Synthesis of β-hydroxypiperidine alkaloids by anodic oxidation of carbamates and hydroboration

Mark Plehiers and Claude Hootelé

Abstract: The β-hydroxypiperidine alkaloids (±)-pseudoconhydrine, (±)-*N*-methylpseudoconhydrine, (−)-5-hydroxysedamine, and (+)-sedacryptine were synthesized. Successive functionalization of the piperidine ring via anodic methoxylation allowed the regio- and stereoselective introduction of the substituents. The α and α′ substituents were introduced by application of the sequence elimination – nucleophilic addition from 2- or 2,5-substituted 6-methoxycarbamates. Hydroboration – oxidation of enecarbamates, obtained by elimination of methanol from α-methoxycarbamates, allowed the introduction of the β-hydroxy function.

Key words: alkaloid, Sedum, *N*-acyliminium, enecarbamate.

Résumé : La synthèse des alcaloïdes pipéridiniques β-hydroxylés tels que la (±)-pseudoconhydrine, la (±)-*N*-méthylpseudoconhydrine, la (−)-5-hydroxysédamine et la (+)-sédacryptine est décrite. L'oxydation anodique de carbamates permet l'introduction successive, de manière régio- et stéréosélective, des substituants sur le cycle pipéridinique. Les substituants α et α′ sont introduits par application de la séquence élimination–addition nucléophile aux carbamates 6-méthoxylés, 2- ou 2,5-substitués. La fonction β-hydroxy est aménagée par hydroboration–oxydation d'ènecarbamates obtenus, au départ d'α-méthoxycarbamates, par élimination de méthanol.

Mots clés : alcaloïde, Sedum, *N*-acyliminium, ènecarbamate.

Development of efficient methods for the elaboration of polysubstituted piperidine compounds is an important goal in the area of natural product synthesis. Indeed, the increasing interest observed in this field is related to the search for new strategies for the synthesis of potentially bioactive compounds and was stimulated recently, among others, by the glycosidase inhibitory properties of polyhydroxylated piperidine derivatives (1). While numerous methods are known for the introduction of a substituent α to the nitrogen atom of the piperidine nucleus, functionalization of β and (or) γ positions has seldom been described in the literature.

The anodic methoxylation of carbamates followed by elimination and nucleophilic substitution now emerges as a powerful method for the synthesis of 2- and 2,6-substituted piperidine derivatives (2–4); the success of this method rests on the highly regioselective preparation of intermediate α-methoxycarbamates from the parent heterocycles. These intermediates are protected forms of reactive *N*-acyliminium cations that can be generated by treatment with Lewis acids and can add a number of nucleophiles. On the other hand, treatment of α-methoxycarbamates in acidic or thermolytic conditions leads to the formation of enecarbamates; these enamine-type compounds allow the introduction of electrophiles at the β position on the piperidine ring (5, 6).

Received June 5, 1996.

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In this paper, we wish to report a new route for the synthesis of β-hydroxy α- and α,α′-substituted piperidine derivatives based on successive functionalizations via anodic oxidation. As an illustration, norsedamine **10** was efficiently functionalized at position 5 (via hydroboration of the enecarbamate **12**) to yield 5-hydroxysedamine **20**; the immediate precursor of ent-**20** was substituted at position 6 to furnish (+)-sedacryptine **28** after functional group transformations.

Results and discussion

Synthesis of β-hydroxypiperidine derivatives

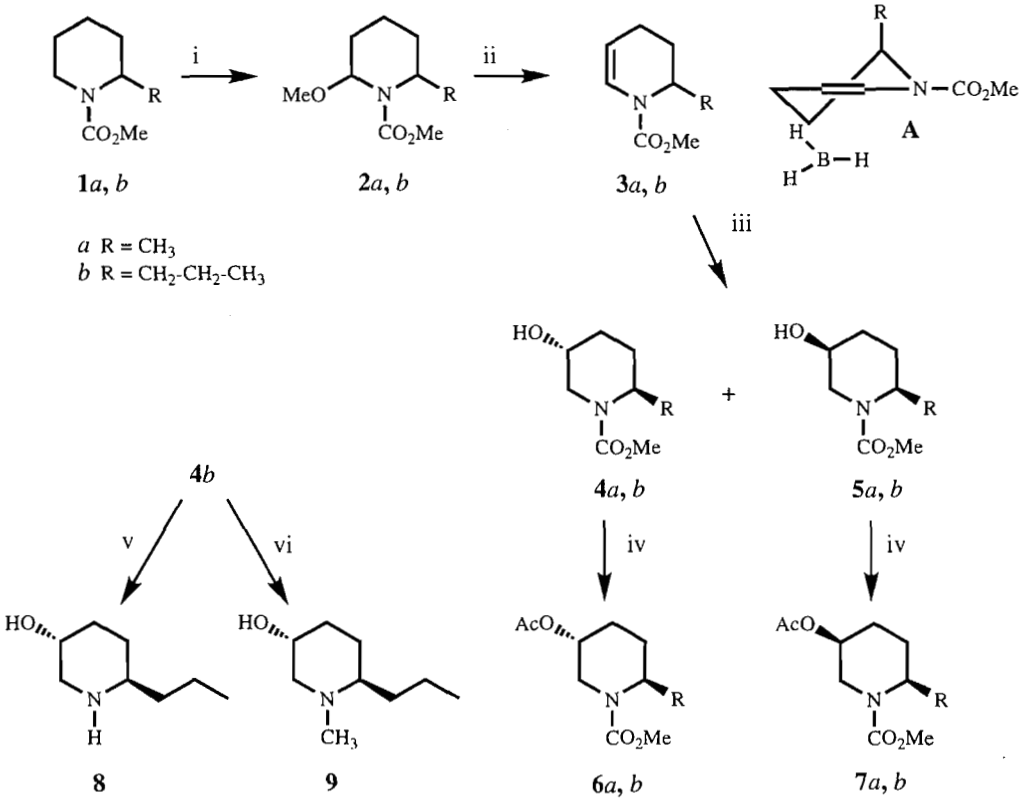
In a preceding communication (6), we briefly reported that hydroboration–oxidation of piperidine enecarbamates constitutes an efficient procedure for the preparation of β-hydroxypiperidine derivatives; the reaction proceeds with good yields to furnish *trans*/*cis* isomers in ratios ranging from 2/1 (20°C) to 6/1 (−78°C to −10°C). Although the last ratio was recently questioned (7), it appears reproducible in our hands. The stereoselectivity observed in favour of the *trans* compound results from a preferential attack of borane from the less hindered side of the enecarbamate **A** (Scheme 1).

Enecarbamate hydroboration was first applied to the model derivative ***3a*** and then exploited to realize short syntheses of pseudoconhydrine **8** (8) and *N*-methylpseudoconhydrine **9** (9), which have a 2,5-*trans* relative stereochemistry (Scheme 1).

On the other hand, we established that alcohols possessing a 2,5-*cis* relative stereochemistry can be efficiently obtained by stereoselective reduction of the corresponding ketone. The method is illustrated by the synthesis of (−)-5-hydroxysedamine **20**.

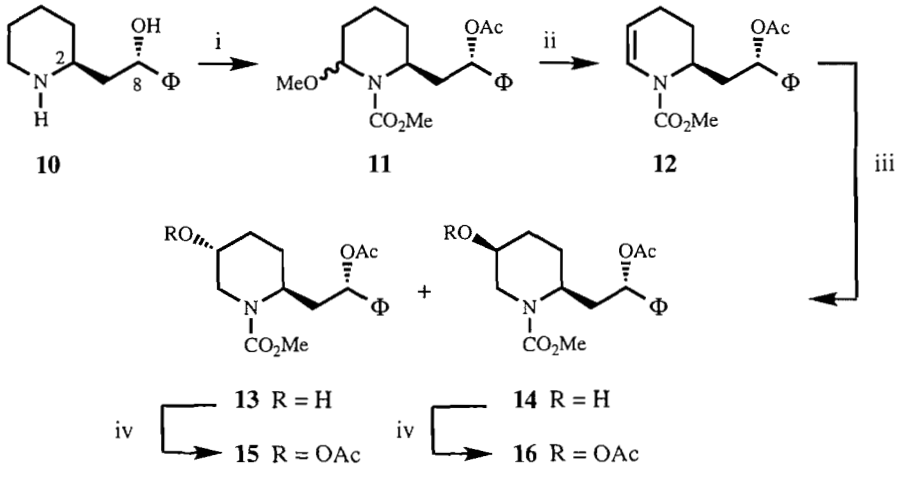
(2*S*,8*S*)-Norsedamine **10** was prepared in optically pure form, protected, and anodically oxidized in methanol to give

Scheme 1.



i: MeOH, $Et_4N^+OTs^-$, 8 V, **2***a*: 2.6 F/mol, 77%, **2***b*: 3 F/mol; ii: *p*-TSA (10% w/w); ΦH, **3***a*: 80%, **3***b*: 91% from **1***b*; iii: from **3***a*: (1) $BH_3{\cdot}SMe_2$, THF, rt; (2) H_2O_2, NaOH, 71% (*c*/*t*: 1/2); from **3***b*: (1) $BH_3{\cdot}SMe_2$, THF, −78°C to −10°C; (2) H_2O_2, NaOH, 71% (*c*/*t*: 1/6); iv: Ac_2O, pyridine; v: (1) TMSI, CH_2Cl_2; (2) MeOH, 89%; vi: $LiAlH_4$, THF, 80%.

