methoxyisoquinoline-3,4-dione (5; 200 mg, 0.75 mmol) in DME (10 mL) containing trichloroacetic acid (20 mg, 0.125 mmol) with 2a generated from anthranillic acid (608 mg, 4.43 mmol) and isoamyl nitrite (855 mg, 7.31 mmol).

1-Benzyldibenzo[*cd*,*f*]-2*H*-indol-2-one (Aristolactam, 9). Reaction of *N*-benzyl-3-methylenephthalimidine[12] (8; 235 mg, 1 mmol) and benzyne (2a, generated from anthranillic acid (800 mg, 5.8 mmol) and isoamyl nitrite (1.12 g, 9.57 mmol) furnished compounds 9 (84 mg, 27% isolated yield) and 10 (194 mg, 63% isolated yield).

9,10-Dihydro-5*H*,7*H*-benzo[*f*][1,3]dioxolo[6,7]isoquino-[8,1,2-*hij*][3,1]benzoxazine (Duguenaine, 11). A stirred solution of (trifluoroacetyl)dehydroanonaine (3e; 100 mg, 0.27 mmol) in dry EtOH (15 mL) was reacted with $NaBH_4$ (excess). When the reaction was over (TLC, 10 min), the mixture was concentrated to dryness and the residue dissolved in dichloromethane (25 mL) and washed with water (3 × 10 mL). Evaporation of the dichloromethane gave 6a,7-dehydroanonaine (3i)[21] as an oil (70 mg, 95%) that was converted into duguenaine[20] (11; 68 mg, 84%) following the reported procedure.[21]

1,2-Dimethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (Lysicamine, 12a). $NaBH_4$ (excess) was added portionwise to a solution of 3d (50 mg, 0.13 mmol) in absolute EtOH (10 mL). After 5 min, the reaction was over (TLC monitoring). The usual workup gave dehydronornuciferine (3j,[21] 37 mg, quantitative).

To a solution of crude dehydronornuciferine (3j; 20 mg, 0.072 mmol) in methanol (10 mL) was added excess Fremy's salt[24] in 4% aqueous sodium carbonate. After the solution was stirred overnight, the usual workup[23] yielded 12a (15 mg, 70%), which was identical in all respects with an authentic sample of lysicamine.[25]

1,2,9,10-Tetramethoxy-7*H*-dibenzo[*de*,*g*]quinolin-7-one (*O*-Methylatheroline, 12b). Successive lots of sodium borohydride were added to a solution of 3h (35 mg, 0.08 mmol) in absolute ethanol (10 mL). The reaction was over (TLC) in ca. 5 min. Standard extractive workup provided dehydronorglaucine (3k,[21] 18 mg, 67% yield).

A solution of crude dehydronorglaucine (3k; 13 mg, 0.04 mmol) in 10 mL of MeOH was treated with excess Fremy's salt[24] in 4% aqueous sodium carbonate and stirred overnight. The usual Workup[23] yielded 12b (6 mg, 30%), identical in all respects with an authentic sample of *O*-methylatheroline.[25]

1-Oxy-2,11-dimethoxy-6-methyl-7-oxo-7*H*-dibenzo[*de*,*g*]-quinolinium (Alkaloid PO-3, 13). Sodium borohydride (excess) was added portionwise to a solution of 3g (29 mg, 0.072 mmol) in ethanol (10 mL). After 5 min, the reaction was over (TLC monitoring). The usual workup furnished a quantitative yield of 1,2,11-trimethoxydehydronoraporphine (nororientidine, 3l), which was used in the next step without further purification: ^{1}H NMR (250 MHz) 3.20 (t, J = 5.9 Hz, 2 H), 3.46 (t, J = 5.9 Hz, 2 H), 3.56 (s, 3 H), 4.00 (s, 6 H), 6.47 (s, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 7.01 (s, 1 H), 7.12 (d, J = 7.8 Hz, 1 H), 7.38 (t, J = 7.8 Hz, 1 H) ppm.

To a stirred solution of 3l (19 mg, 0.06 mmol) in methanol was added excess Fremy's salt[24] dissolved in 4% aqueous sodium carbonate, and the mixture was stirred for 18 h. After the usual workup,[23] oxoaporphine 12c was isolated (14 mg, 71%): ^{1}H NMR (250 MHz) 3.73 (s, 3 H), 4.00 (s, 3 H), 4.08 (s, 3 H), 7.13 (s, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.55 (t, J = 7.9 Hz, 1 H), 7.74 (d, J = 5.2 H, 1 Hz), 8.10 (d, J = 7.9 Hz, 1 H), 8.81 (d, J = 5.2 Hz, 1 H) ppm; MS m/e 321 (M^+, 100). HRMS calcd for $C_{19}H_{14}NO_4$ 321.10010, found, 321.09990.

The crude oxoaporphine 12c (14 mg) was dissolved in acetone (10 mL), treated with excess methyl iodide, and stirred for 24 h at room temperature. The resulting methiodide (16 mg, 79%) was used without purification in the next step: ^{1}H NMR (250 MHz) 3.88 (s, 3 H), 4.02 (s, 3 H), 4.27 (s, 3 H), 4.82 (s, 3 H), 7.39 (d, J = 8 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 7.88–7.91 (s+d, J = 8 Hz, 2 H), 8.90 (d, J = 5.8 Hz, 1 H), 9.22 (d, J = 5.8 Hz, 1 H) ppm.

The previous methiodide was heated in refluxing acetone for 24 h. The resulting green solution was evaporated to dryness. The residue obtained was chromatographed on silica gel plates (CH_2Cl_2:MeOH = 9:1), giving alkaloid PO-3 (13; 7 mg) and 1 mg of 1,2,11-trimethoxyoxoaporphine (12c). The synthetic PO-3 exhibited properties identical with those reported[26] (an authentic sample was not available).

Acknowledgment. Financial support from the Spanish Ministry of Education (CAICYT and DGICYT Project No PB87-0663-C02-01) and the Xunta de Galicia is gratefully acknowledged. We thank Prof. H. Itokawa for providing us with a sample of natural cepharadione B.

Registry No. 1a, 57621-04-2; 1b, 92029-23-7; 1c, 82044-05-1; 1d, 101064-78-2; 1e, 132646-13-0; 2a, 462-80-6; 2b, 54632-05-2; 2c, 33543-19-0; 3a, 82359-82-8; 3b, 13555-30-1; 3c, 132646-11-8; 3d, 101064-64-6; 3e, 132646-12-9; 3f, 86826-87-1; 3g, 101064-65-7; 3h, 101064-63-5; 3i, 41679-82-7; 3j, 92664-95-4; 3k, 39945-38-5; 3l, 101124-45-2; 4, 16535-98-1; 5, 82359-80-6; 7a, 57576-41-7; 7b, 55610-02-1; 7c, 68244-16-6; 7d, 34647-65-9; 8, 82359-81-7; 9, 82359-83-9; 10, 132646-14-1; 11, 80550-24-9; 12a, 15444-20-9; 12b, 5574-24-3; 12c, 101064-62-4; 13, 101064-66-8; 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 4721-98-6; 1-methyl-6,7-(methylenedioxy)-3,4-dihydroisoquinoline, 17104-27-7; anthranilic acid, 118-92-3; 2-amino-6-methoxybenzoic acid, 53600-33-2; 2-amino-4,5-dimethoxybenzoic acid, 5653-40-7; benzenediazonium-2-carboxylate, 1608-42-0.

