trogen. After the flask cooled, 45 mg (8.5×10^{-2} mmol) of $NiCl_2$(dppe) (4) and 1.0 g (7.6 mmol) of 3-bromofuran (**1b**)[22b] [2-bromofuran(**1a**)[22a] was prepared by decarboxylation of 5-bromofuroic acid[22b] by using the procedure of Burness[22c] for the synthesis of 3-methylfuran] were added to 75 mL of dry ether. The flask was fitted with a neoprene septum, and *m*-tolylmagnesium bromide (1.2 equiv) was added under positive nitrogen pressure via syringe. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 16 h and then poured onto 50 mL of aqueous ammonium chloride. The organic layer was removed and the aqueous layer extracted several times with ether. The combined and dried ($MgSO_4$) ether layers were concentrated to an oil which was distilled to yield **3d**: 1.1 g (7.06 mmol, 93%); IR (film) 3040, 2920, 1610, 1510, 1170, 1055, 1020, 870, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (m, 1 H), 7.5–7.0 (m, 5 H), 6.65 (m, 1 H), 2.4 (s, 3 H); mass spectrum, *m/e* 158 (parent peak).

Anal. Calcd for $C_{11}H_{10}O$: C, 83.52; H, 6.37. Found: C, 83.26; H, 6.20.

2-(3,4-Dimethylphenyl)furan (3c) was prepared as described above: IR (film) 2925, 1480, 1450, 1010, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–6.9 (m, 4 H), 6.55 (q, 2 H), 2.32 (s, 6 H); high-resolution mass spectrum, *m/e* 172.090 (M^+; $C_{12}H_{12}O$ requires 172.089).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.19; H, 7.06.

2-(4-Ethylphenyl)furan (3e) was prepared as described above: IR (film) 2970, 1520, 1485, 1005, 835, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (m, 1 H), 7.41 (q, 4 H), 6.55 (q, 2 H), 2.7 (q, 2 H), 1.25 (t, 3 H); mass spectrum, *m/e* 172 (parent peak).

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.56; H, 7.38.

3-(*n*-Propyl)furan (3h) was prepared as described above: IR (film) 2950, 1500, 1160, 1020, 870, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (d, 2 H), 6.3 (s, 1 H), 2.4 (t, 2 H), 1.5 (sextet, 2 H), 0.9 (t, 3 H); high-resolution mass spectrum, *m/e* 110.072 (M^+; $C_7H_{10}O$ requires 110.073).

2-Phenyl-5-*n*-butylfuran (3i) was prepared as described above but by using **1c**:[23] IR (film) 2620, 1540, 910, 750, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (m, 5 H), 6.55 (d, 1 H), 6.05 (d, 1 H), 2.7 (t, 2 H), 1.55 (m, 4 H), 1.0 (m, 3 H); high-resolution mass spectrum, *m/e* 200.119 (M^+; $C_{14}H_{16}O$ requires 200.120).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.17; H, 8.02.

Registry No. **1a**, 584-12-3; **1b**, 22037-28-1; **1c**, 80866-21-3; **3a**, 17113-33-6; **3b**, 17113-32-5; **3c**, 80866-22-4; **3d**, 80866-23-5; **3e**, 80866-24-6; **3f**, 13679-41-9; **3g**, 80866-25-7; **3h**, 42908-61-2; **3i**, 80866-26-8; **4**, 38754-20-0.

(22) (a) Shepard, A. F.; Winslow, N. R.; Johnson, J. R. *J. Am. Chem. Soc.* **1930**, *52*, 2083. (b) Available from Aldrich Chem. Co. (c) Burness, D. M. "Organic Synthesis"; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 628.

(23) Furan **1c** as prepared by using the procedure of Cohen.[19a] NMR, IR, and mass spectral data are satisfactory.

