Synthesis of (−)- and (+)-2-hydroxy-6-keto-*N*-methylmorphinans, their *O*-methyl ethers, and 2-deoxy congeners

HELMUT SCHMIDHAMMER AND ARNOLD BROSSI[1]

Section on Medicinal Chemistry, Laboratory of Chemistry, Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20205, U.S.A.

Received June 7, 1982

HELMUT SCHMIDHAMMER and ARNOLD BROSSI. Can. J. Chem. **60**, 3055 (1982).

Bischler–Napieralski cyclization of the known phenylacetamide **1**, followed by selective ether cleavage of the 3,4-dihydroisoquinoline **2** and sodium borohydride reduction, afforded the tetrahydroisoquinoline **4**. Optical resolution of **4** with tartaric acid gave the optical isomers **4***a*, *b*, which were converted into the 6-ketomorphinans **9***a*, *b* and their *O*-methyl ethers **10***a*, *b* by the following reaction sequence: Birch reduction, *N*-formylation of the dihydro bases, Grewe cyclization, removal of the *N*-formyl protecting groups, reductive *N*-methylation, and *O*-methylation. The 2-deoxy congeners **12***a*, *b* were obtained from **9***a*, *b* by phenyltetrazolylation, and catalytic removal of the heterocyclic ether function. The (−)-enantiomer **12***a* obtained by this synthesis was identical with material prepared from natural morphine, and exhibited the high antinociceptive potency already reported.

HELMUT SCHMIDHAMMER et ARNOLD BROSSI. Can. J. Chem. **60**, 3055 (1982).

La réaction de cyclisation de Bischler–Napieralski de la phénylacétamide **1** suivie du clivage sélectif de l'éther de la dihydro-3,4 isoquinoléine **2** et de la réduction par le borohydrure de sodium, conduit à la tétrahydroisoquinoléine **4**. La résolution optique du composé **4** avec l'acide tartrique permet d'obtenir les isomères optiques **4***a*,*b* que l'on transforme en céto-6 morphinans **9***a*,*b* et en leurs éthers *O*-méthyliques **10***a*,*b* selon les réactions suivantes: la réduction de Birch, la *N*-formylation des bases dihydro, la cyclisation de Grewe, le clivage des groupes protecteurs *N*-formyle, la *N*-méthylation réductive et l'*O*-méthylation. On obtient les congénères déoxy-2 **12***a*,*b* à partir d'une phényltétrazolylation de **9***a*,*b* et de l'élimination catalysée de la fonction éther hétérocyclique. L'énantiomère (−) **12***a* obtenue de cette façon est identique au produit préparé à partir de la morphine naturelle et exhibe le même pouvoir antinociceptif déjà rapporté.

[Traduit par le journal]

The aromatic unsubstituted 6-keto-*N*-methylmorphinan **12***a*, first prepared from natural morphine, showed high antinociceptive potency in the hot-plate assay in mice (1). This result was astonishing, since it was assumed that the presence of a phenolic hydroxy group at C-3 (2) or a methyl ether group at C-4 (3) were essential to manifest good analgetic activity in this group of compounds. The little known pharmacological profiles of the (+)-enantiomers of 6-keto-morphinans suggested that a total synthesis of **12***a* be conceived, which would allow at the same time the preparation of its optical isomer **12***b*. The Grewe cyclization of appropriately substituted octahydroisoquinolines, chosen as the key reaction in the synthesis of **12***a*, *b*, is greatly facilitated by the presence of an electron withdrawing group on the amine nitrogen (4), and a hydroxy group *para*-positioned at the point of ring closure (5). It seemed therefore advisable to first attempt the synthesis of 2-hydroxy substituted 6-ketomorphinans, also needed for our SAR studies, and to eliminate the phenolic 2-hydroxy group afterwards. Elimination of phenolic hydroxy groups has been carried out in several alkaloidal systems and was not expected to give rise to any difficulties (6). This plan has now been accomplished and afforded, as expected, an easy entry into the groups of optically active 2-hydroxy-6-keto-*N*-methylmorphinans and their 2-deoxy congeners.

