **21** being a pure compound, the presence of **24** in the hydrolysis mixture must result from a partial epimerization of C-6 during the basic work-up after the deprotection step. While β-aminoketones such as **23** and **24** epimerize readily in basic medium, or simply in methanol, their salts are stereochemically stable. The epimerization therefore involves the nitrogen lone pair and may be accounted for by the path depicted in Scheme 6, as described for pelletierine and related compounds (23). As sedinone **23** is the major compound of the



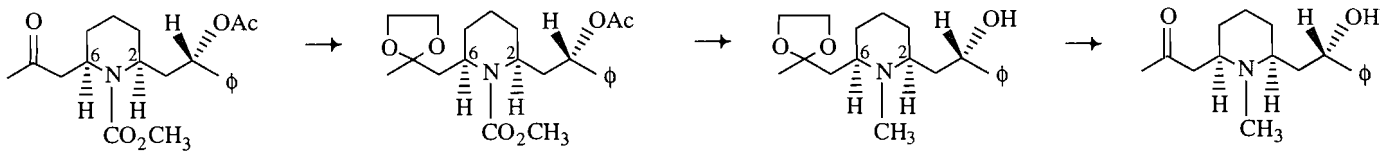
14 15 16 17

SCHEME 3

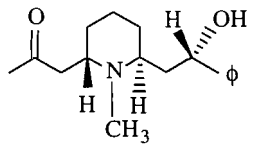


20 18 19

SCHEME 4



18 21 22 23



24

SCHEME 5

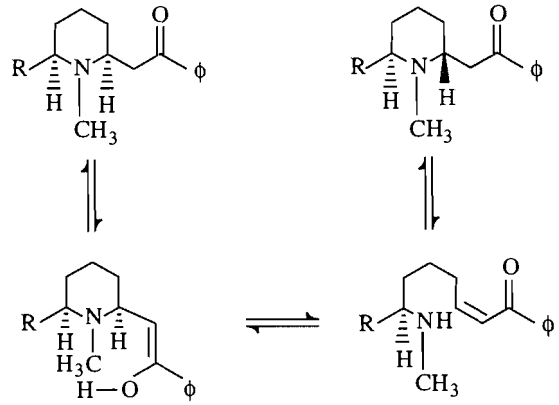
mixture, which is not the equilibrium mixture (8), the relative 2,6 configuration of **18** has to be *cis*.

The same sequence of reactions was applied to (−)-norsedamine **9** (12) as the starting material. After hydrolysis of the optically active acetal **22**, (−)-sedinone hydrochloride was isolated by fractional crystallization from the mixture of the hydrochlorides. The physical properties of the synthetic sample, including the optical rotation, were identical with those of the hydrochloride prepared from a natural sample of (−)-sedinone **23**.

Synthesis of sedacrine 33

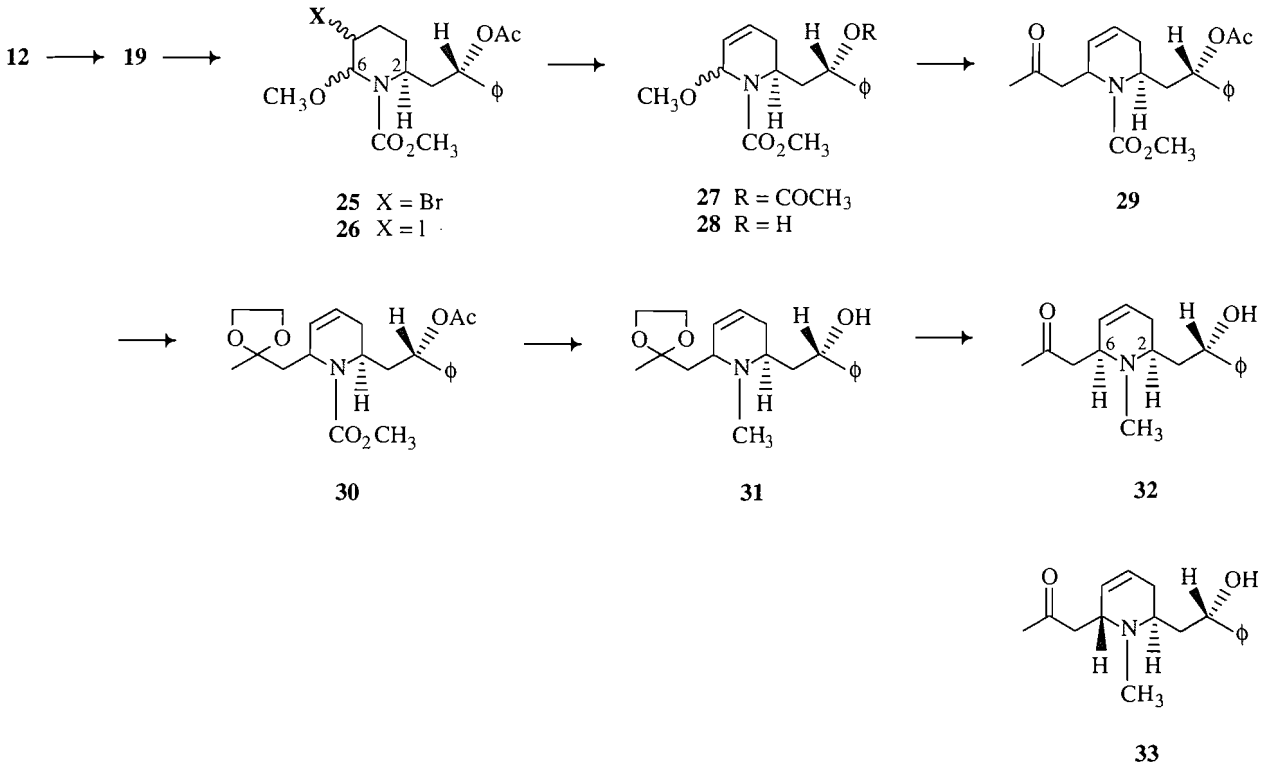
The synthesis of sedacrine **33** from the precursor **12** (Scheme 7) requires the introduction of a C=C double bond in position 4. Recently, Shono *et al.* (13) and Torii *et al.* (14) reported that enecarbamates, which are easily obtained from α-methoxycarbamates (15), are suitable precursors of 2-alkyl-6-methoxy-1,2,3,6-tetrahydropyridine derivatives via halomethoxylation followed by dehydrohalogenation. Consequently, the enecarbamate **19** was prepared by treatment of **12** with *p*-toluenesulfonic acid in benzene at room temperature (yield 96%).

