Synthesis and Central Dopaminergic Activities of (±)-Hexahydro-7*H*-indolo[3,4-*gh*][1,4]benzoxazine Derivatives [(±)-9-Oxaergolines]

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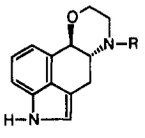
The synthesis and biological activities of a series of (±)-hexahydro-7*H*-indolo[3,4-*gh*][1,4]benzoxazine derivatives [(±)-*trans*-9-oxaergolines] with central dopamine (DA) agonist properties are described. The compounds were prepared from [2a*RS*-(2aα,4β,5α)]-4-amino-1,2,2a,3,4,5-hexahydro-1-(phenylmethyl)benz[*cd*]indol-5-ol (**6b**) by alkaline cyclization of the corresponding *N*-chloracetamide **7b**, followed by reduction of the amido group [5a*RS*-(5aα,6aβ,10aα)]-4,5,5a,6,6a,7,9,10a-octahydro-4-(phenylmethyl)-7*H*-indolo[3,4-*gh*][1,4]benzoxazin-8-one (**8b**) with $LiAlH_4$. After debenzylation of the resulting amine **9a**, the indoline ring of [5a*RS*-(5aα,6aβ,10aα)]-4,5,5a,6,6a,8,9,10a-octahydro-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (**10a**) was dehydrogenated with MnO_2 to give (±)-*trans*-9-oxaergoline (**11a**), which can be alkylated on the nitrogen (**11b,c** and **12**) and brominated in position 2 (**13a,b**). The compounds were examined in vitro for their ability to bind to DA receptors and to inhibit prolactin (PRL) secretion in pituitary cells in culture, in vivo both for their DA stimulant effects at the striatal level (circling in 6-OHDA-lesioned animals, DA turnover, and stereotypy) and inhibitory effects on plasma PRL levels in rats, and for their emetic effects in dogs. Most of the tested compounds were active in these tests, and the potency of (±)-*trans*-6-*n*-propyl-9-oxaergoline (**11c**) was comparable to that of pergolide mesylate.

Various ergoline derivatives with predominant dopaminergic agonist properties have been extensively investigated over the last 10 years, and some of them are now used in the treatment of Parkinson's disease and prolactin-dependent diseases. All of these compounds are natural or semisynthetic derivatives of *d*-lysergic acid; recently, however, structurally simplified analogues, which might exhibit a more specific pharmacological activity and allow one not to be dependent upon raw material of natural origin, have been described.[1-6] It is also with this aim that the synthesis of the 9-oxaergolines of the general formula I has been undertaken.



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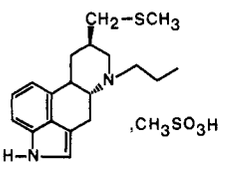


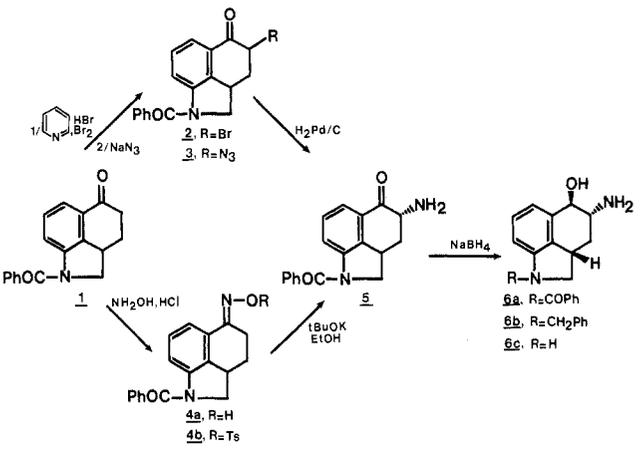
II

The recent publication of Merck's patent[7] on derivatives of this series prompted us to report our own results. The new compounds have been tested for their dopaminergic properties in comparison with the potent and long-lasting structurally related dopamine (DA) agonist pergolide II.

Chemistry The indolobenzoxazines of the general formula I have been prepared following the steps depicted in Scheme I by the intermediacy of the hitherto unknown amino alcohol **6a** obtained by reduction of the amino ketone **5** (Scheme I). In order to have access to this latter derivative, we started from the tricyclic ketone **1**,[8] which was easily accessible starting from indolepropionic acid.

In a first approach to the introduction of the amino group in the α position of the ketone, **1** was brominated with pyridinium perbromide in acetic acid, and the resulting α-bromo ketone **2**[8] was converted into the azide derivative **3** by treatment with NaN_3 in aqueous DMF. Subsequent catalytic hydrogenation of **3** in acidic medium (EtOH–HCl) over Pd/C gave the desired amino ketone **5**, which was not isolated but immediately reduced with $NaBH_4$ in EtOH to the trans amino alcohol **6a** with an overall yield of 38% from **1**.

Scheme I



A more efficient route to this key intermediate involved the Neber rearrangement of the tosyl oxime **4b**,[8] readily produced from the oxime of the tricyclic ketone **1**. Thus, treatment of **4b** with KO-*t*-Bu (1 equiv) for 15 h in a cooled (0 °C) mixture of $CHCl_3$–EtOH, followed by acid hydrolysis of the crude product, led to the isolation of the amino ketone **5** as the chlorhydrate salt. This derivative

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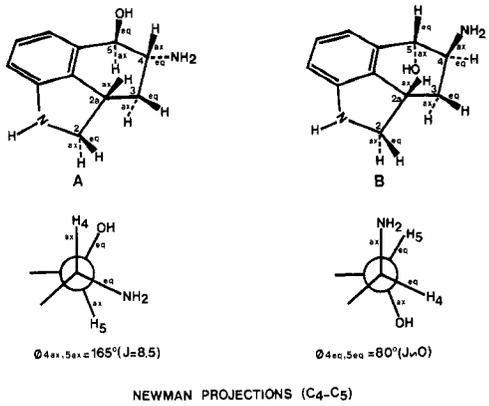


Figure 1.