A Simple Stereospecific Synthesis of 14-Hydroxymorphinans

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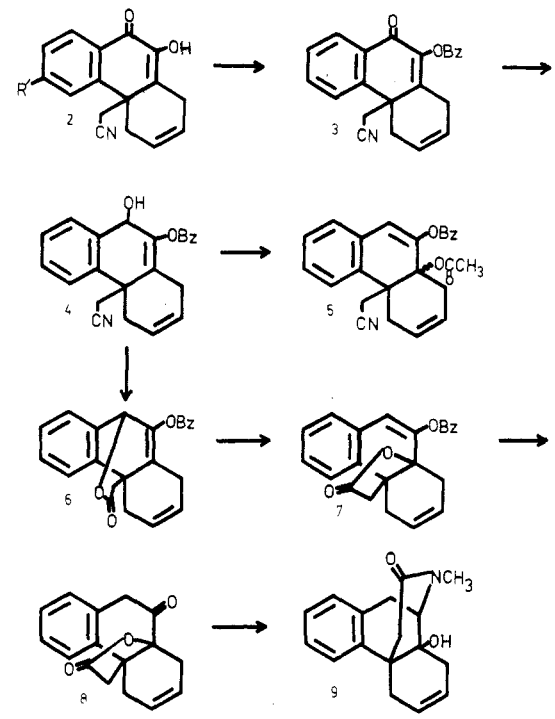
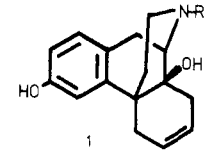
The 3,14-dihydroxymorphinan N-substituted derivatives (**1**, R = allyl, cyclopropylmethyl, cyclobutylmethyl) have interesting pharmacological properties.[1] We report herein a new method for the synthesis of the 14-hydroxymorphinan system that is short, efficient, and adaptable to a wide variety of derivatives.

Scheme I





In this synthesis the (cyanomethyl)hydrophenanthrene system **2** (R = H) of years past[2] once again serves as starting material for a morphinan, this time with a hydroxyl group stereospecifically placed in the 14-position. The method employed is first to fix the oxidation state at C_9 by alkylation to give the enol ether **3**, which is then reduced (sodium borohydride, methanol) to the benzylic alcohol **4** (Scheme I). This benzylic alcohol or its acetate can be rearranged in very high yield (*p*-toluenesulfonic acid (PTSA), acetic acid, acetic anhydride) to a mixture of the C_{14} acetoxy epimers of **5**. The conditions for this rearrangement are similar to those reported by Babler for the rearrangement of allylic alcohols and acetates under acidic conditions.[3] When the lactone **6**, produced by hydrolysis of the nitrile **4**, is similarly rearranged, the lactone **7** of defined stereochemistry is obtained in 80% overall yield from **3**.[4]

Hydrolysis of the enol ether of **7** (HCl, acetic acid, H_2O) gives the ketone **8**. Reductive amination of **8** ($NaCNBH_3$, CH_3NH_2) yields the morphinan lactone **9** (40% overall from **7**). Consistent with this structure, the morphinan lactam is reduced with lithium aluminum hydride in high

(1) Present methods of synthesis: (a) from Theibaine, Y. K. Sawa and H. Tadu, *Tetrahedron*, **24**, 6185 (1968); (b) I. Monkovic, H. Wong, T. T. Conway, Y. G. Perron, I. J. Pachter, and B. Belleau, *J. Am. Chem. Soc.*, **95**, 7910 (1973); (c) I. Monkovic, C. Bachand, and H. Wong, *ibid.*, **100**, 4609 (1978).

(2) M. Gates, R. B. Woodward, W. Newhall, and R. Kunzi, *J. Am. Chem. Soc.*, **72**, 1141 (1950), and other papers in this series.

(3) J. Babler, *Tetrahedron Lett.* **4**, 351 (1974).

(4) The generality of this rearrangement will be reported elsewhere.

0022-3263/82/1947-1592$01.25/0

yield to the corresponding tertiary amine; overall yields of 30% are obtained.

