Simple and selective one-pot replacement of the *N*-methyl group of tertiary amines by quaternization and demethylation with sodium sulfide or potassium thioacetate: an application to the synthesis of pergolide

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The paper describes a mild, selective, and rapid replacement of an *N*-methyl group of tertiary amines with other alkyl groups *via* a simple one-pot procedure. This transformation is easily achieved by preparation of the appropriate quaternary ammonium salt in sulfolane and *in situ* treatment with sodium sulfide or potassium thioacetate. The protocol is successfully applied to the transformation of dihydrolysergol, dextromethorphan and laudanosine (as models of ergot and opium *N*-methyl alkaloids) into various *N*-alkyl congeners.

Introduction

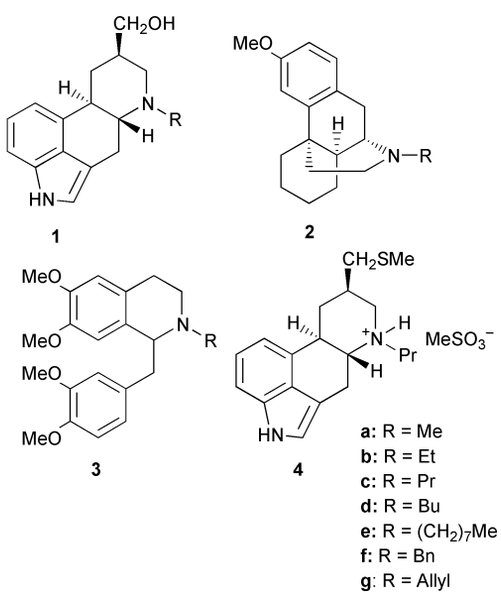
The replacement of an *N*-methyl group of tertiary amines with other alkyl groups is a crucial transformation especially in alkaloid chemistry, as many clinically used compounds possessing different *N*-alkyl groups are prepared from cheap *N*-methyl-substituted analogues of compounds of natural origin. Traditional processes,[1] allowing the replacement of the *N*-methyl group, imply involved protocols, consisting in the conversion of *N*-methyl-substituted compounds to the corresponding cyanamides (by the von Braun reaction[2] with cyanogen bromide), or carbamates[3] [by reaction with alkyl carbonochlorides (alkyl chloroformates)] which are subsequently cleaved to give *N*-noralkaloids. A successive *N*-alkylation accomplishes the desired substitution. This procedure has been recently improved, for the synthesis of opium alkaloids, by using L-selectride as the *N*-demethoxycarbonylation agent.[4]

An alternative procedure involves the intermediate quaternization of the starting tertiary amine, by alkylation with the appropriate alkyl halide, followed by a selective S_N2 demethylation, which can be performed with variable results, using cuprous [copper(I)] or sodium thiophenoxide in refluxing pyridine,[5] butanone[6] or acetonitrile–butanone,[7] thiopropoxide in HMPA,[8] or excess of thiomethoxide (freshly prepared) in 1-methylpyrrolidin-2-one (NMP).[9,10]

Our interest in the transformation of dihydrolysergol **1a** into its congeners having different alkyl groups on the aliphatic nitrogen atom prompted us to seek for a simpler procedure for the exchange of the *N*-methyl group of **1a**. In particular we were looking for a new procedure that would avoid some hassle encountered with the known methods, caused by the use of pyridine[5] or HMPA,[8] the need of a large excess of freshly prepared thioalkoxides, even in the best method to date,[9,10] and the long handling of hazardous intermediates.

As a result of our studies we herein report a simple protocol for the selective one-pot exchange of the *N*-methyl group of tertiary amines, applied to dihydrolysergol **1a**, and also to dextromethorphan **2a** and laudanosine **3a**, two compounds chosen as representative models of opium alkaloids.

The synthetic utility of the method is demonstrated, *inter alia*, by the transformation of dihydrolysergol **1a** into its homologue **1c**, a key intermediate for the synthesis[11] of the pergolide mesylester **4** (8β-[(methylthio)methyl]-6-propylergoline mesylester; Permax®), a semisynthetic ergot alkaloid clinically used as an adjunct to levodopa-carbidopa in the treatment of symptoms of Parkinson's disease.[12]



Results and discussion

The one-pot replacement of the *N*-methyl group of dihydrolysergol **1a** with various alkyl groups (Table 1) was performed by a quantitative quaternization of the tertiary *N*-methyl amine of **1a**, with the appropriate halogenoalkane (1.25 molar equiv.) in sulfolane (tetramethylene sulfone) buffered by catalytic amounts of K_3PO_4 (0.1 molar equiv.), followed by addition of $Na_2S{\cdot}9H_2O$ (1.0 molar equiv.) and heating at 120 °C for 5 h. The use of K_3PO_4 in the quaternization reaction distinctly improves both the level of conversion and the rate of the reac-

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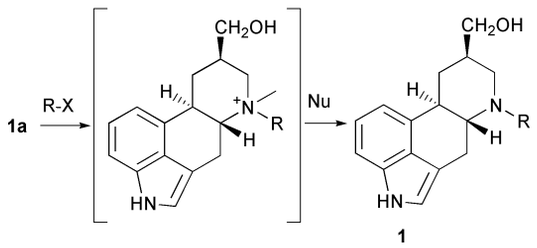
Table 1 Replacement of the methyl group of the dihydrolysergol **1a**



Entry	R-X	Nu	Compound (yield %)[a]	Selectivity[b] **1x** : **1a**
1	$MeCH_2I$	Na_2S	**1b**[c]	81 : 19
2	$Me[CH_2]_2I$	Na_2S	**1c** (85)	96 : 4
3	$Me[CH_2]_3I$	Na_2S	**1d** (90)	98 : 2
4	$Me[CH_2]_7I$	Na_2S	**1e** (87)	98 : 2
5	$C_6H_5CH_2Br$	Na_2S	**1a** (89)	1.4 : 98.6
6	CH_2=CHCHBr	Na_2S	**1a** (84)	9 : 91

[a] Isolated yields after rapid chromatography. [b] Determined by GLC and GLC-MS. [c] Separable with difficulty from starting material **1a**, an analytical sample was obtained by traditional column chromatography.

tion.† The selective removal of the methyl group occurs with very good to excellent yields affording the desired congener **1b**–**e** (Table 1). On the other hand, in the case of benzyl- and allyl-ammonium derivatives, the benzyl and allyl groups are quantitatively eliminated with high selectivity (Table 1, entries 5 and 6) and the demethylation is not of synthetic utility. This preferential removal of benzyl and allyl substituents is in agreement with the results already observed using thiophenoxide[5,13] and could be due to electronic effects.