Supplementary Material Available: NMR spectra of compounds 1d, 1e, 3c, 3l, and 11c (6 pages). Ordering information is given on any current masthead page.

Syntheses of (±)-α- and (±)-γ-Lycorane via a Stereocontrolled Organopalladium Route

Jan-E. Bäckvall,* Pher G. Andersson, Guy B. Stone, and Adolf Gogoll

Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden

Received April 17, 1990

Total syntheses of (±)-α- and (±)-γ-lycorane are described. The key steps in the syntheses are the stereocontrolled palladium-catalyzed intramolecular 1,4-chloroamidation of 12 to 13 and the subsequent anti-stereoselective copper-catalyzed S_N2' reaction of allylic chloride 13 with [3,4-(methylenedioxy)phenyl]magnesium bromide to give 14. Hexahydroindole 14 has the required relative stereochemistry between carbons 3a, 7, and 7a for α-lycorane (1a) and was transformed to the latter via 15 and 16. The epimeric γ-lycorane (2) was obtained by performing the Bischler–Napieralski cyclization on 14, which led to a highly stereoselective isomerization to give exclusively 17. Compound 17 was subsequently transformed to 2. The overall yield from ester 8 to (±)-α- and (±)-γ-lycorane was 40 and 36%, respectively.

The amaryllidaceae alkaloids constitute an important class of naturally occurring compounds.[1] In particular, the lycorine-type alkaloids have attracted considerable interest and a number of total syntheses of the latter have

0022-3263/91/1956-2988$02.50/0

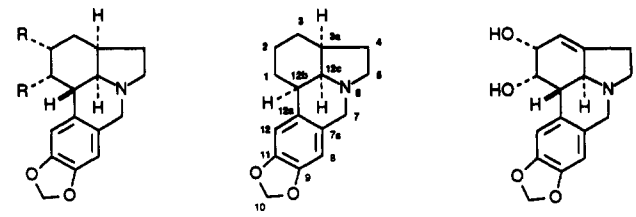


Figure 1.

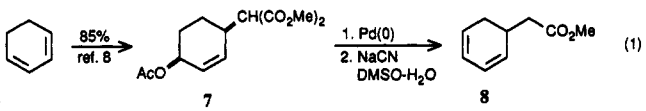
been reported.[1-6] A few examples of lycorine-type alkaloids are shown in Figure 1.

We have recently developed a procedure for palladium-catalyzed intramolecular 1,4-additions to cyclic dienes **4** involving amides as nucleophiles.[7] These reactions lead to synthetically useful hexahydroindoles **5**, which can be further functionalized in a stereospecific manner. It occurred to us that an S_N2' displacement of the allylic leaving group by the appropriate aryl group would provide useful synthetic intermediates **6** for further transformations to lycorine-type alkaloids **1** and **2** (Scheme I). The use of **5a** and **5b** in combination with a stereoselective S_N2' reaction would give access to both α- and γ-lycorane. In this paper, we report a synthesis of (±)-α- and (±)-γ-lycorane (**1a** and **2**) that is partly based on this approach.

Results and Discussion

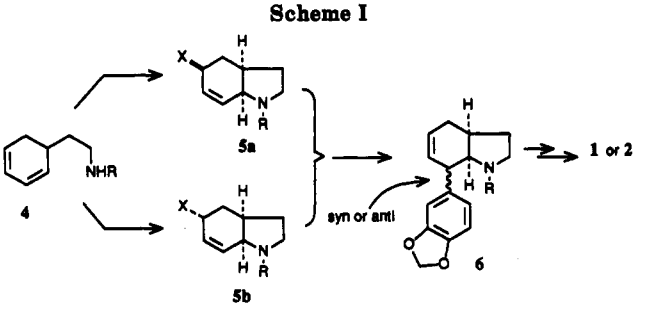
After the preparation of the hexahydroindole **5**, the aryl group could be introduced via a metal-catalyzed Grignard reaction. The intermediate **6** could then be cyclized via a Bischler–Napieralski-type reaction if R is a formyl or an alkoxycarbonyl group.

The syntheses of α- and γ-lycorane start with diene ester **8**, which is readily obtained via **7**[8] on a multigram scale in good yield according to eq 1 (see Experimental Section).



The whole synthesis is outlined in Scheme II. Reduction of diene ester **8** with diisobutylaluminum hydride (DIBAL) gave alcohol **9**, which in a subsequent Mitsunobu reaction[9] was transformed to phthalimide **10**. The latter reaction was very efficient and superior to the procedure previously utilized (via the mesylate).[7] Cleavage of the phthalimide by hydrazine hydrate gave hydrochloride **11**, which on treatment with benzyl chloroformate and $NaHCO_3$ in a two-phase system afforded carbamate **12** in high yield. Palladium-catalyzed intramolecular 1,4-chloroamidation of **12** proceeded smoothly with high regio- and stereoselectivity (>98% selectivity) to give the chlorocarbamate **13** in 95% yield. The regio- and stereochemistry of this and related chloroamidation products have previously been established.[7]

Scheme I



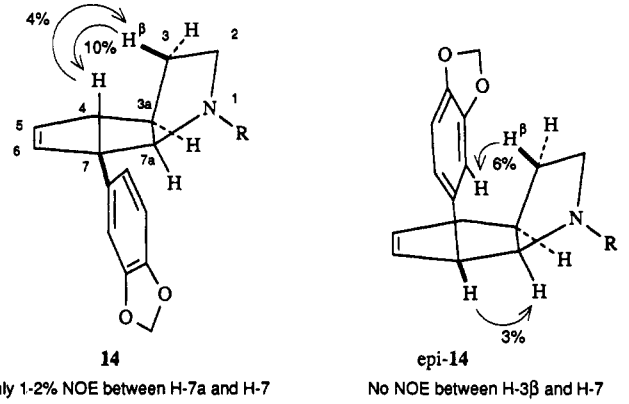
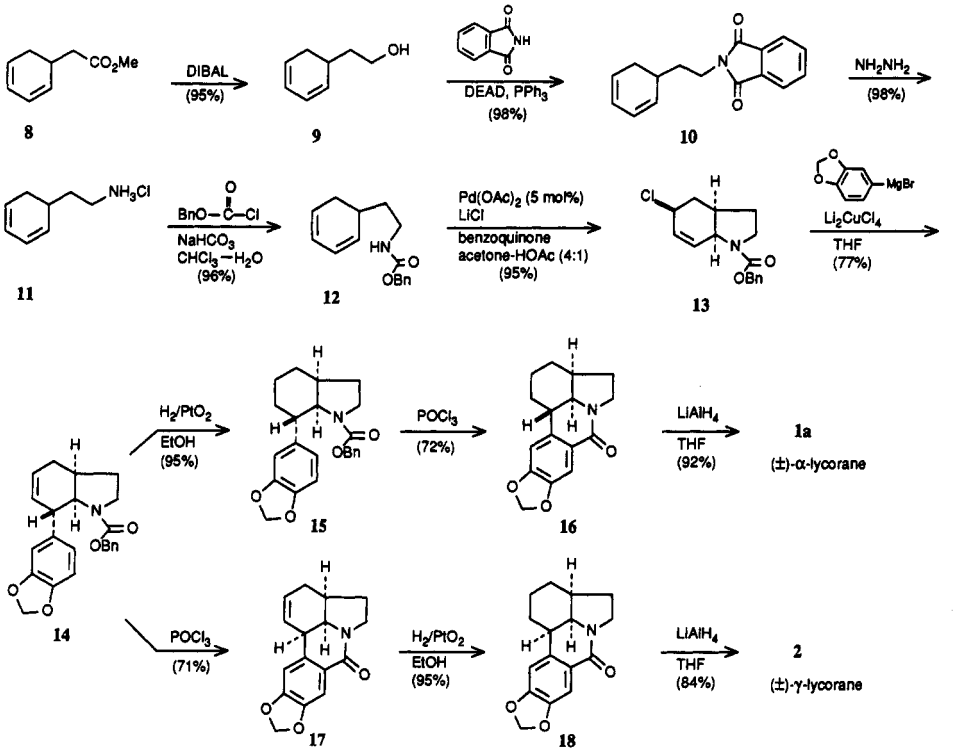