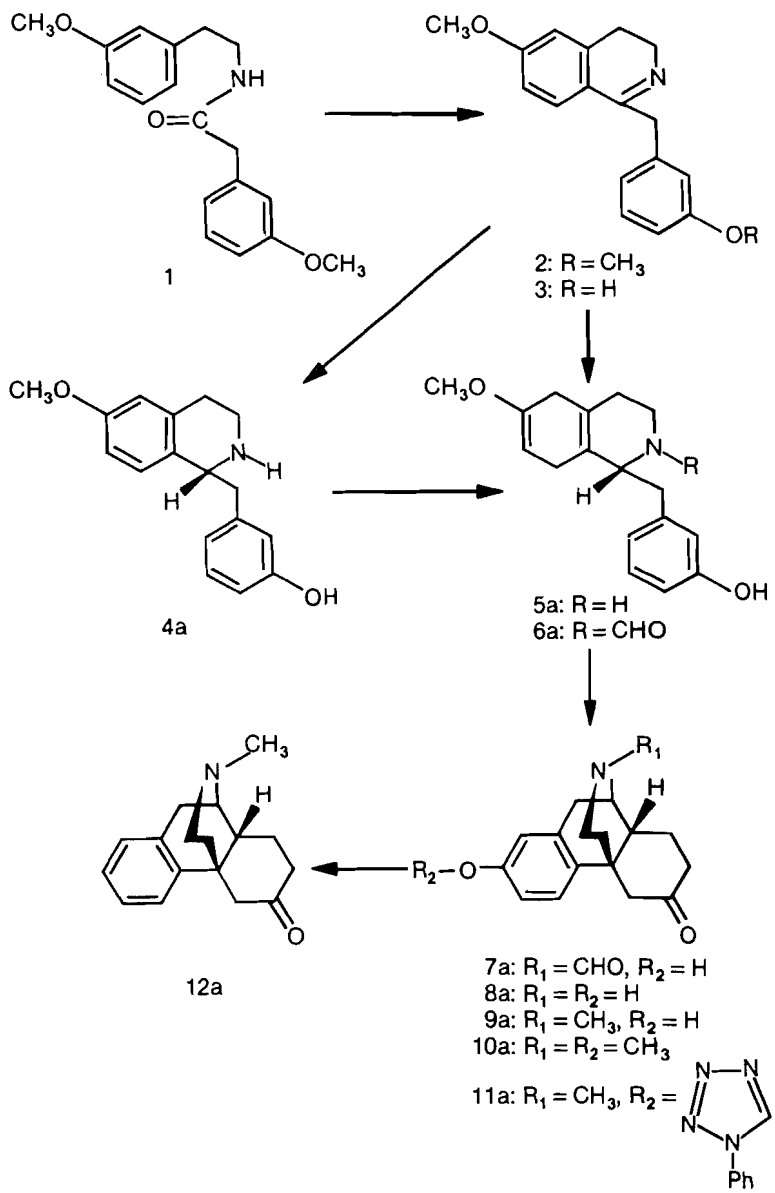
The synthesis of **9***a*, *b* by the route suggested had precedent in Beyerman's synthesis of 3-hydroxy-6-keto-*N*-methylmorphinan (7), and proceeded as follows. Bischler–Napieralski cyclization of the known amide **1** (8, 9), readily available from *m*-methoxybenzaldehyde, afforded the 3,4-dihydroisoquinoline (DIQ) **2**. The DIQ **2** underwent smooth *O*-demethylation at C-3′ with 48% HBr to afford the phenolic DIQ **3** (10). Reduction of **3** was carried out with $NaBH_4$ and afforded the tetrahydroisoquinoline (TIQ) **4**. Optical resolution of **4** with *d*- and *l*-tartaric acid afforded the optical isomers **4***a*, *b*. Their optical purity was determined by ^1H nmr analysis of the methylbenzyl urea derivatives, obtained from both isomers and optically active 1-methylbenzyl isocyanate (11). The individual diastereomers obtained showed little diastereomeric contamination and proved that **4***a*, *b* were optically > 99% pure.

The synthesis of **9***a*, *b* was carried through with the optical isomers **4***a*, *b*, employing identical reaction conditions. Since **12***a* prepared from **4***a* via **9***a* proved to be identical with material prepared from natural morphine (1), only the *a*-series will be discussed in detail. The physical data of the com-

[1]Author to whom correspondence should be addressed.

0008-4042/82/243055-06$01.00/0

©1982 National Research Council of Canada/Conseil national de recherches du Canada



The compounds of the a-series shown above belong to the natural series of 6-ketomorphinans.

SCHEME 1

pounds belonging to the *b*-series and the data for **4**, **5**, **6**, **7**, **8**, and **9** of the racemic series will be listed in the experimental part.

Birch reduction of **4***a* afforded the dihydro base **5***a*, which was *N*-formylated with ethyl formate prior to cyclization. The Grewe cyclization proceeded best in 80% sulfuric acid at 25°C and afforded the *N*-formyl-2-hydroxy-6-ketomorphinan (**7***a*) in 82% yield. The isomeric 4-hydroxy-6-ketomorphinans could only be detected as trace impurities by tlc analysis. This material proved to be a mixture of rotamers, already encountered in other series of *N*-formylated TIQ (12) and morphinans (13). Acid hydrolysis of **7***a* afforded **8***a*, which was converted into **9***a* by a reductive *N*-methylation, and into the *O*-methyl ether **10***a* with phenyltrimethylammonium chloride in DMF. Wolff–Kishner reduction of **8***b*, the optical anti-

