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Synthetic Studies of (±)-Lysergic Acid and Related Compounds[1)]

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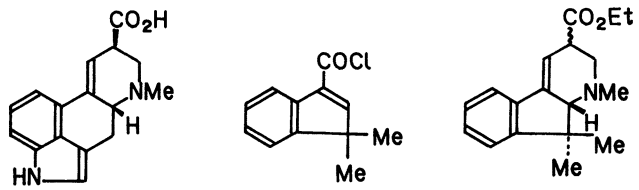
A new and simple method for a formal synthesis of (±)-lysergic acid (**1**), *via* a four-step sequence starting from the aldehyde (**13**), is described. A very high yield of the product was obtained after purification by column chromatography at the end of the process, without isolation of intermediates.

Keywords——(±)-lysergic acid; Uhle's ketone; benz[*cd*]indole-5-carbaldehyde; ethyl 3-aminopropionate; lithium diisopropylamide; indolo[3,4,5-*gh*]isoquinoline; 1,8-diazabicyclo[5.4.0]-7-undecene; mesyl chloride; 2D-NMR; NOE

While a number of syntheses of lysergic acid (**1**), which has been regarded as a central target molecule among Ergot alkaloids, have been reported,[2)] no methodology suitable for practical use has hitherto been presented. Thus, establishment of a simple method to produce large quantities of lysergic acid (**1**) continues to attract the interest of synthetic chemists. We report here a simple and facile synthetic route to (±)-lysergic acid (**1**) according to the methodology developed for tetrahydroindeno[2,1-*b*]pyridine (**3**) as a model compound starting from indene-3-carbonyl chloride (**2**).[3)] The advantage of this methodology is that the

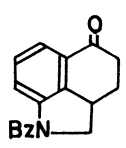


1 2 3

Chart 1

final product is obtained after purification by column chromatography at the end of the process, without purification of intermediates. Application of this methodology for the total synthesis of lysergic acid (**1**) requires the preparation of the 1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carbonyl chloride (**11**), which has a masked indolic system, in order to avoid the possible introduction of aromaticity of the C-ring.[2a)] Thus, the carbonyl chloride (**11**) was prepared as follows. Cyanophosphorylation of Uhle's ketone (**4**),[2a)] which has been utilized as a starting material for the total synthesis of **1**, with diethyl phosphorocyanidate (DEPC) and lithium cyanide (LiCN)[4)] gave the cyanophosphate (**5**), which was then treated with boron trifluoride etherate ($BF_3 \cdot OEt_2$) to afford the α,β-unsaturated nitrile (**6**).[2a)] *Hydrolysis of the cyanide function of* **6** *was successfully achieved via a stepwise route, which* involves the initial isolation of an amide (**7**) by heating of **6** with 77% sulfuric acid (H_2SO_4), then refluxing of **7** in concentrated hydrochloric acid (HCl)–acetic acid (AcOH) (1 : 1) solution

to give an amino acid (**8**) isolated as a hydrochloride salt. Schotten–Baumann reaction of **8** with benzoyl chloride gave a benzoate (**9**) in 72% overall yield from **4**. This was then chlorinated with thionyl chloride ($SOCl_2$) to give 1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]-indole-5-carbonyl chloride (**11**) quantitatively. Numerous attempts to hydrolyze the CN function in **6** directly to **8** were unsuccessful under both acidic and basic conditions. The



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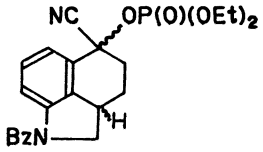

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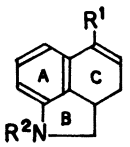


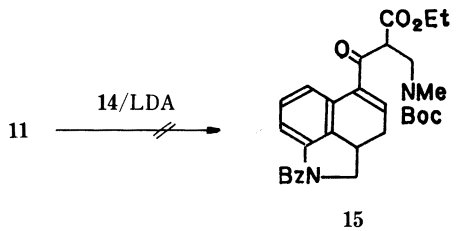
Boc R
$MeNCH_2CHCO_2Et$
14: R = H
33: R = Me

Bz = benzoyl
Boc = *tert*-butoxycarbonyl

6: $R^1 = CN$, $R^2 = Bz$
7: $R^1 = CONH_2$, $R^2 = Bz$
8: $R^1 = CO_2H$, $R^2 = H$
9: $R^1 = CO_2H$, $R^2 = Bz$
10: $R^1 = CO_2H$, $R^2 = CO_2Et$
11: $R^1 = COCl$, $R^2 = Bz$
12: $R^1 = COCl$, $R^2 = CO_2Et$
13: $R^1 = CHO$, $R^2 = Bz$

Chart 2

carbonyl chloride (**11**) thus obtained, however, was only slightly soluble in tetrahydrofuran (THF) and the condensation of **11** with ethyl 3-(*N-tert*-butoxycarbonyl-*N*-methyl-amino)propionate (**14**) in the presence of lithium diisopropylamide (LDA) in THF at −78 °C gave a complex mixture, from which the product (**15**) could not be obtained. In order to overcome the problem of the solubility in THF, the protective group of **11** was changed to an ethoxycarbonyl group. The corresponding carbonyl chloride (**12**) was analogously prepared from **8** *via* Schotten–Baumann reaction (with ethyl chloroformate) followed by chlorination in 84% overall yield. Although the solubility in THF was not greatly improved, reaction of **12** with **14** proceeded smoothly to yield a viscous oil, whose mass spectrum (MS) showed a parent peak at *m/z* 718 ($M^+ + 1$). However, the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of this product was not sufficiently well resolved for the assignment of the protons (300 MHz, $CDCl_3$). Thus, without further investigation, this was submitted to the



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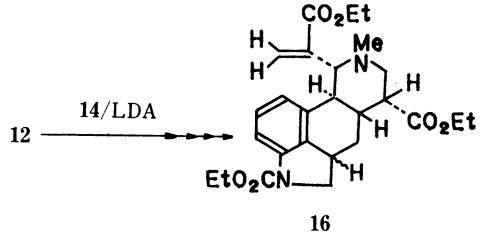

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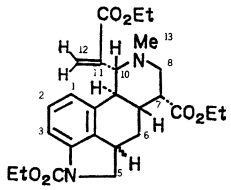
Chart 3

following reaction sequences developed for the model compound, namely i) sodium borohydride ($NaBH_4$) reduction ii) mesylation with methanesulfonyl chloride (MsCl) and pyridine iii) de-*tert*-butoxycarbonylation sequence [2.3 N HCl in ethyl acetate (EtOAc)] iv) treatment with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in dimethyl sulfoxide (DMSO), without purification of the resulting intermediates.[3] The crude oil finally obtained was purified by silica gel (SiO_2) column chromatography to give a crystalline product (**16**) [mp 140—141 °C, MS *m/z*: 470 (M^+), high-resolution MS Calcd for $C_{26}H_{34}N_2O_6$: 470.2418. Found: 470.2415] in 18% overall yield from **12**. The infrared (IR) spectrum of **16** showed strong carbonyl absorptions at