Figure 2. NOE data for **14** and epi-**14** (DMSO-d_6 at 100 °C).

In the next step, it was required that the 3,4-(methylenedioxy)phenyl group be introduced via regioselective γ-attack. Goering has reported that CuCN as catalyst usually leads to a high γ-selectivity in organocopper reactions with allylic compounds.[10] However, attempts to use CuCN as catalyst in the reaction between [3,4-(methylenedioxy)phenyl]magnesium bromide and **13** gave a poor selectivity for γ-attack, and the product from α-attack was always the predominant isomer. We have recently studied the regioselectivity of copper-catalyzed Grignard reactions and identified the factors governing the α/γ-selectivity.[11] In our study, we found that Li_2CuCl_4 in combination with a slow addition of the Grignard reagent favors γ-attack. Indeed, when the latter catalyst was used and [3,4-(methylenedioxy)phenyl]magnesium bromide was added to a solution of **13** and the catalyst over 7 h, the γ-product was the major isomer ($\alpha/\gamma \approx 20/80$), and **14** was isolated in 77% yield. NMR analysis of the γ-product **14** by 2D NOE and NOE difference experiments (Figure 2) made it possible to establish its configuration, which showed that **14** had been formed via an anti-substitution.[12] This is consistent with the stereochemistry usually observed in organocopper reactions.[10b,11b,13,14]

(1) Martin, S. In *The Alkaloids*; Brossi, A. Ed.; Academic Press: New York, 1987; Vol. 30, pp 251-376.
(2) (a) Kotera, K. *Tetrahedron* **1961**, *12*, 240. (b) Ganem, B. *Tetrahedron Lett.* **1971**, 4105. (c) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sato, S.; Numao, N. *J. Org. Chem.* **1977**, *42*, 4272. (d) Hwang, G. J.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1983**, 693.
(3) (a) Wang, C. L. J.; Ripka, W. C.; Confalone, P. N. *Tetrahedron Lett.* **1984**, *41*, 4613. (b) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502. (c) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1074.
(4) Tanaka, H.; Nagai, Y.; Irie, H.; Uyeo, S.; Kuno, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 874.
(5) Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Takagi, S.; Yamaki, M.; Murata, M.; Irie, H.; Tanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1358.
(6) Tanaka, H.; Irie, H.; Baba, S.; Uyeo, S.; Kuno, A.; Ishiguro, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 535.
(7) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683.
(8) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.
(9) Mitsunobu, O. *Synthesis* **1981**, 1.
(10) (a) Tseng, C. C.; Paisly, S. D. Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (b) Tseng, C. C.; Yen, S. J.; Goering, H. L *Ibid* **1986**, *51*, 2892.
(11) (a) Bäckvall, J. E.; Sellén, M. *J. Chem. Soc., Chem. Commun.* **1987**, 827. (b) Bäckvall, J. E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615.
(12) The stereochemistry of the α-product has not yet been securely assigned, although it is most likely the anti-substitution product.
(13) (a) Goering, H. L.; Singleton, V. D.; Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854. (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422. (c) Bäckvall, J. E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396. (d) Ibuka, T.; Tanaka, M.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 967.

Scheme II



The double bond in **14** was selectively hydrogenated without any cleavage of the benzyloxy bond by the use of PtO_2 as catalyst to give **15**.[15] The configuration of **15** was independently established from its ^1H NMR data (see Experimental Section). Subsequent cyclization of **15** to **16** was accomplished via a Bishler–Napieralski-type cyclization.[16] This reaction was run in neat $POCl_3$ at 70 °C, which afforded **16** in 72% yield. Compound **16** was transformed to α-lycorane **1a** via a $LiAlH_4$ reduction.

The initial strategy to reach the epimeric alkaloid γ-lycorane (**2**) involved the use of isomer **5b** (X = OAc) and employing an anti S_N2' organocopper reaction. Attempts to prepare the required γ-substitution product epi-**14** from **5b** (X = OAc, R = CO_2Bn) were discouraging since the α-substitution predominated under all conditions tried. A yield of 77% was realized with an α/γ ratio of 7:1. The γ-isomer (epi-**14**) was isolated and characterized by NMR.[17] The NOE data for **14** and epi-**14** are given in Figure 2. When H-3β was irradiated in these compounds, the NOE on H-7 was 10% for **14** but 0% for epi-**14**. On the other hand, epi-**14** showed an NOE of 6% on the aromatic proton 2′ in this experiment. These data are only consistent with the stereochemistries assigned (Figure 2).

By changing the leaving group and the R group of **5b** it should in principle be possible to increase the relative amount of the γ-substitution product, which on Bischler–Napieralski cyclization would give **17**. However, by chance we found a simple route to **17** via intermediate **14**. It turned out that if the order of hydrogenation and cyclization was reversed, a highly stereoselective isomerization took place in the Bischler–Napieralski cyclization. Thus, treatment of **14** with $POCl_3$ (neat) at 75 °C afforded the cyclized product **17** (>95% isomerically pure) in a yield of 71%.

The transformation of **17** to γ-lycorane **2** in two steps in 82% overall yield was done by first hydrogenating the double bond (PtO_2/H_2) followed by $LiAlH_4$ reduction. The reversed reaction order was avoided since $LiAlH_4$ reduction of **15** gave an additional isomer where the cyclohexene double bond had been moved into conjugation with the aromatic ring (α-anhydrodihydrocaranine[3b]). The present syntheses of α- and γ-lycorane from ester **8** are efficient compared with previous methods. The stereocontrolled palladium-catalyzed intramolecular 1,4-oxidation provides a useful synthon that can be regio- and stereoselectively functionalized via a copper-catalyzed reaction. Thus, **14** is obtained with full stereocontrol. The overall yields of (±)-α- and (±)-γ-lycorane (**1a** and **2**) from **8** are 40 and 36%, respectively. The overall yields of previous syntheses are in the range 2–10%.[2,3]

Experimental Section

NMR spectra were, unless stated otherwise, recorded for $CDCl_3$ solutions with a Varian XL 300 spectrometer, ^1H at 300 MHz and ^{13}C at 75.4 MHz, with tetramethylsilane (δ 0.0, ^1H) or chloroform-d_1 (δ 77.0, ^{13}C) as internal standard. Spectral assignments were made with the aid of two-dimensional proton–proton correlation spectroscopy COSY-45[18a] and 2D NOE (NOESY)[18b] experiments. Selected NOEs were quantified by NOE difference

(14) A syn-directive effect of carbamates has previously been observed in organocopper reactions with allylic compounds: (a) Gallina, C.; Cittani, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035. (b) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715. See also: Greene, A. E.; Coelho, F.; Deprés, J. P.; Brocksom, T. J. *Tetrahedron Lett.* **1988**, *29*, 5661.