The use of amines other than methylamine can presumably be used to give other N-substituents[5] such as allyl, cyclopropylmethyl, and cyclobutylmethyl. A double bond has also been carried through the synthesis in ring C and through it also further functionalization should be possible in this ring.

Experimental Section

General Methods. All reactions were performed under nitrogen with magnetic stirring unless otherwise indicated. Melting points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 137 sodium chloride spectrophotometer. NMR spectra were obtained with a JEOL MH-100 nuclear magnetic resonance spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Du Pont 21-490B mass spectrometer. Thin-layer chromatography was performed with 0.25-mm layers of silica gel from Analtech Corp. Elemental analyses were performed by Chemalytics, Inc.

10-Oxo-9-benzoxy-13-(cyanomethyl)-5,8,13,14-tetrahydrophenanthrene (3). Sodium hydride (0.8 g, 57%) was washed with hexane and 200 mL of distilled tetrahydrofuran (from $LiAlH_4$) was added under nitrogen. Next 9,10-dioxo-13-(cyanomethyl)-5,8,9,10,13,14-hexahydrophenanthrene (**2**; 3.4 g, 14 mmol) was added. The resulting orange solution was stirred under nitrogen 45 min and then 4 mL of benzyl bromide (5.75 g, 34 mmol) was added and the reaction mixture was stirred for 48 h. At the end of this time no orange color remained and a colorless precipitate was formed. The reaction mixture was poured into an equal volume of ice water containing ammonium chloride and extracted with methylene chloride (3 × 50 mL), and the combined organic fractions were washed with brine, dried (Na_2SO_4), and concentrated to yield after two recrystallizations from toluene 3.20 g (70%) of the colorless solid benzyl ether with mp 160.5–162.5 °C. Further recrystallization gave an analytiucal sample with the following: mp 163–163.5 °C; NMR ($CDCl_3$) δ 1.80–330 (m, 5.2), 4.90–5.25 (dd, 2.0), 5.76 (br, s 2), 6.00 (s, 1), 7.2–7.8 (m, 2.0), 8.29–8.35 (2 s, 2.0); IR ($CHCl_3$), 1625, 1660, 1690 cm^{-1}; UV (EtOH) λ_{max} 257.2 (ϵ 102 000), 285.2 (ϵ 5800); mass spectrum (20 eV), m/e 341 (parent). Anal. Calcd for $C_{23}H_{19}NO$: C, 80.91; H, 5.61. Found: C, 80.83; H, 5.84.

10-Hydroxy-9-benzoxy-13-(cyanomethyl)-5,8,13,14-tetrahydrophenanthrene (4). Sodium borohydride (1.21 g, excess) was added to a solution of 10-oxo-9-benzoxy-13-(cyanomethyl)-5,8,13,14-tetrahydrophenanthrene (7.75 g, 22.7 mmol) in 100 mL of methanol. The reaction mixture was stirred for 48 h and a monitor of the reaction at this time showed the reaction to be complete (single strong absorption at 1680 cm^{-1}). The reaction mixture was then evaporated to dryness at reduced pressure. Dilute acetic acid (60 mL) was added to the resulting solid; this mixture was then extracted with methylene chloride (3 × 60 mL), and the combined organic layers were washed with brine (2 × 20 mL), dried ($NaSO_4$), and concentrated under reduced pressure to give a 7.7-g sample (99%), which was used in the following reaction without further purificaiton. This crude sample had a melting point of 122–130 °C. Recrystallization from ethanol gave an analytical sample: mp 131.5–133 °C; NMR ($CDCl_3$) δ 1.65–3.15 (m, 6), 4.70–5.22 (m, 3.7), 5.61–5.92 (m, 2), 7.00–7.70 (m, 10); IR ($CHCl_3$) 1675, 3400–3600 cm^{-1}; UV (EtOH) λ_{max} 257 nm (ϵ 69 500); mass spectrum (20 eV), m/e 343 (parent). Anal. Calcd for $C_{23}H_{21}NO$: C, 79.97; H, 6.71; N, 4.05. Found: C, 80.33; H, 6.60; N, 3.88.