TABLE I. Selected ^{13}C- and ^{1}H-NMR Data for Compound **16** δ in $CDCl_3$



Number	Carbon	Proton J (Hz)	Number	Carbon	Proton J (Hz)
1	113.73 d	6.56 (d, $J=8$)	8	60.34 t	2.45 (dd, $J=12$, 3, -H)
2	128.20 d	7.04 (br t, $J=8$)			3.30 dd, $J=12$, 3, -H)
3	119.43 d	7.56 (br)	10	65.22 d	3.44 (d, $J=11$)
5	57.19 t		10a	43.22 d	3.50 (t, $J=11$)
5a	34.45 d		11[b]	134.97 s	
6	34.48 t	1.58,[a] 2.22 (m)	12[b]	128.73 t	6.04 (s), 6.44 (s)
6a	40.51 d	1.58 (m)	13[b]	43.51 q	2.17 (s)
7	46.49 d	2.79 (q, $J=3$)			

a) Overlapped with 6a-H. *b*) Numberings 11, 12, and 13 were used for convenience.

1720 and 1710 cm^{-1}. The ^{1}H-NMR spectrum showed the presence of three $CO_2CH_2CH_3$ groups, N-CH_3 protons at δ 2.18, and terminal methylene protons at δ 6.04 and 6.44 as well as the protons of the 1,2,2a,3,4,5-hexahydrobenz[*cd*]indole skeleton. Selected ^{1}H-NMR and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectral data are summarized in Table I. On the basis of these results, the structure of **16** was supposed to be ethyl 2-(4,7-diethoxycarbonyl-9-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo-[3,4,5-*gh*]isoquinolin-10-yl)propenoate. From the two-dimensional (2D) ^{1}H–^{13}C chemical shift correlation spectrum (H–C COSY) of **16**, it was found that signal due to 10a-H appears as a triplet at δ 3.50 with $J=11$ Hz. This signal was collapsed to a sharp doublet ($J=11$ Hz) by irradiation of the signal at δ 1.58 (6-H_{ax} and 6a-H). This clearly indicates that 10a-H also couples with 10-H with $J=$ 11 Hz. Thus, the C/D-*trans* fusion, as well as the *trans* relative configuration between 10- and 10a-H, was deduced. This is consistent with the structure of the Ergot alkaloid, paspaclavine.[5] Furthermore, the α-configuration of the ethoxycarbonyl group at C-7 was deduced from the signal of 7-H, which appeared as a sharp quartet with $J=3$ Hz.[6]

Chart 4 shows how **12** could give rise to the final product **16** *via* the reaction sequences mentioned above: namely condensation of the carbonyl chloride (**12**) with **14** in the presence of LDA followed by Michael addition of **14** to the resulting β-keto ester (**17**) gives **18**. Reduction of **18** with $NaBH_4$ gives the alcohol (**19**), which was then mesylated to **20**. De-*tert*-butoxycarbonylation of **20** and heating of **21** with DBU in DMSO gives the cyclized product (**16**) with liberations of methanesulfonic acid and methylamine.

Attempts to synthesize the β-keto esters such as **15** or **17** through the carbonyl chlorides (**11** and **12**) were unsuccessful. Thus, our effort was directed at the reaction of the aldehyde (**13**) with **14**. The aldehyde (**13**) had been prepared by Woodward *et al.*,[2a] and afterward Ramage *et al.*[2c] optimized the procedure to allow satisfactory production of **13** as a key intermediate for the synthesis of lysergic acid (**1**). However, since the nitrile (**6**) is readily available in a large quantity and high yield (100%) from Uhle's ketone (**4**), in our case, **13** was alternatively prepared by reduction of **6** with diisobutylaluminum hydride (DIBAL) in 47% yield. Reaction of the aldehyde (**13**) with **14** in the presence of LDA in THF at -78 °C gave the alcohol (**22**) [MS m/z: 520 (M^+)] as an oily mixture of diastereoisomers in quantitatives yield, after purification by column chromatography on SiO_2. The IR spectrum of **22** showed