(15) The use of Pd/C as catalyst not only led to hydrogenation of the double bond but also caused cleavage of the benzyloxy bond, and 7-[3,4-(methylenedioxy)phenyl]octahydroindole was isolated in an almost quantitative yield.

(16) For a related cyclization leading to a double bond isomer of **15**, see ref 2d.

(17) epi-**14** was isolated by preparative TLC (hexane/EtOAc = 80/20): ^1H NMR (DMSO-d_6, 100 °C) δ 7.35 (m, 5 H, Ph), 6.70–6.53 (m, 3 H, Ar*H*), 6.00 (m, 1 H, H-5), 5.92 (s, 2 H, OCH_2O), 5.83 (m, 1 H, H-6), 5.13 (d, J = 12.6 Hz, 1 H, one of OCH_2Ph), 5.05 (d, J = 12.6 Hz, 1 H, one of OCH_2Ph), 4.17 (d, J = 7.7, 7.8 Hz, 1 H, H-7a), 3.80 (m, 1 H, H-7), 3.14 (ddd, J = 10.8, 10.0, 8.0 Hz, 1 H, H-2α), 2.55, (m, 1 H, H-2β), 2.50 (m, 1 H, H-4α), 2.43 (m, 1 H, H-3a), 2.15 (m, 1 H, H-4β), 1.84 (ddd, J = 12.4, 7.7, 1.7 Hz, 1 H, H-3α), 1.39 (m, 1 H, H-3β).

(18) (a) Bax, A.; Freeman, R.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 164. (b) Wider, G.; Macura, S.; Kumar, A.; Ernst, R. R.; Wüthrich, K. *J. Magn. Reson.* **1984**, *56*, 207. (c) Sanders, J. K. M.; Mersh, J. D. *Progr. NMR Spectrosc.* **1982**, *15*, 353.

spectra.[18c] Samples for NOE measurements were prepared in the appropriate solvent and degassed by flushing with argon for 15 min. NOESY spectra were obtained with a 1-s mixing time and NOE difference spectra with 10–15-s preirradiation. NOE effects were corrected for incomplete saturation of the target proton. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer with a 0.1-mm KBr cell with CCl_4 as solvent. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument in either the electron-impact mode with a potential of 70 eV or in the chemical ionization mode with methane as reagent gas. Microanalyses were performed by Analytische Laboratorien, Engelskirchen, FRG, and Mikrokemi AB, Uppsala, Sweden. Grignard solutions were titrated with 0.80 M benzyl alcohol with 1,10-phenanthroline as indicator. Slow addition of Grignard reagents was performed by the use of a Sage Instruments Model 355 syringe pump. Hydrogenations were performed with a Parr pressure reaction apparatus. Ether and THF were distilled under nitrogen from sodium benzophenone. Toluene and methylene chloride were distilled under nitrogen from calcium hydride. Commercial acetone (99.5%), acetic acid (99.8%), and carbon tetrachloride (99.9%) were used as delivered. Li_2CuCl_4 (0.10 M in THF) was purchased from ALFA products. DIBAL (1 M in hexane), 1,4-benzoquinone, lithium chloride, lithium acetate dihydrate, and 4-bromo-1,2-(methylenedioxy)benzene were purchased from Aldrich and used without further purification. Palladium acetate (47.09% Pd) was purchased from Engelhard, Gloucestershire, England. Merck silica gel 60 (240–400 mesh) was used for column chromatography.

Acronyms for ligands used are as follows: dba, dibenzylideneacetone; dppe, 1,2-bis(diphenylphosphino)ethane.

Dimethyl (*cis*-4-acetoxycyclohex-2-en-1-yl)malonate (7) was prepared according to ref 8.

2-(2,4-Cyclohexadienyl)acetic Acid Methyl Ester (8). Elimination of acetic acid was performed via Pd(0)-catalysis.[19] Compound 7 (47.0 g, 0.173 mol) was dissolved in toluene (700 mL) under nitrogen atmosphere. To the stirred solution were added $Pd(dba)_2$ (2.0 g, 3.47 mmol), dppe (2.8 g, 6.95 mmol), and triisobutylamine (48.3 g, 0.2606 mol). The resulting solution was heated to reflux for 2 h, at which point the reaction was complete according to TLC. The reaction flask was cooled to room temperature, and ether (400 mL) was added. The solution was washed with 2 M HCl (2 × 150 mL), H_2O (150 mL), and brine (100 mL) and dried with $MgSO_4$. The solvent was removed in vacuo and the crude product purified by chromatography (pentane/ether (75:25)) to yield 32.5 g (89%) of a 5:1 mixture of dienes. The two dienes were not separated, the mixture being used directly in the next step.

The Krapcho procedure was used for the decarboxylation.[20] The mixture of dienes (32.5 g, 0.1546 mol) was dissolved in DMSO (450 mL) together with NaCN (37.9 g, 0.773 mol) and H_2O (13.9 g, 0.773 mol). The reaction mixture was heated to 75 °C for 30 h and then cooled to room temperature. Water (400 mL) was added, and the resulting solution was extracted with pentane/ether (90:10, 4 × 200 mL). The combined organic fractions were washed with H_2O (2 × 100 mL) and brine (100 mL) and dried ($MgSO_4$). The solvent was distilled off at atmospheric pressure, and subsequent distillation of the residual oil afforded 16.9 g (72%) of 8 (bp 80 °C (14 mm)) as one single isomer. Spectral data of the product are in accordance with those reported in the literature.[20b]

2-(2,4-Cyclohexadienyl)ethanol (9). A dry, nitrogen-purged reaction flask containing DIBAL (87 mL of 1 M solution in hexane, 87 mmol) and a stir bar was cooled in ice–water. Ester 8 (6.0 g, 39.43 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise during 30 min, and after an additional 1 h, 2 M NaOH (100 mL) was added and the resulting mixture was stirred for 30 min. The mixture was extracted with ether (3 × 50 mL), and the combined organic fractions were washed with H_2O (2 × 25 mL), brine (25 mL), and dried with $MgSO_4$. The solvent was removed under reduced pressure to give a colorless oil that was purfied on a silica gel column with pentane/ether (75:25) as eluent. Evaporation of the eluent yielded 4.65 g (95%) of the alcohol 9: ^1H NMR δ 5.94–5.84 (m, 2 H, olefin), 5.81–5.68 (m, 2 H, olefin), 3.70 (m, 2 H, CH_2O), 2.53–2.39 (m, 1 H), 2.37–2.25 (dddd, J = 16.8, 9.0, 4.6, 1.2 Hz, 1 H), 2.07–1.94 (dddd, J = 16.8, 11.3, 3.7, 1.7 Hz, 1 H), 1.80–1.56 (m, 3 H); ^{13}C NMR δ 130.7, 125.7, 124.0, 124.9, 60.5, 37.1, 29.4, 28.4; IR (neat) 3331, 3034, 2928, 1428, 1056, 1018, 679 cm^{-1}; MS m/z 124 (M^+, 28%), 92 (16), 91 (90), 80 (29), 79 (79), 78 (100), 77 (67). Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 76.8; H, 9.9.