Quantitative bromomethoxylation of **19** was carried out by addition of bromine to a methanolic solution of **19** in the presence of sodium methoxide to give **25**, which is likely to be a mixture of diastereoisomers. The 5-bromo derivative **25** was then subjected to dehydrohalogenation conditions (DBU in

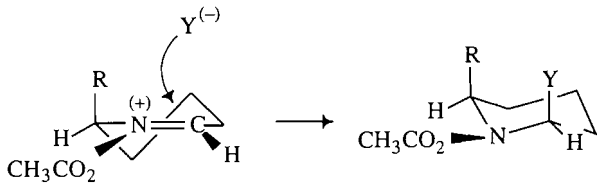


SCHEME 6

toluene at 87°C for 3 h). However, no elimination of HBr occurred. On the other hand, similar treatment of the corresponding 5-iodo derivative **26** (prepared from **19** in 85% yield) furnished a mixture of **27** and the corresponding alcohol **28**; the presence of the alcohol **28** is not surprising since DBU is known as a deprotective agent for acetyl groups (16). Treatment of the crude reaction mixture with acetic anhydride in pyridine led to the isolation of **27** in 93% yield from **26**. The nmr spectra did not allow us to establish whether **27** is a pure compound or a mix-



SCHEME 7



SCHEME 8

ture of diastereoisomers. The nucleophilic substitution of the methoxy group of **27** by an acetonyl chain was carried out in CH_2Cl_2 at −78°C in the presence of $TiCl_4$; after chromatography, the substitution product was isolated in 64% yield. The stereochemistry at C-6 was not established at this stage but the product must contain at least 90% of the *cis* compound **29**, as can be inferred from the isolation of a 9:1 mixture (by ^1H nmr) of episedacrine **32** and sedacrine **33** (84% overall yield) after a sequence of reactions identical with that described above for the synthesis of sedinone **23**: i.e., protection of the keto group of **29**, $LiAlH_4$ reduction of the acetal **30**, and deacetalization. After equilibration in methanol, a 6:1 mixture (by ^1H nmr) of **33** and **32** was obtained.

When the same sequence was applied to (−)-**12** as the starting material, (−)-sedacrine **33**, identical in all respects with the natural compound, was obtained.

In the two examples discussed above, the nucleophilic substitution of the methoxy group leads with high stereoselectivity to the *cis* 2,6-disubstituted piperidine derivative; this stereochemical control of the C-6 configuration is worthy of note and results from the stereoelectronically preferred axial attack of the nucleophile (8, 17) on the *N*-acyliminium intermediate, whose favoured conformation has an axial alkyl group at C-2 (18, 19) (Scheme 8). Other examples of *cis* stereoselectivity in the substitution of a methoxy group by a nucleophile have already been reported (24, 25).

Experimental

Melting points were determined on a Kofler microscope and are uncorrected. Mass spectral data were obtained on a Micromass 7070 spectrometer. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ with TMS as internal standard on a Bruker WM 250 spectrometer. Optical rotations were measured on a Perkin Elmer 141 polarimeter.