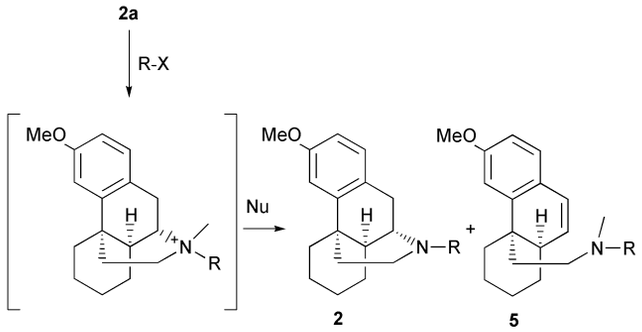
The use of the inorganic sodium sulfide as a selective demethylation agent of quaternary ammonium salts is unprecedented, in spite of the fact that other organic sulfides, such as thiophenoxides or thioalkoxides, are good dealkylants. This salt was chosen for the high nucleophilicity of the sulfide ion (S^{2-}), and because the thiomethoxide ion (CH_3S^-), resulting from a hypothetical S_N2 attack, is still able to continue the dealkylation. Therefore, the selective dealkylation of the ammonium salts was achieved using only a 1 : 1 molar ratio of Na_2S and the ammonium salt, to afford tertiary amines with both high yields and selectivity (Table 1). The selectivity of the demethylation enhances with an increase in the steric hindrance of the alkyl groups used as replacement of the starting methyl (Table 1).

Thus the method was also practically useful for a large-scale preparation of the *N*-propyl compound **1c**, a key intermediate for the synthesis of pergolide **4**. Starting from dihydrolysergol **1a** (10 g) the homologous compound **1c** was obtained in high yield (76%) and purity (99.2% by GLC), after a single crystallization form diisopropyl ether. The replacement of the alcoholic group of **1c** with a thiomethoxy group[11] affords, first, highly pure pergolide (99.5% pure by GLC) after a single crystallization, and successively the pergolide mesylester **4** (99.6% pure by GLC as free base) in satisfactory overall yield (42%) from dihydrolysergol **1a**.

These results clearly confirm the potentials of this new protocol, and allowed us to achieve a new, simple and efficient synthesis of pergolide mesylester **4**, alternative to the best known method,[9] which has a major drawback, since it requires a tandem chromatographic purification to remove some by-products closely related to pergolide.

† Unfortunately any attempt to perform the *N*-alkylation of **1a** or **2a** with secondary halogenoalkanes was not successful due to the incomplete tetraalkylation of the starting amine. In fact the reaction of **1a** or **2a** with 2-iodopropane (6 molar equiv.) in sulfolane or NMP at 120 °C for 26 h afforded a mixture of the tetraalkyl compound (20–30%) and the unchanged starting amine (70–80%).

Table 2 Replacement of the methyl group of the dextromethorphan **2a**



Entry	R-X	Nu	Compound (yield %)[a]	Selectivity[b] **2a** : **2x** : **5x**
1	$MeCH_2I$	Na_2S	**5b** (83)	1 : 2: 97
2	$Me[CH_2]_2I$	Na_2S	**5c** (84)	1 : 6 : 93
3	$Me[CH_2]_7I$	Na_2S	**5e** (74)	1 : 14 : 85
4	$C_6H_5CH_2Br$	Na_2S	**2a** (86)	93 : 2 : 5
5	$MeCH_2I$	MeCOSK	**2b** (75)	16 : 81 : 3
6	$Me[CH_2]_2I$	MeCOSK	**2c** (84)	5 : 92 : 3
7	$Me[CH_2]_7I$	MeCOSK	**2e** (86)	1 : 94 : 5
8	$C_6H_5CH_2Br$	MeCOSK	**2a** (82)	90 : 9 : 1
9	CH_2=CHCHBr	MeCOSK	**2a** (78)	87 : 12 : 1
10	$Me[CH_2]_2I$	MeSNa	**5c** (70)	1 : 20 : 79
11[c]	$Me[CH_2]_2I$	MeSNa	**5c** (69)	4 : 20 : 76

[a] Isolated yields after rapid chromatography. [b] Determined by GLC and GLC-MS. [c] In NMP at 100 °C for 6 h.

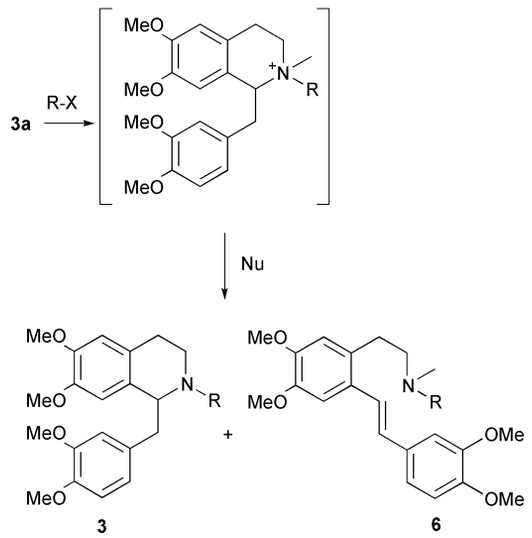
In order to evaluate the generality of our protocol we tested its application to the replacement of the methyl group of dextromethorphan **2a**† and of laudanosine **3a**. Unfortunately, using sodium sulfide, a competitive Hofmann elimination occurred and, in the case of dextromethorphan **2a**, the desired S_N2 products were obtained in negligible to poor amounts (2.0–14.0%, Table 2; entries 1–3) accompanied by the relative elimination products **5b**, **5c** and **5e** lacking the heterocyclic ring. Superior but still modest results were obtained in the case of laudanosine **3a**. In fact, with this substrate, the desired compounds of substitution (Table 3; entries 1–3) were formed as major products in good yields (61–71%), but they were still accompanied by significant amounts of Hofmann elimination products, of assigned structures **6b**, **6c** and **6e**.

The proposed structures **5** and **6** for the Hofmann elimination products were confirmed by MS (molecular ions) and ^{1}H-NMR data. In particular, the presence of only two olefinic proton signals in the ^{1}H-NMR spectra is diagnostic and allows exclusion of any possible alternative structure. Moreover, the couplings-constant values (16.0 Hz) associated with the olefinic protons of compounds **6** are diagnostic for the *E* configuration of the formed double bond.

Formation of an elimination product (20%) was already observed for a similar *N*-methyl group exchange reaction performed on quaternized thebaine, a compound structurally related to **2a**, using thiophenoxide in butanone–acetonitrile.[7] Also the use of sodium thiomethoxide, a nucleophile which shows good results with ergot ammonium salts,[9] afforded, in our hands, similar poor results due to the formation of consistent amounts of elimination products (Table 2; entries 10 and 11).