pode of **8***a*, afforded (+)-2-hydroxy-*N*-methylmorphinan identical by mp and optical rotation with material prepared by a different procedure (4). Phenyltetrazolylation of **9***a* afforded the ether **11***a*, which after catalytic hydrogenation over Pd/C in acetic acid gave the aromatic unsubstituted ketomorphinan **12***a*, identical in every respect with material prepared from morphine (1). This characterizes the TIQ **4***a* as the *R*-isomer and **9***a* and **12***a* as the isomers belonging to the series of (−)-morphinans originating from natural morphine (1, 14). The enantiomers **9***b* and **12***b*, prepared similarly from **4***b*, showed the expected opposite optical behaviour and belong to the series of (+)-morphinans similarly related to (+)-morphine. The analgesic activity of the ketomorphinans prepared here was measured in mice after sc injection by the hot-plate assay. The 2-OH ketone **9***a* (ED_{50} 20.7 mg/kg) was found to be about 20 times and the *O*-methyl ether **10***a* (ED_{50} 8.6 mg/kg) about 10 times less potent than morphine (ED_{50} 0.87 mg/kg). The aromatic unsubstituted ketone **12***a* (ED_{50} 0.33 mg/kg), however, was found to be about 3 times more potent than morphine. It is thus clearly demonstrated that the position of the aromatic oxygenation in oxygenated 6-ketomorphinans is critical for antinociception. Details concerning the biological properties of 6-ketomorphinans are reported elsewhere (15).

Experimental

Melting points (corrected) were determined with a Fisher–Johns apparatus. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. Infrared spectra were recorded on a Beckman IR 4230 spectrometer. Optical rotations were measured by using a Perkin–Elmer Model 241 MC polarimeter with the solvents and concentrations specified. Nuclear magnetic resonance spectra were determined by using a Varian HR-220 spectrometer or a JEOL JNM-FX 100 spectrometer with TMS as internal reference (s = singlet, d = doublet, dd = doublet of doublets, m = multiplet). Chemical ionization mass spectra (ci ms) were obtained by using a Finnigan 1015 D spectrometer with a Model 6000 data collection system. Electron ionization mass spectra (ei ms) were obtained with a Hitachi Perkin–Elmer RMU-6E spectrometer (70 eV).

*1-(3-Methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline hydrogen bromide (**2**·HBr)*

To a solution of 97.6 g (328 mmol) of **1** in 400 mL acetonitrile were added 50 mL (0.53 mol) of $POCl_3$. At room temperature argon was passed through this mixture during 30 min. Then the mixture was refluxed for 1.0 h under argon, evaporated, cooled to 0–5°C and basified with concentrated NaOH. Extraction with CH_2Cl_2, followed by washings with H_2O and brine, drying, and evaporation gave 91.4 g of an oily residue, which was dissolved in 60 mL MeOH. To this solution sufficient 48% HBr (55 mL) was added to give a pH of 1. Addition of Et_2O and cooling to 4°C overnight yielded 91.8 g of **2**·HBr (77%). An analytical sample of **2**·HBr was provided by recrystallization from MeOH/Et_2O; mp 221–223°C; nmr ($CDCl_3$) δ: 3.77, 3.88 (2s, 6H, $2OCH_3$), 4.58 (s, 2H, exchanges with D_2O, benzylic H), 6.70–7.16 (m, 6H, ArH), 7.84 (d, 1H, ArH, J = 8 Hz); ei ms *m/e*: 281 (M^+). *Anal.* calcd. for $C_{18}H_{19}NO_2$·HBr: C 59.67, H 5.57, N 3.82, Br 22.06; found: C 59.82, H 5.56, N 4.03, Br 22.34.

*1-(3-Hydroxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (**3**)*

A solution of 85 g (235 mmol) of **2**·HBr in 200 mL of 48% HBr was refluxed for 50 min, evaporated, and the residue dissolved in 50 mL MeOH. After addition of Et_2O the resulting mixture was kept at 4°C overnight to yield 67.1 g (82%) of **3**·HBr, mp 106–108°C. A portion of this material was converted to the free base **3**; mp 132–134°C (EtOH); ir ($CHCl_3$): 3600 (OH) cm^{-1}; nmr ($CDCl_3$) δ: 2.68, 3.62 (2t, 4H, $2CH_2$, J = 8Hz), 3.82 (s, 3H, OCH_3), 4.01 (s, 2H, exchanges with D_2O, benzylic H), 6.66–7.50 (m, 7H, ArH); ei ms *m/e*: 267 (M^+). *Anal.* calcd. for $C_{17}H_{17}NO_2$: C 76.38, H 6.41, N 5.24; found: C 76.11, H 6.48, N 5.15.

*(±)-1-(3-Hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**)*

A stirred solution of 52 g (149 mmol) of **3**·HBr in 400 mL EtOH was treated with 8 g (211 mmol) $NaBH_4$ in small portions during 20 min while maintaining the temperature at 20–30°C with an ice bath. After the addition of $NaBH_4$ was complete, the mixture was stirred for 15 min at room temperature, then cooled to 0–5°C and the excess $NaBH_4$ was destroyed with 30% AcOH to give a final pH of 5. After evaporation, the residue was dissolved in H_2O, rendered alkaline with concentrated aqueous NH_3, and extracted with $CHCl_3$/2-propanol (2:1). The organic layer was washed with brine, dried, and evaporated to yield 39.4 g (98%) crystalline product. This crude **4** was used for optical resolution. A sample was recrystallized from MeOH to give pure **4**; mp 155–156°C; ir ($CHCl_3$): 3600 (OH) cm^{-1}; nmr (DMSO-d_6) δ: 3.66 (s, 3H, OCH_3), 6.48–6.76 (m, 5H, ArH), 6.96–7.14 (m, 2H, ArH), 9.20 (s, broad, 1H, OH); ci ms *m/e*: 270 (M^+ + 1), 162 (M^+ − 3-hydroxybenzyl). *Anal.* calcd. for $C_{17}H_{19}NO_2$: C 75.81, H 7.11, N 5.20; found: C 75.93, H 6.98, N 5.47.