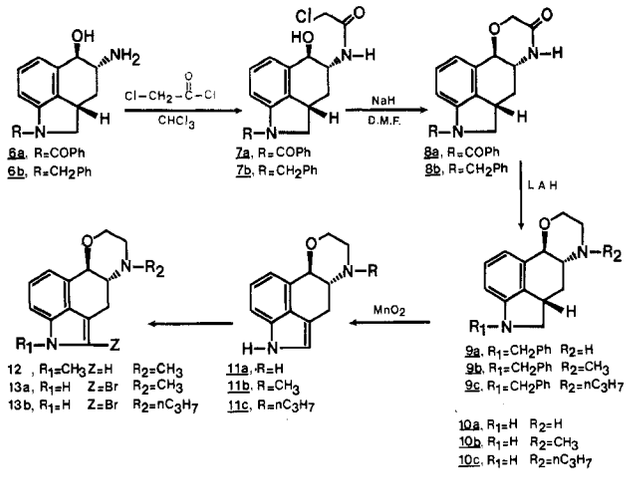
was then reduced to **6a** as already described with a satisfactory yield of 78% from **1**.

The stereochemistry attributed to the amino alcohol **6a** was established by 250-MHz ^1H NMR studies carried out in $CDCl_3$ and at 50 °C to eliminate the splitting of the signals due to the rotamers of the amide. The spectrum analysis (cf. Experimental Section) clearly showed that the hydrogens located in the 2aβ-, 3α-, 4β-, and 5α-positions (structure A, Figure 1) are all in the trans-diaxial configurations in the most stable half-chair conformation of the C ring.

These results are in perfect agreement with the conformational analysis carried out on the corresponding desbenzoylated amino alcohol **6c** with the aid of the SCRIPT program,[9] which allows one to automatically generate all the possible conformers of a molecule with their geometrical parameters. Thus, for the most stable conformation of **6c** (structure A), Figure 1), the theoretical coupling constant between $H_{4\beta}$ and $H_{5\alpha}$ (J = 8 Hz) calculated from the dihedral angle (between C_4H_4 and C_5H_5 = 165°) corresponds well with the experimental value (J = 8.5 Hz). In the case of the preferred conformation of the isomer B where the axial hydrogen at C_{2a} is located on the same side of the amino group, the coupling constant $H_{4\alpha}$–$H_{5\beta}$ would have been very low due to their trans diequatorial configuration (between C_4H_4 and C_5H_5 = 80°, $J_{H_4H_5} \approx 0$).

In a first attempt to build the D morpholine ring, the amino alcohol **6a** was acylated with chloracetyl chloride, and the resulting amide **7a** was treated with NaH in various conditions to carry out the cyclization (Scheme II). Although numerous solvents were used (DME, DMF, and HMPT), this method did not give satisfactory yields of the cyclized derivative **8a**, and, in addition, the $LiAlH_4$ reduction of the latter only afforded poor yields of the desired amine **9a**. To avoid these difficulties, probably due to the very low solubility of the amides **7a** and **8a**, we first reduced the benzoyl group of the starting amino alcohol **6a**, by $LiAlH_4$ and $AlCl_3$ in refluxing dioxane, to the benzyl group to give **6b**. The cyclization of the resulting chloracetamide **7b** by means of NaH in DME at room temperature then gave good yields (87%) of **8b**, which in turn was easily reduced to **9a**. After hydrogenolysis of the *N*-benzyl group, the indoline ring of **10a** was oxidized to the indole by treatment with MnO_2, as previously described in the 2,3-dihydroergoline series.[10] Finally, the 9-oxaergoline **11a** was alkylated to produce **11b** and **11c** by the usual methods. Using an alternative route to prepare the *N*-*n*-propyl derivative **11c**, one of the most interesting products of the series, we introduced the *N*-*n*-propyl substituent on the 2,3-dihydro-9-oxaergoline **9a**, since it was observed that the conversion of the indoline into the indole by MnO_2 gave better yields when it was carried out on the tertiary amine **10b** rather than on the secondary amine **10a**. In this way, the *N*-*n*-propyl-9-oxaergoline **11c** can be prepared with a yield of 25% from the intermediate **6a**.

Scheme II



For biological evaluation, some structural modifications, usually done in the ergoline series, were made on compounds **11b** and **11c** following the usual methods: **11b** was methylated by means of MeI and NaH in liquid NH_3 to give **12**, whereas a bromine was introduced in the 2-position of **11b** and **11c** to give **13a** and **13b**, respectively.

Pharmacology. The new 9-oxaergoline derivatives have been tested for their DA agonist properties in brain structures having well-known predominant dopaminergic functional activities. Thus, the ability of drugs to displace the DA blocking agent [^3H]spiroperidol ([^3H]spiro) and the DA agonist [^3H]dihydroergocriptine ([^3H]DHEC) from striatal and adenopituitary membrane sites, respectively, is parallel to their affinity for DA receptors in these two corresponding brain structures. Induction of rotations in rats with unilateral lesion in the nigrostriatal pathway, decrease of striatal DA turnover, and production of stereotypies are the features of potential striatal effects. Reduction of prolactin (PRL) secretion in adenopituitary cells in culture and lowering of plasma PRL in reserpinized rats are indicative of effects at the pituitary level. Moreover, emesis reflects an impact at the level of the area postrema. Methodological details are given under Experimental Section.

Results and Discussion

The results obtained with the new compounds and pergolide are listed in Table I. From these results, it clearly appears that the *N*-*n*-propyl derivative **11c** exhibits the most intensive activity in all the biochemical and pharmacological tests used. The secondary amine **11a** appears to be weakly active compared to the *N*-methyl derivative **11b**, which in turn is much less potent than **11c**. The influence of the alkyl side chain attached to the nitrogen on the biological effects is comparable to that usually observed in other series endowed with dopaminergic activity.[11] Methylation of the *N*-indole ring (**12**),