Preparation of the carbamate **6**

K_2CO_3 (5.805 g) and methyl chloroformate (3.9 mL) were successively added to a stirred solution of 2-phenacylpiperidine **5** (3.870 g) in water (100 mL). After 15 h, NH_4OH was added and the basic solution was extracted with $CHCl_3$ (2 × 100 mL). The combined $CHCl_3$ layers were evaporated and the residue was filtered through a short column of alumina to afford quantitatively the carbamate **6** (4.966 g), mp 92°C after crystallization from hexane/ethyl acetate 5:1 (lit. (6) mp 89.2°C); ^1H nmr δ: 7.98 (2H), 7.5 (3H), 4.86 (1H, m, H2), 4.06 (1H, m, H6e), 3.62 (3H, s, CO_2CH_3), 3.29 (1H, dd, J = 9 and 15 Hz, H7), 3.15 (1H, dd, J = 6 and 15 Hz, H7′), 2.93 (1H, dt, H6a), 1.69–1.38 (6H, m); ^{13}C nmr δ: 198.3 (C8), 156.0 (NCO), 137.0, 133.1, 128.7, 128.2, 52.4 (CH_3), 48.3 (C2), 40.0 and 39.3 (C6 and C7), 28.0 and 25.3 (C3 and C5), 18.9 (C4); ms, *m/z*: 261 (11%), 230 (2), 202 (39), 156 (6), 142 (100), 141 (35), 105 (47), 77 (31), 70 (11).

Reduction of **6** *with Li(tBuO)$_3$AlH*

The carbamate **6** (152 mg) was dissolved in THF (15 mL) and Li(tBuO)$_3$AlH (1.480 g) was added. The mixture was then refluxed for 4 h. After cooling, some drops of water were added and the mixture was filtered through Celite and evaporated to dryness. The residue was dissolved in water (70 mL), basified with NH_4OH, and extracted with $CHCl_3$ (2 × 70 mL). Evaporation of the solvent gave a mixture (153 mg) of **7** and **8** (98:2 by ^1H nmr). **7** and **8** were separated by chromatography on alumina ($CHCl_3$); **7** (oil): ^1H nmr δ: 7.3 (5H, m), 4.74 (1H, m, H8), 4.43 (1H, m, H2), 3.92 (1H, m, H6e), 3.66 (3H, s), 2.80 (1H, m, H6a), 2.17 (1H, m, H7), 1.89 (1H, m, H7′), 1.61–1.36 (6H, m); ^{13}C nmr δ: 156.5 (NCO), 144.7, 128.3, 127.4, 125.8, 72.4 (C8), 52.5 (CH_3), 48.7 (C2), 39.9 and 39.6 (C6 and C7), 29.0 (C3), 25.4 (C5), 19.1 (C4); ms, *m/z*: 263 (7%), 186 (3), 142 (100). **8** (oil): ^1H nmr δ: 7.3 (5H, m), 4.60 (1H, m), 4.47 (1H, m), 4.05 (1H, m), 3.75 (3H, s),

.85 (1H, m, H6a), 2.22 (1H, m, H7), 2–1.3 (7H, m); ms, *m/z*: 263 (7%), 186 (3), 142 (100).

Reduction of ***6*** *with* $NaBH_4$

The carbamate **6** (131 mg) was dissolved in methanol (5 mL) and $NaBH_4$ (100 mg) was added. After 2 h at room temperature, the solvent was evaporated and water was added to the residue; extraction with $CHCl_3$ afforded, after evaporation of the solvent, 132 mg of a 70:30 mixture (by ^1H nmr) of **7** and **8**.

Reduction of 2-phenacylpiperidine ***5*** *with* $Li(tBuO)_3AlH$

2-Phenacylpiperidine **5** (143 mg) was treated with $Li(tBuO)_3AlH$ (358 mg) in refluxing THF (10 mL) for 15 h. After addition of some drops of water, the mixture was filtered through Celite and the solvent was evaporated. The residue was dissolved in water (50 mL), basified with NH_4OH, and extracted with $CHCl_3$ (3 × 50 mL). Evaporation of the combined organic layers gave a mixture (140 mg) of norsedamine **9** and norallosedamine **10** (35:65 by ^1H nmr (20)).

Preparation of norsedamine ***9*** *from* ***7***

A solution of **7** (144 mg) and KOH (750 mg) in EtOH (7.5 mL) was heated under reflux for 6 h. After evaporation of the solvent, the residue was dissolved in water (15 mL), basified with NH_4OH, and extracted with $CHCl_3$ (2 × 15 mL). Evaporation of the combined organic layers afforded norsedamine **9** (98 mg, 87% yield), whose ^1H nmr and mass spectra were identical with those reported in the literature (20).

Preparation of sedamine ***1*** *from* ***7***

To a solution of the carbamate **7** (120 mg) in THF (15 mL) was added $LiAlH_4$ (115 mg) and the mixture was refluxed for 6 h. Some drops of AcOEt and water were added and the mixture was filtered through Celite and evaporated to dryness. The residue was dissolved in 0.2 N aqueous HCl (50 mL) and extracted with $CHCl_3$ (2 × 3 mL). The aqueous phase was then basified with NH_4OH and extracted with $CHCl_3$ (3 × 50 mL). Evaporation of the combined $CHCl_3$ phases and filtration through a short column of alumina afforded homogeneous sedamine **1** (95 mg); the mass and ^1H nmr spectra of the base are identical with those reported in the literature (20).