Rearranged Lactone 7. To 1.81 g (5.3 mmol) of **4** (R = CH_2Ph) in 126 mL of methanol at 110 °C was added 18 g of potassium hydroxide in 54 mL of water. The reaction mixture was heated under reflux (bath temperature, 110 °C) for 48 h. The reaction mixture was cooled, 50 mL of 60% acetic acid was added, and the mixture was concentrated under reduced pressure; the residue was extracted with chloroform (3 × 60 mL); the combined organic fractions were washed with brine, dried (Na_2SO_4), and concentrated to give a mixture containing lactone **6**. This reaction mixture was then diluted with 40 mL of acetic acid, 10 mg of PTSA, and 10 mL of acetic anhydride. The reaction was sealed and the mixture was allowed to stir for 13 h. It was then cooled to 0 °C and 20 mL of water was added. This clear solution was stirred at 0 °C for 3.5 h. By this time crystals had appeared. The reaction mixture was diluted with water to twice its volume, cooled, and filtered to give 1.5 g (87%; further dilution gave 57 mg more) of the rearranged lactone. Recrystallization from methanol give white crystals: mp 126.5–127 °C; NMR ($CDCl_3$) δ 1.95–3.06 (m, 6), 5.00–5.02 (2 s, 3), 5.52 (s, 1), 5.90 (s, 2), 6.90–7.50 (m, 9); IR ($CHCl_3$) 1650, 1780 cm^{-1}; UV (EtOH) λ_{max} 211 (ϵ 2300), 223 (ϵ 22 000), 272 (ϵ 12 600); mass spectrum (20 eV), m/e 344 (parent). Anal. Calcd for $C_{23}H_{20}O_3$: C, 80.23; H, 5.85. Found: C, 80.56; H, 5.91.

Hydrolysis of the Enol Benzyl Ether to Ketone 8. A mixture containing the enol benzyl ether **6** (226 mg, 0.66 mmol), 4.0 mL of acetic acid, and 0.8 mL of water was heated to 74 °C and then 1.8 mL of concentrated hydrochloric acid was added. The solid dissolved and after 6 min the reaction mixture was cooled in ice and diluted with water containing ammonium hydroxide. A solid separated and was filtered, washed first with 3 mL of water and then with 3 mL of hexane, and allowed to dry. This crude ketone (mp 120–129 °C, 162.5 mg (97%) was used without further purification, although purer samples were obtained by recrystallization from THF–hexane: NMR ($CDCl_3$) δ 2.10–2.80 (m, 5), 3.66 (d, 1, J_{gem} = 17 Hz), 4.89 (s, 1), 5.82–6.00 (m, 2), 7.00–7.80 (m, 4); IR ($CHCl_3$) 1790, 1749 cm^{-1}; UV (EtOH λ_{max} 269 (br adsorption); ethanolic NaOH gives another spectrum with λ_{max} (ϵ 6830) and 305 (ϵ 7200); mass spectrum, m/e 254 (parent). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 74.82; H, 5.64.

Reductive Amination to Morphinan Amide 9. A mixture of methylamine hydrochloride (960 mg, 14 mmol) and sodium acetate (780 mg, 9.5 mmol) in 7.0 mL of methanol was stirred at 0 °C; the keto lactone **8** (0.266 g, 1.0 mmol) was added and the reaction mixture was stirred another 30 min at 0 °C. Sodium cyanoborohydride (1.6 g, 27 mmol) in 10 mL of methanol was then added over 30 min. The reaction mixture was stirred under nitrogen for 28 h and then potassium hydroxide (1.7 g, 30 mmol) was added. Fifteen minutes later all the potassium hydroxide had dissolved. Acetic acid (3.0 mL) was added and the reaction mixture was stirred for 16 h and then filtered. The resulting solid was washed with several portions of methanol, and the combined organic fractions were concentrated to one-fourth of their original volume. To this concentrate was added 70 mL of brine and the resulting mixture was extracted with ethyl acetate (3 × 70 mL), dried over sodium sulfate, and concentrated from toluene to give 1.44 g of an oil.