Scheme 2.

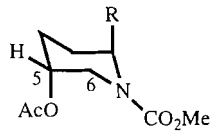


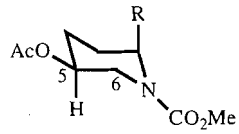
i: (1) $ClCO_2CH_3$, K_2CO_3, H_2O; (2) Ac_2O, pyridine; (3) MeOH, $Et_4N^+OTs^-$, 8 V, 8 F/mol, 95%; ii: *p*-TSA 10%, ΦH, 93%; iii: (1) $BH_3{\cdot}SMe_2$, THF, 20°C; (2) H_2O_2, NaOH, 75%, *t*/*c* 3/1; iv: Ac_2O, pyridine.

11 (3); the enecarbamate **12** was readily obtained by smooth elimination of MeOH from **11** using *p*-toluenesulfonic acid (10% w/w) in benzene as described previously (6) (Scheme 2).

Hydroboration of the enecarbamate **12** (Scheme 2) at room temperature, using the commercially available borane dimethyl sulfide complex, and subsequent hydrogen peroxide oxidation of the intermediate boranes furnished a 3:1 mixture of the alcohols **13** and **14**, which were easily separated by flash

Table 1. Selected ^{1}H NMR chemical shifts of **6***a*, **15**, **7***a*, and **16** (250 MHz, $CDCl_3$, *J* in Hz).

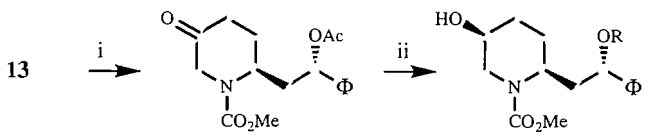




6*a* R = CH_3 **7***a* R = CH_3
15 R = $CH_2CH(OAc)\Phi$ **16** R = $CH_2CH(OAc)\Phi$

Derivative	H5	H6e	H6a
6*a*	4.87, m	4.13, bd (15)	3.03, dd (15, 2)
15	4.87, m	4.23, bd (15)	3.11, dd (15, 2)
7*a*	4.64, tt (11, 5)	4.14, ddd (13, 5, 2)	2.76, dd (13, 11)
16	4.65, tt (11, 5)	4.2, m	2.84, dd (13, 11)

Scheme 3.



17

18 R = H
14 R = Ac

i: PCC 4 equiv., CH_2Cl_2, reflux, 1 h, 71% or Swern oxidation, 3 equiv., 92%; ii: $LiAl(O\text{-}t\text{Bu})_3H$, THF, 0°C, 2 h, 88%.

chromatography. Attribution of the 2,5 relative stereochemistry of alcohols **13** and **14** rests on the analysis of the ^{1}H (coupling connectivity by 2D-COSY) and ^{13}C NMR spectra of the corresponding diacetyl derivatives **15** and **16** and comparison with those of the model compounds **6***a* and **7***a*. In all these compounds, $A^{(1,3)}$ interactions between the N-acyl moiety and the C2 substituent force this last one in an axial orientation (10). Selected diagnostical values from the ^{1}H NMR spectra are reported in Table 1.

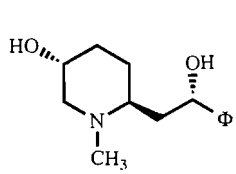
Attempts to prepare ketone **17** by oxidation of the intermediate boranes only proceeded with low yield but we observed that this unstable ketone was readily obtained by oxidation of the alcohol **13** or the mixture of **13** and **14** (Scheme 3). Swern oxidation (11) was found to give higher and more reproducible yields of **17** than PCC (12).

Reduction of the keto function of **17** with $NaBH_4$ yielded a 1/8 ratio of the alcohols **13** and **14**. Use of lithium tri-*tert*-butoxyaluminium hydride resulted in the formation of the *cis* alcohol **14** only, with concomitant deacetylation (88% global yield of *cis* derivatives **14** and **18**).

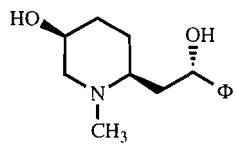
The procedure described above provides the 2,5-*cis* alcohol **14** in a global yield of 60% from the enecarbamate **12**.

Lithium aluminium hydride reduction of the carbamates **14** and **13** furnished (−)-5-hydroxysedamine **20** and its C5 epimer **19**. Spectral and specific rotation values of synthetic and natural **20** (13) are in perfect agreement.

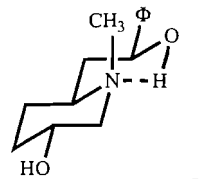
The preferred solution conformation of sedamine was established previously (14): the hydroxyl function at C8 is involved in an intramolecular hydrogen bonding with the nitrogen lone pair and the base exists predominantly in a *cis*-fused conformation. The ^{1}H NMR spectra of **19** and **20** indicate that the hydroxyl function at C5 and the phenyl group are both equatorial in the two diols; the C2 side chain is therefore equatorial in **19** and axial in 5-hydroxysedamine **20**. On the other hand, the diacetyl derivatives (13) obtained from **19** and **20** present a chair conformation in which the C2 substituent has an equatorial orientation and the acetoxy at C5 occupies, respectively, an equatorial and an axial orientation.

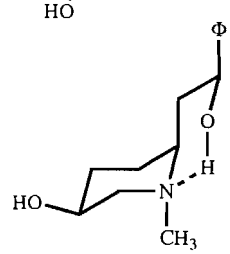


19



20





Synthesis of 2,5,6-trisubstituted piperidine compounds

To our knowledge, no example of transformation of a 2,5-disubstituted piperidine into a 2,5,6-trisubstituted derivative by anodic methoxylation has been described in the literature. The anodic oxidations of piperidine carbamates we described previously were generally carried out in MeOH containing $Et_4N^+OTs^-$ as supporting electrolyte in an undivided cell equipped with two vitreous carbon electrodes (3, 4) and the electrolysis was performed by application of a constant potential of 8 V between the electrodes. Before undertaking the oxidation of compound ent-**16**, precursor of (+)-sedacryptine **28**, we studied the influence of the supporting electrolyte ($Et_4N^+OTs^-$ and $Bu_4N^+BF_4^-$) and of the electrode (carbon and platinum) on the oxidation of the model compound **7***a*. Some significant results are given in Table 2.

It appeared that the anodic oxidation performed under our usual conditions (3, 4) (entry 1) furnished the methoxy compound **21** with a moderate yield. The replacement of the carbon rod anode by a platinum foil allowed a substantial

Table 2. Anodic oxidation of acetate 7*a*.

Entry	Electrolyte	Mol. ratio electrolyte/ acetate 7*a*	Anode	*n*, F/mol	Yield[a] of **21** (%)
1	$Et_4N^+OTs^-$	1/16	C	8	50
2	$Et_4N^+OTs^-$	1/7	Pt	8	50
3	$Et_4N^+OTs^-$	1/14	Pt	8	75
4	$Bu_4N^+BF_4^-$	1/4	Pt	5	71

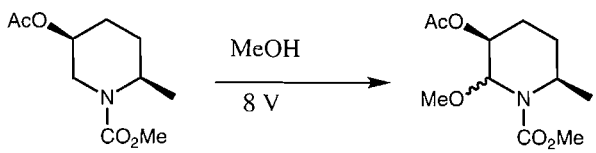
[a]Isolated yields.

Table 3. Anodic oxidation of acetate ent-**16**.