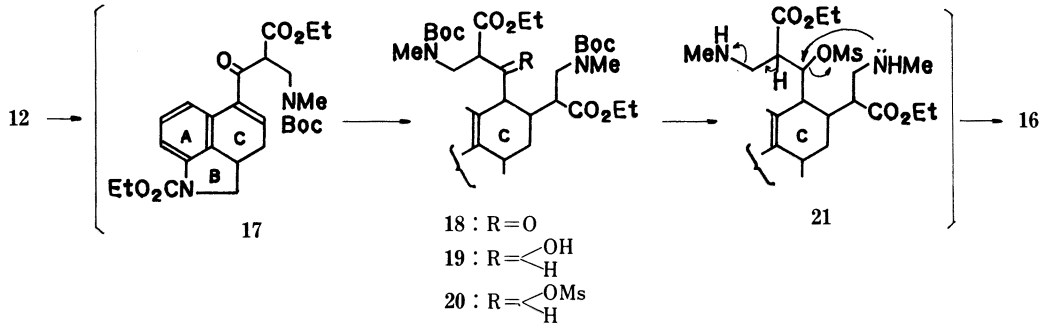


Chart 4

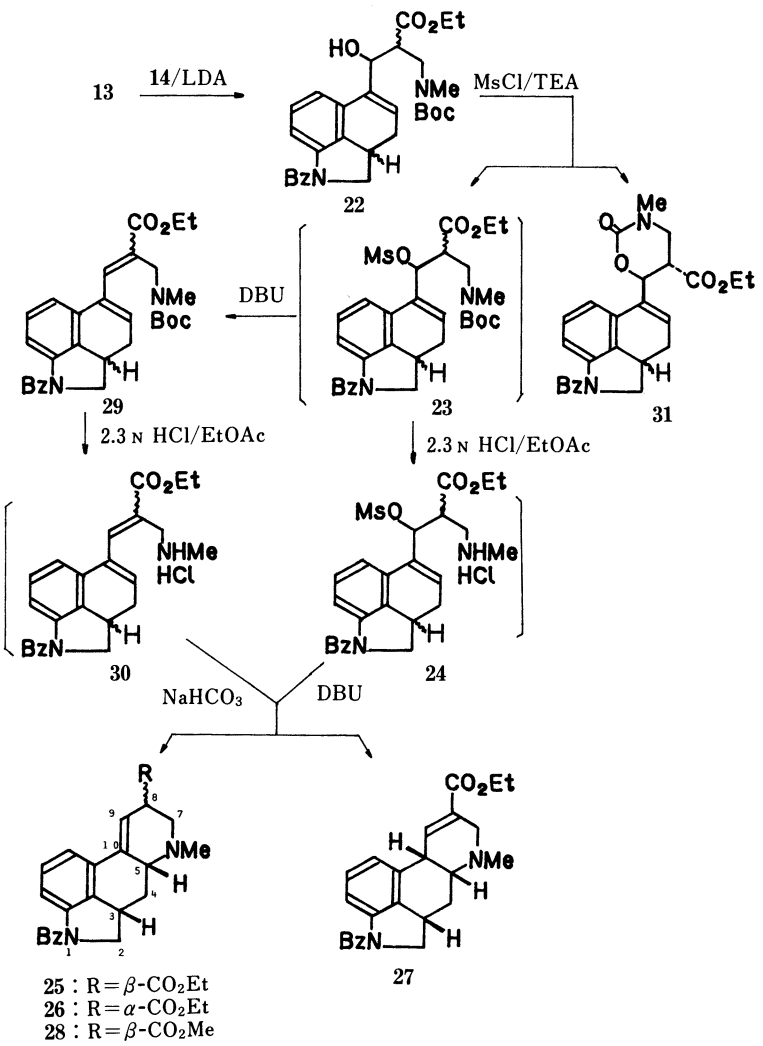


Chart 5

three carbonyl absorptions at 1720, 1680, and 1640 cm^{-1}, as well as a hydroxy absorption at 3400 cm^{-1}. This product was treated with MsCl and triethylamine (TEA) in dichloromethane (CH_2Cl_2) at room temperature to give the mesylate (**23**), which was, without purification,

TABLE II. ^{1}H-NMR, IR, UV, and Mass Spectral Data for Compounds **25** (**26**), and **27**

Compd.	**25**	**26**[a]	**27**
^{1}H-NMR ($CDCl_3$)			
δ J (Hz)			
Protons			
3-H	3.41 (m)		3.44—3.70 (m)
4-H_{eq}	2.55 (m)		2.53 (br)
4-H_{ax}	1.39 (q, J=11.5)	1.42 (q, J=11.5)	1.54 (td, J=13, 3)
5-H	3.04 (br d, J=11.5)	2.89 (br d, J=11.5)	2.82 (q, J=3.6)
7-H_{eq}	3.26 (dd, J=11.5, 6.1)	3.44 (d, J=11.5)	3.44—3.70 (m)
7-H_{ax}	2.67 (t, J=11.5)	2.57 (dd, J=11.5, 5)	2.98 (dt, J=16.2, 3)
8-H	3.62 (m)		
9-H	6.55 (br s)		7.33 (t, J=3)
N–CH_3	2.50 (s)	2.47 (s)	2.46 (s)
IR (KBr) ν			
cm^{-1} (C=O)	1730, 1640		1710, 1645
UV (EtOH)			
nm ($\log\varepsilon$)	254 (4.51), 307 (3.80)		267 (4.09), 293 (3.95)
MS m/z	402 (M^+)		402 (M^+)

a) The ^{1}H-NMR spectral data for **26** were obtained from the spectrum of a mixture of the two isomers (**25** and **26**).

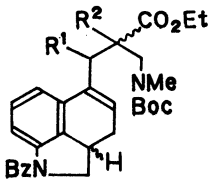
submitted to the usual cleavage of the *tert*-butoxycarbonyl (*tert*-Boc) group by 2.3 N HCl–EtOAc. Cyclization of the resulting hydrochloride (**24**) was performed by treatment with DBU in DMSO at room temperature to afford the desired ethyl *N*-benzoyl-2,3-dihydrolysergates (**25** and **26**) in 54% combined yield from **22** as an isomeric mixture in the ratio of 2 : 1 (by ^{1}H-NMR spectroscopy), along with the isomer (**27**), mp 178—180 °C, in 8% overall yield from **22**. Recrystallization of the above mixture from EtOAc afforded the homogeneous 8β-isomer (**25**), mp 147—148 °C, whose spectroscopic data were very similar to those of the corresponding methyl ester (**28**).[2e] Hydrolysis of **25** with concentrated HCl in methanol (MeOH) and ordinary esterification (dry HCl and MeOH) of the carboxylic acid followed by mild benzoylation[2f] afforded **28**, mp 165—168 °C, the IR and ^{1}H-NMR spectra of which were identical with those of the authentic **28**, provided by Ninomiya. Since **28** has already been converted to lysergic acid,[2a,c,e] the present work amounts to a formal synthesis of (±)-lysergic acid (**1**).

Table II shows the IR, ultraviolet (UV), MS, and selected ^{1}H-NMR spectral data of compounds **25** (**26**), and **27**. The IR and UV spectra clearly indicate the presence of an α,β-unsaturated ester moiety in the structure **27**. The C/D-*cis* ring junction of **27** was determined from the signal pattern of 5-H which appeared as a quartet with J=3.6 Hz at δ2.82 and collapsed to a broad singlet on irradiation of 4-H_α or 4-H_β.

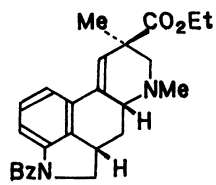
Another approach to the tetracyclic compounds was investigated. When the crude product obtained by mesylation of **22** was first treated with DBU in DMSO, the diene ester (**29**) was obtained as an unstable oil, but the yield was very poor (18%). Usual cleavage of the *tert*-Boc group of **29** followed by treatment with saturated $NaHCO_3$ afforded a mixture of unsaturated esters (**25**/**26**) and the conjugate ester (**27**) in 44% combined yield and 12% yield from **29**, respectively. Therefore, the former approach is superior to the latter. Even on a 9 g scale, the four-step sequence starting from the aldehyde (**13**) can be run without isolation of intermediates to produce **25** (**26**) and **27** in 62% (7.95 g) overall yield. Hence, we have developed a new and simple method for the synthesis of **25** (**26**).