Acetylation of the alcohol ***7***

The alcohol **7** (1.560 g) was treated at room temperature for 15 h with a mixture of pyridine (7 mL) and Ac_2O (7 mL). After evaporation of the solvent, filtration of the residue through a short column of alumina ($CHCl_3$) yielded **11** quantitatively (1.805 g; oil); ^1H nmr δ: 7.3 (5H), 5.73 (1H, dd, *J* = 6 and 8 Hz, H8), 4.32 (1H, m, H2), 4.04 (1H, m, H6e), 3.65 (3H, s), 2.93 (1H, m, H6a), 2.37 (1H, m, H7), 2.04 (3H, s), 1.89 (1H, m, H7′), 1.62–1.37 (6H, m); ^{13}C nmr δ: 170.1, 156.0 (NCO), 140.7, 128.5, 128.1, 126.7, 74.3 (C8), 52.4, 48.3 (C2), 39.4 and 36.7 (C6 and C7), 28.6 (C3), 25.5 (C5), 21.1, 19.1 (C4); ms, *m/z*: 305 (1%), 262 (2), 245 (17), 186 (10), 142 (100).

Preparation of the bicyclic derivative ***14***

A solution of the carbamate **7** (169 mg) and KOH (17 mg) in methanol (10 mL) was heated under reflux for 3.5 h. After the solvent was evaporated, the residue was dissolved in water (15 mL), basified with NH_4OH, and extracted with $CHCl_3$ (2 × 15 mL). Evaporation of the $CHCl_3$ and crystallization from hexane afforded **14** (127 mg, 86% yield); mp 97–98°C; ^1H nmr δ: 7.32 (5H), 5.17 (1H, dd, *J* = 2 and 12 Hz, H8), 4.54 (1H, m, H6e), 3.46 (1H, ddt, *J* = 2.5 and 11 Hz, H2), 2.73 (1H, dt, *J* = 3 and 13 Hz, H6a), 2.29 (1H, ddd, *J* = 2.5 and 14 Hz, H7), 1.97–1.20 (7H, m); ms, *m/z*: 231 (34%), 187 (16), 186 (24), 127 (28), 104 (100).

Anodic methoxylations

All anodic methoxylations were carried out at room temperature in methanol (analytical grade) containing Et_4NOTs as a supporting electrolyte, in an undivided cell equipped with two vitreous carbon electrodes, an exit tube (containing $CaCl_2$) for venting purposes, and a magnetic stirring bar. The carbon electrodes (0.3 cm in diameter, immersed 3.5 cm into the solution) were spaced 1.0 cm apart. The potentiostat was a homemade apparatus. I_0 is the current intensity at the beginning of the anodic oxidation.

Preparation of ***12*** *by anodic methoxylation*

Into the electrolysis cell were placed **11** (313 mg), Et_4NOTs (80 mg), and 15 mL of methanol. The solution was stirred for 10 min and a constant potential of 8.00 V was applied. After 8 F/mol of electricity was passed (15.5 h, I_0 = 17.1 mA), some drops of NH_4OH were added to the solution and the solvent was evaporated; the residue was dissolved in water (70 mL), basified with NH_4OH, and extracted with $CHCl_3$ (2 × 70 mL). The combined $CHCl_3$ layers were evaporated and the residue was filtered ($CHCl_3$) through a short column of alumina to afford quantitatively the 6-methoxylated derivative **12** (oil, 343 mg); ^1H nmr δ: 7.3 (5H, m), 5.80 (1H, dd, H8), 5.40 (1H, m, H6), 4.28 (1H, m, H2), 3.72 (3H, s, NCO_2CH_3), 3.28 (3H, br, C6-OCH_3), 2.08 (3H, s), 2.4–1.4 (8H, m); ^{13}C nmr δ: 170.3, 156.7, 82.5 (C6), 73.9 (C8), 55.4 (C6-OCH_3), 52.6, 47.9 (C2), 40.0 (C7), 30.5 (C5), 27.5 (C3), 21.2 ($OCOCH_3$), 13.7 (C4); ms, *m/z*: 303 ($M^{+\cdot} - CH_3OH$, 4%), 275 (12), 260 (2), 243 (5), 214 (11), 172 (54), 140 (58), 71 (100).

Preparation of ***13*** *by anodic methoxylation*

Ketone **6** (82 mg) and Et_4NOTs (45 mg) in 15 mL of methanol were electrolyzed as described above to afford, after 8F/mol of electricity was passed (8.5 h, I_0 = 11.0 mA), the 6-methoxylated derivative **13** (oil, 88 mg, 96% yield), ^1H nmr δ: 8.1–7.3 (5H), 5.44 (1H, m, H6), 4.84 (1H, m, H2), 3.73 (3H, m, NCO_2CH_3), 3.34 (3H, m, C6-OCH_3); ^{13}C nmr δ: 198.7 (C8), 156.8, 137.2, 133.1, 128.6, 82.6 (C6), 55.5 (C6-OCH_3), 52.7, 47.4 (C2), 42.0 (C7), 30.1 and 27.6 (C3 and C5), 13.6 (C4); ms, *m/z*: 259 ($M^{+\cdot} - CH_3OH$, 17%), 172 (21), 154 (60), 140 (43), 105 (52), 77 (28), 75 (16), 71 (100).