*Optical resolution of (±)-1-(3-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**)*

A mixture of 38.0 g (141 mmol) of **4** and 22.2 g (148 mmol) of *d*-tartaric acid was dissolved in 90 mL MeOH at the boiling point. This mixture was kept at 4°C for 15 h. Then the formed crystals were collected to give 17.8 g nearly pure **4***b*·*d*-tartrate. This material was recrystallized from 40 mL MeOH to yield 12.5 g of pure **4***b*·*d*-tartrate. From combined mother liquors another 14.3 g of pure **4***b*·*d*-tartrate were obtained. Together 26.8 g (91%) of optically > 99% pure **4***b*·*d*-tartrate were obtained;[2] mp 183–185°C; $[\alpha]_D^{26}$ −10.4° (*c* 0.92, H_2O). *Anal.* calcd. for $C_{21}H_{25}NO_8$: C 60.13, H 6.01, N 3.34; found: C 59.77, H 5.86, N 3.25.

Compound **4***b*·*d*-tartrate was converted to the free base in the usual way (described below). After recrystallization from MeOH, 16.1 g of *(−)-1-(3-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline* (**4***b*) were obtained; mp 179–180°C; $[\alpha]_D^{26}$ −35.6° (*c* 0.84, 95% EtOH).

The mother liquor of the first crystallization of **4***b*·*d*-tartrate was evaporated, dissolved in H_2O, rendered alkaline with concentrated aqueous NH_3, and extracted with $CHCl_3$/2-propanol (2:1). The organic layer was washed with brine, dried, and evaporated to give 29.1 g of a solid. Following this, 17.0 g (113 mmol) l-tartaric acid and 60 mL MeOH were added. This

[2]The optical purity was determined by reaction of the bases **4***a*, *b* with (*R*)-(+)-α-methylbenzyl isocyanate in deuteriochloroform followed by 220 MHz nmr analysis of the resulting diastereomeric urea derivatives (11).

mixture was stirred at the boiling point until a clear solution was obtained. After 18 h at 4°C, 21.9 g of nearly pure **4***a*·l-tartrate could be collected. This material was recrystallized from 50 mL MeOH to give 16.7 g pure **4***a*·l-tartrate. From combined mother liquors another 11.2 g of pure **4***a*·l-tartrate were obtained. Together 27.9 g (94%) of optically > 99% pure **4***a*·l-tartrate·H_2O were obtained;[2] mp 174–176°C; $[\alpha]_D^{24}$ +10.3° (*c* 0.86, H_2O). *Anal.* calcd. for $C_{21}H_{25}NO_8 \cdot H_2O$: C 57.66, H 6.22, N 3.20; found: C 57.84, H 6.13, N 3.13.

Compound **4***a*·l-tartrate was converted to the free base in the usual way. Recrystallization from MeOH yielded 15.8 g of *(+)-1-(3-hydroxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline* (**4***a*); mp 179–180°C; $[\alpha]_D^{26}$ +35.4° (*c* 0.98, 95% EtOH).

(±)-1-(3-Hydroxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (5)

To 500 mL distilled NH_3 were added 5.5 g (0.79 mol) Li metal and 250 mL of a 1:1 mixture of dry *t*-BuOH/dry Et_2O at −70°C. Into this well stirred mixture a solution of 13.5 g (50 mmol) of **3** in 400 mL dry *t*-BuOH/dry Et_2O (1:1) was dropped during 30 min. This mixture was stirred at −70°C for 1 h, then 100 mL MeOH were added dropwise. The mixture was allowed to warm up slowly and was then kept at room temperature overnight. After evaporation the resulting solid was dissolved in H_2O and an aqueous solution of 45 g (0.84 mol) NH_4Cl was added. The precipitate was collected and washed with MeOH and n-hexane to yield 12.3 g (90%) of **5**. An analytical sample of **5** was obtained by recrystallization from MeOH; mp 183–185°C; ir (KBr): 3400 and 3300 (OH, NH), 1700 and 1670 (C=C) cm^{-1}; nmr ($CDCl_3$) δ: 3.58 (s, 3H, OCH_3), 4.66 (s, 1H, C7—H), 6.64 (m, 3H, ArH), 7.12 (dd, 1H, ArH, *J* = 8, 8 Hz); ci ms *m/e*: 272 (M^+ + 1). *Anal.* calcd. for $C_{17}H_{21}NO_2$: C 75.24, H 7.80, N 5.16; found: C 74.92, H 7.90, N 5.11.