Entry	Electrolyte	Mol. ratio electrolyte/ acetate ent-**16**	Anode	*n*, F/mol	Yield[a] of **23** (%)
1	$Bu_4N^+BF_4^-$	1/4	Pt	6	43
2	$Et_4N^+OTs^-$	1/10	Pt	8	40
3	$Et_4N^+OTs^-$	1/10	C	8	58[b]
4	$Et_4N^+OTs^-$	1/10	C	10	32

[a]Isolated yields.
[b]28% of recovered starting material.

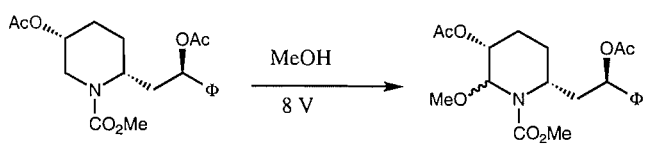
increase of the yield (entry 3). During our systematic study we observed that in the case of $Et_4N^+OTs^-$ as electrolyte the best yields were obtained when the electrolyte/carbamate molar ratio was kept below a 0.1 value; on the other hand, in the case of $Bu_4N^+BF_4^-$, electrolyte/carbamate ratios ranging from 0.1 to 1 gave comparable yields. Of course, a high relative concentration of the electrolyte is suitable in that it allows shorter reaction times.



7*a* **21**

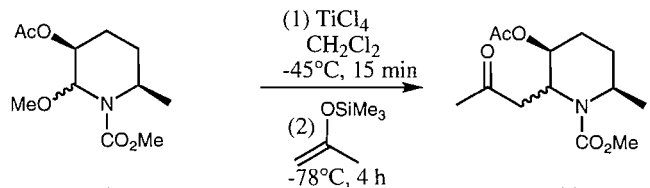
Application to the diacetoxy derivative ent-**16** (2*R*,5*R*,8*R*) of the best conditions found for the oxidation of 7*a* appeared disappointing as a yield of less than 50% of **23** was obtained. A new series of experiments was therefore undertaken and the results are reported in Table 3.

For the anodic oxidation of ent-**16**, the highest yield of the methoxy derivative **23** was achieved using $Et_4N^+OTs^-$ as supporting electrolyte and a vitreous carbon rod as anode. In all cases the reaction appeared incomplete and a substantial amount of starting material could be recovered. It was observed that an increase in the number of Faraday did not improve the yield (entry 4) but led to the formation of degradation products. The α-methoxycarbamates **21** and **23** were found to be stable compounds and they can be stored for months without noticeable degradation.



ent-**16** **23**

The elimination – nucleophilic addition sequence was first performed on the model compound **21**. The iminium cation was formed at −45°C with $TiCl_4$ as a Lewis acid and reacted with 2-trimethylsilyloxypropene at −78°C to yield a 76/24 mixture of the expected ketones **22** in 73% yield.

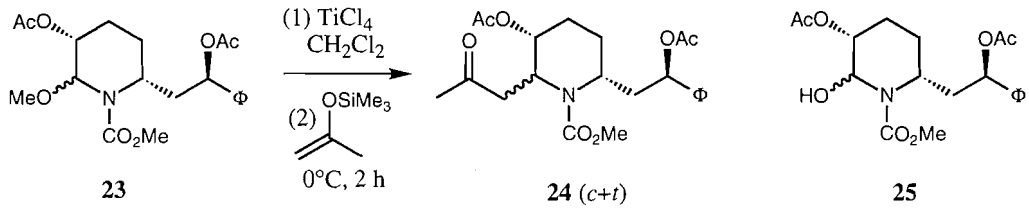


21 **22** (*c*+*t*)

The same sequence was applied to the methoxy derivative **23**. The reaction was first conducted at low temperature (−78°C to −45°C, 4 h), furnishing a mixture in which the expected *cis* and *trans* compounds **24** were present in low yield (ca. 25%); the other major constituents were identified as the starting material (ca. 50%) and a 6-hydroxy derivative **25** (ca. 25%) originating from the addition of water to the iminium cation during the work-up. These observations indicate that the formation of the iminium cation was not complete under these conditions. When the two steps were conducted at 0°C a 77/23 mixture of the two expected diastereoisomers was isolated in 60% yield. The *cis* relative stereochemistry is attributed to the major compound on the basis of our previous results on related compounds.

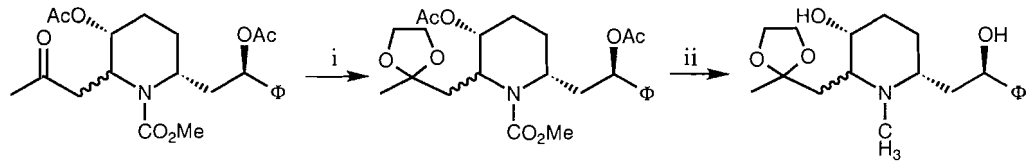
Simple functional group transformations of **24** allowed the synthesis of (+)-sedacryptine **28** (Scheme 4).

After protection of the keto group of the *cis* and *trans*

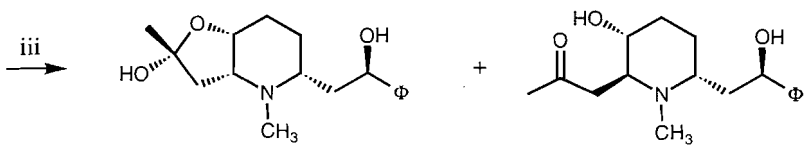


23 **24** (*c+t*) **25**

Scheme 4.



24 (*c+t*) **26** (*c+t*) **27** (*c+t*)



28 **29**

i: ethylene glycol, $TsOH \cdot H_2O$, benzene, reflux; ii: $LiAlH_4$, THF, reflux, 67% from **24**; iii: 0.1 N HCl, reflux.

trisubstituted compounds **24**, reduction of the carbamate and acetate functions furnished the corresponding amino alcohols **27** in 67% yield without modification of the diastereoisomeric ratio. Deprotection of the acetal function was performed in boiling 0.1 N aqueous hydrogen chloride, providing, after neutralization, a mixture of (+)-sedacryptine **28** and its C6-epimer **29** in a 60/40 ratio.

Compounds possessing a β-amino ketone moiety are able to epimerize under a variety of conditions (4, 15). We observed that pure sedacryptine as well as the above 60/40 mixture epimerizes in methanol at room temperature affording a 80/20 mixture of **28** and **29**. On the other hand, this last ratio shifted to >95/5 in cyclohexane. Spectral properties of our synthetic (+)-sedacryptine **28** were identical with those of the natural compound; the optical rotations of both samples were identical in magnitude but of opposite sign. The above synthesis confirms the absolute configuration (2*S*,5*S*,6*S*,8*S*,10*S*) previously attributed to the alkaloid (16).

Experimental

Mass spectral data were obtained on a Micromass 7070 spectrometer or a Fisons Autospec spectrometer. Unless otherwise stated, NMR spectra were recorded on a Bruker WM 250 spectrometer in $CDCl_3$ with TMS as internal standard. IR spectral data were recorded on a Brucker IFS 25 spectrometer. Analytical thin-layer chromatography was performed on Polygram Sil G/UV254 plates and on Merck aluminium sheets, aluminium oxide 60 F_{254} neutral, type E. Visualization was accomplished either by ethanolic phosphomolybdic acid solution followed by heating or by iodine followed by spraying Dragendorff reagent.

Anodic methoxylations were carried out at room temperature in methanol (analytical grade) containing the supporting electrolyte, in an undivided cell equipped with two vitreous carbon electrodes (unless otherwise stated) and a magnetic stirring bar. The carbon electrodes (0.3 cm diameter, immersed 3.5 cm into the solution) were placed 1.0 cm apart. The platinum foil anode (0.3 × 4 cm) was immersed 2 cm into the solution at 1 cm of the carbon cathode. The potentiostat was a homemade apparatus; the potential between the electrodes was fixed at 8 V.

Anodic oxidation of 1*a*

The carbamate **1***a* (521 mg, 3.3 mmol), $Et_4N^+OTs^-$ (50 mg, 0.16 mmol), and 15 mL of methanol were introduced into the electrolysis cell. The solution was stirred for 10 min and then a constant potential of 8 V was applied. After 2.6 F/mol of electricity was passed, some drops of NH_4OH were added to the solution and the solvent was evaporated; the residue was dissolved in water (30 mL), basified with NH_4OH, and extracted with $CHCl_3$ (2 × 30 mL). The combined $CHCl_3$ layers were evaporated and the residue was filtered through a short column of silica gel (ethyl acetate/hexane 1:2) to afford the 6-methoxy derivative **2***a* (oil, 476 mg, 2.54 mmol, 77%): ^1H NMR δ: 5.39 (1H, m, H6), 4.33 (1H, m, H2), 3.72 (3H, s, NCO_2CH_3), 3.26 (3H, broad s, CH_3O), 1.2–2.1 (6H, m), 1.28 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR δ: 82.6, 55.3, 52.9, 47.0, 30.8, 30.5, 19.9, 14.0; MS, *m/z*: 187 ($M^{+\bullet}$, 3%), 186 (5), 172 (33), 156 (100), 142 (76), 71 (86).