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Table I. Dopaminergic Activities of the 9-Oxaergoline Derivatives

compd	X	R	in vitro binding: IC_{50}, [d] nM [^{3}H]spiro	[^{3}H]DHEC	induction rotations: [a] MED [e]	decrease in DA turnover: [a] MED [f]	induction stereo: [a] MED [g]	inhibn of PRL secretion cell cult: IC_{50}, [h] nM	plasma PRL submax. decrease: [b] duration, h	induction emesis: [c] MED [g]	acute toxicity: LD_{50} [i]
11a	H	H	5000	7000	0.5	1	5	300	3	>0.5	150
11b	H	CH_3	800	2500	0.2	0.1	0.5	17	4–8	0.1	100
11c	H	*n*-C_3H_7	70	40	0.01	0.05	0.1	0.06	>22	0.01	150
12	1-CH_3	CH_3	4500	4800	2	10	20	>10 000	3–4	1	>200
13a	2-Br	CH_3	1000	3000	1	1	20	100	3–6	0.5	35
13b	2-Br	*n*-C_3H_7	250	500	0.2	0.5	0.2	0.2	>12	>0.5	>200
10c	2-H, 3-H	*n*-C_3H_7	600	300	0.1	0.1	0.1	0.1	>12	0.1	150
pergolide mesylate			70	50	0.02	0.05	0.1	0.07	>22	0.05	100

[a] Each drug was tested on groups of four or eight rats per dose. It was injected ip at three to five doses as tenfold multiples of 0.01, 0.02, and 0.05 mg/kg. The corresponding data are the minimal effective dose (MED) in milligrams per kilogram, the signification of which is given in the following footnotes. [b] Each drug was administered po to groups of five rats at the standard dose of 5 mg/kg. Mean duration for a submaximal inhibition was approximatively evaluated. [c] Each drug was injected sc to groups of two or four dogs per dose. Dose scale and interpretation as described in footnote *a*. [d] IC_{50} is the nanomolar concentration of a drug giving 50% competition of specific binding. It is derived from a dose-response curve that calculated by using a weighted iterative nonlinear least-squares regression. The standard error is within ±20%. [e] MED is the lowest dose inducing at least a mean total of 300 contralateral turns. [f] MED is the lowest mean dose significantly reducing ($p < 0.05$) the αMPT-induced disappearance of striatal DA content in treated animals vs. controls. [g] MED is the lowest dose producing a clear effect in at least half the treated animals. [h] IC_{50} is the nanomolar concentration of a drug reducing PRL release by 50%. Calculation as described in footnote *d*. [i] LD_{50}, in milligrams per kilogram, by ip route was approximately estimated from a dose-related number of deaths in groups of five mice per dose.

as well as bromination in the 2-position (**13a,b**) or saturation of the 2,3 double bond (**10c**), decreases the dopaminergic activity compared to the corresponding unsubstituted compounds.

It should be pointed out that the results obtained in the in vitro binding assays with dihydroergocriptine and spiroperidol used as ligands are roughly similar and parallel to those obtained in the in vivo experiments, which are characteristic of DA-stimulating properties.

The DA agonist activity of the most potent derivative, **11c** (RU 29 717), is close to that of pergolide, the results of which are in good agreement with those previously reported.[12-15] A more detailed comparative study of the central dopaminergic properties of both compounds will be published elsewhere.[16]

From this study, no specificity in the site of action of the new compounds emerges from the results obtained, and their clinical application as either anti-Parkinsonian or antiprolactin drugs might be accompanied by emetic side effects as already observed with all the ergoline derivatives hitherto tested.

From the overall results, it is apparent that replacement of the *D*-piperidine ring in the ergoline skeleton by a 1,4-morpholine ring allows the DA agonist properties of the ergoline derivatives of natural origin to be retained. Moreover, the presence of the usual substituent in the 8-position of the ergolines does not seem to be necessary for the dopaminergic activity, as it has already been observed with decarboxylysergic acid.[17]

Experimental Section

Chemistry. All melting points were determined on a Kofler block. IR spectra were recorded on a Perkin-Elmer 580 spectrometer and absorption spectra on a Cary 14 instrument. ^{1}H NMR spectra were measured with a Brucker WP 60 DS, WH 90, or WM 250 with $CDCl_3$ as solvent (except where noted) and $(CH_3)_4Si$ as an internal standard. Deuterium exchanges were performed on all compounds possessing labile hydrogens. NMR abbreviations used are as follows: s = singlet; d = doublet; t = triplet; dd = doublet of doublets; m = multiplet; q = quadruplet. TLC and column chromatography were done on SiO_2 (silica gel 60 F 254 and silica gel 60, 0.040–0.060 mm).

4-Bromo-1-benzoyl-2,2a,3,4-tetrahydrobenz[*cd*]indol-5-(1*H*)-one (2). Pyridine hydrobromide perbromide (3.54 g, 22 mmol) was added to a solution of 5.54 g (20 mmol) of ketone **1** in 80 mL of acetic acid. The mixture was heated for 15 min to 50 °C, then poured into water, extracted with methylene chloride, washed with water, dried (Na_2SO_4), and evaporated. The residual product (6.8 g) was crystallized from ether: yield 6.6 g (94%); mp 180–181 °C (lit.[8] mp 180 °C); IR ($CHCl_3$) ν_{max} 1694 (CO) 1658, 1650, 1644 ($NCOC_6H_5$), 1611, 1596, 1581, 1493 (aromatic) cm^{-1}; NMR δ 4.68 (t, J = 5 Hz, H_4), 3.6–4.6 (m, 2-CH_2 and H_{2a}), 2.0–2.8 (3-CH_2).

4-Azido-1-benzoyl-2,2a,3,4-tetrahydrobenz[*cd*]indol-5-(1*H*)-one (3). Sodium azide (2.42 g, 37 mmol) in 25 mL of water was added to a solution of 6.6 g (18.7 mmol) of bromo ketone **2** in 100 mL of dimethylformamide and 5 mL of acetic acid cooled to 10 °C. The temperature rose to 20 °C, and the reaction was stopped after 1 h. After water was added to the solution, the

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(16) Boissier, J. R.; Euvrard, C.; Oberlander, C.; Laurent, J.; Dumont, C.; Labrie, F., submitted for publication in *Eur. J. Pharmacol.*
(17) Bach, N. J.; Hall, D. A.; Kornfeld, E. C. *J. Med. Chem.* **1974**, *17*, 312.

resulting yellow precipitate was filtered and extracted with methylene chloride, washed with water, dried, and evaporated.

The crude product (6.2 g) was crystallized from ether and used as such for a later stage: yield 3.4 g (58%); mp 161 °C; IR ($CHCl_3$) ν_{max} 2104 (N_3), 1703 (CO), 1659, 1651, 1645 ($NCOC_6H_5$), 1613, 1593, 1582, 1495 (aromatic) cm^{-1}; NMR δ 3.3–4.7 (2-CH_2, H_{2a}, H_4), 1.5–2.8 (3-CH_2).