(+)-1-(3-Hydroxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (5a)

To 400 mL distilled NH_3 were added 7.0 g (1.0 mol) Li metal and 400 mL of a 1:1 mixture of dry *t*-BuOH/dry Et_2O at −70°C. To this well stirred mixture 15.0 g (56 mmol) of powdered **4***a* were added at once. This mixture was stirred at −70°C for 1 h, then 100 mL MeOH were added dropwise. The mixture was allowed to warm up slowly and was then kept at room temperature overnight. After evaporation the resulting solid was dissolved in H_2O and an aqueous solution of 60 g (1.12 mol) NH_4Cl was added. The precipitate was collected, washed subsequently with H_2O, MeOH, and petroleum ether to yield 14.5 g (96%) of **5***a*, mp 190–193°C. Recrystallization of a portion of this material from MeOH afforded an analytical sample of **5***a*; mp 195–196°C; $[\alpha]_D^{25}$ +101.9° (*c* 0.95, 95% EtOH). *Anal.* calcd. for $C_{17}H_{21}NO_2$: C 75.24, H 7.80, N 5.16; found: C 75.11, H 7.56, N 5.07.

(−)-1-(3-Hydroxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (5b)

Preparation of this compound from **4***b* on the same scale and essentially as described above for the enantiomer afforded 14.6 g (97%) of **5***b*, mp 192–194°C. Recrystallization from MeOH afforded the analytical sample; mp 195–196°C; $[\alpha]_D^{26}$ −102.0° (*c* 1.10, 95% EtOH). *Anal.* calcd. for $C_{17}H_{21}NO_2$: C 75.24, H 7.80, N 5.16; found: C 75.23, H 7.71, N 5.06.

(+)-N-Formyl-1-(3-hydroxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (6a)

To a solution of 14.0 g (51.6 mmol) of **5***a* in 120 mL dry DMF were added 180 mL dry ethyl formate at 90°C (bath temperature) during 30 min. The resulting solution was refluxed for 60 h under argon. Evaporation yielded a crystalline solid, which was treated with 50 mL MeOH to give 14.6 g (95%) of **6***a*, mp 225–228°C. An analytical sample was prepared by recrystallization of a portion of this material with 2-propanol; mp 226–229°C; $[\alpha]_D^{24}$ +3.5° (*c* 1.03, DMSO); ir (KBr): 3180 (OH), 1705 and 1675 (C=C), 1640 (NCHO) cm^{-1}; nmr (DMSO-d_6) δ: 3.47 (s, 3H, OCH_3), 4.70 (s, 1H, C7—H), 6.56 (m, 3H, ArH), 7.00 (dd, 1H, ArH, *J* = 8, 8 Hz), 7.35 (s, 1H, CHO), 9.24 (s, 1H, OH); ci ms *m/e*: 300 (M^+ + 1). *Anal.* calcd. for $C_{18}H_{21}NO_3$: C 72.21, H 7.07, N 4.68; found: C 72.12, H 6.89, N 4.41.

(−)-N-Formyl-1-(3-hydroxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (6b)

Preparation of this compound from **5***b* on the same scale and exactly as described above for the enantiomer afforded 14.8 g (96%) **6***b*, mp 223–227°C. Recrystallization from 2-propanol gave an analytical sample; mp 227–229°C; $[\alpha]_D^{25}$ −0.6° (*c* 0.93, DMSO). *Anal.* calcd. for $C_{18}H_{21}NO_3$: C 72.21, H 7.07, N 4.68; found: C 72.08, H 7.11, N 4.57.

(±)-N-Formyl-1-(3-hydroxybenzyl)-6-methoxy-1,2,3,4,5,8-hexahydroisoquinoline (6)

This compound was prepared from 5.5 g of **5** essentially as described above to afford 5.5 g (91%) of **6**, mp 201–204°C. An analytical sample was obtained by recrystallization from 2-propanol; mp 204–206°C. *Anal.* calcd. for $C_{18}H_{21}NO_3$: C 72.21, H 7.07, N 4.68; found: C 72.01, H 6.96, N 4.44.

(−)-N-Formyl-2-hydroxymorphinan-6-one (7a)

To a well stirred mixture of 14.0 g (46.8 mmol) **6***a* and 500 mL Et_2O were added dropwise 300 mL 80% H_2SO_4 at 0°C under an argon atmosphere during 3.5 h. The resulting solution was then kept at room temperature for 20 h, poured on 1.0 L ice water, and the organic solvent was evaporated. The aqueous solution was extracted with 6 × 200 mL $CHCl_3$/2-propanol (3:1). The organic layer was washed with water, dried, and evaporated to give 10.9 g (82%) **7***a* as a foam, which was used for the next step without further purification. An analytical sample was prepared by crystallization with MeOH; mp 259–261°C; $[\alpha]_D^{24}$ −219.1° (*c* 0.82, DMSO); ir (KBr): 3260 (OH), 1705 (CO), 1650 and 1620 (NCHO); nmr (DMSO-d_6) δ: 4.58 (m, 1H, C9—H), 6.52 (m, 2H, ArH), 7.04 (d, 1H, ArH, *J* = 8 Hz), 7.95 (s, 1H, CHO), 9.20 (s, 1H, OH); ei ms *m/e*: 285 (M^+). *Anal.* calcd. for $C_{17}H_{19}NO_3$: C 71.56, H 6.71, N 4.91; found: C 71.49, H 6.47, N 4.79.