1-(2,4-Cyclohexadienyl)-2-phthalimidoethane (10). 2-(2,4-Cyclohexadienyl)ethanol (9) (4.10 g, 33.02 mmol), triphenylphosphine (10.39 g, 39.6 mmol), and phthalimide (5.83 g, 39.6 mmol) were dissolved in dry THF (100 mL) at 0 °C under nitrogen. To the resulting suspension was added slowly diethyl azadicarboxylate (6.9 g, 39.6 mmol). After the addition was complete, the homogeneous mixture was stirred for 3 h at 0 °C and then diluted with n-hexane (200 mL). The resulting slurry was filtered and the solid residue washed with 3 × 25 mL pentane/ether (90:10). The combined filtrate and washings were evaporated, and the residue was purified by column chromatography on silica gel (pentane/ether (90:10)) to yield 8.2 g (98%) of 10: ^1H NMR δ 7.84 (dd, J = 5.1, 3.0 Hz, 2 H, Ar*H*), 7.71 (dd, J = 5.1, 3.0 Hz, 2 H, Ar*H*), 5.95–5.85 (m, 2 H, olefin), 5.81–5.74 (m, 2 H, olefin), 3.84 (t, J = 7.3 Hz, 2 H, CH_2N), 2.44–2.22 (m, 2 H), 2.12–2.00 (m, 1 H), 1.91–1.77 (m, 2 H); ^{13}C NMR δ 168.4, 133.9, 132.1, 130.0, 125.6, 124.3, 124.0, 123.2, 35.7, 32.9, 30.2, 28.2; IR (CCl_4) 3038, 2940, 1774, 1744, 1717, 1395, 1366 cm^{-1}; MS m/z 253 (M^+, 33.6%), 160 (100), 133 (29.6), 130 (30.6), 106 (39.0), 105 (82.6), 104 (40.4), 91 (36.5), 77 (81.7), 76 (34.8). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.68; H, 6.09.

[2-(2,4-Cyclohexadienyl)ethyl]ammonium Chloride (11). To a solution of 10 (3.0 g, 11.84 mmol) in 95% ethanol (15 mL) was added hydrazine hydrate (80%, 0.74 g, 11.84 mmol). The reaction mixture was then refluxed for 3 h and cooled to 0 °C. The cold solution was acidified to pH 1–2 with ice-cold concd. HCl and filtered. The solid residue was washed with 3 × 5 mL of 95% ethanol. Evaporation of the combined filtrate and washings yielded 1.86 g (98 %) of the hydrochloride 11: ^1H NMR δ 8.45–8.20 (br s, 3 H, NH_3Cl), 5.97–5.84 (m, 2 H, olefin), 5.79–5.71 (m, 1 H, olefin), 5.66 (dd, J = 9.2, 3.9 Hz, 1 H, olefin), 3.04 (m, 2 H, CH_2N), 2.49–2.30 (m, 2 H), 2.07–1.75 (m, 3 H); ^{13}C NMR δ 128.6, 125.5, 125.1, 124.2, 37.6, 31.9, 29.7, 27.8; MS m/z 123 (M^+ – HCl, 3.8%), 122 (8.7), 106 (13.6), 105 (39.5), 92 (10.4), 91 (76.5), 79 (65.3), 78 (100), 77 (90.9). Anal. Calcd for $C_8H_{14}NCl$: C, 60.18; H, 8.84. Found: C, 60.06; H, 8.68.

***O*-Benzyl *N*-[2-(2,4-Cyclohexadienyl)ethyl]carbamate (12).** Compound 11 (1.1 g, 6.89 mmol) was dissolved in chloroform (20 mL). Benzyl chloroformate (1.41 g, 8.27 mmol) and saturated aqueous $NaHCO_3$ (30 mL) were added in portions during 30 min. After another 2 h, the two phases were separated and the aqueous phase was extracted with chloroform (20 mL). The combined organic phases were dried with $MgSO_4$, and the solvent was evaporated. The resulting solid was purified on a column of silica gel (pentane:ether = 75:25) to yield 1.57 g (96%) of 12: ^1H NMR δ 7.37–7.32 (br s, 5 H, Ar*H*), 5.93–5.84 (m, 2 H, olefin), 5.80–5.74 (m, 1 H, olefin), 5.72–5.64 (m, 1 H, olefin), 5.09 (br s, 2 H, benzylic), 4.77–4.67 (br s, 1 H, N*H*), 3.25 (q, J = 5.0 Hz, 2 H, CH_2N), 2.40–2.23 (M, 2 H), 2.06–1.91 (m, 1 H), 1.73–1.49 (m, 2 H); ^{13}C NMR δ 156.3, 136.6, 130.2, 128.5, 128.1, 128.0, 125.6, 124.2, 124.0, 66.6, 38.7, 34.5, 30.2, 28.3; IR (CCl_4) 3460, 3040, 2930, 1730, 1510, 1230, 1130 cm^{-1}; MS m/z 257 (M^+, 0.3%), 166 (9.1), 106 (7.4), 105 (74.9), 92 (15.8), 91 (100), 79 (14.9), 77 (18.3), 65 (11.9). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.66; H, 7.23.

1-(Benzyloxycarbonyl)-*r*-5-chloro-2,3,*c*-3a,4,5,*c*-7a-hexahydroindole (13). LiCl (0.55 g, 12.98 mmol), 1,4-benzoquinone (1.40 g, 12.98 mmol), and $Pd(OAc)_2$ (73 mg, 0.324 mmol) were dissolved in HOAc/acetone (1:4, 30 mL). A solution of carbamate 12 (1.54 g, 6.49 mmol) in acetone (5 mL) was added to the reaction flask over 5 h. The reaction mixture was then stirred for an additional 5 h. Water (40 mL) was added, and the resulting mixture was extracted with ether (3 × 20 mL). The combined ethereal fractions were washed with 2 M NaOH (2 × 15 mL) and brine (10 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue filtered through a short silica gel column,

(19) (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Ibid.* **1979**, 2301. (c) Bäckvall, J. E.; Vågberg, J. O.; Zercher, C.; Genêt, J. P.; Denis, A. *J. Org. Chem.* **1987**, *52*, 5430.