Preparation of the enecarbamate 3*a* from 2*a*

The 6-methoxy derivative **2***a* (100 mg, 0.53 mmol) was dissolved in dry benzene (10 mL); $TsOH \cdot H_2O$ (10 mg, 0.052

mmol) was added and the reaction mixture was stirred at room temperature. After 1.5 h, some drops of NH_4OH were added to the reaction mixture and the solvent was evaporated; the residue was dissolved in water (30 mL) and the solution extracted with $CHCl_3$ (2 × 30 mL). The combined organic layers were evaporated and the residue was filtered through a short column of alumina to afford the enecarbamate **3***a* (65 mg, 0.42 mmol, 80%) as a colourless oil: ^{1}H NMR δ: 6.69 (1H, m, H6), 4.86 (1H, m, H2), 4.40 (1H, m, H5), 3.75 (3H, s, NCO_2CH_3), 1.7–2.2 (4H, m), 1.12 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR δ: 124.1, 105.8, 53.1, 46.7, 26.9, 17.6, 17.1; MS, *m/z*: 155 ($M^{+\bullet}$, 36%), 140 (100).

Synthesis of *N*-carbomethoxyconiine 1*b*

N-Carbomethoxypiperidine (5.04 g, 35 mmol), $Et_4N^+OTs^-$ (550 mg, 1.8 mmol), and 50 mL of methanol were introduced into the electrolysis cell. The solution was stirred for 10 min and a constant potential of 8 V was applied. After 2.7 F/mol of electricity was passed, some drops of NH_4OH were added to the solution and the solvent was evaporated; the residue was dissolved in water (400 mL), basified with NH_4OH, and extracted with $CHCl_3$ (3 × 400 mL). The combined $CHCl_3$ layers were evaporated and the residue was filtered through a short column of silica gel (ethyl acetate/hexane 1:2) to afford 2-methoxy-*N*-carbomethoxypiperidine (6 g, 34 mmol).

To a solution of $TiCl_4$ (7.2 g, 38 mmol) in CH_2Cl_2 at −78°C, under an atmosphere of nitrogen, was added dropwise a solution of allyltrimethylsilane (9.5 g, 59 mmol) and 2-methoxy-*N*-carbomethoxypiperidine (6 g) in 40 mL of CH_2Cl_2. After 1 h at −78°C, the reaction mixture was poured into 400 mL of water and extracted with 2 × 400 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were evaporated to dryness. Distillation of the residue under reduced pressure afforded the substitution derivative (4.98 g, 27.2 mmol, 77% global yield) as a colourless oil, bp 94–98°C (3 Torr;): ^{1}H NMR δ: 5.7 (1H, ddt, J = 17, 10 and 7 Hz), 5.01 (1H, dd, J = 17 and 2 Hz), 4.98 (1H, dt, J = 2 and 10 Hz), 4.28 (1H, m, H2), 3.96 (1H, broad d, J = 14 Hz, H6e), 3.64 (3H, s, NCO_2CH_3), 2.79 (1H, td, J = 2 and 14 Hz, H6a), 2.35 (1H, dt, J = 14 and 7 Hz), 2.26 (1H, dt, J = 14 and 7 Hz), 1.3–1.6 (6H, m); ^{13}C NMR δ: 156.6, 135.7, 117.1, 52.8, 50.8, 39.7, 34.8, 28.0, 25.9, 19.2; MS, *m/z*: 182 ($M^{+\bullet}$ − 1, 4%), 142 (100).

The above derivative (4.5 g, 24.5 mmol) in 300 mL of ethanol containing 10% Pd/C (0.5 g) was hydrogenated (1 atm (101.3 kPa)). After filtration through Celite and evaporation of the solvent, a distillation under reduced pressure of the residue furnished *N*-carbomethoxyconiine **1***b* (3.7 g, 20 mmol, 81%), bp 92–96°C (2 Torr; 1 Torr = 133.3 Pa): ^{1}H NMR δ: 4.24 (1H, m, H2), 3.98 (1H, broad d, J = 13 Hz, H6e), 3.67 (3H, s, NCO_2CH_3), 2.80 (1H, td, J = 13 and 3 Hz, H6a), 1.2–1.7 (10H, m), 0.91 (3H, t, J = 7 Hz); ^{13}C NMR δ: 156.7, 52.8, 51.0, 39.5, 32.3, 28.8, 26.1, 19.9, 19.4, 14.4; MS, *m/z*: 185 ($M^{+\bullet}$, 2%), 142 (100).

Preparation of the enecarbamate 3*b* from 1*b*

The carbamate **1***b* (2.52 g, 13 mmol), $Et_4N^+OTs^-$ (250 mg, 0.83 mmol), and 50 mL of methanol were introduced into the electrolysis cell. The solution was stirred for 10 min and a constant potential of 8 V was applied. After 3F/mol of electricity was passed, some drops of NH_4OH were added to the solution and the solvent was evaporated; the residue was dissolved in water (400 mL), basified with NH_4OH, and extracted with $CHCl_3$ (3 × 400 mL). The combined $CHCl_3$ layers were evaporated to dryness to afford the 6-methoxy derivative **2***b* (2.8 g, 13 mmol): ^{1}H NMR δ: 5.45 (1H, m, H6), 4.14 (1H, m, H2), 3.71 (3H, s, NCO_2CH_3), 3.28 (3H, s, OCH_3), 1.2–1.9 (10H, m), 0.92 (3H, t, J = 7 Hz); ^{13}C NMR δ: 82.9, 55.8, 53.0, 51.3, 36.3, 31.1, 27.9, 20.9, 14.4, 14.2; MS, *m/z*: 215 ($M^{+\bullet}$, <1%), 200 (4), 184 (32), 172 (64), 142 (22), 140 (20), 71 (100).

The crude 6-methoxy derivative **2***b* was dissolved in dry benzene (200 mL); $TsOH{\cdot}H_2O$ (300 mg, 1.57 mmol) was added and the reaction mixture was stirred at room temperature. After 1 h, some drops of NH_4OH were added to the reaction mixture and the solvent was evaporated. The residue was dissolved in 30 mL of dilute NH_4OH and extracted with 2 × 30 mL of $CHCl_3$. The combined $CHCl_3$ layers were evaporated to dryness and the residue was filtered through a short column of alumina ($CHCl_3$) to afford the enecarbamate **3***b* (2.18 g, 11.9 mmol, 91% from **1***b*): ^{1}H NMR δ: 6.75 (1H, m, H6), 4.8 (1H, m, H2), 4.3 (1H, m, H5), 3.74 (3H, s, NCO_2CH_3), 1.2–2.1 (8H, m), 0.92 (3H, t, J = 7 Hz); ^{13}C NMR δ: 124.2, 106.4, 53.2, 50.7, 33.2, 24.5, 19.6, 18.0, 14.4; MS, *m/z*: 183 ($M^{+\bullet}$, 12%), 140 (100).

General procedure for the acetylation reactions

The alcohol was treated with a mixture of pyridine and acetic anhydride for 1 night at room temperature. After addition of ethanol and chloroform, the solvents were evaporated and the residue was filtered through a short column of alumina to yield the corresponding O-acetyl derivative.

General procedure for the hydroboration of enecarbamates

All the glassware was dried in an oven, assembled hot, and cooled under a stream of dry nitrogen. THF was distillated from lithium aluminium hydride, into the reaction flask containing the enecarbamate; the flask was then equipped with a rubber septum and a positive pressure of nitrogen was maintained. The hydroboration was carried out by adding a 2 M solution of borane in THF (Aldrich) through the septum via a hypodermic syringe previously flushed with dry nitrogen. After the reaction was complete, the reaction flask was immersed in a cooling bath at 0°C, and the excess of borane was destroyed by adding some drops of water. The oxidation step was carried out under magnetic stirring at room temperature by adding the proper amounts of aqueous NaOH and hydrogen peroxide.