Anodic methoxylation of ***14***

The bicyclic compound **14** (296 mg) and Et_4NOTs (150 mg) in 15 mL of methanol were electrolyzed as described above. After 7 F/mol of electricity was passed (9.5 h, I_0 = 28.1 mA) the mixture was treated in the usual way. Fractionation of the residue by chromatography on alumina ($CHCl_3$) afforded four fractions. The first fraction contained the pure 2-methoxylated derivative **15** (or **16**) (oil, 59 mg); ^1H nmr δ: 7.35 (5H, m), 5.11 (1H, dd, *J* = 2 and 12 Hz, H8), 4.12 (1H, m, H6e), 3.15 (3H, s, OCH_3), 2.93 (1H, dt, *J* = 3 and 13 Hz, H6a), 2.48 (1H, dd, *J* = 12 and 14 Hz, H7a), 1.96 (1H, dd, *J* = 2 and 14 Hz, H7e); ms, *m/z*: 261 (2%), 260 (4), 230 (56), 216 (19), 186 (100), 105 (76), 104 (55), 82 (69), 77 (48), 71 (51), 55 (58). The second fraction (85 mg) was a mixture of the same 2-methoxylated derivative **15** (or **16**) and the 6-methoxylated derivative **17** (1:3 by ^1H nmr); ms *m/z*: 261. **17**: ^1H nmr δ: 7.35 (m), 5.70 (m, H6), 5.18 (dd, *J* = 2 and 12 Hz, H8), 3.36 (s, OCH_3). The third fraction (34 mg) was a mixture of **17** and the other 2-methoxylated derivative **16** (or **15**) (1:1 by ^1H nmr). The last fraction contained the pure 2-methoxylated derivative **16** (or **15**) (oil, 71 mg): ^1H nmr δ: 7.35 (5H, m), 5.35 (1H, dd, *J* = 2 and 12 Hz, H8), 4.28 (1H, m, H6e), 3.31 (3H, s, OCH_3), 3.09 (1H, dt, *J* = 3 and 13 Hz, H6a), 2.45 (1H, dd, *J* = 2 and 15 Hz, H7e), 1.94 (1H, dd, *J* = 12 and 15 Hz, H7a); ms, *m/z*: 261 (4%), 260 (2), 230 (73), 186 (100), 105 (30), 104 (75), 82 (63), 77 (29), 55 (48).

Nucleophilic displacement of the methoxy group of ***12***

To a stirred solution of $TiCl_4$ (638 mg) in dichloromethane (10 mL) at −78°C, under an atmosphere of nitrogen, was added dropwise a solution of **12** (1012 mg) in the same solvent (10 mL). After the mixture was stirred for 5 min, a solution of 2-trimethylsilyloxypropene (21) (770 mg), contaminated by ca. 25% of $(CH_3)_3SiOSi(CH_3)_3$) in dichloromethane (10 mL), was added dropwise. The resulting reaction mixture was stirred for 2 h at −78°C and then allowed to reach room temperature (2 h). Cold water (100 mL) was then added and the solution was stirred for 10 min. After basification with NH_4OH, the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were evaporated and the residue was fractionated by chromatography on alumina ($CHCl_3$) to afford **18** (oil, 766 mg, 70% yield) and the enecarbamate **19** (oil, 90 mg, 10% yield). **18**: ^1H nmr δ: 7.3 (5H, m), 5.77 (1H, dd, *J* = 4 and 10 Hz, H8), 4.67 (1H, m, H6), 4.30 (1H, m, H2), 3.69 (3H, s), 2.65 (2H, m, H9 and H9′), 2.16 and 2.10 (2 × 3H), 2.07–1.5 (8H, m); ^{13}C nmr δ: 206.5, 170.3, 156.2, 140.6, 128.6, 128.1, 126.5, 73.7 (C8), 52.6, 48.4 (C9), 47.5 and 46.4 (C2 and C6), 41.3 (C7), 30.0 (C11), 28.0 and 27.3 (C3 and C5), 21.2,

13.9 (C4); ms, *m/z*: 361 (<0.5%), 318 (0.5), 301 (15), 242 (10), 212 (4), 198 (19), 154 (10), 140 (100), 85 (11), 83 (18), 75 (6), 43 (16). **19**: ^{1}H nmr δ: 7.29 (5H, m), 6.72 (1H, m, H6), 5.84 (1H, dd, J = 4 and 9 Hz, H8), 4.88 (1H, m, H5), 4.38 (1H, m, H2), 3.75 (3H, s), 2.06 (3H, s), 2.26–1.55 (6H, m); ^{13}C nmr δ: 170.4, 153.8, 140.9, 128.7, 128.2, 126.7, 124.0 (C6), 105.9 (C5), 73.4 (C8), 53.0, 47.7 (C2), 37.7 (C7), 24.2 (C3), 21.3, 17.7 (C4); ms, *m/z*: 303 (8%), 260 (2), 243 (11), 186 (4), 184 (8), 142 (16), 141 (38), 140 (100), 139 (81), 138 (90), 124 (15), 43 (28).