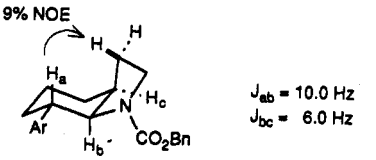
(20) (a) Krapcho, A. P. *Synthesis* **1982**, 805. (b) Pearson, A. J.; Ray, T. *Tetrahedron* **1985**, *41*, 5765.

eluting with pentane/ether (50:50). Evaporation of the solvent yielded 1.80 g (95%) of **13** (>98% *r*-5,*c*-3a,*c*-7a):[7] ^{1}H NMR (two rotamers) δ 7.40–7.28 (m, 5 H, Ar*H*), 6.20 and 5.97 (each d, *J* = 10.2 Hz, rotamers, 1 H, CH=C*H*CHN), 5.87 and 5.84 (each d, *J* = 10.2 Hz, rotamers, 1 H, ClCHC*H*=CH), 5.12 (m, 2 H, benzylic), 4.55 (m, 1 H, ClC*H*CH=CH), 4.18 (m, 1 H, CH=CHC*H*N), 3.58–3.44 (m, 2 H, CH_2N), 2.47 (m, 1 H) 2.32–1.88 (m, 4 H); ^{13}C NMR (two rotamers) δ 154.9, 136.5, 129.3, 128.9, 128.6, 128.4, 128.3, 127.9, 127.8, 66.9, 66.7, 54.4, 53.9, 52.9, 52.4, 45.8, 45.3, 36.0, 35.3, 32.9, 32.6, 29.1, 28.9; IR (CCl_4) 3035, 2954, 1705, 1412, 1354, 1105 cm^{-1}; MS (CI, CH_4) *m*/*z* 292 (M^+ + 1, 13%), 256 (54), 166 (33), 122 (30), 93 (30), 91 (100). Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 66.0; H, 6.5; N, 4.8.

1-(Benzyloxycarbonyl)-*r*-7-[3,4-(methylenedioxy)-phenyl]-2,3,*t*-3a,4,7,*t*-7a-hexahydroindole (14). To a flame-dried, nitrogen-purged reaction flask containing Mg turnings (0.145 g, 6 mmol), dry THF (2 mL), and a magnetic stir bar was slowly added 4-bromo-1,2-(methylenedioxy)benzene (1 g, 5 mmol). The reaction was kept at a moderate reflux by slow addition of dry THF (~13 mL). After addition was complete, the mixture was left for 1 h and the concentration of the resulting Grignard solution was determined to be 0.33 M by titration. Compound **13** (400 mg, 1.37 mmol) was placed in a flame-dried, nitrogen-purged reaction flask together with Li_2CuCl_4 (4.6 mL of 0.10 M in THF, 0.45 mmol) and a magnetic stir bar. The reaction mixture was then cooled to 0 °C and the Grignard solution (7 mL of 0.33 M, 2.31 mmol) was added via a syringe pump during 7 h. After the addition was complete, a solution of 2 M ammonia (3 mL) and aqueous NH_4Cl (7 mL) was added and the resulting two phases were separated. The aqueous phase was extracted with ether (3 × 10 mL), and the combined ethereal fractions were washed with brine (5 mL) and then dried ($MgSO_4$). Evaporation of the solvent and chromatography on silica gel (pentane/ether (75:25)) gave 0.40 g (77 %) of **14**: ^{1}H NMR (DMSO-d_6, 100 °C[21]) δ 7.28 (br s, 3 H, Ar*H*), 7.10 (m, 2 H, Ar*H*) 6.75–6.55 (m, 3 H, Ar*H*), 5.89, 5.87 (two s, 2 H, OCH_2O), 5.80 (m, 1 H, olefin), 5.52 (m, 1 H, olefin), 4.92 (d, *J* = 12.5 Hz, 1 H, benzylic), 4.69 (br d, *J* = 12.5 Hz, 1 H, benzylic), 3.86 (dd, *J* = 6.5, 6.6 Hz, 1 H, C*H*N), 3.46 (m, 2 H, CH_2N) 3.34 (m, 1 H, CH=CHC*H*Ar), 2.45 (m, 1 H, one of H-4) 2.35 (m, 1 H, H-3a), 2.05 (m, 1 H, one of H-4) 1.95 (m, 1 H, H-7α), 1.79 (m, 1 H, H-7β); NOE measurements were performed in DMSO-d_6 at 100 °C; ^{13}C NMR (chloroform-d_1, 60 °C[21]) δ 154.7, 147.1, 145,4, 139.3, 136.5, 129.3, 128.9, 128.6, 127.8, 125.6, 122.1, 109.4, 108.5, 101.0, 67.0, 62.6, 45.4, 44.7, 35.8, 30.6, 27.0; IR (CCl_4) 3030, 2956, 2892, 1699, 1504, 1484, 1443, 1416, 1360, 1329, 1246, 1228, 1114, 1044 cm^{-1}; MS *m*/*z* 377 (M^+, 1.5%), 286 (6.1), 242 (5.4), 174 (77.2), 144 (14.7), 116 (20.1), 115 (16.9), 91 (100), 82 (10.1), 65 (11.8). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14. Found: C, 73.05; H, 6.10.

1-(Benzyloxycarbonyl)-*r*-7-[3,4-(methylenedioxy)-phenyl]-2,3,*t*-3a,4,5,6,7,*t*-7a-octahydroindole (15). In a dry, nitrogen-purged reaction flask were placed **14** (100 mg, 0.265 mmol) and PtO_2 (6.0 mg, 0.265 mmol, 10 mol%). Ethanol (99.5%, 8 mL) was added, and the reaction flask was purged with hydrogen at 1 atm of pressure. The reaction mixture was stirred for 3 h at room temperature and then filtered through Celite. Evaporation and chromatography on silica gel (pentane/ether (75:25)) gave 94 mg (95%) of **15**: ^{1}H NMR (DMSO-d_6, 100 °C[21]) δ 7.33–7.05 (m, 5 H, Ar*H*), 6.73 (s, 1 H, H-2′), 6.66–6.57 (m, 2 H, Ar*H*), 5.81 and 5.87 (two br s, 2 H, OCH_2O), 4.83 (d, *J* = 12.5 Hz, 1 H, one of OCH_2Ph), 4.40 (m, 1 H, one of OCH_2Ph), 3.88 (dd, *J* = 10.0, 6.0 Hz, H-7a), 3.45 (m, 2 H, H-2), 2.45 (m, 1 H, H-7), 2.30 (m, 1 H, H-3a), 2.04 (ddd, *J* = 21, 12, 9 Hz, 1 H, H-3β), 1.84 (m, 1 H, H-3α), 1.75 (m, 1 H, H-4α), 1.65–1.50 (m, 4 H, H-4, H-5); NOE measurements were performed in DMSO-d_6 at 100 °C; ^{13}C NMR (chloroform-d_1, 60 °C[21]), 155.0, 148.4, 146.8, 138.9, 129.3, 127.6, 128.3, 127.5, 121.7, 108.7, 108.1, 100.8, 66.7, 63.0, 46.0, 44.9, 38.9, 32.6, 26.9, 26.7, 21.5; IR (CCl_4) 3034, 2933, 1683, 1504, 1492, 1444, 1424, 1249 cm^{-1}; HRMS calcd 379.1784 ($C_{23}H_{25}NO_4$), found 379.1780.