Hydroboration of the enecarbamate 3*a*

The enecarbamate **3***a* (267 mg, 1.72 mmol) was subjected to hydroboration, according to the general procedure described above, in 25 mL of THF with addition of a 2 M $BH_3{\cdot}SMe_2$ solution (0.86 mL, 1.72 mmol). After 3 h, the reaction was stopped and the oxidation was performed by adding 1 mL of 3 M NaOH and 1 mL of H_2O_2 (35% w/w). After 2 h at room temperature, the reaction mixture was basified by addition of 100 mL of dilute NH_4OH and extracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ layers were evaporated to dryness and the residue was submitted to flash chromatography (silica gel, ethyl acetate/hexane 1:1) to furnish successively the *cis* alcohol **5***a* (69 mg, 0.39 mmol, 22%), and the *trans* alcohol **4***a* (148 mg, 0.85 mmol, 49%); **4***a*: ^{1}H NMR δ: 4.44 (1H, m, H2),

4.02 (1H, broad d, J = 14 Hz, H6e), 3.93 (1H, m, H5), 3.69 (3H, s, NCO_2CH_3), 3.06 (1H, dd, J = 14 and 2 Hz, H6a), 1.3–2.1 (4H, m), 1.15 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR δ: 157.4, 64.8, 53.0, 46.7, 45.1, 25.6, 24.1, 15.8; MS, *m/z*: 173 ($M^{+\bullet}$, 10%), 158 (100), 140 (48), 125.9 (m*), 124.0 (m*), 114 (16), 102 (11), 88 (11); **5***a*: ^1H NMR δ: 4.36 (1H, m, H2), 4.12 (1H, ddd, J = 13, 5 and 1 Hz, H6e), 3.68 (3H, s, NCO_2CH_3), 3.57 (1H, tt, J = 5 and 11 Hz, H5), 2.66 (1H, dd, J = 11 and 13 Hz, H6a), 1.5–1.8 (4H, m), 1.15 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR δ: 156.4, 67.7, 53.1, 45.9, 45.7, 28.9, 28.5, 16.0; MS, *m/z*: 173 ($M^{+\bullet}$, 28%), 158 (100), 140 (69), 126 (17), 116 (32), 114 (16), 102 (24), 88 (22).

The O-acetyl derivatives **6***a* and **7***a* were prepared according to the procedure described above; **6***a*: ^1H NMR δ: 4.87 (1H, m, H5), 4.47 (1H, m, H2), 4.13 (1H, broad d, J = 15 Hz, H6e), 3.67 (3H, s, NCO_2CH_3), 3.03 (1H, dd, J = 15 and 2 Hz, H6a), 1.2–2 (4H, m), 2.01 (3H, s, OAc), 1.15 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR δ: 170.8, 156.8, 67.5, 52.9, 46.3, 42.2, 24.7, 23.2, 21.5, 15.9; MS, *m/z*: 215 ($M^{+\bullet}$, <1%), 200 (3; calcd. for $C_9H_{14}NO_4$: 200.0922; found: 200.0927), 155 (66), 140 (100), 126.4 (m*). **7***a*: ^1H NMR δ: 4.64 (1H, tt, J = 5 and 11 Hz, H5), 4.39 (1H, m, H2), 4.14 (1H, ddd, J = 13, 5, and 2 Hz, H6e), 3.68 (3H, s, NCO_2CH_3), 2.76 (1H, dd, J = 13 and 11 Hz, H6a), 2.03 (3H, s, OAc), 1.5–1.9 (4H, m), 1.15 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR δ: 170.4, 156.2, 69.6, 53.0, 45.9, 42.3, 28.5, 25.2, 21.5, 15.9; MS, *m/z*: 215 ($M^{+\bullet}$, <1%), 200 (2; calcd. for $C_9H_{14}NO_4$: 200.0922; found: 200.0920), 155 (66), 140 (100), 126.4 (m*).

Hydroboration of the enecarbamate 3*b*

The enecarbamate **3***b* (108 mg, 0.59 mmol) was submitted to hydroboration, according to the general procedure described above, in 5 mL of THF with the addition, at −78°C, of a 2 M $BH_3 \cdot SMe_2$ solution (0.3 mL, 0.59 mmol). Once the addition was complete, the reaction mixture was maintained at −10°C for 20 h; the reaction was then stopped and the oxidation was performed by adding 0.5 mL of 3 M NaOH and 0.5 mL of H_2O_2 (35% w/w). After 2 h at room temperature, the reaction mixture was poured into 20 mL of dilute NH_4OH and extracted with $CHCl_3$ (3 × 20 mL). The combined $CHCl_3$ layers were evaporated to dryness and the residue was submitted to flash chromatography (silica gel, ethyl acetate/hexane 1:1) to furnish successively the *cis* alcohol **5***b* (11 mg, 0.054 mmol, 9%) and the *trans* alcohol **4***b* (74 mg, 0.36 mmol, 62%). **4***b*: ^1H NMR δ: 4.27 (1H, m, H2), 4.05 (1H, broad d, J = 14 Hz, H6e), 3.91 (1H, m, H5), 3.69 (3H, s, NCO_2CH_3), 3.0 (1H, dd, J = 14 and 2 Hz, H6a), 1.1–2.1 (8H, m), 0.92 (3H, t, J = 7 Hz, CH_3); ^{13}C NMR δ: 64.6, 52.6, 50.4, 44.8, 31.3, 25.5, 22.1, 19.5, 13.9; MS, *m/z*: 201 ($M^{+\bullet}$, 3%), 170 (3), 158 (100), 140 (50); **5***b*: ^1H NMR δ: 4.1 (2H, m, H2 and H6e), 3.66 (3H, s, NCO_2CH_3), 3.55 (1H, tt, J = 10.5 and 5 Hz, H5), 2.58 (1H, dd, J = 13 and 10.5 Hz, H6a), 1.2–1.9 (8H, m), 0.89 (3H, t, J = 7 Hz, CH_3); ^{13}C NMR δ: 67.2, 52.6, 49.5, 45.4, 31.5, 28.5, 26.8, 19.4, 13.9; MS, *m/z*: 201 ($M^{+\bullet}$, 3%), 170 (3), 158 (100), 140 (51).

The O-acetyl derivatives **6***b* and **7***b* were prepared according to the procedure described above; **6***b*: ^1H NMR δ: 4.86 (1H, m, H5), 4.33 (1H, m, H2), 4.18 (1H, broad d, J = 15 Hz, H6e), 3.68 (3H, s, NCO_2CH_3), 2.97 (1H, dd, J = 15 and 2 Hz, H6a), 2.02 (3H, s, OAc), 1.2–2.0 (8H, m), 0.92 (3H, t, J= 7 Hz, CH_3); ^{13}C NMR δ: 170.9, 157.2, 67.5, 52.9, 50.4, 42.2, 31.8, 23.6, 23.2, 21.5, 19.9, 14.3; MS, *m/z*: 243 ($M^{+\bullet}$, 2%), 212 (2), 200 (42; calcd. for $C_9H_{14}NO_4$: 200.0922; found: 200.0922), 183 (15), 158 (6), 140 (100); **7***b*: ^1H NMR δ: 4.67 (1H, tt, J = 5 and 11 Hz, H5), 4.2 (2H, m, H2 and H6e), 3.71 (3H, s, NCO_2CH_3), 2.74 (1H, dd, J = 11 and 13 Hz, H6a), 2.06 (3H, s, OAc), 1.2–1.9 (8H, m), 0.95 (3H, t, J = 7Hz, CH_3); ^{13}C NMR δ: 170.4, 156.8, 69.5, 53.1, 50.1, 42.4, 31.9, 26.9, 25.6, 21.5, 19.9, 14.4; MS, *m/z*: 242 ($M^{+\bullet}$, <1%), 212 (1), 200 (30; calcd. for $C_9H_{14}NO_4$: 200.0922; found: 200.0926), 183 (28), 158 (13), 140 (100).