(+)-N-Formyl-2-hydroxymorphinan-6-one (7b)

Preparation of this compound from **6***b* on the same scale and essentially as described above for the enantiomer afforded 11.2 g (84%) **7***b* as a foam, which was used for the next step without further purification. Crystallization with MeOH gave an analytical sample; mp 260–262°C; $[\alpha]_D^{24}$ +222.5° (*c* 0.87, DMSO). *Anal.* calcd. for $C_{17}H_{19}NO_3$: C 71.56, H 6.71, N 4.91; found: C 71.34, H 6.64, N 4.68.

(±)-N-Formyl-2-hydroxymorphinan-6-one (7)

This compound was prepared in a similar manner as described for both enantiomers, from 4.3 g **6** to give 3.5 g (85%) **7** as a foam, which was used for the next step without further purification. Crystallization with MeOH afforded an analytical sample; mp 244–247°C; *Anal.* calcd. for $C_{17}H_{19}NO_3 \cdot 0.5H_2O$: C 69.37, H 6.85, N 4.76; found: C 69.70, H 6.74, N 4.66.

(−)-2-Hydroxymorphinan-6-one (8a)

A solution of 8.0 g (28.0 mmol) **7***a* in 81 mL MeOH and 9 mL concentrated HCl was refluxed for 16 h and then evaporated. The oily residue was dissolved in H_2O, basified with concentrated aqueous NH_3, and extracted with a total amount of 250 mL $CHCl_3$/2-propanol (3:1). The organic layer was washed with brine, dried, and evaporated to give a crystalline residue, which yielded after treatment with MeOH 6.1 g (85%) of **8***a*. An analytical sample was recrystallized with MeOH; mp 282–286°C (dec.); $[\alpha]_D^{25}$ −116.9° (*c* 0.95, DMSO); ir (KBr): 3400 (broad,

OH), 3280 (NH); nmr (DMSO-d_6) δ: 6.48 (m, 2H, ArH), 6.96 (d, 1H, ArH, J = 8 Hz); ei ms *m/e*: 257 (M^+). *Anal.* calcd. for $C_{16}H_{19}NO_2$: C 74.68, H 7.44, N 5.44; found: C 74.40, H 7.65, N 5.36.

(+)-2-Hydroxymorphinan-6-one (8b)

Preparation of this compound from **7b** in the same scale and manner as described above afforded 6.2 g (86%) of **8b**. An analytical sample was obtained by recrystallization from MeOH; mp 281–284°C (dec.); $[\alpha]_D^{25}$ +117.6° (*c* 1.03, DMSO). *Anal.* calcd. for $C_{16}H_{19}NO_2$: C 74.68, H 7.44, N 5.44; found: C 74.40, H 7.63, N 5.68.

(±)-2-Hydroxymorphinan-6-one (8)

Preparation of this compound from 3.5 g **7** in the same manner as described above afforded 2.45 g (78%) of **8**. An analytical sample was obtained by recrystallization from MeOH; mp > 270°C (dec.). *Anal.* calcd. for $C_{16}H_{19}NO_2 \cdot 0.5H_2O$: C 72.15, H 7.57, N 5.26; found: C 72.29, H 7.28, N 5.31.

*(−)-2-Hydroxy-*N*-methylmorphinan-6-one (9a)*

A mixture of 5.5 g (21.4 mmol) of **8a**, 5.5 g (40.4 mmol) of $NaOAc \cdot 3H_2O$, 17.6 mL of 37% formaline, and 1.5 g 10% Pd/C catalyst was hydrogenated in 150 mL 2 *N* AcOH at 50 psi and room temperature for 2 h. The mixture was filtered, washed with 2 *N* AcOH, the filtrate was basified with concentrated aqueous NH_3 and extracted with a total amount of 200 mL $CHCl_3$/2-propanol (3:1). The organic layer was washed with H_2O, dried, and evaporated to give a foam, which after crystallization from MeOH yielded 5.4 g (93%) **9a**. An analytical sample was formed by recrystallization from MeOH; mp 115–117°C; $[\alpha]_D^{24}$ −130.2° (*c* 0.89, DMF); ir (KBr): 3400 (OH), 1705 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 2.24 (s, 3H, NCH_3), 6.48 (m, 2H, ArH), 6.92 (d, 1H, ArH, J = 8 Hz), 8.92 (s, 1H, OH); ci ms *m/e*: 272 ($M^+ + 1$). *Anal.* calcd. for $C_{17}H_{21}NO_2 \cdot CH_3OH$: C 71.25, H 8.31, N 4.62; found: C 71.26, H 8.73, N 4.43.