*Preparation of **21** from **18***

A solution of **18** (117 mg), ethylene glycol (128 mg), and $TsOH \cdot H_2O$ (3 mg) in 20 mL of benzene was heated under reflux for 20 h in a Dean–Stark apparatus. After evaporation of the solvent, the residue was dissolved in water (20 mL), basified with NH_4OH, and extracted with chloroform ((2 × 20 mL). The combined organic layers were evaporated and the residue was filtered through a short column of alumina ($CHCl_3$) to yield quantitatively **21** (oil, 131 mg) after evaporation: ^{1}H nmr δ: 7.3 (5H), 5.76 (1H, dd, J = 4 and 10 Hz, H8), 4.4 and 4.3 (2H, m, H6 and H2), 3.92 (4H, m, OCH_2CH_2O), 3.70 (3H, s), 2.09 (3H, s), 1.37 (3H, s), 2.1–1.4 (10H, m); ^{13}C nmr δ: 170.3, 156.1, 140.8, 128.0, 126.5, 109.4 (C10), 73.8 (C8), 64.6 and 64.1 (OCH_2CH_2O), 52.4 (NCO_2CH_3), 47.6 and 47.1 (C2 and C6), 43.1 and 41.3 (C7 and C9), 28.3 and 27.4 (C3 and C5), 23.8 (C11), 21.1 (CH_3COO), 14.0 (C4); ms, *m/z*: 405 (0.5%), 345 (3), 242 (12), 154 (3), 143 (4), 140 (100), 87 (55), 43 (24).

*Preparation of **22** from **21***

To a solution of **21** (125 mg) in THF (15 mL) was added $LiAlH_4$ (117 mg). The mixture was then heated under reflux for 17 h. Some drops of AcOEt and then water were added and the mixture was filtered through Celite and evaporated to dryness. The residue was dissolved in 0.2 N aqueous HCl (30 mL) and extracted with $CHCl_3$ (3 × 7 mL). The organic phases were discarded and the aqueous phase was basified with NH_4OH and extracted with chloroform (2 × 30 mL). Evaporation of the chloroform afforded **22** (oil, 81 mg, 82% yield): ^{1}H nmr δ: 7.25 (5H, m), 4.94 (1H, dd, J = 3 and 11 Hz, H8), 3.92 (4H, m), 3.24–3.04 (2H, m, H2 and H6), 2.26 (3H, s, NCH_3), 1.36 (3H, s), 1.99–1.30 (10H, m); ^{13}C nmr δ: 145.3, 128.2, 126.9, 125.6, 109.5 (C10), 76.1 (C8), 64.9 (C6), 64.6 and 64.3 (OCH_2CH_2O), 59.1 (C2), 43.0 (C9), 40.7 (C7), 26.2 (NCH_3), 24.1 (C11), 25.3, 24.0, and 23.2 (C3, C4, C5); ms, *m/z*: 319 (7%), 276 (8), 218 (47), 198 (100), 98 (17), 96 (34), 87 (50), 43 (21).

*Hydrolysis of the acetal **22***

A solution of the acetal **22** (93 mg) in 0.12 N aqueous HCl (20 mL) was heated under reflux for 30 min. The mixture was then cooled, basified with NH_4OH, and extracted with $CHCl_3$ (2 × 30 mL). Evaporation of the combined organic layers afforded a mixture (77 mg) of sedinone **23** and 6-episedinone **24** (9:1 by ^{1}H nmr).

*Preparation of (−)sedinone **23** from (−)-norsedamine **9***

K_2CO_3 (600 mg) and methylchloroformate (0.4 mL) were successively added to a stirred solution of (−)-norsedamine **9** (401 mg) in water (30 mL). After 4 h, NH_4OH was added and the solution was extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were evaporated and the residue was filtered through a short column of alumina ($CHCl_3$) to afford quantitatively (−)-**7** (oil, 512 mg) after evaporation of the solvent; acetylation of the alcohol (−)-**7**, as described for racemic **7**, yielded (−)-**11** (oil), $[\alpha]_D$ −98° (*c* 1.7, MeOH), Anodic methoxylation of (−)-**11** afforded (−)-**12** (oil), $[\alpha]_D$ −96° (*c* 1.9, MeOH).

Starting from (−)-**12**, the sequence described for the racemic compound (nucleophilic displacement, acetalization, $LiAlH_4$ reduction, and hydrolysis) afforded a 90:10 mixture (by ^{1}H nmr) of (−)-sedinone **23** (^{1}H nmr, NCH_3 δ: 2.26) and 6-episedinone **24** (^{1}H nmr, NCH_3 δ: 2.33); 184 mg of the above mixture was dissolved in ether (25 mL) and treated with gaseous HCl. Crystallization of the precipitate from 2-butanone afforded (−)-sedinone hydrochloride (138 mg), mp 175–177°C; $[\alpha]_D$ −79° (*c* 2, MeOH) (lit. (22) mp 175°C; $[\alpha]_D$ −79.4° (*c* 1, MeOH)). The mass and ^{1}H nmr spectra of the free base were identical with those reported in the literature (7, 22).