Hydroboration of the enecarbamate 12

The enecarbamate **12** (252 mg, 0.83 mmol) was subjected to hydroboration, according to the general procedure described above, in 20 mL of THF with addition of a 2 M $BH_3 \cdot SMe_2$ solution (0.45 mL, 0.91 mmol). After 1.5 h, the reaction was stopped and the oxidation was performed by adding 1 mL of 3 M NaOH and 1 mL of H_2O_2 (35% w/w). After 2 h at room temperature, the reaction mixture was basified with 50 mL of dilute NH_4OH and extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ layers were evaporated to dryness and the residue was submitted to flash chromatography (silica gel, ethyl acetate/hexane 9:1) to furnish successively the *cis* alcohol **14** (49 mg, 0.15 mmol, 18%) and the *trans* alcohol **13** (154 mg, 0.47 mmol, 57%). **13**: ^1H NMR δ: 7.3 (5H, m), 5.71 (1H, dd, J = 6 and 7 Hz, H8), 4.32 (1H, m, H2), 4.12 (1H, m H6e), 3.95 (1H, m, H5), 3.66 (3H, s, NCO_2CH_3), 3.15 (1H, dd, J = 2 and 14 Hz, H6a), 2.05 (3H, s, OAc), 1.2–2.4 (7H, m); ^{13}C NMR δ: 157.1, 140.2, 128.5, 128.2, 126.7, 74.4, 64.4, 52.7, 48.3, 45.1, 36.1, 25.6, 22.5, 21.3; MS, *m/z*: 321 ($M^{+\bullet}$, 1%), 261 (25), 202 (15), 158 (100), 156.3 (m*), 140 (41), 124.0 (m*). **14**: ^1H NMR δ: 7.3 (5H, m), 5.7 (1H, dd, J = 5 and 8 Hz, H8), 4.17 (2H, m, H2 and H6e), 3.66 (3H, s, NCO_2CH_3), 3.58 (1H, m, H5), 2.73 (1H, dd, J = 11 and 13 Hz, H6a), 2.04 (3H, s, OAc), 1.4–2.4 (7H, m); ^{13}C NMR δ: 170.6, 156.3, 140.7, 128.9, 128.5, 127.0, 74.7, 67.4, 53.2, 47.9, 46.1, 36.7, 28.9, 27.6, 21.6; MS, *m/z*: 321 ($M^{+\bullet}$, <1%), 278 (6), 261 (55), 202 (35), 158 (100), 140 (50).

The O-acetyl derivatives **15** and **16** were prepared according to the procedure described above. **15**: ^1H NMR δ: 7.3 (5H, m), 5.72 (1H, dd, J = 6 and 8 Hz, H8), 4.87 (1H, m, H5), 4.37 (1H, m, H2), 4.23 (1H, broad d, J = 15 Hz, H6e), 3.66 (3H, s, NCO_2CH_3), 3.11 (1H, dd, J = 15 and 2 Hz, H6a), 2.04 (3H, s, OAc), 2.01 (3H, s, OAc), 1.3–2.4 (6H, m); ^{13}C NMR δ: 170.8, 170.5, 156.9, 140.6, 128.9, 128.5, 127.0, 74.6, 67.2, 53.0, 48.2, 42.5, 36.5, 23.6, 23.4, 21.5; MS, *m/z*: 363 ($M^{+\bullet}$, <1%; calcd. for $C_{19}H_{25}NO_6$: 363.1681; found: 363.1688), 320 (2), 303 (17), 252.9 (m*), 244 (12), 243 (9), 200 (40), 194.8 (m*), 158 (10), 156 (10), 140 (100), 110.2 (m*), 98 (m*); **16**: ^1H NMR δ: 7.3 (5H, m), 5.72 (1H, dd, J = 6 and 8 Hz, H8), 4.65 (1H, tt, J = 5 and 11 Hz, H5), 4.2 (2H, m, H2 and H6e), 3.67 (3H, s, NCO_2CH_3), 2.84 (1H, dd, J = 11 and 13 Hz, H6a), 2.04 (3H, s, OAc), 2.05 (3H, s, OAc), 1.2–2.4 (6H, m); ^{13}C NMR δ: 170.1, 169.9, 155.8, 140.2, 128.5, 128.2, 126.6, 74.2, 68.9, 52.8, 47.4, 42.3, 36.3, 26.7 25.2, 21.2, 21.1; MS, *m/z*: 363 ($M^{+\bullet}$, <1%; calcd. for $C_{19}H_{25}NO_6$: 363.1681; found: 363.1687), 304 (4), 303 (7), 260 (4), 244 (10), 243 (8), 200 (37), 140 (100), 110.2 (m*), 98 (m*).

Preparation of pseudoconhydrine 8

To a solution of **4***b* (46 mg, 0.22 mmol) in 5 mL of CH_2Cl_2 was added TMSI (0.32 mL, 2.28 mmol) distilled over copper pow-

der just before use. The reaction mixture was refluxed for 1 h and after addition of some drops of MeOH was allowed to stand at room temperature during 10 min. The solvent was evaporated to dryness and the residue was dissolved in dilute NH_4OH and extracted with $CHCl_3$ (3 × 15 mL). Evaporation of the $CHCl_3$ layers furnished **8** as a colourless oil (28 mg, 0.19 mmol, 89 %). Mass and ^1H NMR spectra were identical with those reported in the literature (17).

Preparation of *N*-methylpseudoconhydrine 9

To a solution of **4***b* (30 mg, 0.15 mmol) in THF (10 mL) was added $LiAlH_4$ (50 mg). The mixture was refluxed for 2.5 h. Some drops of water were added at room temperature, the mixture was filtered through Celite, and the solvent was evaporated to dryness. The residue was dissolved into 10 mL of $CHCl_3$ and extracted with 0.1 N HCl (2 × 10 mL). The organic phase was discarded and the aqueous phase basified with NH_4OH and extracted with $CHCl_3$ (2 × 100 mL). The combined $CHCl_3$ layers were evaporated to dryness and the residue was filtered through a short column of alumina ($CHCl_3$/MeOH 9:1) to afford **9** (20 mg, 0.12 mmol, 80%). Mass and ^1H NMR spectra were identical with those reported in the literature (18).

Swern oxidation of alcohol 13

DMSO (102 μL, 1.45 mmol) was added to a stirred solution of oxalyl chloride (126 μL, 1.45 mmol) in 2 mL of CH_2Cl_2 at −78°C under a nitrogen atmosphere. After 10 min, alcohol **13** (156 mg, 0.48 mmol) dissolved in 1 mL of CH_2Cl_2 was added; the reaction flask was then cooled at −40°C and after 10 min at −78°C triethylamine (1 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and after 15 min poured into 30 mL of water. After neutralization with concentrated HCl and extraction with CH_2Cl_2 (30 mL), the organic phase was washed with dilute NH_4OH, dried, evaporated, and filtered through a short column of silica gel (ethyl acetate/hexane 4:1) to give the ketone **17** (142 mg, 0.44 mmol, 92%). IR: (CCl_4 solution) cm^{-1}: 2955, 1739, 1708, 1450, 1234; ^1H NMR δ: 7.3 (5H, m), 5.83 (1H, dd, J = 5 and 9 Hz, H8), 4.3 (2H, m, H2 and H6e), 3.71 (3H, s, NCO_2CH_3), 3.62 (1H, d, J = 19Hz, H6a), 2.07 (3H, s, OAc), 1.6–2.4 (6H, m); ^{13}C NMR δ: 206.8, 170.6, 156.2, 140.5, 129.0, 128.7, 126.9, 73.8, 53.5, 50.9, 48.8, 39.7, 36.0, 26.7, 21.6; MS, *m/z*: 319 ($M^{+\bullet}$, 1%), 291 (2), 275 (15), 260 (11), 156 (100),128 (32).

PCC oxidation of the alcohol 13

PCC adsorbed on alumina (1 g, 0.9 mmol) was added under stirring to a solution of **13** (73 mg, 0.22 mol) in 10 mL of CH_2Cl_2. The mixture was refluxed and stirred for 1 h, cooled, and then filtered through a column of Florisil (CH_2Cl_2, then AcOEt). The combined organic layers were evaporated to dryness and the residue was filtered through a short column of silica gel (AcOEt). Evaporation of the solvent furnished the ketone **17** as a colourless oil (50 mg, 0.15 mmol, 71%).

Reduction of ketone 17 with $NaBH_4$

$NaBH_4$ (60 mg, 1.6 mmol) was added to a solution of ketone **17** (103 mg, 0.32 mmol) in 5 mL of absolute ethanol at 0°C. After 15 min some drops of water were added and the solvent was evaporated to dryness. The residue was dissolved in 10 mL of dilute NH_4OH and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layers were evaporated and the residue was submitted to flash chromatography (silica gel, ethyl acetate/hexane 4:1) to furnish successively the alcohols **14** (84 mg, 0.26 mmol, 81%) and **13** (10 mg, 0.031 mmol, 10%).