In order to overcome this limitation of our method (as well as of the previous ones), we decided to test the behaviour of a less basic nucleophile. We found that treatment of quaternized **2a** or **3a** dissolved in sulfolane with commercial potassium thioacetate (3 molar equiv.) for 6 h at 120 °C, affords the desired *N*-alkylamino homologues with high yields and selectivity (Table 2 and Table 3; entries 5–7). The reaction proceeded with the same good results also when we used NMP in place of

Table 3 Replacement of the methyl group of the (±)-laudanosine **3a**



Entry	R-X	Nu	Compound (yield %)[a]	Selectivity[b] **3a** : **3x** : **6x**
1	$MeCH_2I$	Na_2S	**3b** (58)	18 : 62 : 20
2	$Me[CH_2]_2I$	Na_2S	**3c** (55)	6 : 61 : 33
3	$Me[CH_2]_7I$	Na_2S	**3e** (65)	6 : 71 : 23
4	$C_6H_5CH_2Br$	Na_2S	**3a** (86)	95 : 4 : 1
5	$MeCH_2I$	MeCOSK	**3b** (78)	11 : 85 : 4
6	$Me[CH_2]_2I$	MeCOSK	**3c** (82)	7 : 88 : 5
7	$Me[CH_2]_7I$	MeCOSK	**3e** (86)	1 : 94 : 5
8	$C_6H_5CH_2Br$	MeCOSK	**3a** (84)	93 : 6 : 1

[a] Isolated yields after rapid chromatography. [b] Determined by GLC and GLC-MS.

sulfolane and appears to be a general and interesting alternative to known methods, in particular for the modification of substrates prone to suffer elimination.

Unfortunately, a limitation of our exchange protocol is represented by the impossibility to efficiently replace a methyl group with a benzyl or allyl group since the new substituent is preferably eliminated (Table 2; entries 4, 8 and 9 and Table 3; entries 4 and 8). However, the clean and selective new protocol for the debenzylation of the quaternary benzylammonium salts promoted by potassium thioacetate herein reported is of great interest, since it offers the possibility to regenerate, under milder conditions, the starting amine in all cases in which its protection as quaternary benzylammonium salt is required or could be useful.

Experimental

General

Mps were measured on a SMP3 mp apparatus (Stuart Scientific, USA) and are not corrected. Proton nuclear magnetic resonance spectra were recorded in $CDCl_3$ or [$^2H_6$]-DMSO at 303 K on Bruker AM-500 spectrometer operating at 500.13 MHz. Chemical shifts are reported as δ-values in ppm, relative to residual $CHCl_3$ (δ 7.24) or DMSO (δ 2.50) as internal standard. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet. Coupling constants (J) are reported in Hz. Optical rotations were taken at 24 °C on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. GLC analyses were carried out on a Hewlett-Packard 5890 gas chromatography equipped with an HP-5 (Hewlett-Packard) capillary column (5 m, 0.32 mm ID, 0.25 μm, He 15 kPa) for dihydrolysergol derivatives and with an HP-1 (Hewlett-Packard) capillary column (12 m, 0.20 mm ID, 0.20 μm, He 65 kPa) for laudanosine and dextromethorphan derivatives. Mass spectra were obtained on a Hewlett-Packard 5988A, by using either electron impact (EI) or chemical ionization (CI) with NH_3 as reagent gas. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}) using UV light, 50% sulfuric acid and heat or iodine as developing agent. E. Merck 230–400 mesh silica gel was used for rapid column chromatography.[14]

General procedure for the one-pot replacement of the *N*-methyl group of tertiary amines

The starting tertiary amine (**1a**, **2a** and **3a**; 1.00 mmol) and the appropriate halogenoalkane (1.25 mmol) were dissolved in sulfolane (80 cm^3) containing $K_3PO_4 \cdot 3H_2O$ (0.1 mmol) and the solution was heated at 110 °C for 2 h. At this time, the disappearance of the starting amine was monitored (by TLC), the nucleophile ($Na_2S \cdot 9H_2O$, 1 mmol; MeSNa, 3 mmol; MeCOSK, 9 mmol) was added and the mixture was heated at 120 °C [for 5 h ($Na_2S \cdot 9H_2O$, MeSNa) or 6 h (MeCOSK)]. The mixture was then poured in ice-cold water (10 cm^3) and the resulting suspension was extracted with ethyl acetate. The organic layer was then washed with water, and dried over Na_2SO_4 to afford, after evaporation under reduced pressure, a crude residue which was finally chromatographed.

(1) Using chloroethane, dihydrolysergol 1a and $Na_2S \cdot 9H_2O$. The obtained crude product was a mixture of the starting amine **1a** and of its homologues **1b** in a 19 : 81 ratio. Purification by traditional chromatography on silica gel G-Celite (1 : 1 v/v, starting elution with AcOEt and going on with addition of increasing amounts of MeOH), allowed the isolation of an analytical sample of pure **1b** as a solid (Found: C, 75.3; H, 8.4; N, 10.5. $C_{17}H_{22}N_2O$ requires C, 75.5; H, 8.2; N, 10.4%); mp 251–254 °C (from EtOH–CH_2Cl_2) (lit.,[15] 252–254 °C); GLC (240 °C) t_R 2.22 min; δ_H (500 MHz; $CDCl_3$) 0.86 (3 H, t, J 7.1, NCH_2CH_3), 0.92 (1 H, ddd, J 12.2, 12.2, 12.4, 9-Ha), 1.89 (1 H, m, 8-H), 1.96 (1 H, dd, J 10.8 and 10.8, 7-Ha), 2.26 (1 H, ddd, J 4.0, 9.6, 11, 5-H), 2.52–2.60 (3 H, overlapping, 4-Ha, 9-Hb, $NCHHCH_3$), 2.71–2.78 (2 H, overlapping, 10-H and $NCHHCH_3$), 3.08 (1 H, dd, J 2.9 and 10.8, 7-Hb), 3.28 (2 H, m, 8′-H_2), 3.36–3.47 (overlapping DHO and 4-Hb), 4.53 (1 H, dd, J 4.0 and 4.0, 8′-OH), 6.76 (1 H, d, J 6.8, 12-H), 6.95 (1 H, br s, 2-H), 7.01 (1 H, dd, J 6.8 and 6.8, 13-H), 7.11 (1 H, d, J 6.8, 14-H), 10.80 (1 H, br s, 1-H); m/z (CI, NH_3) 271 ($M^+ + 1$, 100%); m/z (EI) 270 (M^+, 100%), 255 (14), 168 (14), 154 (49), 144 (34), 127 (18).

