

After workup and chromatography on silica gel (20% ether-hexanes), 241 mg (57%) of alcohol **21** was obtained as a 75:25 mixture of erythro and threo isomers: IR film ν 3400, 2940, 2865, 2840, 1640, 1470, 1260, 1105 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.07 (s, CH_3Si), 0.91 (s, *tert*-butyl), 1.23–1.38, 1.41–1.50, 1.51–1.67 (m, CH_2 's), 1.73 (p, $J = 6$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.83 (d, $J = 6$ Hz, OH), 2.10–2.18 (m, threo allylic CH), 2.26–2.34 (m, erythro allylic CH), 2.53–2.64 (m, allylic CH_2 's), 2.56–2.66 (m, CH_2OSi), 4.12–4.8 (m, threo carbinyl CH), 4.22–4.28 (m, erythro carbinyl CH), 5.08–5.25 (m, vinyl H's), 5.53–5.72 (m, vinyl H's); MS, calcd for $\text{C}_{24}\text{H}_{49}\text{O}_3\text{Si}_2\text{I}$ m/e 568.7, found m/e ($\text{M}^+ - \text{C}(\text{CH}_3)_3$) 511. Anal.

Calcd for $\text{C}_{24}\text{H}_{49}\text{O}_3\text{Si}_2\text{I}$: C, 50.69; H, 8.68. Found: C, 50.79; H, 8.70.

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An Asymmetric Synthesis of (+)-Morphinans in High Enantiomeric Purity

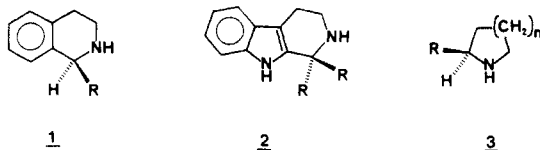
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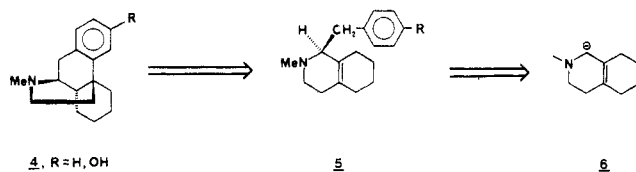
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The synthesis of the narcotic analgesic dextrorphan (**4**) and its desoxy derivative has been accomplished via an asymmetric alkylation of octahydroisoquinoline **10**. The latter, converted to its chiral formamidine **13**, underwent highly selective alkylation to give the 1-benzyl derivative **16** in >98% ee. Grewe cyclization then produced the title compounds.

In the continuing study on chiral formamidines, as precursors to α -lithio anions, which have thus far led to asymmetric synthetic methods for tetrahydroisoquinolines **1**,¹ β -carbolines **2**,² piperidines and pyrrolidines **3**, and



benzomorphans,^{3,4} we describe an efficient synthesis of morphinans which includes the preparation of dextrorphan (**4**) and its unsubstituted derivative. These substances

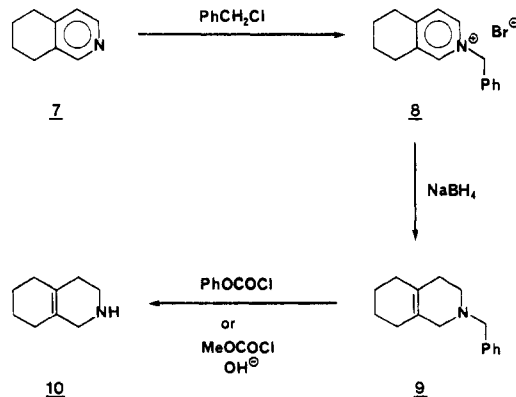


have been the subject of considerable effort over the past 35 years due to their analgesic and antitussive properties. Synthetic approaches to the morphine-based system have also enjoyed considerable success⁵ and continue even in recent years.⁶ However, there are no reported asymmetric

syntheses to these systems and it is the purpose of this paper to disclose a successful entry into enantiomerically enriched (>98%) morphinans.

Our approach is to generate a chiral carbanion from the octahydroisoquinoline **6** via formamidines and to alkylate, in a stereoselective manner, to the benzyl derivative **5**. The final construction to the morphinan **4** makes use of the well-known Grewe cyclization⁷ under acidic conditions.