Reduction of ketone 17 with LiAl(O-*t*Bu)$_3$H

(tBuO)$_3$AlLiH (24 mg, 0.094 mmol) was added to a solution of ketone **17** (20 mg, 0.062 mmol) in THF (2 mL) at 0°C. After 2 h some drops of water were added and the mixture was filtered through Celite. After evaporation of the solvent, dilute NH_4OH was added to the residue and the solution was extracted with $CHCl_3$. Evaporation of the solvent followed by a flash chromatography (silica gel, AcOEt/hexane 1:9) furnished the *cis* acetate **14** (12 mg, 0.037 mmol, 60%) and the *cis* diol **18** (5 mg, 0.017 mmol, 28%). **18**: ^1H NMR δ: 7.3 (5H, m), 4.73 (1H, m, H8), 4.36 (1H, m, H2), 4.07 (H, m, H6e), 3.66 (3H, s, NCO_2CH_3), 3.58 (1H, m, H5), 2.61 (1H, dd, J = 11 and 12 Hz, H6a), 1.4–2.2 (8H, m); MS, *m/z*: 279 ($M^{+\bullet}$, 3%), 261 (4), 244 (m*), 202 (4), 186 (4), 173 (3), 158 (100), 140 (78), 124.0 (m*).

Preparation of alcohol 19

To a solution of the carbamate **13** (33 mg, 0.1 mmol) in THF (5 mL) was added $LiAlH_4$ (35 mg). The mixture was then refluxed for 3.5 h. After addition of some drops of water the mixture was filtered through Celite and the solvent was evaporated to dryness. The residue was filtered through a short column of alumina ($CHCl_3$, MeOH 5%, NH_4OH) to give **19** as a colourless oil (15 mg, 0.063 mmol, 63%): $[\alpha]_D^{20}$ −80.5 (c = 0.9, MeOH); ^1H NMR δ: 7.34 (5H, m), 4.82 (1H, dd, J = 3 and 10 Hz, H8), 3.79 (1H, tt, J = 4 and 8 Hz, H5), 2.99 (1H, ddd, J = 12, 4, and 1 Hz, H6e), 2.56 (1H, m, H2), 2.40 (3H, s, NCH_3), 2.26 (1H, dd, J = 8 and 12 Hz, H6a), 1.36–2.08 (6H, m); ^{13}C NMR δ: 128.8, 127.7, 125.9, 73.5, 65.7, 61.2, 60.3, 41.4, 39.9, 32.5, 25.9; MS, *m/z*: 235 ($M^{+\bullet}$, 3%), 128 (3), 114 (100), 96 (10).

Preparation of (−)-5-hydroxysedamine 20

The alcohol **14** (18 mg, 0.056 mmol) was reduced with $LiAlH_4$ (20 mg) in THF (5 mL) as described for **13** to afford alcohol **20** as a colourless oil (10 mg, 0.045 mmol, 80%). The mass, ^1H, and ^{13}C spectra were identical with those reported in the literature (13); $[\alpha]_D^{20}$ −53 (c = 0.3, MeOH).

Anodic oxidation of carbamate 7*a*

The carbamate **7***a* (59 mg, 0.27 mmol), $Bu_4N^+BF_4^-$ (22 mg, 0.068 mmol), and 5 mL of methanol were introduced into the electrolysis cell equipped with a platinum anode and a vitreous carbon cathode. A constant potential of 8 V was applied. After 5F/mol of electricity was passed, the usual work-up was applied; the crude fraction (68 mg) was flash chromatographed (silica gel, AcOEt/hexane 1:2) to give **21** (47 mg, 0.19 mmol, 71%): ^1H NMR δ: 5.5 (1H, m, H6), 4.70 (1H, dt, J ≈ 4 and 12 Hz, H5), 4.3 (1H, m, H2), 3.73 (3H, s, NCO_2CH_3), 3.33 (3H, broad s, OCH_3), 2.10 (3H, s, OAc), 1.64–2.14 (4H, m), 1.29 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR δ: 170.7, 156.3, 82.9, 72.2, 55.8, 53.2, 46.2, 29.1, 21.5, 19.8; MS, *m/z*: 245 ($M^{+\bullet}$, <1%), 214 (8), 202 (4), 198 (5), 185 (23), 172 (11), 170.4 (m*), 170 (7), 142 (25), 140 (11), 118 (100).

Preparation of 22 from 21

To a solution of $TiCl_4$ (21 μL, 0.19 mmol) in 0.2 mL of

CH_2Cl_2 at −45°C, under an atmosphere of nitrogen, was added a solution of **21** (32 mg, 0.13 mmol) in 0.6 mL of CH_2Cl_2. After 15 min the solution was cooled to −78°C and 2-trimethylsilyloxypropene (112 mg, 0.65 mmol) contaminated by ca. 25% of $(CH_3)_3SiOSi(CH_3)_3$ was added. After 4 h at −78°C, the solution was poured into 10 mL of water and NaCl was added; extraction with CH_2Cl_2 (2 × 10 mL), evaporation to dryness, and two successive flash chromatographies (silica gel, ethyl acetate/hexane 1:1) furnished **22** as a 76:24 mixture of diastereoisomers (26 mg, 0.096 mmol, 73%): MS, *m/z* (*c* + *t*): 271 ($M^{+\bullet}$, <1%), 256 (2), 240 (2), 214 (14), 211 (100), 198 (16), 196 (17), 172 (50), 171 (46), 169 (65), 168 (54), 156 (28), 154 (47), 152 (30), 140 (64), 102 (75), 85 (86). The following NMR values were extracted from the spectra of the mixture: major constituent: ^{1}H NMR δ: 4.8–5.07 (2H, m, H5 and H6), 4.35 (1H, m, H2), 3.69 (3H, s, NCO_2CH_3), 2.99 (1H, dd, *J* = 16 and 9 Hz, H7), 2.35 (1H, dd, *J* = 16 and 3 Hz, H7′), 2.19 (3H, s, CH_3), 1.95 (3H, s, OAc), 1.6–1.8 (4H, m), 1.18 (3H, d, *J* = 7 Hz, CH_3); ^{13}C NMR δ: 205.4, 169.7, 156.1, 70.4, 53.0, 48.6, 45.6, 45.4, 30.0, 28.3, 21.0, 20.2, 20.1; minor constituent: ^{1}H NMR δ: 4.78 (1H, m), 4.27 (1H, m), 4.01 (1H, m), 3.64 (3H, s, NCO_2CH_3), 3.12 (1H, dd, *J* = 16 and 8 Hz, H7), 2.60 (1H, dd, *J* = 16 and 7 Hz, H7′), 2.19 (3H, s, CH_3), 2.03 (3H, s, OAc), 1.3–1.9 (4H, m), 1.33 (3H, d, *J* = 7 Hz, CH_3); ^{13}C NMR δ: 205.8, 169.7, 156.2, 70.9, 52.4, 51.4, 49.0, 44.9, 30.0, 26.9, 24.8, 21.3, 18.4.

Anodic oxidation of ent-16

(+)-ent-**16** (93 mg, 0.25 mmol), $Et_4N^+OTs^-$ (8 mg, 0.026 mmol), and 5 mL of methanol were introduced into the electrolysis cell. The solution was stirred for 10 min and a constant potential of 8 V was applied. After 8F/mol of electricity was passed, some drops of NH_4OH, were added to the solution and the solvent was evaporated; the residue was dissolved in water (50 mL), basified with NH_4OH, and extracted with $CHCl_3$ (2 × 50 mL). The combined $CHCl_3$ layers were evaporated and the residue was filtered through a short column of silica gel (ethyl acetate/hexane 1:1) to afford a mixture of **23** and unreacted ent-**16**. This mixture was submitted to column chromatography on alumina (ethanol-free $CHCl_3$) to furnish the mixture of the diastereomeric methoxy compounds **23** (57 mg, 0.145 mmol, 58%): MS, *m/z* (*cis* and *trans*): 362 ($M^{+\bullet}-CH_3O^\bullet$, 3%), 333 (17), 319 (20), 259 (27), 231 (41), 230 (20), 202 (23), 198 (100), 170.4 (m*), 170 (18), 156 (61). The following NMR values were extracted from the spectra of the mixture: major constituent: ^{1}H NMR δ: (330 K): 7.31 (5H, m), 5.79 (1H, dd, *J* = 7 Hz, H8), 5.5 (1H, m, H6), 4.67 (1H, dt, *J* = 12 and 4 Hz, H5), 4.24 (1H, m, H2), 3.72 (3H, s, NCO_2CH_3), 3.35 (3H, s, OCH_3), 2.28 (m, 2H), 2.06 (6H, s, OAc), 1.6–1.94 (4H); ^{13}C NMR δ: (330 K): 170.7, 156.9, 141.2, 129.0, 128.5, 127.0, 83.5, 74.2, 72.2, 57.0, 53.3, 47.8, 40.5, 26.6, 21.4, 20.0; minor constituent: ^{1}H NMR δ (330K): 7.3 (5H, m), 5.8 (1H, m, H8), 5.19 (1H, d, *J* = 2 Hz, H6), 4.91 (1H, dt, *J* = 6 and 3 Hz, H5), 3.70 (3H, s, NCO_2CH_3), 3.60 (1H, m, H2), 3.28 (3H, s, OCH_3), 2.58 (1H, ddd, *J* = 5, 9, and 14 Hz, H7), 2.25 (1H, m, H7′), 2.04 (3H, s, OAc), 1.96 (3H, s, OAc), 1.6–1.9 (4H, m); ^{13}C NMR δ (330 K): 170.7, 170.3, 157.7, 141.2, 129.0, 128.5, 127.1, 85.8, 74.5, 69.2, 56.0, 52.6, 49.2, 39.8, 23.7, 23.4, 21.3, 21.2.