(2) Using 1-chloropropane and dihydrolysergol 1a with $Na_2S \cdot 9H_2O$. Purification by rapid chromatography, eluting with AcOEt–MeOH 75 : 25 v/v, afforded the amine **1c** (241 mg, 85%) as a solid (Found: C, 76.1; H, 8.6; N, 9.8. $C_{18}H_{24}N_2O$ requires C, 76.0; H, 8.5; N, 9.85%); mp 179–181 °C (from diisopropyl ether) (lit.,[15] 181–182 °C); $[\alpha]_D$ −52.2 (c 1 in MeOH) (lit.,[15] −66); GLC (240 °C) t_R 2.61 min; δ_H (500 MHz; $CDCl_3$) 0.86 (3 H, t, J 7.3, $NCH_2CH_2CH_3$), 0.92 (1 H, ddd, J 12.2, 12.2, 12.4, 9-Ha), 1.46 (2 H, m, $NCH_2CH_2CH_3$), 1.88 (1 H, m, 8-H), 1.96 (1 H, dd, J 11.0 and 11.0, 7-Ha), 2.27 (1 H, ddd, J 3.9, 9.6, 10.7, 5-H), 2.53–2.59 (3 H, overlapping, 4-Ha, 9-Hb, $NCHHCH_2CH_3$), 2.71–2.77 (2 H, overlapping, 10-H and $NCHHCH_2CH_3$), 3.08 (1 H, dd, J 2.9 and 11.0, 7-Hb), 3.28 (2 H, m, 8′-H_2), 3.36–3.46 (overlapping DHO and 4-Hb), 4.54 (1 H, dd, J 4.0 and 4.0, 8′-OH), 6.76 (1 H, d, J 6.8, 12-H), 6.95 (1 H, br s, 2-H), 7.00 (1 H, dd, J 6.8 and 6.8, 13-H), 7.10 (1 H, d, J 6.8, 14-H), 10.80 (1 H, br s, 1-H); m/z (CI, NH_3) 285 ($M^+ + 1$, 100%); m/z (EI) 284 (M^+, 100%), 255 (81), 168 (22), 154 (69), 144 (22), 127 (24).

(3) Using 1-chlorobutane, dihydrolysergol 1a and $Na_2S \cdot 9H_2O$. Purification by rapid chromatography, eluting with AcOEt–MeOH 80 : 20 v/v, afforded the amine **1d** (268 mg, 90%) as a

solid (Found: C, 72.2; H, 9.0; N, 8.7. $C_{19}H_{26}N_2O{\cdot}H_2O$ requires C, 72.1; H, 8.9; N, 8.85%); mp 151–153 °C (from diisopropyl ether) (lit.,[15] 152–154 °C); $[\alpha]_D$ −51.4 (*c* 1 in MeOH) (lit.,[15] −68.2); GLC (240 °C) t_R 2.88 min; δ_H (500 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.3, $N[CH_2]_3CH_3$), 0.93 (1 H, ddd, *J* 12.2, 12.2, 12.4, 9-Ha), 1.28 (2 H, tq, *J* 7.3 and 7.3, $N[CH_2]_2CH_2CH_3$), 1.42 (2 H, m, $NCH_2CH_2CH_2CH_3$), 1.89 (1 H, m, 8-H), 1.97 (1 H, dd, *J* 11.0 and 11.0, 7-Ha), 2.28 (1 H, ddd, *J* 3.8, 9.8, 10.8, 5-H), 2.51–2.62 (3 H, overlapping, 4-Ha, 9-Hb, $NCH[CH_2]_2CH_3$), 2.73–2.82 (2 H, overlapping, 10-H and $NCH[CH_2]_2CH_3$), 3.08 (1 H, dd, *J* 3.0 and 10.3, 7-Hb), 3.29 (2 H, m, 8′-H_2), 3.40–3.49 (overlapping DHO and 4-Hb), 4.59 (1 H, dd, *J* 4.0 and 4.0, 8′-OH), 6.76 (1 H, d, *J* 7.0, 12-H), 6.96 (1 H, br s, 2-H), 7.00 (1 H, dd, *J* 7.0 and 7.0, 13-H), 7.11 (1 H, d, *J* 7.0, 14-H), 10.82 (1 H, br s, 1-H); *m*/*z* (CI, NH_3) 299 (M^+ + 1, 100%).

(4) Using 1-chlorooctane, dihydrolysergol 1a and $Na_2S{\cdot}9H_2O$. Purification by rapid chromatography, eluting with AcOEt–MeOH 90 : 10 v/v, afforded the amine **1e** (252 mg, 87%) as a solid (Found: C, 78.0; H, 9.6; N, 7.9. $C_{23}H_{34}N_2O$ requires C, 77.9; H, 9.7; N, 7.9%); mp 138–140 °C (from diisopropyl ether); $[\alpha]_D$ −44.6 (*c* 1 in MeOH); GLC (240 °C) t_R 11.01 min; δ_H (500 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 6.7, $NCH_2[CH_2]_6CH_3$), 0.91 (1 H, ddd, *J* 12.2, 12.2, 12.4, 9-Ha), 1.23–1.30 (10 H, overlapping, 5 × CH_2), 1.43 (2 H, m, $NCH_2CH_2[CH_2]_5CH_3$), 1.87 (1 H, m, 8-H), 1.95 (1 H, dd, *J* 10.3 and 11.0, 7-Ha), 2.26 (1 H, ddd, *J* 4.0, 9.8, 10.9, 5-H), 2.51–2.62 (3 H, overlapping, 4-Ha, 9-Hb, $NCH[CH_2]_6CH_3$), 2.71–2.80 (2 H, overlapping, 10-H and $NCH[CH_2]_6CH_3$), 3.06 (1 H, dd, *J* 1.7 and 10.3, 7-Hb), 3.28 (2 H, m, 8′-H_2), 3.35–3.46 (overlapping DHO and 4-Hb), 4.56 (1 H, dd, *J* 4.0 and 4.0, 8′-OH), 6.75 (1 H, d, *J* 7.1, 12-H), 6.96 (1 H, br s, 2-H), 6.99 (1 H, dd, *J* 7.1 and 6.8, 13-H), 7.10 (1 H, d, *J* 7.1, 14-H), 10.79 (1 H, br s, 1-H); *m*/*z* (CI, NH_3) 355 (M^+ + 1, 100%); *m*/*z* (EI) 354 (M^+, 90%), 255 (100), 168 (21), 154 (62), 144 (21), 127 (16).

(5) Using benzyl bromide, dihydrolysergol 1a and $Na_2S{\cdot}9H_2O$. Purification by rapid chromatography, eluting with AcOEt–MeOH 70 : 30 v/v, afforded the starting dihydrolysergol **1a** (228 mg, 89% recovery); GLC (240 °C) t_R 2.02 min.

(6) Using allyl bromide, dihydrolysergol 1a and $Na_2S{\cdot}9H_2O$. Purification by rapid chromatography, eluting with AcOEt–MeOH 70 : 30 v/v, afforded the starting dihydrolysergol **1a** (215 mg, 84% recovery); GLC (240 °C) t_R 2.02 min.