The main disadvantage during the synthetic route described above is that in the mesylation of **22** a side reaction occurs with the formation of a polar compound (**31**). Thus,

the isolation of the side product was attempted. After usual mesylation of **22**, the crude product was purified by SiO_2 column chromatography [benzene–EtOAc (2:1)] to yield a crystalline product (**31**) in 30% yield.[7] The molecular formula was determined by high-resolution MS, indicating $C_{26}H_{26}N_2O_5$ for **31**. The ^{1}H-NMR spectrum exhibited no *tert*-butyl group, although three carbonyl absorptions (1720, 1710, and 1640 cm^{-1}) are observed in the IR spectrum. Consequently, the structure of **31** was determined as ethyl 3-methyl-6-(1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indol-5-yl)-2-oxo-3,4,5,6-tetrahydro-1,3-oxazine-5-carboxylate. The *trans* stereochemistry between 5-H and 6-H was deduced from the signal pattern of 6-H_{ax} which appeared as a doublet with $J=9$ Hz. Although the mechanistic details of this side reaction have not been established,[8] it was suggested that the methanesulfonyloxy group may participate in the formation of **31**, because no reaction took place on heating of **22** with TEA in the absence of MsCl in CH_2Cl_2. Thus, **22** was chlorinated with *N*-chlorosuccinimide (NCS) and triphenylphosphine (Ph_3P)[9] to give the chloride (**32**), which was then submitted to the de-*tert*-Boc sequence followed by treatment with DBU in DMSO to give a mixture of unsaturated esters (**25** and **26**) (43% from **22**) and **27** (6% from **22**), the yields of which could not be improved.



32: R^1=Cl, R^2=H
34: R^1=OH, R^2=Me
35: R^1=Cl, R^2=Me



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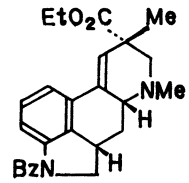

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Chart 6

Next, synthesis of (±)-lysergine, along with development of the methodology of the synthesis of (±)-lysergic acid (**1**), was attempted. The condensation of the aldehyde (**13**) with **33** under the same conditions as described for the preparation of **22** gave the alcohol (**34**) as diastereomixtures in 95% yield. The alcohol (**34**) did not afford the mesylate on treatment with MsCl in the presence of TEA, pyridine, or even *n*-butyllithium. Therefore, **34** was chlorinated with $SOCl_2$ (method A) or NCS-Ph_3P[9] (method B) to give the chloride (**35**) as an oil (mixture of diastereoisomers) in 23% and 36% yields, respectively. Cleavage of the *tert*-Boc group of **35** (obtained *via* methods A and B) followed by treatment with DBU in DMSO at 60 °C gave a mixture of the desired unsaturated esters [**36**/**37**: 30%/26% from **35** (method A) and **36**/**37**: 65%/6.5% from **35** (method B)]. The ^{1}H-NMR spectrum of **36** was very similar to that of **37**, except for the chemical shifts of 8-CH_3 (δ 1.48 in **36** and δ 1.28 in **37**) and 7-H_2 [**36**: δ 2.68 (d, $J=11.5$ Hz, 7-H_{ax}), 2.89 (dd, $J=11.5$, 1.4 Hz, 7-H_{eq}) and **37**: δ 2.15 (d, $J=11.5$ Hz, 7-H_{ax}), 3.49 (d, $J=11.5$ Hz, 7-H_{eq})]. The two compounds (**36** and **37**) are therefore epimeric at C-8. Upon irradiation of 8-CH_3, a nuclear Overhauser effect (NOE) enhancement was observed at 7-H_{ax} and 5-H, and irradiation of 5-H gave NOE enhancement at 3-H and 7-H_{ax} in compound **37**. Thus, the relative configuration between 8-CH_3 and 3-H, 5-H, and 7-H_{ax} was deduced as being all-*cis* in compound **37**. It is considered that the distinct difference of the products (**36**/**37**) ratios is responsible for the result that the respective chlorides obtained *via* methods A and B have different ratios of diastereoisomers.

Finally, hydrolysis of **36** (**37**) and subsequent decarboxylation aiming at the preparation of *N*-benzoyl-2,3-dihydrolysergine was attempted, but so far without success.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR and UV spectra were recorded on a Shimadzu IR-435 and a JASCO UVIDEC-505 spectrophotometers. MS were taken on a Hitachi M-80 spectrometer. ^{1}H- and ^{13}C-NMR spectra were taken with tetramethylsilane as an internal standard on a Varian XL-300 spectrometer, in $CDCl_3$ unless otherwise noted. The solvent for extraction was a mixture of benzene–EtOAc (1 : 1) unless otherwise noted, and was dried over anhydrous Na_2SO_4. For column chromatography, SiO_2 (Merck 7734 and 9385) was used.

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carbonitrile (6)——A solution of a mixture of DEPC (19.07 g, 117 mmol) and Uhle's ketone (**4**) (10.86 g, 39 mmol) in THF (75 ml) was added to LiCN (3.86 g, 117 mmol) suspended in THF (100 ml) with ice cooling, and the mixture was stirred for 30 min at room temperature. The mixture was concentrated *in vacuo*, water (20 ml) was added to the residue and the aqueous mixture was extracted. The extract was washed with H_2O, and brine, and dried. Removal of the solvent gave an oil (**5**), which was dissolved in dry benzene (30 ml). $BF_3 \cdot OEt_2$ (16.59 g, 117 mmol) was added to the benzene solution and the mixture was stirred for 1.5 h at room temperature. Water was added with ice cooling under vigorous stirring and the aqueous mixture was extracted. The extract was washed with H_2O, and brine, then dried, and evaporated. The resulting solid was recrystallized from benzene–petroleum ether to give **6** (10.05 g, 90%) as colorless crystals, mp 149—150 °C (lit.[2a] 142—144 °C). IR ν_{max}^{Nujol} cm^{-1}: 2200 (CN), 1630 (CO). ^{1}H-NMR δ: 2.34 (1H, ddd, J=18, 15.5, 2.6 Hz, 3-H), 2.84 (1H, m, 3-H), 3.62 (1H, m, 2a-H), 3.83 (1H, t, J=11 Hz, 2-H), 4.50 (1H, br, 2-H), 6.83 (1H, dd, J=6.3, 2.6 Hz, 4-H), 7.1—7.7 (8H, m, Ph).

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carboxamide (7)——Compound **6** (8.59 g, 30 mmol) was added to a 77% H_2SO_4 solution (90 ml) in limited amounts at room temperature and the mixture was heated at 90 °C for 2.2 h. The solution was poured into ice-water under stirring, and the resulting white precipitate was collected by filtration, washed with H_2O, and dried to give **7** (9.13 g, 100%). Recrystallization from dimethylformamide (DMF)–H_2O gave colorless crystals, mp 270—273 °C. IR ν_{max}^{Nujol} cm^{-1}: 3400—3100 (NH_2), 1670 ($CONH_2$), 1620 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.18 (1H, t, J=16 Hz, 3-H), 2.66 (1H, m, 3-H), 3.48 (1H, m, 2a-H), 3.89 (1H, br s, 2-H), 4.20 (1H, br, 2-H), 6.55 (1H, d, J=5.9 Hz, 4-H), 7.0—8.0 (10H, m, Ph and $CONH_2$). *Anal.* Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.68; H, 5.59; N, 9.48.