Nucleophilic displacement of the methoxy group of 23

To a stirred solution of $TiCl_4$ (43 μL, 0.39 mmol) in 1 mL of CH_2Cl_2 at 0°C, under an atmosphere of nitrogen, was added a solution of **23** (139 mg, 0.35 mmol) in 3 mL of CH_2Cl_2 and 2-trimethylsilyloxypropene (303 mg, 1.75 mmol) contaminated by ca. 25% of $(CH_3)_3SiOSi(CH_3)_3$. The solution was stirred for 2 h at 0°C, then poured into 50 mL of water and, after addition of NaCl, extracted with CH_2Cl_2 (4 × 50 mL). The combined CH_2Cl_2 layers were evaporated to dryness and the residue was submitted to two successive flash chromatographies (silica gel ethyl acetate/hexane 1:1) to furnish **24** as a 77/23 mixture of *c/t* diastereoisomers (88 mg, 0.21 mmol, 60%): MS, *m/z* (*cis* + *trans*): 419 ($M^{+\bullet}$, <1%; calcd. for $C_{22}H_{29}NO_7$: 419.1944; found: 419.1938), 362 (2), 359 (38), 316 (6), 299 (61), 298 (21), 270 (6), 256 (64), 249.0 (m*), 198 (70), 197 (27), 196 (37), 195 (50), 194 (35), 156 (61), 154 (60), 153.1 (m*), 150.0 (m*), 138 (40), 114 (100). The following NMR values were extracted from the spectra of the mixture: major constituent: ^{1}H NMR δ: 7.35 (5H, m), 5.76 (1H, dd, *J* = 10 and 4 Hz, H8), 5.07 and 4.93 (2H, m, H5 and H6), 4.29 (1H, m, H2), 3.69 (3H, s, NCO_2CH_3), 2.92 (1H, dd, *J* = 16 and 9 Hz, H9), 2.39 (1H, dd, *J* = 16 and 3 Hz, H9′), 2.17 (3H, s, CH_3), 2.09 (3H, s, OAc), 1.93 (3H, s, OAc), 1.9–2.2 (2H, m, H7), 1.2–1.7 (4H, m); ^{13}C NMR δ: 205.4, 170.5, 169.7, 156.1, 140.4, 128.8, 128.4, 126.6, 73.7, 70.1, 53.2, 48.5, 46.9, 45.2, 40.9, 30.1, 25.8, 21.8, 21.4, 20.3; minor constituent: ^{1}H NMR δ (characteristic values): 5.87 (1H, dd, *J* = 8 and 6 Hz, H8), 4.73 (1H, m), 4.2 (1H, m), 3.8 (1H, m), 3.58 (3H, s, NCO_2CH_3), 3.10 (1H, dd, *J* = 17 and 8 Hz, H9), 2.58 (2H, m), 2.17 (3H, s, CH_3), 2.06 (3H, s, OAc), 2.00 (3H, s, OAc), 1.6–2.1 (5H, m).

25: ^{1}H NMR δ: 7.3 (5H, m), 5.90 (1H, broad s, H6), 5.78 (1H, dd, *J* = 5 and 9 Hz, H8), 4.72 (1H, dt, *J* = 12 and 4 Hz, H5), 4.23(1H, m, H2), 3.72 (3H, s, NCO_2CH_3), 2.98 (1H, m, OH), 1.79 (1H, m, H7), 2.09 and 2.07 (6H, 2s, 2 × OAc), 1.7–2.1 (5H, m); MS, *m/z*: 379 ($M^{+\bullet}$, <1%), 319 (9), 318 (5), 301 (5), 259 (16), 241 (6), 231 (11), 216 (8), 198 (33), 156 (100), 121 (73).

Preparation of 27

A solution of **24** (68 mg, 0.16 mmol), ethylene glycol (17 mg, 3.2 mmol), and $TsOH{\cdot}H_2O$ (7 mg) in 20 mL of benzene was refluxed for 3 h in a Dean–Stark apparatus. After evaporation of the solvent, the residue was dissolved in dilute NH_4OH and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were evaporated to dryness to furnish **26** as a colourless oil (70 mg).

To a solution of the crude acetal **26** in THF (15 mL) was added $LiAlH_4$ (116 mg). The mixture was heated under reflux for 3 h. Some drops of water were added and the mixture was filtered through Celite and evaporated to dryness. The combined CH_2Cl_2 layers were evaporated and a chromatography on alumina of the residue furnished the diol **27** as a *c/t* mixture (36 mg, 1.1 mmol, 67% from **24**). The following NMR values (major constituent) were extracted from the spectra of the mixture: ^{1}H NMR δ: 7.3 (5H, m), 4.90 (1H, dd, *J* = 3 and 11 Hz, H8), 3.96 (4H, m, -OCH_2CH_2O-), 3.92 (1H, m, H5), 3.04 (1H, m), 2.91 (1H, td, *J* = 5 and 2 Hz, H6), 2.49 (3H, s, NCH_3), 1.2–2.1 (10H, m), 1.35 (3H, s, CH_3); ^{13}C NMR δ: 145.6, 128.6, 127.4, 125.9, 109.6, 75.9, 68.2, 65.0, 64.7, 64.2, 61.1, 40.8, 39.1, 32.4, 32.3, 24.4, 20.7; MS, *m/z*: 335 ($M^{+\bullet}$, 8%), 320 (2), 292 (6), 234 (14), 214 (97), 112 (29), 87 (100), 58.6 (m*).

Preparation of sedacryptine 28 from 27

A solution of the acetal **27** (36 mg, 1.1 mmol) in 0.1 N aqueous HCl (5 mL) was heated under reflux for 30 min. The mixture was then cooled, basified with NH_4OH, and extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 layers were evaporated to dryness to furnish a mixture of sedacryptine **28** and **29** in a 60/40 ratio (25 mg, 0.086 mmol, 80 %). After epimerization in MeOH the diastereoisomeric ratio moved to 80/20. Crystallization from cyclohexane furnished pure (+)-sedacryptine **28** as colourless crystals, mp 122–123°C; $[\alpha]_D^{20}$ +14 (c = 0.54, $CHCl_3$); ^{1}H NMR δ (360 MHz): 7.34 (5H, m), 4.85 (1H, dd, J = 10 and 3 Hz, H8), 4.07 (1H, q, J = 3 Hz, H5), 2.69 (1H, t, J = 3 Hz, H6), 2.31 (1H, m, H2), 2.28 (3H, s, NCH_3), 2.24 (1H, d, J = 13 Hz, H9), 2.20 (1H, m, H7), 2.09 (1H, ddt, J = 14, 3 and 3 Hz, H4e), 1.91 (1H, dd, J =13 and 4 Hz, H9′), 1.83 (1H, m, H3e), 1.54–1.65 (3H, m, H3a, H4a, H7′), 1.5–1.9 (2H, OH), 1.48 (3H, s, CH_3); MS, m/z: 291 ($M^{+\bullet}$, 4%), 273 (12), 234 (2), 230 (4), 170 (100), 152 (83), 135.9 (m*), 112 (44), 95 (75).

Acknowledgements

M.P. wishes to thank the "Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" (IRSIA) for the award of a fellowship. C.H. is a Research Associate of the National Fund for Scientific Research (FNRS).

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