(7) Using chloroethane and dextromethorphan 2a. *(a) With $Na_2S{\cdot}9H_2O$.* Purification by rapid chromatography, eluting with MeOH, afforded the elimination compound **5b** (248 mg, 83%) as an oil (Found: C, 80.4; H, 9.75; N, 4.8. $C_{20}H_{29}NO$ requires C, 80.2; H, 9.8; N, 4.7%); GLC (220 °C) t_R 2.76 min; δ_H (500 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.0, NCH_2CH_3), 0.97 (1 H, dddd, *J* 3.1, 11.2, 12.3, 12.3, 8-Ha), 1.21 (1 H, m, 7-Ha), 1.29–1.43 (3 H, overlapping, 5-Ha, 6-Ha, 15-Ha), 1.52–1.58 (3 H, overlapping, 5-Hb, 7-Hb, 8-Hb), 1.92 (1 H, ddd, *J* 4.6, 12.0, 12.8, 15-Hb), 1.97–2.04 (2 H, overlapping, 14-H and 16-Ha), 2.05 (3 H, s, NMe), 2.25 (2 H, q, *J* 7.0, NCH_2CH_3), 2.29–2.37 (2 H, overlapping, 6-Hb and 16-Hb), 3.79 (3 H, s, OMe), 5.78 (1 H, dd, *J* 6.1 and 9.5, 9-H), 6.27 (1 H, d, *J* 9.5, 10-H), 6.65 (1 H, dd, *J* 2.4 and 8.3, 2-H), 6.77 (1 H, d, *J* 2.4, 4-H), 6.95 (1 H, d, *J* 8.3, 1-H); *m*/*z* (CI, NH_3) 300 (M^+ + 1, 100%); *m*/*z* (EI) 299 (M^+, 0.9%), 285 (1.2), 270 (5.6), 214 (39.7), 171 (100).

(b) With MeCOSK. Rapid chromatography, eluting with MeOH, afforded, first, the amine **2b** (214 mg, 75%) as an oil (Found: C, 79.8; H, 9.6; N, 4.8. $C_{19}H_{27}NO$ requires C, 79.95; H, 9.6; N, 4.9%); $[\alpha]_D$ +51.6 (*c* 1 in $CHCl_3$); GLC (220 °C) t_R 2.86 min; δ_H (500 MHz; $CDCl_3$) 1.07 (3 H, t, *J* 7.1, NCH_2CH_3), 1.11 (1 H, dddd, *J* 3.4, 12.4, 12.5, 12.5, 8-Ha), 1.25–1.40 (5 H, overlapping, 5-Ha, 6-Ha, 7-Ha, 8-Hb, 15-Ha), 1.49 (1 H, ddd, *J* 2.6, 3.3, 10.9, 5-Hb), 1.62 (1 H, m, 7-Hb), 1.71 (1 H, ddd, *J* 4.7, 12.6, 12.6, 15-Hb), 1.79 (1 H, ddd, *J* 2.9, 3.3, 12.5, 14-H), 1.98 (1 H, ddd, *J* 3.3, 12.2, 12.6, 16-Ha), 2.32 (1 H, m, 6-Hb), 2.50–2.58 (4 H, overlapping, 10-Ha, 16-Hb, NCH_2CH_3), 2.90 (1 H, dd, *J* <1, 17.8, 10-Hb), 2.90 (1 H, ddd, *J* <1, 3.3, 4.4, 9-H), 3.76 (3 H, OMe), 6.66 (1 H, dd, *J* 2.7, 8.4, 2-H), 6.78 (1 H, d, *J* 2.7, 4-H), 6.98 (1 H, d, *J* 8.4, 1-H); *m*/*z* (CI, NH_3) 286 (M^+ + 1, 100%). Further elution afforded the starting dextromethorphan **2a** (35 mg, 13% recovery).

(8) Using 1-chloropropane and dextromethorphan 2a. *(a) With $Na_2S{\cdot}9H_2O$.* Purification by rapid chromatography, eluting with MeOH, afforded the elimination compound **5c** (263 mg, 84%) as an oil (Found: C, 80.5; H, 9.9; N, 4.5. $C_{21}H_{31}NO$ requires C, 80.5; H, 10.0; N, 4.5%); GLC (220 °C) t_R 3.34 min; δ_H (500 MHz; $CDCl_3$) 0.79 (3 H, t, *J* 7.4, $NCH_2CH_2CH_3$), 0.96 (1 H, dddd, *J* 2.7, 11.0, 12.1, 12.1, 8-Ha), 1.21 (1 H, m, 7-Ha), 1.29–1.43 (5 H, overlapping, 5-Ha, 6-Ha, 15-Ha, $NCH_2CH_2CH_3$), 1.52–1.57 (3 H, overlapping, 5-Hb, 7-Hb, 8-Hb), 1.91 (1 H, ddd, *J* 4.3, 11.9, 12.8, 15-Hb), 1.96–2.04 (2 H, overlapping, 14-H and 16-Ha), 2.05 (3 H, s, NMe), 2.12 (2 H, t, *J* 7.4, $NCH_2CH_2CH_3$), 2.28–2.35 (2 H, overlapping, 6-Hb and 16-Hb), 3.79 (3 H, s, OMe), 5.78 (1 H, dd, *J* 6.1 and 9.5, 9-H), 6.27 (1 H, d, *J* 9.5, 10-H), 6.65 (1 H, dd, *J* 2.4 and 8.3, 2-H), 6.77 (1 H, d, *J* 2.4, 4-H), 6.95 (1 H, d, *J* 8.3, 1-H); *m*/*z* (CI, NH_3) 314 (M^+ + 1, 100%); *m*/*z* (EI) 313 (M^+, 1.0%), 299 (0.6), 284 (1.0), 270 (8.7), 214 (44.2), 171 (100).

(b) With MeCOSK. Purification by rapid chromatography, eluting with MeOH, afforded the amine **2c** (251 mg, 84%) as an oil (Found: C, 80.1; H, 9.5; N, 4.7. $C_{20}H_{29}NO$ requires C, 80.2; H, 9.8; N, 4.7%); $[\alpha]_D$ +66.4 (*c* 1 in $CHCl_3$); GLC (220 °C) t_R 3.47 min; δ_H (500 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.3, $NCH_2CH_2CH_3$), 1.10 (1 H, dddd, *J* 3.5, 12.3, 12.5, 12.5, 8-Ha), 1.25–1.39 (5 H, overlapping, 5-Ha, 6-Ha, 7-Ha, 8-Hb, 15-Ha), 1.44–1.52 (3 H, overlapping, 5-Hb and $NCH_2CH_2CH_3$), 1.62 (1 H, m, 7-Hb), 1.70 (1 H, ddd, *J* 4.7, 12.6, 12.6, 15-Hb), 1.79 (1 H, ddd, *J* 2.9, 3.3, 12.5, 14-H), 2.01 (1 H, ddd, *J* 3.2, 12.2, 12.6, 16-Ha), 2.32 (1 H, m, 6-Hb), 2.41 (2 H, t, *J* 7.3, $NCH_2CH_2CH_3$), 2.49 (1 H, ddd, *J* 1.3, 4.7, 12.2, 16-Hb), 2.55 (1 H, dd, *J* 5.9, 18.0, 10-Ha), 2.85 (1 H, ddd, *J* <1, 3.3, 5.9, 9-H), 2.91 (1 H, dd, *J* <1, 18.0, 10-Hb), 3.76 (3 H, OMe), 6.66 (1 H, dd, *J* 2.8, 8.2, 2-H), 6.78 (1 H, d, *J* 2.8, 4-H), 6.99 (1 H, d, *J* 8.2, 1-H); *m*/*z* (CI, NH_3) 300 (M^+ + 1, 100%).