1,2,2a,3-Tetrahydrobenz[*cd*]indole-5-carboxylic Acid Hydrochloride (8)——A solution of **7** (9.13 g, 3 mmol) in concentrated HCl–AcOH (1 : 1) (200 ml) was refluxed for 15 h. After removal of the solvents by evaporation *in vacuo*, the residue was dissolved in H_2O (400 ml). The aqueous solution was extracted with EtOAc in order to remove the soluble material. The aqueous portion was concentrated to dryness to give the hydrochloride of **8** (7.12 g, 100%). Recrystallization from MeOH–ether gave colorless crystals, mp 216—217 °C. IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.32 (1H, td, J=17, 2.6 Hz, 3-H), 2.84 (1H, dt, J=17, 7 Hz, 3-H), 3.42 (1H, t, J=10 Hz, 2-H), 3.50 (1H, m, 2a-H), 4.08 (1H, dd, J=10, 7 Hz, 2-H), 7.21 (1H, dd, J=7, 2.6 Hz, 4-H), 7.25—7.83 (3H, m, Ph). *Anal.* Calcd for $C_{12}H_{12}ClNO_2$: C, 60.63; H, 5.09; N, 5.89. Found: C, 60.74; H, 5.09; N, 5.87.

Schotten–Baumann Reaction of Amino Acid (8) with Benzoyl Chloride (or Ethyl Chloroformate)——General Procedure: Benzoyl chloride (843 mg, 6 mmol) [ethyl chloroformate (651 mg, 6 mmol)] was added to a solution of **8** (1.19 g, 5 mmol) in 0.2 N NaOH solution (30 ml) with ice cooling. The mixture was stirred for 1 h at room temperature and acidified by the addition of 10% HCl with cooling. The resulting precipitate was collected by filtration, washed with H_2O, and dried. Recrystallization from DMF–H_2O gave a grayish powder.

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carboxylic Acid (9)——Yield, 80%. mp 237—240 °C. IR ν_{max}^{Nujol} cm^{-1}: 1710 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.24 (1H, td, J=15, 2.3 Hz, 3-H), 2.70 (1H, m, 3-H), 3.48 (1H, m, 2a-H), 3.88 (1H, br s, 2-H), 4.20 (1H, br, 2-H), 7.08—8.0 (9H, m, Ph and 4-H), 12.70 (1H, br, CO_2H). *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.73; H, 4.98; N, 4.71.

1-Ethoxycarbonyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carboxylic Acid (10)——Yield, 84%. mp 255—256 °C. IR ν_{max}^{Nujol} cm^{-1}: 1700, 1670 (CO). ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, J=7 Hz, $CO_2CH_2CH_3$), 2.24 (1H, t, J=17 Hz, 3-H), 2.75 (1H, dt, J=17, 7.1 Hz, 3-H), 3.43 (1H, m, 2a-H), 3.60 (1H, t, J=10.5 Hz, 2-H), 4.20 (2H, br, $CO_2CH_2CH_3$), 4.32 (1H, t, J=10.5 Hz, 2-H), 7.06—7.60 (4H, m, Ph and 4-H), 12.70 (1H, s, CO_2H). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.97; H, 5.43; N, 4.99.

Without purification of the intermediates, the ketone (**4**) (30.34 g, 109 mmol) was successfully converted to **9** (72% overall yield from **4**) under the same conditions as described above.

Chlorination of the Carboxylic Acids (9 and 10)——General Procedure: $SOCl_2$ (2.6 ml, 35 mmol) was added to a solution of a carboxylic acid (8.8 mmol) in dry benzene (50 ml), and the mixture was heated at 95 °C for 2.5 h with stirring. After the mixture had been concentrated *in vacuo*, the residue was recrystallized from dry benzene with the aid of Norite to give the corresponding carbonyl chloride.

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carbonyl Chloride (11)——Yield, 100%. mp 180—181 °C. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1630 (CO). ^{1}H-NMR δ: 2.38 (1H, t, J=16 Hz, 3-H), 2.90 (1H, m, 3-H), 3.58 (1H, br s, 2a-H), 3.82 (1H, t, J=10.2 Hz, 2-H), 4.45 (1H, br, 2-H), 6.80—7.80 (9H, m, Ph and 4-H). *Anal.* Calcd for $C_{15}H_{14}ClNO_3$: C, 70.48; H, 4.36; N, 4.33. Found: C, 70.53; H, 4.27; N, 4.22.

1-Ethoxycarbonyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carbonyl Chloride (12)——Yield, 100%. mp 128—130 °C. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1690 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.39 (1H, ddd, J=17.7, 15.2, 2.5 Hz, 3-H), 2.95 (1H, dt, J=17.7, 6.6 Hz, 3-H), 3.52 (1H, m, 2a-H), 3.63 (1H, t, J=10.3 Hz, 2-H), 4.32 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.45 (1H, br, 2-H), 7.20—7.80 (4H, m, Ph and 4-H). *Anal.* Calcd for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.84; N, 4.80. Found: C, 61.76; H, 4.78; N, 4.68.

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole-5-carbaldehyde (13)——DIBAL (1.5 M toluene solution, 3.3 ml, 5 mmol) was added to a solution of **6** (573 mg, 2 mmol) in dry benzene (30 ml) with ice cooling, and the mixture was stirred for 2 h at 65 °C, then cooled to room temperature. Benzoyl chloride (1.4 g, 10 mmol) and TEA (1.01 g, 10 mmol) were added, and the mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of H_2O (5 ml) and saturated NH_4Cl solution (8 ml), and then the mixture was neutralized by the addition of 10% H_2SO_4 (3.3 ml). The whole was extracted with EtOAc and the extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography [benzene–EtOAc (5 : 1)] to give **13** (268 mg, 47%), which was recrystallized from EtOH as colorless crystals, mp 175—176 °C (lit.[2a] mp 179.5—180.5 °C).[10] IR ν_{max}^{KBr} cm^{-1}: 1680, 1620 (CO). ^{1}H-NMR δ: 2.41 (1H, ddd, J=17.6, 15.1, 2.6 Hz, 3-H), 2.92 (1H, br s, 3-H), 3.59 (1H, m, 2a-H), 3.83 (1H, t, J=10.9 Hz, 2-H), 4.45 (1H, br, 2-H), 6.95 (1H, br d, J=6.1 Hz, 4-H), 7.0—7.90 (8H, m, Ph), 9.73 (1H, s, CHO).