*Preparation of the enecarbamate **19** from **12***

A mixture of **12** (655 mg) and $TsOH \cdot H_2O$ (68 mg) in benzene (50 mL) was stirred for 30 min at room temperature. The solvent was then evaporated and the residue was filtered through a short column of alumina ($CHCl_3$) to afford, after evaporation, the enecarbamate **19** (oil, 570 mg, 96% yield). The spectra of **19** are described above.

*Bromomethoxylation of the enecarbamate **19***

To a mixture of **19** (101 mg) and sodium (8.4 mg) in anhydrous methanol (8 mL) was added dropwise a solution of bromine (68 mg) in anhydrous methanol (7 mL). The mixture was then stirred for 15 min at room temperature. After evaporation of the solvent, the residue was dissolved in dilute NH_4OH (70 mL) and extracted with $CHCl_3$ (2 × 70 mL). The combined organic layers were evaporated and the residue was filtered through a short column of alumina ($CHCl_3$) to yield quantitatively the bromo derivative **25** (oil, 139 mg): ^{1}H nmr δ: 7.3 (5H, m), 5.75 (1H, dd, H8), 5.5 (1H, m, H6), 4.35 (2H, m, H2 and H5), 3.7 (3H, s, $NCOOCH_3$), 3.4 and 3.3 (3H, 2s, C6-OCH_3), 2.1 (3H, s), 2.6–1.4 (6H, m); ms, *m/z*: 383 (18%), 381 (18), 323 (17), 321 (17), 220 (77), 219 (100), 218 (>100), 217 (95), 216 (63), 204 (26), 202 (26), 140 (65), 94 (57), 43 (69).

*Iodomethoxylation of the enecarbamate **19***

To the enecarbamate **19** (288 mg) and sodium (24.2 mg) in anhydrous methanol (10 mL) was added dropwise a solution of iodine (271 mg) in anhydrous methanol (10 mL). After stirring for 1 h, the mixture was treated as described above to afford the 5-iodo derivative **26** (oil, 374 mg, 85% yield): ^{1}H nmr δ: 7.32 (5H, m), 5.79 (1H, dd, J = 5 and 9 Hz, H8), 5.64 and 5.48 (1H, 2m, H6), 4.5–4.2 (2H, m, H2 and H5), 3.76 (3H, s, $NCOOCH_3$), 3.34 (3H, m, C6-OCH_3), 2.09 (3H, s), 2.4–1.6 (6H, m); ms, *m/z*: 430 (2%), 401 (22), 302 (8), 274 (19), 266 (21), 261 (24), 242 (25), 197 (75), 170 (40), 140 (83), 138 (51), 43 (78).

*Dehydroiodation of **26***

(a) A mixture of **26** (154 mg) and DBU (161 mg) in anhydrous toluene (0.5 mL) was heated at 87°C for 4 h. After cooling, pyridine (1 mL) and acetic anhydride (1 mL) were added and the solution was allowed to stand for 16 h at room temperature. Water and NH_4OH were then added and the mixture was extracted with chloroform (2 × 50 mL). The combined $CHCl_3$ layers were evaporated and the residue was filtered through a short column of alumina ($CHCl_3$). Evaporation of the solvent afforded **27** (oil, 103 mg, 93% yield): ^{1}H nmr δ: 7.30 (5H, m), 5.90–5.73 (3H, H4, H5, and H8), 5.47 (1H, m, H6), 4.40 (1H, m, H2), 3.73 (3H, m), 3.40 (3H, m, C6-OCH_3), 2.05 (3H, s), 2.5–1.7 (4H, m); ^{13}C nmr δ: 170.1, 156.5, 140.4, 128.4, 128.0, 126.9, 125.8 and 124.8 (C4 and C5), 80.0 (C6), 73.9 (C8), 56.4 (C6-OCH_3), 52.8, 44.9 (C2), 39.8 (C7), 28.2 (C3), 21.2; ms, *m/z*: 333 (<0.5%), 302 (3), 273 (8), 242 (5), 241 (5), 170 (18), 138 (100), 94 (25), 43 (16).

(b) The iodo derivative **26** (687 mg) in anhydrous toluene (1.5 mL) was treated with DBU (717 mg). After 4 h at 87°C, fractionation of the mixture by chromatography on alumina ($CHCl_3$) afforded the acetyl derivative **27** (oil, 213 mg, 43% yield) and the alcohol **28** (oil, 99 mg, 23% yield): ^{1}H nmr δ: 7.3 (5H), 5.80 (2H, m, H4 and H5), 5.16 (1H, m, H6), 4.77 (1H, dd, J = 3 and 12 Hz, H8), 4.46 (1H, m, H2), 3.82 (3H, m, $NCOOCH_3$), 3.60 (3H, m, C6-OCH_3), 2.5–1.6 (4H, m); ms, *m/z*: 291 (<0.5%), 259 (13), 170 (13), 153 (21), 139 (89), 138 (100), 94 (30).