(c) With MeSNa. Rapid chromatography, eluting with MeOH, afforded, first, the amine **2c** (50 mg, 17%) and then the elimination product **5c** (219 mg, 70%).

(d) With MeSNa in NMP at 100 °C for 6 h. Rapid chromatography, eluting with MeOH, afforded, first, the amine **2c** (48 mg, 16%) and then the elimination product **5c** (216 mg, 69%).

(9) Using 1-chlorooctane and dextromethorphan 2a. *(a) With $Na_2S{\cdot}9H_2O$.* Purification by rapid chromatography, eluting with hexane–AcOEt 70–30 v/v, afforded the elimination compound **5e** (283 mg, 74%) as an oil (Found: C, 81.6; H, 10.9; N, 3.7. $C_{26}H_{41}NO$ requires C, 81.4; H, 10.9; N, 3.65%); GLC (220 °C for 5 min, 20 °C min^{-1} until 290 °C) t_R 7.62 min; δ_H (500 MHz; $CDCl_3$) 0.77 (3 H, t, *J* 7.0, $NCH_2[CH_2]_6CH_3$), 0.96 (1 H, dddd, *J* 2.7, 11.0, 12.1, 12.1, 8-Ha), 1.16–1.26 (11 H, overlapping, 7-Ha and 5 × CH_2), 1.29–1.46 (5 H, overlapping, 5-Ha, 6-Ha, 15-Ha, CH_2), 1.52–1.57 (3 H, overlapping, 5-Hb, 7-Hb, 8-Hb), 1.91 (1 H, ddd, *J* 4.0, 11.2, 12.3, 15-Hb), 1.96–2.04 (2 H, overlapping, 14-H and 16-Ha), 2.05 (3 H, s, NMe), 2.16 (2 H, t, *J* 7.0, $NCH_2[CH_2]_6CH_3$), 2.28–2.35 (2 H, overlapping, 6-Hb and 16-Hb), 3.79 (3 H, s, OMe), 5.78 (1 H, dd, *J* 6.0 and 9.5, 9-H), 6.27 (1 H, d, *J* 9.5, 10-H), 6.65 (1 H, dd, *J* 2.5 and 8.3, 2-H), 6.77 (1 H, d, *J* 2.5, 4-H), 6.95 (1 H, d, *J* 8.3, 1-H); *m*/*z* (CI, NH_3) 384 (M^+ + 1, 100%); *m*/*z* (EI) 383 (M^+, 2.3%), 340 (0.6), 284 (3.4), 270 (1.7), 214 (97.1), 171 (100).

(b) With MeCOSK. Purification by rapid chromatography, eluting with hexane–AcOEt 60 : 40 v/v, afforded the amine **2e** (317 mg, 86%) as an oil (Found: C, 81.1; H, 10.7; N, 4.2.

$C_{25}H_{39}NO$ requires C, 81.25; H, 10.7; N, 4.3%); $[\alpha]_D$ +111.6 (*c* 1 in $CHCl_3$); GLC (220 °C for 5 min, 20 °C min^{-1} until 290 °C) t_R 8.10 min; δ_H (500 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.0, $NCH_2[CH_2]_6CH_3$), 1.10 (1 H, dddd, *J* 3.2, 12.3, 12.5, 12.5, 8-Ha), 1.23–1.39 (15 H, overlapping, 5-Ha, 6-Ha, 7-Ha, 8-Hb, 15-Ha, 5 × CH_2), 1.45–1.52 (3 H, overlapping, 5-Hb and CH_2), 1.61 (1 H, m, 7-Hb), 1.74 (1 H, ddd, *J* 4.5, 12.6, 12.6, 15-Hb), 1.83 (1 H, ddd, *J* 3.0, 3.3, 12.5, 14-H), 2.03 (1 H, ddd, *J* 3.2, 12.2, 12.6, 16-Ha), 2.32 (1 H, m, 6-Hb), 2.46 (2 H, t, *J* 7.0, $NCH_2CH_2CH_3$), 2.53 (1 H, ddd, *J* 1.3, 4.5, 12.2, 16-Hb), 2.58 (1 H, dd, *J* 5.9, 18.0, 10-Ha), 2.90 (1 H, ddd, *J* <1, 3.3, 5.9, 9-H), 2.91 (1 H, dd, *J* <1, 18.0, 10-Hb), 3.76 (3 H, OMe), 6.66 (1 H, dd, *J* 3.0, 8.2, 2-H), 6.78 (1 H, d, *J* 3.0, 4-H), 6.99 (1 H, d, *J* 8.2, 1-H); *m*/*z* (CI, NH_3) 370 (M^+ + 1, 100%).

(10) Using benzyl bromide and dextromethorphan 2a. *(a) With $Na_2S{\cdot}9H_2O$.* Purification by rapid chromatography, eluting with MeOH, afforded the starting dextromethorphan **2a** (233 mg, 86% recovery); GLC (220 °C) t_R 2.52 min.

(b) With MeCOSK. Purification by rapid chromatography, eluting with MeOH, afforded the starting dextromethorphan **2a** (222 mg, 82% recovery); GLC (220 °C) t_R 2.52 min.

(11) Using allyl bromide, dextromethorphan 2a and MeCOSK. Purification by rapid chromatography, eluting with MeOH, afforded the starting dextromethorphan **2a** (211 mg, 78%); GLC (220 °C) t_R 2.52 min.