Ethyl 2-(4,7-Diethoxycarbonyl-9-methyl-4,5,5a,6,6a,7,8,9,10,10a-decahydroindolo[3,4,5-*gh*]isoquinolin-10-yl)-propenoate (16)——The preparation of LDA was carried out as follows: *n*-butyllithium (1.6 M hexane solution, 6.9 ml, 10.8 mmol) was added to a solution of diisopropylamine (1.09 g, 10.8 mmol) in THF (10 ml) at −78 °C under N_2, and the mixture was stirred for 20 min. A solution of ethyl 3-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)propionate (**14**) (2.5 g, 10.8 mmol) in THF (5 ml) was then added to the solution at −78 °C, and the mixture was stirred for 20 min. A solution of **12** (1.04 g, 3.6 mmol) in THF (25 ml) was added dropwise, and the whole was stirred for another 20 min at this temperature. The reaction was quenched by the addition of H_2O, and THF was removed by evaporation. The residue was extracted, and the extract was washed with brine, dried, and concentrated. The residue was dissolved in EtOH (75 ml), and the $NaBH_4$ (680 mg, 18 mmol) was added. After the mixture had been stirred for 4 h, acetic acid was added to decompose excess $NaBH_4$, and EtOH was removed by evaporation. The residue was extracted, and the extract was washed with H_2O and brine, dried, and concentrated. To a solution of this residue in dry pyridine (28 ml) was added MsCl (3.3 g, 29 mmol), and the mixture was stirred for 4 h at room temperature. The reaction mixture was made alkaline by the addition of 10% NH_4OH, diluted with H_2O (100 ml), and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The residue was dissolved in 2.3 N HCl in EtOAc (16 ml) and the mixture was stirred for 1.5 h at room temperature. After removal of the solvent by evaporation, the residue was dissolved in DMSO (3 ml) containing DBU (2.18 g, 18 mmol). The mixture was allowed to stand for 3 h, diluted with cold H_2O (10 ml), then extracted. The extract was washed with H_2O and brine, dried, and evaporated. The residue was purified by column chromatography [benzene–EtOAc (1 : 1)] to give **16** (300 mg, 18% overall yield from **12**). Recrystallization from EtOH gave colorless crystals, mp 141—142 °C. IR ν_{max}^{KBr} cm^{-1}: 1720, 1710 (CO). ^{1}H-NMR δ: 1.28—1.38 (9H, m, 3 × $CO_2CH_2C\underline{H}_3$), 1.58 (2H, m, 6-H, 6a-H), 2.17 (3H, s, NCH_3), 2.22 (1H, m, 6-H), 2.45 (1H, dd, J=12, 3 Hz, 8-H), 2.79 (1H, q, J=3 Hz, 7-H), 3.30 (1H, dd, J=12, 3 Hz, 8-H), 3.44 (1H, d, J=11 Hz, 10-H), 3.50 (1H, t, J=11 Hz, 10a-H), 4.20—4.44 (7H, m, 3 × $CO_2C\underline{H}_2CH_3$, 5-H), 6.04 and 6.44 (each 1H, each s, $=CH_2$), 6.56 (1H, d, J=8 Hz, 1-H), 7.04 (1H, br t, J=8 Hz, 2-H), 7.56 (1H, br, 3-H). MS *m/z*: 470 (M^+). High-resolution MS (HRMS) Calcd for $C_{26}H_{34}N_2O_6$: 470.2418. Found: 470.2415. *Anal.* Calcd for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.43; H, 7.29; N, 5.84.

Ethyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)methyl-3-hydroxy-3-(1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indol-5-yl)propionate (22)——A solution of **14** (1.46 g, 6.3 mmol) in THF (5 ml) was added to a solution of LDA [prepared from diisopropylamine (640 mg, 6.3 mmol)] in THF (5 ml) at −78 °C under N_2, and the mixture was stirred for 20 min. A solution of **13** (1.24 g, 4.2 mmol) in THF (25 ml) was added dropwise at −78 °C, and the whole was stirred for 30 min. The reaction was quenched by the addition of H_2O, and THF was removed by evaporation. The residue was extracted, and the extract was washed with H_2O and brine, dried, and evaporated. The residue was purified by column chromatography [benzene–EtOAc (3 : 1)] to give **22** (2.18 g, 99%) as an oil. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1720, 1680 (CO). The ^{1}H-NMR spectrum was not sufficiently well resolved for assignment of the signals. MS *m/z*: 520 (M^+). HRMS Calcd for $C_{30}H_{36}N_2O_6$: 520.2575. Found: 520.2571.

Ethyl 1-Benzoyl-2,3-dihydrolysergates (25 and 26) and 1-Benzoyl-8-ethoxycarbonyl-2,3-dihydro-6-methyl-$\Delta^{8,9}$-ergoline (27)——Method A: MsCl (504 mg, 4.4 mmol) was added to a solution of **22** (1.77 g, 3.4 mmol) and TEA (516 mg, 5.1 mmol) in CH_2Cl_2 (40 ml), and the mixture was stirred for 15 min at room temperature. Work-up as described for the preparation of **16** gave a mesylate (**23**), which was then dissolved in 2.3 N HCl–EtOAc (16 ml). After being stirred for 1.5 h, the mixture was concentrated, and the residue was dissolved in DMSO (2 ml) and DBU (1.04 g, 6.8 mmol). Work-up gave an oil, which was subjected to column chromatography. The first eluate with EtOAc gave **27** (6.8% from **22**) as colorless crystals and a mixture of **25** and **26** (578 mg, 42% from **22**) as an oil. Crystallization from EtOAc gave homogeneous **25** as colorless crystals.

25: mp 147—148 °C (from EtOAc). IR ν_{max}^{KBr} cm^{-1}: 1730, 1640 (CO). ^{1}H-NMR δ: 1.31 (3H, t, J=7.3 Hz, $CO_2CH_2C\underline{H}_3$), 1.39 (1H, q, J=11.5 Hz, 4-H_{ax}), 2.50 (3H, s, NCH_3), 2.67 (1H, t, J=11.5 Hz, 7-H_{ax}), 3.04 (1H, br d,

J=11.5 Hz, 5-H), 3.26 (1H, dd, J=11.5, 6.1 Hz, 7-H_{eq}), 3.62 (1H, m, 8-H), 3.70 (1H, t, J=11 Hz, 2-H_{α}), 4.22 (2H, q, J=7.3 Hz, $CO_2C\underline{H}_2CH_3$), 4.30 (1H, br s, 9-H), 6.55 (1H, br s, 9-H), 7.26—7.60 (8H, m, Ph). UV λ_{max}^{EtOH} nm (log ε): 254 (4.51), 307 (3.80). *Anal.* Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.33; H, 6.48; N, 6.86.