*Nucleophilic displacement of the methoxy group of **27***

To a stirred solution of $TiCl_4$ (54 mg) in dichloromethane (5 mL) at −78°C, under an atmosphere of nitrogen, was added dropwise a solution of **27** (85 mg) in dichloromethane (5 mL). After the mixture was stirred for 5 min, a solution of 2-trimethylsilyloxypropene (65 mg, contaminated by ca. 25% of $(CH_3)_3SiOSi(CH_3)_3$) in dichloromethane (5 mL), was added dropwise. The solution was stirred for 2 h at −78°C and then allowed to reach room temperature (2 h). Cold water (40 mL) was added and the mixture was stirred for 10 min, basified with NH_4OH, and extracted with $CHCl_3$ (3 × 40 mL). After evaporation of the solvent, chromatography on alumina ($CHCl_3$) of the residue yielded **29** (oil, 59 mg, 64% yield): ^{1}H nmr δ: 7.33 (5H), 5.9–5.7 (3H, m, H4,

H5, and H8), 4.8–4.2 (2H, m, H2 and H6), 3.70 and 3.69 (3H, 2s, $NCOOCH_3$), 2.9–2.6 (2H, m, H9 and H9′), 2.17 and 2.16, 2.11 and 2.09 (2 × 3H, 4s), 2.5–1.8 (4H, m); ms, *m/z*: 302 (7%), 299 (39), 242 (12), 195 (75), 194 (99), 152 (39), 140 (47), 138 (100), 94 (58), 43 (92).

*Preparation of the acetal **30***

A solution of **29** (57 mg), ethylene glycol (62 mg), and $TsOH \cdot H_2O$ (1.5 mg) in benzene was heated under reflux for 16 h in a Dean–Stark apparatus. The solvent was then evaporated and the residue was dissolved in water, basified with NH_4OH, and extracted with $CHCl_3$ (2 × 40 mL) to yield quantitatively the acetal **30** (oil, 64 mg): ^1H nmr δ: 7.3 (5H), 5.98–5.65 (H3, H4, H5, and H8), 4.51 (2H, m, H2 and H6), 3.94 (4H, m), 3.70 (3H, m, $NCOOCH_3$), 2.08 (3H, m, CH_3COO), 1.42 (3H, m), 2.3–1.6 (6H, m); ms, *m/z*: 403 (<0.5%), 344 (3), 343 (2), 302 (7), 242 (7), 194 (9), 140 (39), 138 (100), 87 (91), 43 (43).

*Reduction of **30** with $LiAlH_4$*

To a solution of the acetal **30** (63 mg) in THF (15 mL) was added $LiAlH_4$ (58 mg); the mixture was refluxed for 16 h. Some drops of AcOEt and water were added and the mixture was filtered through Celite and evaporated to dryness. The residue was dissolved in 0.2 N aqueous HCl (50 mL) and extracted with $CHCl_3$ (2 × 3 mL). The aqueous phase was then basified with NH_4OH and extracted with $CHCl_3$ (3 × 50 mL). Evaporation of the combined $CHCl_3$ phases afforded **31** (oil, 43 mg, 86% yield): ^1H nmr δ: 7.3 (5H, m), 5.78–5.56 (2H, m, H4 and H5), 4.95 (1H, dd, J = 2 and 11 Hz, H8), 3.96 (4H, m, OCH_2CH_2O), 3.83 (1H, m, H6), 3.43 (1H, m, H2), 2.21 (3H, s, NCH_3), 1.38 (3H, s), 2.5–1.35 (6H, m); ms, *m/z*: 317 (5%), 216 (72), 196 (28), 98 (71), 96 (81), 94 (100), 87 (93).

*Hydrolysis of the acetal **31***

A solution of the acetal **31** (38 mg) in 0.1 N aqueous HCl (20 mL) was heated under reflux for 30 min. After cooling, NH_4OH was added and the mixture was extracted with $CHCl_3$ (2 × 30 mL) to afford a 9:1 mixture (by ^1H nmr) of 6-episedacrine **32** and sedacrine **33** (32 mg). The mixture was then dissolved in methanol (15 mL) and left at room temperature for 16 h. Evaporation of the solvent yielded a 1:6 mixture (by ^1H nmr) of **32** and **33** (32 mg).

*Synthesis of (−)-sedacrine **33***

Starting from (−)-**12**, the sequence described above afforded a 1:6 mixture of 6-episedacrine **32** and (−)-sedacrine **33**. This mixture was dissolved in 2-butanone and a solution of perchloric acid in acetone was added until neutralization. The solvent was evaporated and fractional crystallizations of the residue from 2-butanone yielded pure (−)-sedacrine perchlorate, mp 168–169°C; $[\alpha]_D$ −114° (*c* 1.7, MeOH) (lit. (7) mp 169°C; $[\alpha]_D$ −115° (*c* 2, MeOH)). The nmr and mass spectra of the free base are identical with those reported in the literature (7, 22).

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