This oil was dissolved in 50 mL of methanol and 150 mg of the sodium borohydride was added (vigorous reaction). The resulting solution was stirred for 24 h. The reaction mixture was then evacuated to dryness and 25 mL of 10% hydrochloric acid was added. The resulting mixture was extracted with ethyl acetate (3 × 75 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to give 0.5124 g of a colorless oil. The IR spectrum of this oil showed the amide absorption at 1635^{-1} cm to be the largest carbonyl absorption. The product mixture was chromatographed on silica gel, using ethyl acetate, to give a product fraction (R_f 0.21) of 99 mg (37%). Crystallization from a drop of ethyl acetate gave the solid amide, mp 191–193.5 °C. An analytical sample was obtained by recrystallization from ethyl acetate: mp 193–194 °C NMR ($CDCl_3$) δ 2.10–3.20 (m with s at 2.90, 10), 3.60–3.80 (m, 1), 4.06 (br s, 2), 5.90 (s, 2), 6.80–7.10 (m, 4); IR 3700–3200, 1635 cm^{-1}; mass spectrum, m/e 269 (parent). Anal. Calcd for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 76.06; H, 7.04.

Reduction to the Morphinan. Lithium aluminum hydride (1 mL of a 1 N ether solution) was added under nitrogen to morphinan amide **8** (50 mg) in 10 mL of ether, and the reaction mixture was refluxed for 48 h. Another 0.5 mL of the lithium aluminum hydride solution was added and the reaction mixture was refluxed for another 12 h. The reaction mixture was then cooled and 1 mL of ethyl acetate was added, followed by 3 mL of 10% hydrochloric acid. The mixture was filtered, and the layers were separated. The ether layer was washed with hydrochloric acid (2 × 25 mL). The combined acid layers were then cooled in an ice bath and made basic by the addition of solid potassium

(5) C. F. Lane, *Synthesis*, 135–144 (1975).

hydroxide. The resulting colorless precipitate was extracted with methylene chloride (3 × 25 mL), dried (Na_2SO_4), and evaporated to dryness to give the *N*-methyl-14-hydroxymorphinan as a colorless solid in high yield (>90%). Recrystallization from ethanol gave material with the following: mp 161.5–163 °C; NMR ($CDCl_3$) 1.8–3.8 (m with s at 2.3, 15), 5.70–5.90 (m, 2), 6.90–7.20 (m, 4.8); IR 3700–3350 cm^{-1}; UV, only end absorption with a shoulder at 215 nm; mass spectrum, *m/e* 255 (parent).

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Registry No. 2 (R = H), 80879-09-0; **3**, 80879-10-3; **4**, 80879-11-4; **5**, 80879-12-5; **6**, 80879-13-6; **7**, 80879-14-7; **8**, 80879-15-8; **9**, 80879-16-9; *N*-methyl-14-hydroxymorphinan, 80879-17-0.

Crystal Structure and Stereochemistry of Amblyodiol[1]