26: (The ^{1}H-NMR spectral data for **26** were obtained from the spectrum of a mixture of two isomers.) ^{1}H-NMR δ: 1.27 (3H, t, J=7.3 Hz, $CO_2CH_2C\underline{H}_3$), 1.42 (1H, q, J=11.5 Hz, 4-H_{ax}), 2.47 (3H, s, NCH_3), 2.57 (1H, dd, J=11.5, 5 Hz, 7-H_{ax}), 2.89 (1H, br d, J=11.3 Hz, 5-H), 3.44 (1H, d, J=11.5 Hz, 7-H_{eq}), 3.16 (1H, br, 8-H), 4.22 (2H, q, J=7.3 Hz, $CO_2C\underline{H}_2CH_3$).

27: mp 178—180 °C (from EtOAc). IR ν_{max}^{KBr} cm^{-1}: 1710, 1645 (CO). ^{1}H-NMR δ: 1.30 (3H, t, J=7.3 Hz, $CO_2CH_2C\underline{H}_3$), 1.54 (1H, td, J=13, 3 Hz, 4-H_{ax}), 2.46 (3H, s, NCH_3), 2.82 (1H, q, J=3.6 Hz, 5-H), 2.98 (1H, dt, J=16.2, 3 Hz, 7-H_{ax}), 4.22 (3H, m, $CO_2C\underline{H}_2CH_3$, 2-H_{α}), 4.50 (1H, br s, 2-H_{β}), 7.33 (1H, d, J=3 Hz, 9-H), 6.80—7.60 (8H, m, Ph). UV λ_{max}^{EtOH} nm (log ε): 267 (4.09), 293 (3.95). *Anal.* Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.60; H, 6.55; N, 6.88.

Even on a 9.0 g (32 mmol) scale, the four-step sequence starting from the aldehyde (**13**) as described above can be run without isolation of intermediates to produce **27** (1.01 g, 8%) and a mixture of **25** (**26**) (6.94 g, 54%).

Method B: A solution of **29** (90 mg) in 2.3 N HCl–EtOAc (2.5 ml) was allowed to stand for 1.5 h. Work-up gave an oil, which was purified by column chromatography (EtOAc) to give **27** (8 mg, 12%) and a mixture of **25** and **26** (30 mg, 44%), the spectra (IR, ^{1}H-NMR) of which were identical with those of the samples prepared in Method A.

Method C: A solution of Ph_3P (435 mg, 1.5 mmol) in THF (5 ml) was added to a solution of NCS (221 mg, 1.5 mmol) in THF (15 ml), and the mixture was stirred for 25 min at room temperature. A solution of **22** (520 mg, 1 mmol) in THF (7 ml) was added to the resulting pasty solution, and the whole was stirred for 1 h. The reaction mixture was diluted with benzene–EtOAc (60 ml) and the whole was washed with H_2O, brine, dried, and evaporated. The residue, including the chloride (**32**), which was unstable during purification by column chromatography (EtOAc), was submitted to de-*tert*-butoxycarbonylation [2.3 N HCl–EtOAc (9 ml)] and cyclization with DBU (456 mg, 3 mmol) in DMSO (2 ml) as usual. The resulting crude oil was purified by column chromatography to give a mixture of **25** and **26** (172 mg, 43%), and **27** (23 mg, 6%). These products were identical with the samples prepared by method A, based on comparison of their IR and ^{1}H-NMR spectra.

Methyl 1-Benzoyl-2,3-dihydrolysergate (28)——A solution of a mixture of **25** and **26** (201 mg, 0.5 mmol) and concentrated HCl (1 ml) in MeOH (20 ml) was refluxed for 6 h. After removal of the solvent by evaporation, the residue was dried *in vacuo* over P_2O_5 for 14 h, then dissolved in dry MeOH (5 ml) and 2 N HCl in MeOH (1 ml). The mixture was stirred for 24 h at room temperature under N_2. The solvent was removed *in vacuo*, and the residue was neutralized with 10% K_2CO_3 and extracted with CH_2Cl_2. The extract was washed with brine, dried and evaporated. The residue was again dissolved in dry MeOH (20 ml) containing benzoyl chloride (0.5 ml) and pyridine (0.5 ml), and the mixture was stirred for 5 min at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried, and concentrated. The residue was purified by column chromatography (EtOAc) to give an oil (116 mg, 60%), which is an epimeric mixture of **28**. Crystallization of the oil from EtOAc gave a solid, which was recrystallized from EtOAc to give **28**, mp 165—168 °C (lit.[2e] mp 165—168 °C). The IR and ^{1}H-NMR spectra were identical with those of an authentic sample.

Ethyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)methyl-3-(1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indol-5-yl)-propenoate (29)——The crude mesylate (**23**) obtained from **22** (520 mg, 1 mmol) was dissolved in DMSO (1.5 ml) and DBU (304 mg, 2 mmol) and the mixture was stirred for 5 min at room temperature. Water was added, and the aqueous solution was extracted. The extract was washed with H_2O and brine, dried, and evaporated. The residue was purified by column chromatography [benzene–EtOAc (5 : 1)] to give **29** (90 mg, 18%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1710, 1690, 1640 (CO). The ^{1}H-NMR spectrum was not sufficiently well resolved for assignment of the signals. MS m/z: 502 (M^+). HRMS Calcd for $C_{30}H_{34}N_2O_5$: 502.2469. Found: 502.2465.

Ethyl 3-Methyl-6-(1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indol-5-yl)-2-oxo-3,4,5,6-tetrahydro-1,3-oxazine-5-carboxylate (31)——The crude product obtained by mesylation of **22** (1.92 g, 3.7 mmol) as described above was subjected to column chromatography. The benzene–EtOAc eluate gave **31** (490 mg, 30%) as a solid, which was recrystallized from EtOAc to give colorless crystals, mp 161—163 °C. IR ν_{max}^{KBr} cm^{-1}: 1720, 1710, 1640 (CO). ^{1}H-NMR δ: 1.17 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.18 (1H, br t, J=16 Hz, 3-H_{ax}), 2.60 (1H, br, 3-H_{eq}), 3.08 (3H, s, NCH_3), 3.73 (1H, dd, J=12, 9 Hz, 4-H), 3.78 (1H, t, J=11.5 Hz, 2-H), 4.11 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.29 (1H, d, J=9 Hz, 6-H), 6.10 (1H, br m, 4-H), 7.0—7.60 (8H, m, Ph). *Anal.* Calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27. Found: C, 69.81; H, 5.93; N, 6.20.

Ethyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)methyl-3-hydroxy-2-methyl-3-(1-benzoyl-1,2,2a,3-tetrahydro-benz[*cd*]indol-5-yl)propionate (34)——A solution of **33** (368 mg, 1.5 mmol) in THF (5 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (152 mg, 1.5 mmol)] in THF (5 ml) at −78 °C, and the mixture was stirred for 20 min at −78 °C. A solution of **13** (289 mg, 1 mmol) in THF (10 ml) was added dropwise to this solution, and the whole was stirred for another 20 min. Work-up as described for the preparation of **22** gave an oil, which was purified by column chromatography [benzene–EtOAc (4 : 1)] to give **32** (494 mg, 95%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1720, 1690, 1640 (CO). The ^{1}H-NMR spectrum was not sufficiently well resolved for assignment of the signals. MS m/z: 534 (M^+). HRMS Calcd for $C_{31}H_{38}N_2O_6$: 534.2731. Found: 534.2726.

Ethyl 2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)methyl-3-chloro-2-methyl-3-(1-benzoyl-1,2,2a,3-tetrahydrobenz-[*cd*]indol-5-yl)propionate (35)——Method A: $SOCl_2$ (2 ml) was added to a solution of **34** (534 mg, 1 mmol) in dry benzene (10 ml), and the mixture was allowed to stand for 30 min at room temperature, then refluxed for 1 h. The mixture was concentrated *in vacuo*, then the residue was made alkaline by the addition of saturated $NaHCO_3$ with cooling, and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated. The residue was purified by column chromatography [benzene–AcOEt (4:1)] to give **35** (153 mg, 23%) as a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1720, 1690, 1645 (CO). The ^{1}H-NMR spectrum was not sufficiently well resolved for assignment of the signals. MS *m/z*: 552 (M^+), 554 ($M^+ + 2$). HRMS Calcd for $C_{31}H_{37}ClN_2O_5$: 552.2393. Found: 552.2388.

Method B: A solution of Ph_3P (263 mg) in THF (5 ml) was added to a solution of NCS (134 mg, 1 mmol) in THF (10 ml) at room temperature. Then a solution of **34** (267 mg, 0.5 mmol) in THF (5 ml) was added to the resulting pasty solution. Work-up as described for the preparation of **32** gave a crude oil, which was purified by column chromatography [benzene–EtOAc (4:1)] to give **35** (101 mg, 36%) as a pale yellow oil, which was identical with a sample prepared by method A, based on comparison of their IR spectra.

Ethyl 1-Benzoyl-8-methyl-2,3-dihydrolysergate (36) and Ethyl 1-Benzoyl-8-methyl-2,3-dihydroisolysergate (37)——Route A: The chloride (**35**) (153 mg, 0.23 mmol) obtained *via* method A was submitted to de-*tert*-butoxycarbonylation [2.3 N HCl–EtOAc (2 ml)], followed by treatment with DBU (105 mg, 0.69 mmol) in DMSO (1 ml) at 60 °C for 3 h. Work-up gave an oil, which was purified by column chromatography (EtOAc) to give **36** (30 mg, 30%) from the earlier fraction and **37** (25 mg, 26%) from the later fraction, each as an oil.

36: IR ν_{max}^{neat} cm^{-1}: 1720, 1640 (CO). ^{1}H-NMR δ: 1.30 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.36 (1H, q, J=11 Hz, 4-H_{ax}), 1.48 (3H, s, CH_3), 2.49 (3H, s, NCH_3), 2.60 (1H, br, 4-H_{eq}), 2.68 (1H, d, J=11.5 Hz, 7-H_{ax}), 2.82 (1H, br d, J=11.5 Hz, 5-H), 2.89 (1H, dd, J=11.5, 1.4 Hz, 7-H_{eq}), 3.40 (1H, m, 3-H), 3.69 (1H, t, J=11 Hz, 2-H_α), 4.20 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.24 (1H, br, 2-H_β), 6.54 (1H, br s, 9-H), 7.10—7.64 (8H, m, Ph). UV λ_{max}^{EtOH} nm (log ε): 255 (4.45), 305 (3.76). MS *m/z*: 416 (M^+). HRMS Calcd for $C_{26}H_{28}N_2O_3$: 416.2101. Found: 416.2099.

37: IR ν_{max}^{neat} cm^{-1}: 1720, 1640 (CO). ^{1}H-NMR δ: 1.23 (3H, t, J=7.3 Hz, $CO_2CH_2C\underline{H}_3$), 1.28 (3H, s, CH_3), 1.37 (1H, q, J=11.9 Hz, 4-H_{ax}), 2.15 (1H, d, J=11.5 Hz, 7-H_{ax}), 2.45 (3H, s, NCH_3), 2.54 (1H, br s, 4-H_{eq}), 2.81 (1H, br d, J=11.5 Hz, 5-H), 3.40 (1H, br m, 3-H), 3.49 (1H, d, J=11.5 Hz, 7-H_{eq}), 3.68 (1H, t, J=11 Hz, 2-H_α), 4.0—4.30 (3H, m, $CO_2C\underline{H}_2CH_3$, 2-H_β)), 6.40 (1H, s, 9-H), 7.0—7.66 (8H, m, Ph). UV λ_{max}^{EtOH} nm (log ε): 254 (4.33), 306 (3.63). MS *m/z*: 416 (M^+). HRMS Calcd for $C_{26}H_{28}N_2O_3$: 416.2101. Found: 416.2099.

Route B: The chloride (**35**) (170 mg, 0.3 mmol) obtained *via* method B was treated as described in route A to give **36** (84 mg, 65%) and **37** (8 mg, 6.5%). These products were identical with the samples obtained by route A, based on comparison of their IR and ^{1}H-NMR spectra.

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References and Notes

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6) The stereochemistry of 5a-H is ambiguous due to overlapping of the signal of this proton with other signals in the ^{1}H-NMR spectrum.
7) Purification of the mesylate (**23**) by column chromatography (SiO_2) was unsuccessful.
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10) As mentioned in a preliminary communication,[1] the aldehyde (**13**) was also prepared by the following method. A stream of H_2 was slowly bubbled through a solution of **11** (1.05 g, 4.6 mmol) in a mixture of EtOAc–xylene (3:1) (200 ml) containing *N*,*N*-dimethylaniline (669 mg, 5.5 mmol) and 10% Pd–$BaSO_4$ (1 g) for 2 h at 90—100 °C. During this period additional 10% Pd–$BaSO_4$ (0.2 g) was added every 30 min. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography [benzene–AcOEt (5:1)] to give **13** (719 mg, 54%).