The synthetic scheme begins with the acquisition of the octahydroisoquinoline (**10**), which was prepared in 30–40% overall yield from isoquinoline. The latter was reduced⁸ with hydrogen–palladium–trifluoroacetic acid to the tetrahydroisoquinoline **7** followed by quaternization with benzyl bromide to furnish the *N*-benzyl salt **8**. Reduction



with sodium borohydride gave the *N*-benzyloctahydroisoquinoline **9**, which was debenzylated to 1,2,3,4,5,6,7,8-octahydroisoquinoline (**10**). Transformation into the chiral

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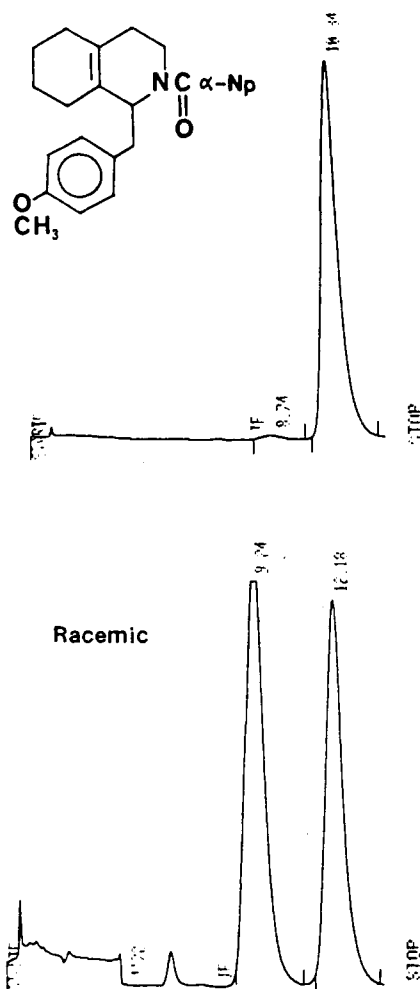
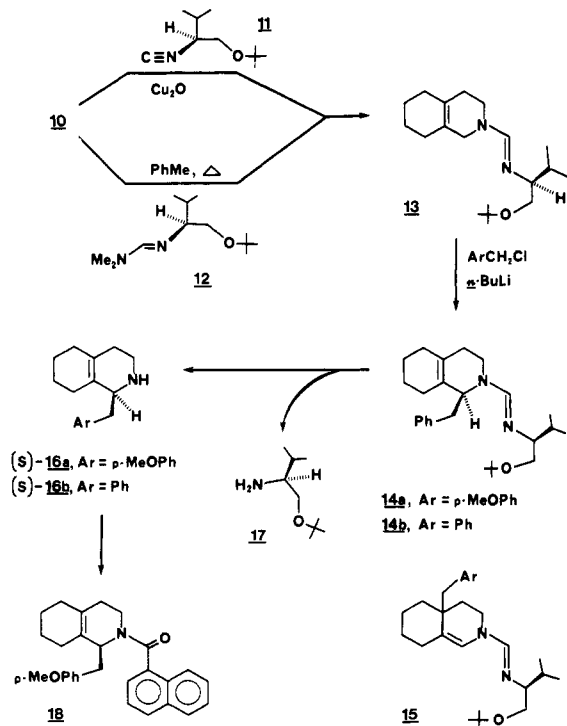


Figure 1. Pirkle column analysis of racemic 18 and (-)-18. Ratios are 98.87 to 1.13 (98% ee).

formamidine 13 was accomplished by treating the octahydroisoquinoline 10 with the isocyanide derived from valinol *tert*-butyl ether 11, in the presence of cuprous



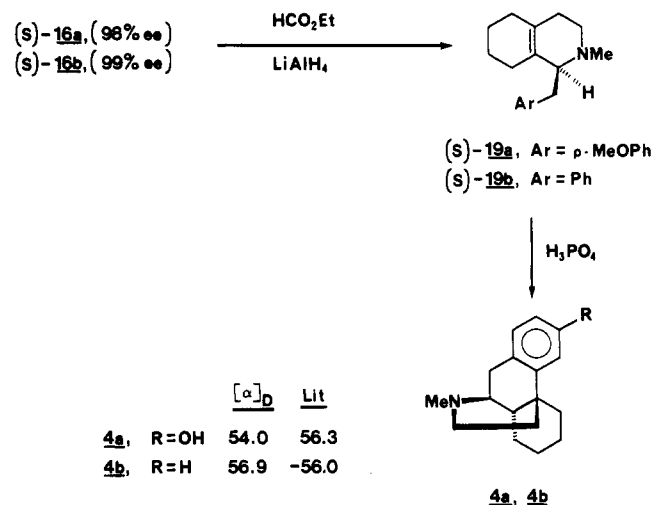
oxide, or the dimethyl formamidine 12³ by simple heating

to eliminate dimethylamine. Although the isocyanide-amine addition to 13 works well (~70%), it was found that for larger scale reactions the (dimethylamino)formamidine 12 gave more consistent yields (~80%). The isocyanide gave lower yields of 13 as the reactions were scaled up.