*(+)-2-Hydroxy-*N*-methylmorphinan-6-one (9b)*

Preparation of this compound from **8b** on the same scale and manner as described above afforded 5.3 g (91%) **9b**. An analytical sample was recrystallized from MeOH; mp 115–117°C; $[\alpha]_D^{24}$ +130.9° (*c* 0.95, DMF). *Anal.* calcd. for $C_{17}H_{21}NO_2 \cdot CH_3OH$: C 71.25, H 8.31, N 4.62; found: C 70.83, H 8.31, N 4.50.

Wolff–Kishner reduction of this material carried out in the usual way afforded the known (+)-2-hydroxy-*N*-methylmorphinan (4); mp 182–184°C (MeOH); $[\alpha]_D^{25}$ +40.8° (*c* 0.92, MeOH) (lit. (4) mp 181–183°C (Et_2O); $[\alpha]_D^{25}$ +41.4° (*c* 0.45, MeOH)).

*(±)-2-Hydroxy-*N*-methylmorphinan-6-one (9)*

Preparation of this compound from 2.5 g **8** essentially as described above yielded 2.2 g (83%) **9**. An analytical sample was prepared by recrystallization from 2-propanol; mp 240–242°C (dec.). *Anal.* calcd. for $C_{17}H_{21}NO_2$: C 75.24, H 7.80, N 5.16; found: C 74.93, H 7.85, N 5.11.

*(−)-2-Methoxy-*N*-methylmorphinan-6-one (10a)*

A mixture of 300 mg (1.1 mmol) of **9a**, 300 mg (2.2 mmol) of anhydrous K_2CO_3, and 380 mg (2.2 mmol) of phenyltrimethylammonium chloride in 20 mL anhydrous DMF was stirred at 80°C (bath temperature) under argon for 6 h. The mixture was filtered, washed with $CHCl_3$, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed with 1 *N* NaOH and brine, dried, and evaporated to give a crystalline solid, which was recrystallized from isopropyl ether to yield 210 mg (67%) of **10a**. An analytical sample was recrystallized from MeOH; mp 149–151°C; $[\alpha]_D^{24}$ −125.8° (*c* 0.97, $CHCl_3$); ir (KBr): 1705 (CO) cm^{-1}; nmr ($CDCl_3$) δ: 2.44 (s, 3H, NCH_3), 3.74 (s, 3H, OCH_3), 6.66 (m, 2H, ArH), 7.14 (d, 1H, ArH, J = 8 Hz); ei ms *m/e*: 285 (M^+). *Anal.* calcd. for $C_{18}H_{23}NO_2$: C 75.75, H 8.12, N 4.91; found: C 75.51, H 8.09, N 4.89.

*(+)-2-Methoxy-*N*-methylmorphinan-6-one (10b)*

Preparation of this compound from **9a** on the same scale and essentially as described above yielded 200 mg (63%) of **10b**. An analytical sample was prepared by recrystallization from MeOH; mp 150–152°C; $[\alpha]_D^{24}$ +126.0° (*c* 1.08, $CHCl_3$). *Anal.* calcd. for $C_{18}H_{23}NO_2$: C 75.75, H 8.12, N 4.91; found: C 75.93, H 8.19, N 4.89.

*(−)-2-[(1-Phenyl-1*H*-tetrazol-5-yl)oxy]-*N*-methylmorphinan-6-one (11a)*

A mixture of 3.7 g (13.6 mmol) of **9a**, 3.7 g (26.8 mmol) of anhydrous K_2CO_3, and 2.6 g (14.4 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole in 40 mL anhydrous DMF was stirred at room temperature under argon atmosphere for 18 h. The mixture was filtered, washed with $CHCl_3$, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and extracted with 10% aqueous tartaric acid. The aqueous layer was washed with Et_2O, rendered alkaline with concentrated NaOH, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to give 5.4 g (95%) of **11a** as an oil, which was used for the next step without further purification. An analytical sample was obtained by crystallization with AcOEt; mp 133–134°C; $[\alpha]_D^{24}$ −80.1° (*c* 1.03, $CHCl_3$); ir (KBr): 1705 (CO) cm^{-1}; nmr ($CDCl_3$) δ: 2.38 (s, 3H, NCH_3), 7.04–7.78 (m, 8H, ArH); ei ms *m/e*: 415 (M^+). *Anal.* calcd. for $C_{24}H_{25}N_5O_2$: C 69.38, H 6.07, N 16.85; found: C 69.66, H 6.25, N 16.68.

*(+)-2-[(1-Phenyl-1*H*-tetrazol-5-yl)oxy]-*N*-methylmorphinan-6-one (11b)*

This compound was prepared from 2 g of **9b** essentially as described above, yielded 2.8 (91%) of **11b** as an oil, which was used for the next step without further purification. An analytical sample was obtained by crystallization with AcOEt; mp 132–134°C; $[\alpha]_D^{24}$ +80.4° (*c* 1.15, $CHCl_3$). *Anal.* calcd. for $C_{24}H_{25}N_5O_2$: C 69.38, H 6.07, N 16.85; found: C 69.51, H 5.93, N 17.08.