[2a*RS*-(2aα,4β,5α)]-4-Amino-1-benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indol-5-ol (6a). A mixture of 0.5 g of 10% palladium on carbon, 2.2 g (6.9 mmol) of keto azide **3**, 500 mL of ethanol, and 2.2 mL of concentrated hydrochloric acid was hydrogenated at 20 °C for 5 h. After the catalyst was separated, the solvent was evaporated and the amino ketone **5** was obtained as the hydrochloride salt and used immediately: yield 2.22 g; mp 218 °C.

To a suspension of 2.2 g (6.9 mmol) of the hydrochloride **5** was slowly added at 5 °C a solution of 0.465 g (12.3 mmol) of sodium borohydride in 10 mL of ethanol. After 1 h, the mixture was acidified with 2 N hydrochloric acid and then evaporated under vacuum; water was first added to the residual product and then aqueous 2 N sodium hydroxide to alkalinize the mixture. The precipitate obtained was filtered and dried: yield 1.8 g. It was purified by chromatography by using $CHCl_3$/20% MeOH as eluant: yield 1.4 g (70% from **3**); mp 168 °C; mp 173 °C (crystallized from CH_2Cl_2); IR ($CHCl_3$) ν_{max} 3615, 3587, 3572 (OH), 1640 ($NCOC_6H_5$) cm^{-1}; UV (EtOH) λ_{max} 266 nm (ϵ 12 000), 294 (8800); NMR (250 MHz, t = 50 °C) δ 4.40 (d, J = 8.5 Hz, H_5), 3.10 (ddd, J = 3.5, 8.5, and 11.5 Hz, H_4), 1.57 (q, J = 11.5 Hz, H_3 axial), 3.42 (m, H_{2a} axial). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

5-Oxime of 1-Benzoyl-2,2a,3,4-tetrahydrobenz[*cd*]indol-5(1*H*)-one (4a). A mixture of 200 g (0.720 mol) of ketone **1**, 74.4 g (1.07 mol) of hydroxylamine hydrochloride, 50 g (0.362 mol) of potassium carbonate, 3 L of ethanol, and 0.3 L of water was stirred and heated under reflux for 1 h. After the starting material was dissolved, the oxime was crystallized into the medium, which was concentrated and then poured into 7 L of cooled water. The precipitate obtained was filtered, washed with water, and dried: yield 207 g (98%); mp 226 °C (lit.[8] mp 210 °C); IR (Nujol) ν_{max} 3210 (=NOH), 1619, 1599, 1570, 1491 (aromatic) cm^{-1}; UV (EtOH) λ_{max} 237 nm (ϵ 25 600, sh), 252 (29 400), 309 (6400); UV λ_{max} (EtOH plus 0.1 N NaOH) 271 nm (ϵ 30 300), 310 (11 000, sh), 321 (8200, sh); NMR (Me_2SO) δ 11.28 (H exchangeable with D_2O), 7.6 (COC_6H_5), 7.0 (aromatic), 3–4.4 (2-CH_2, 4-CH_2, H_{2a}), 1.1–2.5 (3-CH_2). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

[(4-Methylphenyl)sulfonyl]oxime of 1-Benzoyl-2,2a,3,4-tetrahydrobenz[*cd*]indol-5(1*H*)-one (4b). To a solution of 200 g (0.684 mol) of oxime **4a** in 2 L of anhydrous pyridine was added, at 0 °C over a period of 1 h and 40 min, a solution of 520 g (2.73 mol) of tosyl chloride in 1.04 L of pyridine. The mixture was stirred overnight at 0 °C, then poured into water, extracted with methylene chloride, and evaporated. The residual oil obtained was crystallized from ethanol: Yield 290 g (95%); mp 146 °C (lit.[8] mp 155 °C); IR ($CHCl_3$) ν_{max} 1642 (NCO), 1610, 1601, 1580, 1495 (aromatic), 1381, 1188, 1177 (SO_2) cm^{-1}; UV λ_{max} (EtOH) 230 nm (ϵ 33 500), 250 (31 600), 320 (5500); NMR δ 7.93 (d, J = 8 Hz), 7.41 (d, J = 8 Hz) ($SO_2C_6H_5$), 2.45 (s, $CH_3C_6H_5$), 6.9–7.6 (aromatic indol), 7.52 (N=COC_6H_5), 3.0–4.5 (m, 2-CH_2, H_{2a}), 3.9 (3-CH_2, 4-CH_2). Anal. ($C_{25}H_{22}N_2O_4S$) C, H, N, S.

Hydrochloride Salt of 4-Amino-1-benzoyl-2,2a,3,4-tetrahydrobenz[*cd*]indol-5(1*H*)-one (5) and [2a*RS*-(2aα,4β,5α)]-4-Amino-1-benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indol-5-ol (6a). Potassium terbutylate (31 g, 0.276 mol) was dissolved in 500 mL of ethanol over nitrogen and then cooled to 0 °C. A solution of 112 g (0.251 mol) of tosyloxime **4b** in 500 mL of ethanol and 500 mL of chloroform was added over 50 min; the suspension obtained was stirred overnight at 0 °C and then 275 mL of 2 N aqueous hydrochloric acid was added slowly. The mixture was evaporated under vacuum at a low temperature (30 °C). The residual product was extracted with 2 L of ethyl ether and 500, 200, and 200 mL of 2 N hydrochloric acid. The acidic extraction was evaporated under vacuum (30 °C): yield 192 g of crude **5** as the chlorhydrate salt, which was poured immediately into 2.65 L of ethanol at 0 °C and then 31.4 g of sodium borohydride was added over a period of 1 h and 15 min at ~2 °C. The mixture was stirred overnight at 10–15 °C, 125 mL of water and 625 mL of 2 N sodium hydroxide were added, and the mixture was concentrated to exclude the ethanol. Then, 1.2 L of water was added, the precipitate obtained was filtered, and the filtrate was washed with water, triturated with ether, and dried: yield 62.4 g (84.5% from **4b**); mp 173 °C (crystallized from CH_2Cl_2), identical with the same product formed by the azide method.