1,2,3,*r*-3a,4,5,*t*-11b,*c*-11c-Octahydro-9,10-(methylenedioxy)pyrrolo[3,2,1-*de*]phenanthridin-7-one (16). In a dry reaction flask was placed **15** (80 mg, 0.252 mmol), phosphorus oxychloride (1.9 g, 12.6 mmol), and a magnetic stir bar under a dry atmosphere of nitrogen. After 24 h at 70 °C, the reaction flask was cooled to 0 °C and 2 M NaOH (10 mL) was added carefully. The resulting mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a residue that upon silica gel chromatography with EtOAc as eluent gave 49 mg (72 %) of **16** (>99% *trans*-H-11b, H-11c): ^{1}H NMR δ 7.44 (s, 1 H, H-8), 6.64 (s, 1 H, H-11), 5.97 (s, 2 H, OCH_2O), 4.13 (dd, *J* = 7.3, 11.8 Hz, 1 H, one of H-5), 3.47 (dd, *J* = 9.0, 12.9 Hz, 1 H, H-11c), 3.25 (app dt, *J* = 5.6, 11.8 Hz, 1 H, one of H-5), 2.66 (app dt, *J* = 5.0, ~12.4 Hz, 1 H, H-11b), 2.46 (m, 1 H, H-3a), 2.13 (m, 1 H, one of H-1), 2.00 (m, 1 H, one of H-4), 1.85–1.60 (m, 5 H), 1.32 (m, 1 H, one of H-1); ^{13}C δ 163.0, 150.2, 146.2, 138.2, 125.2, 108.3, 103.7, 101.3, 60.8, 45.5, 37.2, 37.0, 30.7, 25.4, 23.1, 20.7; HRMS calcd 271.1208 ($C_{16}H_{17}NO_3$), found 271.1196.



3,*r*-3a,4,5,*c*-11b,*c*-11c-Hexahydro-9,10-(methylenedioxy)-pyrrolo[3,2,1-*de*]phenanthridin-7-one (17). In a dry reaction flask was placed **14** (300 mg, 7.80 mmol), phosphorus oxychloride (6.1 g, 39.7 mmol), and a magnetic stir bar under a dry atmosphere of nitrogen. After 24 h at 75 °C, the reaction flask was cooled to 0 °C and 2 M NaOH (60 mL) was added carefully. The resulting mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a residue that upon silica gel chromatography with EtOAc as eluent gave 152 mg (71 %) of **17** (>95% *cis*-H-11b, H-11c):[22] ^{1}H NMR δ 7.54 (s, 1 H, H-8), 6.71 (s, 1 H, H-11), 6.00 (two d, Δδ = 0.01 ppm, *J* = 1.3 Hz, 2 H, OCH_2O), 5.71–5.64 (m, J_{AB} = 10 Hz, 1 H, H-2), 5.40–5.33 (m, J_{AB} = 10 Hz, 1 H, H-1), 4.03 (dd, *J* = 6.0, 5.0 Hz, 1 H, H-11c), 3.70 (d, *J* = 9.7 Hz, 1 H, one of H-5), 3.68 (dd, *J* = 9.7, 1.0 Hz, 1 H, one of H-5), 3.60 (m, 1 H, H-11b), 2.55–2.45 (m, 1 H, H-3a), 2.31–2.17 (m, 1 H), 2.06–1.93 (m, 1 H), 1.88–1.69 (m, 2 H); ^{13}C NMR δ 161.9, 150.6, 147.0, 135.6, 125.8, 125.2, 123.0, 107.5, 107.3, 101.5, 56.5, 42.3, 36.9, 34.0, 29.8, 25.0; IR (CCl_4) 3029, 2943, 1653, 1615, 1479, 1461, 1414, 1268, 1243, 1043 cm^{-1}; MS *m*/*z* 269 (M^+, 77.2%), 268 (30.1), 228 (23.2), 189 (100), 188 (17.7), 115 (41.5), 86 (16.9), 84 (23.0). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.25; H, 5.50.

1,2,3,*r*-3a,4,5,*c*-11b,*c*-11c-Octahydro-9,10-(methylenedioxy)pyrrolo[3,2,1-*de*]phenanthridin-7-one (18). In a pressure-proof vessel **17** (100 mg, 0.371 mmol) was dissolved in 99.9% ethanol (5 mL). PtO_2 (0.42 mg, 0.019 mmol) was added, and the mixture was shaken in a Parr apparatus at a hydrogen pressure of 6 kg/cm^2. After 3 h, the hydrogenation was complete and the mixture was filtered through Celite. The filter cake was washed with 2 × 2 mL of ethanol, and the combined filtrate and washings were concentrated in vacuo. The residue was chromatographed on a silica gel column with EtOAc as eluent to give 95 mg (95 %) of **18** (> 99% *cis*-H-11b, H-11c): ^{1}H NMR δ 7.54 (s, 1 H, H-8), 6.63 (s, 1 H, H-11), 5.99 (two d, Δδ = 0.01 ppm, *J* = 1.4 Hz, 2 H, OCH_2O), 3.86 (dd, *J* = 4.7, 4.7 Hz, 1 H, H-11c), 3.77 (dd, *J* = 12, 10 Hz, 1 H, one of H-5), 3.69–3.58 (m, 1 H, one of H-5), 2.85–2.75 (ddd, *J* = 12.0, 5.0, 5.0 Hz, 1 H, H-11b), 2.34–2.23 (m, 1 H), 2.02–1.87 (m, 1 H), 1.80–1.59 (m, 4 H), 1.40–1.03 (m, 3 H); ^{13}C NMR δ 162.7, 150.2, 146.7, 138.5, 123.0, 107.7, 107.0, 101.4, 58.0, 42.7, 39.2, 38.2, 30.0, 29.0, 26.3, 23.8; IR (CCl_4) 2935, 1652, 1614, 1478, 1462, 1410, 1355, 1248, 1042 cm^{-1}; MS *m*/*z* 271 (M^+, 93%), 270 (100), 254 (9.8), 242 (15), 229 (14.3), 228 (30.4), 203 (27.3), 189 (24.6), 172 (12.9). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.61; H, 6.19.

(±)-α-Lycorane (1a). To a flame-dried, nitrogen-purged reaction flask containing dry THF (5 mL), $LiAlH_4$ (28 mg, 0.737

(21) In **14** and **15**, two rotamers were present because of hindered rotation around the carbonyl carbon–nitrogen bond. In order to simplify the NMR spectra, they were recorded at elevated temperature.

(22) For an ^{1}H NMR spectrum of the *trans*-11b,11c isomer of **17**, see ref 5. The stereochemistry assigned for **17** was confirmed by NOE experiments ($CDCl_3$, 23 °C). Irradiation of H-11c gave a 6.8% NOE on H-11b and a 6.1% NOE on H-3a.

mmol), and a magnetic stir bar was added 16 (40 mg, 0.147 mmol). The reaction mixture was then heated to 70 °C for 5 h, at which point the reduction was complete according to TLC. The reaction mixture was cooled to room temperature, and H_2O (0.15 mL) was added. The resulting slurry was filtered off and the filtrate evaporated to give a residue that upon silica gel chromatography with $EtOAc/Et_3N$ (90:10) as eluent afforded 35 mg (92 %) of (±)-α-lycorane (1a).[23a] The spectral data are in agreement with those reported in the literature:[3a] ^1H NMR δ 6.70 (s, 1 H, H-12), 6.59 (s, 1 H, H-8), 5.89 (s, 2 H, H-10), 4.10 (d, J = 15.1 Hz, 1 H, one of H-7), 3.76 (d, J = 15.1 Hz, one of H-7), 3.12 (app dt, J = 7.9, 9.4 Hz, 1 H, one of H-5), 2.82 (app dt, J = 3.4, 9.4 Hz, 1 H, one of H-5), 2.50–2.32 (m, 3 H), 2.22 (app dq, J = 3.5, 13.0 Hz, 1 H, one of H-1), 1.94–1.55 (m, 6 H), 1.17 (m, 1 H, one of H-1); ^{13}C δ 146.0, 145.2, 134.9, 128.8, 106.8, 104.4, 100.6, 64.4, 54.6, 54.1, 36.9, 33.8, 27.8, 26.1, 24.8, 20.8; IR (CCl_4) 2933, 1503, 1482, 1456, 1364, 1261, 1242 cm^{-1}.