*(−)-*N*-Methylmorphinan-6-one (12a) (1)*

To a solution of 4.0 g (9.6 mmol) of crude **11a** in 50 mL of glacial acetic acid were added 8.0 g 10% Pd/C catalyst. This mixture was hydrogenated at 50 psi at room temperature for 24 h. The catalyst was filtered off, washed with glacial acetic acid, and the filtrate was evaporated. The residue was dissolved in H_2O, rendered alkaline with concentrated NaOH, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to give a crystalline solid, which was treated with isopropyl ether to yield 1.9 g (77%) of **12a**. An analytical sample was recrystallized with isopropyl ether; mp 165–167°C (lit. (1) mp 164–166°C); $[\alpha]_D^{25}$ −135.8° (*c* 0.86, $CHCl_3$) (lit. (1) $[\alpha]_D^{26}$ −137.8° (*c* 0.92, $CHCl_3$)); ir and nmr were identical with an authentic sample.

*(+)-*N*-Methylmorphinan-6-one (12b)*

This compound was prepared from 2.7 g of crude **11b** essentially as described above, yielded 1.2 g (72%) of **12b**. An analytical sample was recrystallized with isopropyl ether; mp 165–167°C; $[\alpha]_D^{24}$ +136.1° (*c* 1.01, $CHCl_3$). *Anal.* calcd. for $C_{17}H_{21}NO$: C 79.96, H 8.29, N 5.49; found: C 79.93, H 8.32, N 5.36.

Acknowledgement

We thank Dr. A. E. Jacobson and L. Atwell for having provided us with the biological data of the compounds described here.

1. H. Schmidhammer, A. E. Jacobson, and A. Brossi. Heterocycles, **17**, 391 (1982).
2. J. Hellerbach, O. Schnider, H. Besendorf, and B.

PELLMONT. *In* Synthetic analgesics. Part II, a monograph in Organic chemistry. Vol. 8, Pergamon Press, New York. 1966. pp. 74–75.
3. A. E. JACOBSON, F.-L. HSU, M. D. ROZWADOWSKA, H. SCHMIDHAMMER, L. ATWELL, A. BROSSI, and F. MEDZIHRADSKY. Helv. Chim. Acta, **64**, 1298 (1981); A. MANMADE, H. C. DALZELL, J. F. HOWES, and R. K. RAZDAN. J. Med. Chem. **24**, 1437 (1981).
4. E. MOHACSI and W. LEIMGRUBER. U. S. Patent No. 3,914,234 (1975), assigned to Hoffmann-La Roche Inc.
5. R. GREWE and A. MONDON. Chem. Ber. **81**, 279 (1948); R. GREWE, H. FISCHER, and W. I. FRIEDRICHSEN. Chem. Ber. **100**, 1 (1967); H. HENECKA. Ann. **583**, 110 (1949); W. S. JOHNSON. *In* Organic reactions. Vol. II. John Wiley & Sons, New York. 1944. pp. 118–120.
6. A. BROSSI, M. F. RAHMAN, K. C. RICE, M. GERECKE, R. BORER, J. O'BRIEN, and S. TEITEL. Heterocycles, **7**, 277 (1977); J. REDEN, M. REICH, K. C. RICE, A. E. JACOBSON, A. BROSSI, R. A. STREATY, and W. KLEE. J. Med. Chem. **22**, 256 (1979).
7. C. OLIEMAN, PH. NAGELHOUT, A. D. DEGROOT, L. MAAT, and H. C. BEYERMAN. Recl. Trav. Chim. Pays-Bas, **99**, 353 (1980).
8. J. JIRKOWSKY and M. PROTIVA. Collect. Czech. Chem. Commun. **29**, 400 (1964).
9. S. N. CHAKRAVATI, R. D. HAWORTH, and W. H. PERKIN, JR. J. Chem. Soc. 2270 (1927).
10. A. BROSSI and S. TEITEL. Helv. Chim. Acta, **53**, 1779 (1970).
11. K. C. RICE and A. BROSSI. J. Org. Chem. **45**, 592 (1980).
12. K. C. RICE, W. C. RIPKA, J. REDEN, and A. BROSSI. J. Org. Chem. **45**, 601 (1980); A. BROSSI. Proceedings of the 4th Asian Symposium on Medicinal Plants and Spices, Bangkok, Thailand. Unesco Publication. September 1980. p. 261; C. SZÁNTAY, G. BLASKÓ, M. BÁRCZAI-BEKE, and G. DÖRNYEI. Heterocycles, **14**, 1127 (1980); H. VAN KONINGSFELD and C. OLIEMAN. Cryst. Struct. Commun. **10**, 541 (1981).
13. K. C. RICE. J. Org. Chem. **45**, 3135 (1980).
14. A. BROSSI. Proceedings First Int. Conference on Chemistry and Biotechnology of Biologically Active Nat. Products. Vol. 1. *Edited by* Bulgarian Academy of Sciences, Varna. October 1981. p. 114.
15. H. SCHMIDHAMMER, A. E. JACOBSON, and A. BROSSI. Med. Res. Rev. 1983. Submitted.