[2a*RS* (2aα,4β,5α)]-4-Amino-1,2,2a,3,4,5-hexahydro-1-(phenylmethyl)benz[*cd*]indol-5-ol (6b). Aluminium chloride (31.2 g, 0.23 mol) was added with care to a suspension of 62.4 g (1.64 mol) of lithium aluminium hydride in 2 L of anhydrous dioxane, followed by 62.4 g (0.21 mol) of the *N*-benzamide derivative **6a**. The temperature rose to 50 °C, and then the mixture was heated under reflux for 2 h. After cooling, 750 mL of tetrahydrofuran containing 20% water and then 750 mL of 2 N aqueous sodium hydroxide were added. The precipitate obtained was filtered, and the filtrate was extracted with methylene chloride, washed, dried, and treated with charcoal. The decolourized solution was evaporated, and the crude product (50.8 g) was crystallized in ether: yield 44.7 g (75%); mp 166 °C; IR ($CHCl_3$) ν_{max} 3590 (OH), 3375 (NH_2), 1620, 1596, 1492 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 259 nm (ϵ 10 400), 299 (2650); UV λ_{max} (EtOH plus 0.1 N HCl) 259 nm (ϵ 7300), 299 (1700); NMR (250 MHz) δ 6.36 (dd), 6.80 (dd), 6.97 (t,) (aromatic indol), 4.40 (d, J = 8 Hz, H_5), 3.88–4.43 (AB system, J = 14 Hz, $NCH_2C_6H_5$). Anal. ($C_{18}H_{20}N_2O$) C, H, N.

[2a*RS* (2aα,4β,5α)]-2-Chloro-*N*-[5-hydroxy-1-(phenylmethyl)-1,2,2a,3,4,5-hexahydro-4-benz[*cd*]indolyl]acetamide (7b). A solution obtained from 26 g (0.65 mol) of sodium hydroxide in 200 mL of water was added to a solution of 26 g (0.092 mol) of the amino alcohol **6b** in 800 mL of chloroform, and then 14.8 mL (0.184 mol) of chloracetylchloride was added dropwise; the mixture was stirred for 1 h and 30 min, poured into water, and extracted with chloroform, and the extract was washed and evaporated: yield 29.5 g (89%); mp 211 °C; IR (Nujol) ν_{max} 3212 (NH, OH), 1656 (CONH), 1629, 1597, 1571, 1490, 1475 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 257 nm (ϵ 10 700), 296 (2800); UV λ_{max} (EtOH plus 0.1 N HCl) 257 nm (ϵ 4900), 296 (1200); NMR δ 4.0–4.7 (H_4, H_5), 4.1 (CH_2Cl), 1.55 (H exchangeable with D_2O), 6.38 (dd), 6.81 (dd), 6.98 (t) (3 aromatic protons), 7.31 (5 aromatic protons). Anal. ($C_{20}H_{21}N_2O_2Cl$) C, H, N, Cl.

[5a*RS* (5aα,6aβ,10aα)]-4,5,5a,6,6a,7,9,10a-Octahydro-4-(phenylmethyl)-7*H*-indolo[3,4-*gh*][1,4]benzoxazin-8-one (8b). A solution of 32 g (0.089 mol) of chloroacetamido **7b** in 3 L of 1,2-dimethoxyethane, previously obtained by warming to 50 °C and then cooling, was added over 1 h to a suspension of 4.9 g (0.102 mol) of sodium hydride dispersion (50–60% in oil) in 200 mL of anhydrous 1,2-dimethoxyethane. The mixture was stirred for 1 h and 30 min at 20 °C, then poured into water, and extracted thoroughly with chloroform containing 10% methanol, and the extract was washed with water, dried, and evaporated. The residual product was crystallized from ether: yield 25 g (87%); mp 259 °C; IR ($CHCl_3$) ν_{max} 3392, 1678 (NHCO), 1622, 1601, 1496 (aromatic) cm^{-1}; UV λ_{max} (EtOH plus 0.1 N HCl) 259 nm (ϵ 7500), 300 (1900); NMR δ 3–7.4 (m, aromatic), 3.91 (d, J = 15 Hz), 4.43 (d, J = 15 Hz) ($NCH_2C_6H_5$), 4.48 (9-CH_2). Anal. ($C_{20}H_{20}N_2O_2$) C, H, N.

[5a*RS* (5aα,6aβ,10aα)]-4,6,6a,8,9,10a-Hexahydro-4-(phenylmethyl)-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (9a). Oxomorpholine **8b** (25 g, 0.078 mol) was gradually added while stirring to a suspension of 25 g (0.46 mol) of lithium aluminium hydride in 2.5 L of anhydrous tetrahydrofuran. The mixture was heated under reflux for 1 h and 30 min. After the mixture was cooled, 350 mL of tetrahydrofuran containing 10% water was carefully added, and the aluminium hydroxide that precipitated was separated and washed generously with chloroform/10% methanol. The organic layer was washed with water and evaporated in vacuo; the residual product obtained was crystallized from ether: yield 19.3 g (85%); mp 125 °C; IR ($CHCl_3$) ν_{max} 3320 (NH), 1622, 1600, 1497, 1480 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 259 nm (ϵ 10 300), 299 (2600); UV λ_{max} (EtOH plus 0.1 N HCl) 260 nm (ϵ 8800), 301 (2500); NMR δ 7.38 (phenyl), 6.44, 6.82, 7.15 (aromatic indol), 3.87 (d, J = 15 Hz), 4.43 (d, J = 15 Hz) ($NCH_2C_6H_5$), 2.4–4.4 (9-CH_2, 8-CH_2, H_{10a} and H_{6a} angular). Anal. ($C_{20}H_{22}N_2O$) C, H, N.