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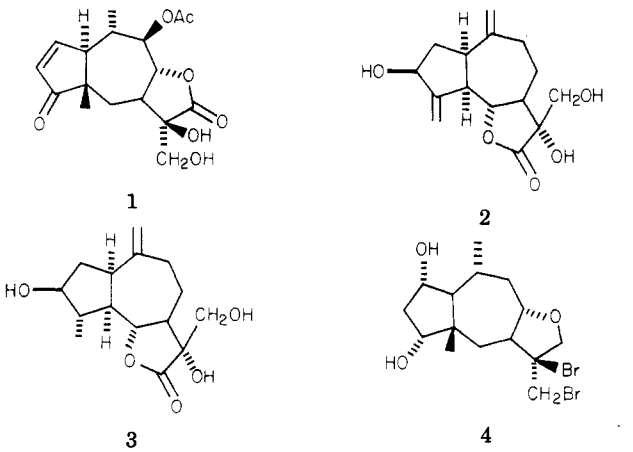
The helenanolide amblyodiol from *Gaillardia amblyodon*[2] is one of a small group of sesquiterpene lactones in which the ubiquitous α-methylene γ-lactone function is oxidized to an 11,13-diol.[3] The stereochemistry of such diol functions is difficult to determine unambiguously by chemical and spectroscopic methods. In the case of amblyodiol the relative and absolute stereochemistry shown in formula 1 (Chart I) for C-1, C-5, C-6, C-7, C-8, C-9, and C-10 has been established,[2] but attempts to use various CD methods[4] for solving the stereochemistry at C-11 failed,[2] and the results of solvent shift studies remained somewhat questionable.

To settle the stereochemistry at C-11 and to continue our study of the conformations of different types of sesquiterpene lactones, we undertook an X-ray analysis of amblyodiol. Crystal data for the substance are listed in the Experimental Section. Figure 1a is a stereoscopic drawing of the molecule which shows that the C-11 hydroxyl group is β and that our earlier[2] stereochemical assignments for the other asymmetric centers were correct. Figure 1 also represents the absolute configuration because of the negative Cotton effect due to the cyclopentenone chromophore.

Chart I



1 2 3 4

Table V. Torsion Angles (in Degrees) in 1 with Standard Deviations in Parentheses

C(1)-C(5)-C(6)-C(7)	35.8 (8)
C(5)-C(6)-C(7)-C(8)	38.8 (7)
C(6)-C(7)-C(8)-C(9)	−84.4 (6)
C(7)-C(8)-C(0)-C(10)	66.6 (8)
C(8)-C(9)-C(10)-C(1)	−47.8 (8)
C(0)-C(10)-C(1)-C(5)	69.2 (8)
C(10)-C(1)-C(5)-C(6)	−86.7 (8)
O(2)-C(8)-C(7)-C(11)	32.6 (5)
C(8)-C(7)-C(11)-C(12)	−33.2 (6)
C(7)-C(11)-C(12)-O(2)	23.2 (6)
C(11)-C(12)-O(2)-C(8)	−2.5 (6)
C(12)-O(2)-C(8)-C(7)	−19.5 (5)
C(1)-C(2)-C(3)-C(4)	1.6 (11)
C(2)-C(3)-C(4)-C(5)	13.8 (10)
C(3)-C(4)-C(5)-C(1)	−22.2 (8)
C(4)-C(5)-C(1)-C(2)	21.9 (8)
C(5)-C(1)-C(2)-C(3)	−15.5 (10)

Tables I–IV listing final atomic and final anistropic thermal parameters, bond lengths, and bond angles are available as supplementary material. Table V lists selected to torsion angles. As is apparent from these and also from Figure 1a and the framework model of Figure 1b, the cycloheptane ring is a twist chair whose twofold axis of symmetry passes through C-6 and the midpoint of the C-9,C-10 bond. Σ_2, the deviation of the ring from C_2 symmetry[5], is only 8°. The two five-membered rings are attached to the cycloheptane ring in the C-5(e), C-1(e) and the C-7(e), C-8(e) positions, respectively. The cyclopentenone is an envelope with C-5 as the flap, and the γ-lactone ring is also an envelope with C-7 as the flap.

The conformation of the cycloheptane ring of amblyodiol seems to be characteristic of helenanolides with a trans lactone ring closed to C-8.[6-8] Amblyodiol and the guaianolide 11,12-triols solstitialin (**2**)[3a] and cynaratriol (**3**)[3c] all have the same *absolute configuration* (*R*) at C-11, although the *orientation* of the 11-hydroxyl group of amblyodiol is opposite that found in **2** and **3** as the result of lactonization

(1) Work at the Florida State University was supported in part by a grant from the U.S. Public Health Service (CA-13121) through the National Cancer Institute.

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