With the octahydroisoquinoline-valineformamidine in hand, the sequence to the morphinans proceeded by metalation-alkylation of 13 to give the benzylated derivatives 14 and 15. The ratio of 1- vs. 5-benzylation with benzyl chloride was 4:1, respectively, while *p*-methoxybenzyl chloride gave a 7:1 ratio for 14 and 15. It was unnecessary to separate 14 from 15 since the next step, which involved hydrazinolysis, selectively destroyed 15 such that the only product isolated was the 2-benzyl-octahydroisoquinoline 16a or 16b. Also isolated during the hydrazine treatment was a 75% recovered yield of the *tert*-butyl ether of valinol 17.

In order to assess the enantiomeric purity of the benzyloctahydroisoquinolines 16a, 16b, they were transformed into their naphthamides 18 and subjected to HPLC analysis utilizing the chiral Pirkle column.⁹ A typical separation is shown in Figure 1. Integration of these peaks showed that 16a and 16b were formed in 99% and 98.5% ee, respectively.

Treatment of 16a and 16b with ethyl formate followed by lithium aluminum hydride reduction gave the *N*-methyl derivatives 19a and 19b in 82–90% yield, which were then



subjected to hot phosphoric acid under Grewe conditions,⁷ affording the morphinans 4a, 4b in 45–50% yield. Comparison of these products with the literature values showed that the optical purities were 99% and 96%, respectively, in agreement with the HPLC enantiomeric analysis.

In summary, we have demonstrated an efficient asymmetric synthesis of morphinans in high enantioselectivity, and this, coupled with the benzomorphan synthesis already described, provides a route into a wide variety of morphine-based alkaloids.

Experimental Section

The NMR spectra were determined on a Bruker-IBM 270 MHz instrument. Optical rotations were taken on a Rudolph AutoPol polarimeter. The HPLC analyses were performed on a Waters 440 unit with flow rates of 3.0 mL/min. The Pirkle column was a Baker (J. T. Baker and Co.) dinitrophenylglycine covalent HPLC column (No. RP-71130), using 5% isopropyl alcohol in hexane as the eluent.

***N*-Benzyl-5,6,7,8-tetrahydroisoquinolinium Bromide (8).** A solution of 10.0 g (7.7 mmol) of distilled isoquinoline in 67 mL

(9) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* 1984, 49, 2504.

of trifluoroacetic acid containing 5.0 g of 5% palladium on carbon was hydrogenated in the manner of Eliel and Vierhapper⁸ at 50 psi of H₂, 50 °C over 48 h. The catalyst was removed by filtration, and the reaction mixture was carefully neutralized with solid KOH and 20% KOH solution. Extraction with CH₂Cl₂, followed by a saturated NaHCO₃ solution wash, afforded, upon concentration, 10.0 g of the crude product contaminated with some overreduced material. The crude 5,6,7,8-tetrahydroisoquinoline was dissolved in 70 mL of reagent grade acetone, 10.3 mL (8.7 mmol) of benzyl bromide was added, and the solution was refluxed for 1 h. Upon cooling, the benzyl bromide salt precipitated from solution as a fine white powder. Filtration provided 16.9 g (72%) of the product. Recrystallization from methanol/ether afforded large prisms: mp 185–186 °C (uncorrected), lit.¹⁰ ml 178–180 °C.