[5a*RS* (5aα,6aβ,10aα)]-4,5,5a,6,6a,8,9,10a-Octahydro-4-(phenylmethyl)-7-propyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (9c). Anhydrous potassium carbonate (9.11 g, 0.085 mol) and 14.2

mL (0.146 mol) of propyl iodide were added to a solution of 10 g (0.032 mol) of **9a** in 500 mL of dimethylformamide. The mixture was stirred for 3 h at 55 °C; after the mixture was cooled, it was poured into water and extracted with ether, and the extract was washed and evaporated in vacuo. The crude residue (11.9 g) was purified by chromatography by using benzene/50% ethyl acetate as eluant: yield 9.8 g (86%); mp 102–103 °C; IR ($CHCl_3$) ν_{max} 1623, 1600, 1495, 1479 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 258 nm (ϵ 9700), 299 (2500); UV λ_{max} (EtOH plus 0.1 N HCl) 258 nm (ϵ 8000), 299 (2050); UV λ_{max} (EtOH plus 0.1 N NaOH) 258 nm (ϵ 9400), 298 (2500); NMR δ 7.36 (phenyl), 7.1, 6.80, 6.39 (aromatic indol), 4.40 (d, J = 8 Hz, H_{10a}), 3.88 (d, J = 15 Hz), 4.15 (d, J = 15 Hz, $NCH_2C_6H_5$), 0.90 (t, J = 7 Hz, CH_3 propyl). Anal. ($C_{23}H_{28}N_2O$) C, H, N.

[5a*RS*(5aα,6aβ,10aα)]-4,5,5a,6,6a,8,9,10a-Octahydro-7-propyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (10c). A mixture of 2.2 g of 10% palladium on carbon, 8.75 g (0.025 mol) of the N-benzylated derivative **9c**, and 100 mL of acetic acid was hydrogenated at 20 °C for 1 h and 30 min. After the catalyst had been separated, the colorless solution was diluted with 150 mL of water, made alkaline by addition of aqueous sodium hydroxide and then extracted with methylene chloride; the extract was then washed and evaporated: yield 6.5 g of crude **10c** as a yellow oil. It was purified by chromatography with chloroform/5% methanol: yield 5.4 g (87%) of **10c**; mp 85 °C (crystallized from isopropyl ether); IR ($CHCl_3$) ν_{max} 3391, 3374 (NH), 1623, 1605, 1472 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 211 nm (ϵ 31 000), 245 (6200), 293 nm (2300); UV λ_{max} (EtOH plus 0.1 N HCl) 265 nm (ϵ 700), 272 (670); NMR δ 7.05, 6.78, 6.51 (aromatic), 4.40 (d, J = 8 Hz, H_{10a}), 0.88 (t, J = 7 Hz, propyl). Anal. ($C_{16}H_{22}N_2O$) C, H, N.

Hydrochloride Salt of (6a*RS*,10a*RS*)-4,6,6a,8,9,10a-Hexahydro-7-propyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (11c). Manganese oxide (20.8 g, 0.24 mol) was added to a solution of 5.2 g (0.02 mol) of **10c** in 250 mL of methylene chloride. The mixture was stirred for 24 h at 20 °C; then the oxidant was separated and washed with methylene chloride. The filtered solution was evaporated in vacuo: yield 5.02 g. This crude product was purified by chromatography with chloroform/5% methanol: yield 3.18 g (61.5%); mp 216 °C. The hydrochloride salt was prepared by dissolving the basic compound in 150 mL of hot methylene chloride. After the solution was cooled, 10 mL of a solution of hydrochloride acid gas in ethyl ether (2.5 N) was slowly added. The salt crystallized in medium and was filtered, and the filtrate was washed with ether and dried: yield 3.09 g of **11c**; mp 236–240 °C; IR (Nujol) ν_{max} 3518, 3435, 3150 (NH), 1616, 1530, 1503 (indol) cm^{-1}; UV λ_{max} (EtOH plus 0.1 N HCl) 222 nm (ϵ 32 700), 275 (6000, sh), 280 (6500), 290 nm (5850); NMR (Me_2SO) δ 11–11.9 (NH and NH^+), 6.8–7.4 (4 aromatic protons), 5.40 (d, J = 8 Hz, H_{10a}), 0.96 (t, J = 7 Hz, CH_3 propyl). Anal. ($C_{16}H_{20}N_2O$·HCl) C, H, N, Cl.

[5a*RS*(5aα,6aβ,10aα)]-4,5,5a,6,6a,8,9,10a-Octahydro-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (10a). The morpholinic *N*-benzyl compound **9a** (8 g, 0.026 mol) was hydrogenated by using the same process as to obtain **10c**: yield 4.75 g (84%) of **10a**; mp 156–158 °C; IR ($CHCl_3$) ν_{max} 3407, 3385 (NH), 1622, 1609, 1478 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 244 nm (ϵ 5500), 292 (2100); UV λ_{max} (EtOH plus 0.1 N HCl) 263 nm (ϵ 760), 272 (650); NMR δ 6.52 (dd), 6.77 (dd), 7.05 (t) (aromatic), 4.29 (d, J = 9 Hz, H_{10a}). Anal. ($C_{13}H_{16}N_2O$) C, H, N.

Hydrochloride Salt of (6a*RS*,10a*RS*)-4,6,6a,8,9,10a-Hexahydro-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (11a). The compound **10a** (4.4 g, 0.020 mol) was oxidized with manganese oxide as above to obtain **11c**: yield 2.38 g (53%); mp 110 °C. This was converted to the hydrochloride salt: yield 1.98 g of **11a**; mp ~280 °C; IR (Nujol) ν_{max} 3340 (NH), 2650 (NH_2^+), 1630, 1618, 1606, 1589, 1507 (NH deform and aromatic) cm^{-1}; UV λ_{max} (EtOH) 223 nm (ϵ 33 100), 282 (6600), 292 (5900); NMR (Me_2SO) δ 2.9–4.4 (H_6, H_8, H_9), 5.13 (d, J = 8 Hz, H_{10a}), 6.8–7.4 (aromatic), 10 and 10.9 (H exchangeable with D_2O). Anal. ($C_{13}H_{14}N_2O$·HCl) C, H, N, Cl.