(12) Using chloroethane and (±)-laudanosine 3a. *(a) With $Na_2S{\cdot}9H_2O$.* Rapid chromatography, eluting with AcOEt–MeOH 60 : 40 v/v, afforded, first, the amine **3b** (215 mg, 58%) as a solid (Found: C, 71.1; H, 7.8; N, 3.7. $C_{22}H_{29}NO_4$ requires C, 71.1; H, 7.9; N, 3.8%); mp 86–88 °C (from EtOH) (lit.,[16] 89 °C); GLC (250 °C) t_R 4.05 min; δ_H (500 MHz; $CDCl_3$) 1.11 (3 H, t, *J* 7.1, NCH_2CH_3), 2.48 (1 H, ddd, *J* 3.9, 4.4, 13.1, 4-Ha), 2.68 (2 H, q, *J* 7.1, NCH_2CH_3), 2.72 (1 H, dd, *J* 7.8 and 13.5, 9-Ha), 2.79–2.89 (2 H, overlapping, 3-Ha and 4-Hb), 3.07 (1 H, dd, *J* 5.5 and 13.3, 9-Hb), 3.17 (1 H, ddd, *J* 4.4, 7.2, 13.7, 3-Hb), 3.54 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.79 (1 H, dd, *J* 5.5 and 7.8, 1-H), 3.81 (3 H, s, OMe), 3.82 (3 H, s, OMe), 5.98 (1 H, s, 8-H), 6.35 (1 H, s, 5-H), 6.60 (1 H, d, *J* 1.5, 2′-H), 6.61 (1 H, dd, *J* 1.5 and 7.7, 6′-H), 6.75 (1 H, d, *J* 7.7, 5′-H); *m*/*z* (CI, NH_3) 372 (M^+ + 1, 100%); *m*/*z* (EI) 220 (100%), 204 (16), 176 (6), 151 (9).

Further elution afforded the elimination products **6b**[17] (65 mg, 17%) as an oil (Found: C, 71.6; H, 8.0; N, 3.6. $C_{23}H_{31}NO_4$ requires C, 71.6; H, 8.1; N, 3.6%); GLC (250 °C) t_R 7.95 min; δ_H (500 MHz; $CDCl_3$) 1.07 (3 H, t, *J* 7.1, NCH_2CH_3), 2.33 (3 H, s, NMe), 2.49 (2 H, q, *J* 7.1, NCH_2CH_3), 2.55 (2 H, t, *J* 8.0, $ArCH_2CH_2N$), 2.87 (2 H, t, *J* 8.0, $ArCH_2CH_2N$), 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.91 (6 H, s, 2 × OMe), 6.68 (1 H, s, ArH), 6.87 (1 H, d, *J* 16.0, olefinic H), 6.85 (1 H, d, *J* 9.0, ArH), 7.02–7.04 (2 H, overlapping, 2 × ArH), 7.09 (1 H, s, ArH), 7.16 (1 H, d, *J* 16.0, olefinic H); *m*/*z* (CI, NH_3) 386 (M^+ + 1, 100%); *m*/*z* (EI) 385 (M^+, 7%), 313 (0.4), 297 (0.4), 282 (0.6), 72 (100).

(b) With MeCOSK. Purification by rapid chromatography, eluting with AcOEt–MeOH 60 : 40 v/v, afforded the amine **3b** (300 mg, 78%), identical in all respects with the compound above described.

(13) Using 1-chloropropane and (±)-laudanosine 3a. *(a) With $Na_2S{\cdot}9H_2O$.* Rapid chromatography, eluting with AcOEt–MeOH 70 : 30 v/v, afforded, first, the amine **3c** (212 mg, 55%) as an oil (Found: C, 71.6; H, 8.1; N, 3.6. $C_{23}H_{31}NO_4$ requires C, 71.7; H, 8.1; N, 3.6%); mp 68–70 °C (from aq. acetone) (lit.,[16] 69–70 °C); GLC (250 °C) t_R 4.78 min; δ_H (500 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 7.3, $NCH_2CH_2CH_3$), 1.50 (2 H, tq, *J* 7.3 and 7.3, $NCH_2CH_2CH_3$), 2.45 (1 H, ddd, *J* 3.8, 4.2, 14.0, 4-Ha), 2.55 (2 H, t, *J* 7.3, $NCH_2CH_2CH_3$), 2.73 (1 H, dd, *J* 7.6 and 13.5, 9-Ha), 2.80–2.87 (2 H, overlapping, 3-Ha and 4-Hb), 3.05 (1 H, dd, *J* 5.8 and 13.5, 9-Hb), 3.19 (1 H, ddd, *J* 4.2, 6.9, 13.6, 3-Hb), 3.57 (3 H, s, OMe), 3.74 (1 H, dd, *J* 5.8 and 7.6, 1-H), 3.78 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.83 (3 H, s, OMe), 6.02 (1 H, s, 8-H), 6.53 (1 H, s, 5-H), 6.60 (1 H, d, *J* 1.5, 2′-H), 6.61 (1 H, dd, *J* 1.5 and 7.7, 6′-H), 6.75 (1 H, d, *J* 7.7, 5′-H); *m*/*z* (CI, NH_3) 386 (M^+ + 1, 100%); *m*/*z* (EI) 234 (100%), 218 (9), 190 (5), 151 (7).

Further elution afforded the elimination products **6c** (115 mg, 29%) as an oil (Found: C, 72.0; H, 8.4; N, 3.5. $C_{24}H_{33}NO_4$ requires C, 72.15; H, 8.3; N, 3.5%); GLC (250 °C) t_R 9.44 min; δ_H (500 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.49 (2 H, tq, *J* 7.4 and 7.4, $NCH_2CH_2CH_3$), 2.34 (3 H, s, NMe), 2.38 (2 H, t, *J* 7.4, $NCH_2CH_2CH_3$), 2.56 (2 H, t, *J* 8.0, $ArCH_2CH_2N$), 2.87 (2 H, t, *J* 8.0, $ArCH_2CH_2N$), 3.87 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.91 (6 H, s, 2 × OMe), 6.68 (1 H, s, ArH), 6.83 (1 H, d, *J* 16.0, olefinic H), 6.84 (1 H, d, *J* 8.7, ArH), 7.01–7.06 (2 H, overlapping, 2 × ArH), 7.08 (1 H, s, ArH), 7.16 (1 H, d, *J* 16.0, olefinic H); *m*/*z* (CI, NH_3) 400 (M^+ + 1, 100%); *m*/*z* (EI) 399 (M^+, 5%), 313 (0.5), 297 (0.5), 282 (0.6), 86 (100).

(b) With MeCOSK. Purification by rapid chromatography, eluting with AcOEt–MeOH 70 : 30 v/v, afforded the amine **3c** (300 mg, 78%), identical in all respects with the compound above described.