N-Benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (9). To a solution of 4.0 g (1.3 mmol) of the pyridinium benzyl bromide 8 in 25 mL of 80% aqueous methanol at 0 °C was slowly added 1.0 g (2.6 mmol) of NaBH₄. After completion of the addition, the reaction mixture was refluxed for 1 h. Upon cooling, the methanol was removed in vacuo, and the crude product was taken up in ether and washed with saturated NaHCO₃ solution, and the organic layer was dried over K₂CO₃. Bulb-to-bulb distillation at 90 °C (0.05 mmHg) provided 2.8 g (93%) of the product as a colorless liquid: ¹H NMR (CDCl₃) δ 1.8 (10 H, m), 2.5 (2 H, t, *J* = 5 Hz), 2.8 (2 H, m), 3.6 (2 H, s), 7.3 (5 H, s); mp (oxalate salt) 179–181 °C, lit.¹⁰ mp 183 °C.

1,2,3,4,5,6,7,8-Octahydroisoquinoline (10). To a solution of 2.826 g (0.024 mol) of the *N*-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline in 40 mL of CH₂Cl₂ was carefully added 2.4 mL (2.5 equiv) of methyl chloroformate (or phenyl chloroformate). After 2 h, the reaction mixture was concentrated in vacuo, and the benzyl chloride generated from the reaction was removed by bulb-to-bulb distillation. The crude urethane was then dissolved in 40 mL of THF containing 5 mol % of 18-crown-6. To this mixture was added 2 g (3 equiv) of powdered KOH and the reaction mixture was refluxed under argon for 2 days. Upon cooling, the solvent was removed in vacuo, and the crude material was taken up in diethyl ether. The ethereal phase was washed with saturated NaHCO₃ solution 3 times and the organic layer was dried over anhydrous K₂CO₃. Bulb-to-bulb distillation (20 mmHg; 105 °C) provided 0.995 g (60%) of the product as a colorless liquid: ¹H NMR (CDCl₃) δ 1.9 (11 H, m), 3.0 (2 H, t, *J* = 5 Hz), 3.2 (2 H, m).⁸ Anal. Calcd for C₉H₁₅N: C, 78.88; H, 11.02. Found: C, 78.97; H, 11.09. Picrate prepared in ethanol, mp 169–170 °C; hydrochloride (MeOH-ether) mp 147–149 °C.

Valineformamide of Octahydroisoquinoline 10. A solution of 0.560 g (4.1 mmol) of 1,2,3,4,5,6,7,8-octahydroisoquinoline (10) and 0.860 g (4.0 mmol) of (*S*)-*N,N*-dimethyl-*O*-*tert*-butylvalinolformamide 12⁹ in 1 mL of toluene was heated at 85 °C for 48 h. Concentration and flash chromatography (silica gel; 5% Et₃N in hexanes) of the crude product afforded 0.998 g (80%) of the product as a colorless oil: IR (film) 2920 (br), 2820, 1640, 1450, 1385, 1355, 1230, 1190, 1075, 1010, 875 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (6 H, d, *J* = 7 Hz), 1.15 (9 H, s), 1.59 (4 H, m), 1.88 (7 H, m), 2.70 (1 H, q, *J* = 6 Hz), 3.18 (1 H, m), 3.30 (2 H, t, *J* = 6 Hz), 3.55 (3 H, m), 7.31 (1 H, s); [α]_D²⁵ -44.6° (c 3.3, CHCl₃). Elemental analyses were not taken due to the ready absorption of oxygen, carbon dioxide, and water. These formamides are best stored under argon after degassing under high vacuum.

Isocyanide of (*S*)-Valinol *tert*-Butyl Ether (11). *N*-Formylvalinol *t*-butyl ether³ (8.52 g) was dissolved in 50 mL of dry DMF and then cooled to -50 °C, and a solution of 5.4 g of thionyl chloride, dissolved in 20 mL of DMF, was added. After the addition was complete the solution was warmed to -30 °C and was recooled to -50 °C. While the solution was stirring at -50 °C, 9.6 g of solid K₂CO₃ was added. The colorless mixture was allowed to warm to room temperature overnight. Extraction of the crude material was done by partitioning it between H₂O and

ether and drying the combined organic layers with MgSO₄. The crude product was distilled, bulb-to-bulb at 78 °C (3 torr), yielding 6.5 g of the isonitrile, 85%: ¹H NMR (CDCl₃) δ 3.45 (3 H, m), 1.22 (9 H, s), 1.05 (3 H, *J* = 7 Hz, d), 1.00 (3 H, *J* = 7 Hz, d); IR (neat 2940, 2120 cm⁻¹; [α]_D²⁴ +1.76° (c 1.19, CHCl₃). Anal. Calcd for C₁₀H₁₉NO: C, 71.00; H, 11.24. Found: C 69.89; H, 11.19.