[5a*RS*(5aα,6aβ,10aα)]-4,5,5a,6,6a,8,9,10a-Octahydro-4-(phenylmethyl)-7-methyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (9b). A mixture of 30% formaldehyde (19.6 mL) and 3.27 g of sodium cyanoborohydride was added to a solution of 10 g (0.032 mol) of the *N*-benzyl compound **9a** in 200 mL of hot acetonitrile after it had been cooled. The mixture was stirred for 1 h at 20 °C; then the solvent was evaporated, and the residual product obtained was extracted with methylene chloride, washed, dried, and purified by chromatography with chloroform/5% methanol as eluant: yield 9 g (86%) of **9b**; mp 104 °C; IR ($CHCl_3$) ν_{max} 2793 (Bohlman's bands), 1623, 1574, 1491, 1475 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 212 nm (ϵ 34 000), 258 (40 400), 299 (2550); UV λ_{max} (EtOH plus 0.1 N HCl) 211 nm (ϵ 30 700), 259 (8500), 300 (2150) with evolution of the solution; NMR δ 2.38 (s, NCH_3), 3.87 (d, J = 15 Hz), 4.45 (d, J = 15 Hz, $NCH_2C_6H_5$), 4.40 (d, J = 8 Hz, H_{10a}), 6.37 (dd), 6.77 (dd), 7.08 (t) (aromatics). Anal. ($C_{21}H_{24}N_2O$) C, H, N.

[5a*RS*-(5aα,6aβ,10aα)]-4,5,5a,6,6a,8,9,10a-Octahydro-7-methyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (10b). The methylmorpholinic *N*-benzyl compound **9b** (9 g, 0.028 mol) was hydrogenated by using the same process as for **10c**: yield 6.1 g (87%) of **10b**; mp 145 °C; IR ($CHCl_3$) ν_{max} 3399 (NH), 2790 (Bohlmann's bands), 1621, 1605, 1474 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 211 nm (ϵ 29 500), 216 (6000), 293 (2200); UV λ_{max} (EtOH plus 0.1 N HCl) 263 nm (ϵ 740), 271 (650); NMR δ 2.4 (s, NCH_3), 4.42 (d, J = 9 Hz, H_{10a}), 6.56 (dd), 6.82 (dd), 7.08 (t) (aromatics). Anal. ($C_{14}H_{18}N_2O$) C, H, N.

Hydrochloride Salt of (6a*RS*,10a*RS*)-4,6,6a,8,9,10a-Hexahydro-7-methyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (11b). The "indoline" **10b** (5.2 g) was oxidized with manganese oxide as above to obtain **11c**: yield 3.4 g (66%); mp 216 °C. This was converted to the hydrochloride salt: yield of 3.03 g of **11b**; mp 250 °C dec; IR (Nujol) ν_{max} 3217 (NH), 2500 (NH^+), 1620, 1613, 1551, 1504 (aromatic indol) cm^{-1}; UV λ_{max} (EtOH plus 0.1 N HCl) 224 nm (ϵ 34 000), 276 (6100), 281 (6650), 291 (6000); NMR (Me_2SO) δ 2.93 (s, N^+-CH_3), 5.26 (d, J = 8 Hz, H_{10a}), 6.8–7.4 (aromatic), 2.8–3.7 (6- and 8-CH_2), 4–4.5 (9-CH_2), 11.0 (NH, exchangeable with D_2O). Anal. ($C_{14}H_{16}N_2O$·HCl) C, H, N, Cl.

Oxalate Salt of (6a*RS*,10a*RS*)-4,6,6a,8,9,10a-Hexahydro-4,7-dimethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (12). Sodium metal (0.5 g, 0.021 mol) and ferric nitrate hydrate (0.05 g, 0.12 mmol) were added in portions to 100 mL of liquid ammonia. The blue solution obtained became brown when the sodium amidine was formed. A suspension of 2.28 g (0.010 mol) of the oxamethylergoline **11b** as base, in 70 mL of ethyl ether, was added and the mixture was stirred for 10 min. Methyl iodide (1.5 mL, 0.021 mol) was then added, and the mixture was left to evaporate slowly for 1 h and 30 min. The residual product was extracted with methylene chloride, washed, and evaporated: yield 2.3 g (95%); mp 128 °C, which was converted to the oxalate salt by addition of a solution of 1.26 g (0.010 mol) of oxalic acid hydrate in 60 mL of isopropyl alcohol: yield 3.1 g (white crystals, 93%) of **12**; mp 228 °C; UV λ_{max} (EtOH plus 0.1 N HCl) 228 nm (ϵ 31 600), 283 (5850, sh), 290 (6350); NMR (Me_2SO) δ 2.78 (s, N^+-CH_3, morpholine), 3.75 (s, N-CH_3, indol), 5.08 (d, J = 7 Hz, H_5), 6.9–7.4 (aromatic). Anal. [($C_{15}H_{18}N_2O$·$(COOH)_2$] C, H, N.

Oxalate Salt of (6a*RS*,10a*RS*)-4,6,6a,8,9,10a-Hexahydro-5-bromo-7-methyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (13a). To a solution of 2.5 g (0.0109 mol) of 9-oxamethylergoline **11b** in 150 mL of anhydrous dioxane was added at 20 °C, while stirring over a period of 20 min, a solution of 8.15 g (0.0155 mol) of pyrrolidone perbromide in 2 L of dioxane. After another 15 min, the solvent was evaporated at a low temperature. The residual product was extracted with methylene chloride, washed with aqueous sodium hydrogen carbonate and water, dried, and purified by chromatography with chloroform/5% methanol as eluant: yield 2 g (65%); mp ~250 °C. This product was converted to the oxalate salt by addition of a solution of 0.82 g (0.0065 mol) of oxalic acid hydrate in 50 mL of isopropyl alcohol: yield 2.5 g of **13a**; mp 275 °C; IR (Nujol) ν_{max} 3200 (OH), 1736–1722, 1697 (C=O), 1614 (COO^-), 1560, 1508, 1490 (aromatic) cm^{-1}; UV λ_{max} (EtOH) 224 nm (ϵ 37 300), 276 (8900, sh), 281 (9100), 290 (7350, sh); NMR (Me_2SO) δ 2.73 (N^+-CH_3), 3.9–4.1 (H_{6a}, 9-CH_2), 5.0 (d, J = 8 Hz, H_5), 6.9–7.2 (aromatic). Anal. [$C_{14}H_{15}BrN_2O$·$(COOH)_2$] C, H, N, Br.