(14) Using 1-chlorooctane and (±)-laudanosine 3a. *(a) With $Na_2S{\cdot}9H_2O$.* Rapid chromatography, eluting with hexane–AcOEt 60 : 40 v/v, afforded, first, the amine **3e** (296 mg, 65%) as an oil (Found: C, 73.8; H, 9.0; N, 3.1. $C_{28}H_{41}NO_4$ requires C, 73.8; H, 9.1; N, 3.1%); GLC (250 °C for 10 min, 20 °C min^{-1} until 290 °C for 5 min) t_R 12.19 min; δ_H (500 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 6.9, $NCH_2[CH_2]_6CH_3$), 1.23–1.29 (10 H, overlapping, 5 × CH_2), 1.48 (2 H, m, CH_2), 2.45 (1 H, ddd, *J* 4.0, 4.3, 14.0, 4-Ha), 2.57 (2 H, t, *J* 7.0, $NCH_2[CH_2]_6CH_3$), 2.72 (1 H, dd, *J* 7.6 and 13.5, 9-Ha), 2.80–2.87 (2 H, overlapping, 3-Ha and 4-Hb), 3.05 (1 H, dd, *J* 5.7 and 13.5, 9-Hb), 3.20 (1 H, ddd, *J* 4.3, 7.1, 13.8, 3-Hb), 3.56 (3 H, s, OMe), 3.75 (1 H, dd, *J* 5.7 and 7.6, 1-H), 3.78 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.83 (3 H, s, OMe), 6.02 (1 H, s, 8-H), 6.53 (1 H, s, 5-H), 6.61 (1 H, d, *J* 1.6, 2′-H), 6.62 (1 H, dd, *J* 1.6 and 7.8, 6′-H), 6.74 (1 H, d, *J* 7.8, 5′-H); *m*/*z* (CI, NH_3) 456 (M^+ + 1, 100%); *m*/*z* (EI) 304 (100%), 288 (5), 260 (1), 151 (13).

Further elution afforded the elimination products **6e** (70 mg, 15%) as an oil (Found: C, 74.1; H, 9.2; N, 2.9. $C_{29}H_{43}NO_4$ requires C, 74.2; H, 9.2; N, 3.0%); GLC (250 °C for 10 min, 20 °C min^{-1} until 290 °C for 5 min) t_R 14.72 min; δ_H (500 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 7.1, $NCH_2[CH_2]_6CH_3$), 1.22–1.26 (10 H, overlapping, 5 × CH_2), 1.46 (2 H, m, CH_2), 2.33 (3 H, s, NMe), 2.39 (2 H, t, *J* 7.1, $NCH_2[CH_2]_6CH_3$), 2.54 (2 H, t, *J* 7.8, $ArCH_2CH_2N$), 2.86 (2 H, t, *J* 7.8, $ArCH_2CH_2N$), 3.87 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.91 (6 H, s, 2 × OMe), 6.68 (1 H, s, ArH), 6.83 (1 H, d, *J* 16.0, olefinic H), 6.84 (1 H, d, *J* 8.7, ArH), 7.02–7.05 (2 H, overlapping, 2 × ArH), 7.08 (1 H, s, ArH), 7.16 (1 H, d, *J* 16.0, olefinic H); *m*/*z* (CI, NH_3) 470 (M^+ + 1, 100%); *m*/*z* (EI) 469 (M^+, 4%), 313 (1), 297 (0.9), 282 (2), 156 (100).

(b) With MeCOSK. Purification by rapid chromatography, eluting with hexane–AcOEt 60 : 40 v/v, afforded the amine **3e** (391 mg, 86%), identical in all respects with the compound above described.

(15) Using benzyl bromide and (±)-laudanosine 3a. *(a) With $Na_2S{\cdot}9H_2O$.* Purification by rapid chromatography, eluting with AcOEt–MeOH 60 : 40 v/v, afforded the starting (±)-laudanosine **3a** (308 mg, 86% recovery); GLC (250 °C) t_R 3.53 min.

(b) With MeCOSK. Purification by rapid chromatography, eluting with AcOEt–MeOH 60 : 40 v/v, afforded the starting (±)-laudanosine **3a** (300 mg, 84% recovery); GLC (250 °C) t_R 3.53 min.

Synthesis of pergolide mesylester 4

A mixture of dihydrolysergol **1a** (10 g, 39 mmol), 1-iodopropane (8.3 g, 48.8 mmol) and $K_3PO_4 \cdot 3H_2O$ (1.04 g, 3.9 mmol) in sulfolane (80 cm^3) was heated at 110 °C under stirring, becoming a dark solution within 45 min. Heating was continued (2 h) until **1a** could no longer be detected by TLC (development with MeOH; R_f **1a** = 0.25). At this time solid $Na_2S \cdot 9H_2O$ (9.36 g, 39 mmol) was added and the mixture was heated, with stirring, at 120 °C for 5 h. The mixture was then slowly poured into water (400 cm^3) under vigorous agitation. The suspension was cooled to 0 °C under stirring and filtered. A green solid was obtained which was dried, dissolved in AcOEt–MeOH (1 : 1 v/v, 400 cm^3), and treated with decolourizing carbon (4 g) for 30 min at room temperature. Filtration and evaporation under reduced pressure gave a light yellow solid (9.98 g), which was crystallized from diisopropyl ether to afford pure *N*-propyl derivative **1c** as a colourless solid (8.43 g, 76%; 99.2% pure by GLC), with all physico-chemical properties identical with those described above.

The obtained compound **1c** (8.43 g, 29.7 mmol) was dissolved in pyridine (45 cm^3) and the solution was chilled to −10 °C under argon. Methanesulfonyl chloride (4.65 cm^3, 60 mmol) was then added dropwise at such a rate as to maintain the temperature at below 0 °C (30 min). The mixture was stirred at 0 °C for 1 h and then was poured in water (450 cm^3). The white suspension was filtered and the resulting white solid was washed with water (2 × 40 cm^3) and dried at room temperature under reduced pressure (6.7 pa) for 6 h, to give the crude methanesulfonate (9.56 g, 89%), which was dissolved in DMF (200 cm^3) and treated with commercial CH_3SNa (5.54 g, 79.1 mmol). The resulting suspension was stirred at room temperature for 2 h and then poured into water (550 cm^3). After filtration, the collected solid was washed with water (2 × 40 cm^3), dried at room temperature under reduced pressure (6.7 pa) for 6 h and triturated in boiling MeOH (300 cm^3) to afford pure pergolide (6.53 g, 78.8%; 99.5% pure by GLC).

The obtained pergolide (6.53 g, 20.8 mmol), suspended in MeOH (60 cm^3), was treated with a solution of methanesulfonic acid (2.0 g, 20.8 mmol) in MeOH (60 cm^3) and the mixture was heated under reflux. When the pergolide had completely dissolved, propan-2-ol (120 cm^3) was added under stirring. Filtration of the suspension afforded a pink solid (7.33 g) which, after treatment with decolourizing carbon and recrystallization from EtOH (180 cm^3), gave pergolide mesylester **4** (6.67 g, 78.3%; 99.6% pure by GLC, as free base) as a white solid: mp 257–259 °C (decomp.) (lit.,[12] 258–260 °C); $[\alpha]_D$ −21.7 (*c* 1 in DMF) (lit.,[12] −18 to −23); GLC (240 °C) t_R 3.07 min (as free base); identical in all respects with authentic material.

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