(±)-γ-Lycorane (2). To a flame-dried, nitrogen-purged reaction flask containing dry THF (5 mL), $LiAlH_4$ (70 mg, 1.84 mmol), and a magnetic stir bar was added 18 (100 mg, 0.369 mmol). The reaction mixture was then heated to 65 °C for 3 h, at which point the reduction was complete according to TLC. Workup as above afforded 80 mg (84 %) of (±)-γ-lycorane (2).[23b] The spectral data are in agreement with those reported in the literature:[3b] ^1H NMR δ 6.61 (s, 1 H, H-12), 6.49 (s, 1 H, H-8), 5.88 (two d, J = 1.4 Hz, 2 H, OCH_2O), 4.00 (d, J = 14.2 Hz, 1 H, one of H-7), 3.37 (ddd, J = 9.0, 9.0, 3.5 Hz, 1 H, one of H-5), 3.20 (d, J = 14.2 Hz, 1 H, one of H-7), 2.73 (ddd, J = 11.5, 5.0 Hz, 1 H, H-12b), 2.36 (dd, J = 5.0, 4.0 Hz, 1 H, H-12c), 2.23–2.08 (m, 2 H), 2.07–1.94 (m, 1 H), 1.80–1.58 (m, 3 H), 1.54–1.23 (m, 4 H); ^{13}C NMR δ 146.0, 145.6, 133.1, 127.3, 108.3, 106.2, 100.6, 62.8, 57.1, 53.7, 39.4, 37.3, 31.7, 30.4, 29.2, 25.2; IR (CCl_4) 2929, 1505, 1482, 1319, 1244, 1231, 1044 cm^{-1}; MS m/z 257 (M^+, 60.2%), 256 (100), 162 (9.1), 128 (7.5), 115 (6.3), 77 (8.2).

Acknowledgment. Financial support from the Swedish Board of Technical Development and the Swedish Natural Science Research Council is gratefully acknowledged. We thank Prof. L. Kenne (University of Stockholm) for running high-resolution MS.

Registry No. (±)-1a, 63814-02-8; (±)-2, 63814-03-9; (±)-7, 132541-04-9; (±)-8, 132541-05-0; (±)-9, 132541-06-1; (±)-10, 132541-07-2; (±)-11, 132541-08-3; (±)-12, 132541-09-4; (±)-13, 132541-10-7; (±)-14, 132541-11-8; (±)-15, 132541-12-9; (±)-16, 66816-53-3; (±)-17, 132618-67-8; (±)-18, 132619-48-8; 4-bromo-1,2-(methylenedioxy)benzene, 2635-13-4.

(23) (a) Nothing of the isomeric γ-lycorane (2)[3b] could be detected in the ^1H NMR spectrum (<0.2%). (b) Nothing of the isomeric α-lycorane (1a)[3a] could be detected in the ^1H NMR spectrum (<0.2%).

Synthesis of 2′,3′-Dideoxy-3′-*C*-hydroxymethyl Nucleosides as Potential Inhibitors of HIV

Lars Svansson and Ingemar Kvarnström

Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden

Björn Classon and Bertil Samuelsson*,†

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

Received October 5, 1990

A novel synthesis of 2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides is described. (2*S*,3*R*)-3-[[(4-Bromobenzyl)oxy]methyl]oxirane-2-methanol (1) was regioselectively alkylated using allylmagnesium bromide. The allyl double bond was oxidatively cleaved, and the product was treated with acidic methanol to give the requisite methyl furanoside derivative 5, which was subsequently condensed with purine and pyrimidine bases. Deblocking and separation of the anomers by chromatography afforded the α- and β-nucleoside analogues.

Introduction

In the early 1980s a new disease, termed acquired immuno deficiency syndrome (AIDS) was discovered which since then has spread so that it now has become a serious epidemic. The causative agent of AIDS is a retrovirus referred to as HIV (human immunodeficiency virus). AIDS is characterized by a profound immunodeficiency which is due to low numbers of a subset of lymphocyte-T-helper cells, which are targeted for the HIV infection, and which makes AIDS patients highly susceptible to a variety of opportunistic infections of bacterial, fungal, protozoal, and viral origin.[1,2] 3′-Azido-3′-deoxythymidine (AZT, zidovudine)[3] is the first and thus far the only drug that has been approved for the treatment of AIDS. The widespread use of zidovudine has raised some concern that viral resistance towards the drug might develop. Recently it was shown that long term use of zidovudine resulted in reduced sensitivity to the drug in isolates of many patients examined,[4] and although the clinical consequences of these findings are unclear, the use of other drugs alone or in combination therapy would considerably reduce this risk. The mechanism for anti-HIV activity of zidovudine is believed to involve activation by cellular kinases to give the corresponding triphosphate which acts as a substrate/inhibitor for viral reversed transcriptase (RT) causing premature termination of chain elongation. There are many other nucleoside analogues in preclinical and clinical development such as 2′,3′-dideoxycytidine,[5] 2′,3′-

† Address also: AB Hässle, S-431 83 Mölndal, Sweden.

(1) Sandström, E. *Drugs* **1989**, *38*, 417.

(2) De Clercq, E.; Walker, R. T. *Antiviral Drug Development. A Multidisciplinary Approach*; Plenum Press: New York, 1988.

(3) Fischl, M. A.; Richman, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King, D. *New Engl. J. Med.* **1987**, *317*, 185. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. L.; Bolognesi, D. P.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.

(4) Larder, B. A.; Sharon, D. K. *Science* **1989**, *246*, 1155.

(5) Merigan, T. C.; Skowron, G.; Bozzette, S. A.; Richman, D.; Uttamchandani, R.; Fischl, M.; Schooley, R.; Hirsch, M.; Soo, W.; Pettinelli, C.; Schaumburg, H. *Ann. Int. Med.* **1989**, *110*, 189. Yarchoan, R.; Thomas, R. V.; Allain, J.-P.; McAtee, N.; Dubinsky, R.; Mitsuya, H.; Lawley, T. J.; Safai, B.; Myers, C. E.; Perno, C. F.; Klecker, R. W.; Wills, R. J.; Fischl, M. A.; McNeely, M. C.; Pluda, J. M.; Leuther, M.; Collins, J. M.; Broder, S. *Lancet* **1988**, Jan. 16, 76.

0022-3263/91/1956-2993$02.50/0