Hydrochloride Salt of (6a*RS*,10a*RS*)-4,6,6a,8,9,10a-Hexahydro-5-bromo-7-propyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (13b). The compound **11c** (3 g, 0.011 mol) was brominated by the same process as above to obtain **13a**: yield 2.7 g (69%) of free base. This was directly converted to the hydrochloride salt from methylene chloride/ether: yield 2.6 g of **13b**; mp 275 °C; (crystallized from ethanol); IR (Nujol) ν_{max} 3080

(NH), 2420 (NH^+), 1620, 1554 (indole) cm^{-1}; UV λ_{max} (EtOH) 224 nm (ϵ 36 500), 276 (8800, sh), 281 (9100), 290 (7350, sh); NMR (Me_2SO) δ 1.0 (t, J = 7 Hz, CH_3 propyl), 5.34 (d, J = 9 Hz, H_{10a}), 7.1–7.6 (aromatic), 4.2–4.3 (9-CH_2). Anal. ($C_{16}H_{19}BrN_2O$·HCl) C, H, N, Br.

Pharmacology. Drugs. Compounds as salts were dissolved in the appropriate volumes of distilled water. The solutions were prepared immediately before use. Pergolide mesylate was synthesized following the method previously described.[18]

Receptor Binding Assays. [^{3}H]Dihydroergocriptine (23 Ci/mmol) and [^{3}H]spiroperidol (30 Ci/mmol) binding was measured by a rapid filtration technique as previously described with bovine anterior pituitary[19] or rat striatal[20] membranes, respectively. The radioligands were purchased from New England Nuclear Corp.

Circling Behavior in Unilaterally 6-OHDA-Lesioned Rats. Male Sprague–Dawley rats weighing 220–250 g were stereotaxically lesioned by injecting 8 μg of 6-hydroxydopamine hydrochloride (6-OHDA) (expressed as the free base) dissolved in 4 μL of saline containing 0.2 μg of ascorbic acid at a speed of 1 μL/min into the right nigrostriatal dopamine pathway, according to König and Klippel[21a] coordinates: A, +4.0; H, −2.8; L, 1.3. The animals were used at least 5 weeks later. Circling behavior was registered by using a rotometer connected to a microcomputer.[21b]

Striatal Dopamine Turnover. Male Sprague–Dawley rats weighting 200–225 g were used. They were sacrificed by decapitation. The brains were rapidly removed in the cold (4 °C), and the striata were immediately dissected and homogenized as previously described.[22]

The DA content was measured spectrofluormetrically according to the method of Laverty and Taylor,[23] after its isolation by ion-exchange chromatography with an Amberlite CG-50 resin.[24] DA turnover was determined by measuring the decline in DA levels 3 h after inhibition of its synthesis with α-methylparatyrosine (αMPT) (300 mg/kg, ip). The latter and the test drug were given simultaneously.

Stereotyped Behavior. Male Sprague–Dawley rats weighting 180–200 g were housed separately in Plexiglas boxes (20 × 25 × 17 cm) with some chips of wood but without food and water and observed for stereotypy every 30 min for 5 h after treatment. The intensity of the stereotypies was evaluated according to the rating method previously reported.[25]

Prolactin Release Inhibiting Activity in Rat Anterior Pituitary Cells in Culture. The preparation of primary cultures of anterior pituitary cells was performed according to Drouin and Labrie.[26] After a 4-h incubation with the drug, prolactin was measured in the medium by radioimmunoassay as previously described.[27]

Inhibitory Effects on Plasma Prolactin Levels. Male Sprague–Dawley rats weighing 200–225 g were housed two per cage in a controlled-temperature (22 ± 2 °C) and sound-attenuated room on a 14 h/10 light/dark cycle (lights on at 05.00 and off at 19.00).

After 1 week in the animal room environment, a catheter was inserted into the right superior vena cava under thiamylal (Surital) anesthesia (5 mg/kg, ip). Two days later, the rats were treated with reserpine (5 mg/kg, ip) 4 h before the experiment. Blood samples (0.7 mL) were taken hourly for 4 h, then at 2-h intervals up to 12 h, and finally 22 h posttreatment in freely moving unanesthetized animals. Prolactin levels were determined in the plasma as mentioned above.

Emetic Activity. Male or female Beagle dogs weighing 10–14 kg were used. On the day of the experiment, the animals were individually observed for vomiting for 5 h after treatment. A 1-week interval at least was maintained between two successive assays in the same animals.

Acute Toxicity. Male mice weighing 18–22 g were used. They were caged (five animals per cage) with a standard chow and water ad libitum. Mortality was numbered 48 h after treatment.

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Note Added in Proof: A synthesis of the (+)- and (−)-*trans*-6-ethyl-9-oxaergolines (**11**, R = C_2H_5) has recently been published (P. S. Anderson and co-workers, *J. Org. Chem.* **1982**, *47*, 2184) following a route analogous to the one described here. The DA activity of the (−)-*N*-ethyl derivative has been evaluated in comparison with apomorphine (G. E. Martin and co-workers, *Life Sci.* **1982**, *30*, 1847). The results obtained in this study are consistent with the results we obtained for the (±)-*N*-propyl derivative **11c**.

Registry No. (±)-**1**, 84131-92-0; **2**, 51867-03-9; **3**, 84131-93-1; (±)-**4a**, 84131-94-2; (±)-**4b**, 84131-95-3; (±)-**5**·HCl, 84131-96-4; (±)-**6a**, 84234-90-2; (±)-**6b**, 84173-34-2; (±)-**7b**, 84173-35-3; (±)-**8b**, 84131-97-5; (±)-**9a**, 84131-98-6; (±)-**9b**, 84131-99-7; (±)-**9c**, 84132-00-3; (±)-**10a**, 84132-01-4; (±)-**10b**, 84132-02-5; (±)-**10c**, 84132-03-6; (±)-**11b**, 77291-63-5; (±)-**11c** (base), 77291-65-7; (±)-**11a**, 80952-17-6; (±)-**11a** (base), 77291-61-3; (±)-**11b** (base), 77306-60-6; (±)-**11c**, 80952-18-7; (±)-**12**, 80917-59-5; (±)-**12** (base), 80917-58-4; (±)-**13a**, 84132-04-7; (±)-**13a** (base), 77291-79-3; (±)-**13b**, 80952-19-8; (±)-**13b** (base), 77291-73-7; chloroacetyl chloride, 79-04-9; PRL, 9002-62-4.

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