Valineformamide 13 from Isocyanide 11. A solution of 0.560 g (4.1 mmol) of 1,2,3,4,5,6,7,8-octahydroisoquinoline and 0.69 g (4.1 mmol) of (*S*)-*O*-*tert*-butylvalinol isocyanide in 10 mL of toluene was heated at reflux for 16 h with a catalytic amount of dry cuprous oxide. Concentration and flash chromatography (silica gel; 5% Et₃N in hexanes) of the crude product afforded 0.87 g (70%) of the product as a colorless oil whose spectral data, [α]_D, and other physical properties were identical with 13 prepared from 12.

1-(*p*-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinolineformamide (14a). To a 0.05 M solution of 0.221 g (0.721 mmol) of the chiral octahydroisoquinolineformamide 13 and 0.22 mL (2 equiv) of *p*-methoxybenzyl chloride in THF at -78 °C, under argon, was added 1.1 equiv of *n*-butyllithium in hexane. The light yellow solution had become completely colorless after 1 h, and after an additional hour at -78 °C, the reaction mixture was allowed to warm to 0 °C. The reaction mixture was poured into hexane, and the organic layer was washed with 1 N HCl solution. After separation of the layers, excess *p*-methoxybenzyl chloride could be recovered from the hexane/THF layer. The acid wash was made basic with 20% KOH solution, and the milky white aqueous phase was extracted with diethyl ether several times. Concentration and passage of the crude product through a small silica gel plug and elution with 5% Et₃N in hexanes ("flash filtration") provided 0.281 g (92%) of a 7:1 ratio of 1- vs. 5-substituted regioisomers (14a, 15). If desired, radial chromatography of this mixture on a 2-mm silica gel plate, eluting with 5% Et₃N in hexanes, separated the regioisomers, affording 0.203 g (66%) of the 1-(*p*-methoxybenzyl)octahydroisoquinolineformamide 14a as a clear, viscous oil: IR (film) 1640 cm⁻¹; ¹H NMR (CDCl₃) δ 0.77 (6 H, m), 1.10 (9 H, s), 1.60 (6 H, m), 1.86 (4 H, m), 2.10 (2 H, m), 2.60 (1 H, m), 2.90 (4 H, m), 3.41 (1 H, m), 3.76 (4 H, 2 s and m), 6.76 (2 H, m), 7.05 (3 H, m). This product was carried on directly to the hydrazine treatment.

(*S*)-1-(*p*-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (16a). A solution of 0.438 g (1.03 mmol) of the 1-(*p*-methoxybenzyl)octahydroisoquinolineformamide 14a in 7 mL of 95% EtOH, 0.27 mL (8 equiv) of hydrazine, and 0.18 mL of glacial acetic acid was heated at 50 °C under argon for 12 h. Upon cooling, the reaction mixture was taken up in diethyl ether, and the organic phase was washed with 20% KOH solution and dried over anhydrous K₂CO₃. Concentration under aspirator pressure (cold!) followed by bulb-to-bulb distillation at 80 °C (20 mmHg) afforded 0.127 g (75%) of the *tert*-butyl ether of (*S*)-valinol (17). Subsequent bulb-to-bulb distillation of the pot residue (0.05 mmHg, 110 °C) provided 0.214 g (81%) of the chiral secondary amine a viscous, colorless oil: ¹H NMR (CDCl₃) δ 1.64 (5 H, m), 1.92 (6 H, m), 2.75 (5 H, complex multiplets), 3.78 (3 H, s), 6.84 (2 H, d, *J* = 8 Hz), 7.14 (2 H, d, *J* = 8 Hz); [α]_D²⁴ -175.8° (c = 1.7 ether). The enantiomeric excess was determined on the α-naphthamide whose preparation follows.

α-Naphthamide 18. General Procedure. A stirred dichloromethane solution containing 16a or 16b (0.1 m) was treated with 5 equiv of triethylamine at room temperature. α-Naphthoyl chloride (1.5 equiv) was added and the mixture was stirred under dry nitrogen overnight. The solution was partitioned between dichloromethane and 10% aqueous KOH (1:1) and the aqueous layer separated. The aqueous phase was extracted (2 × 50 mL) with dichloromethane and combined with the dichloromethane solution previously obtained. After washing with brine, drying (K₂CO₃), and concentration, there remained a light yellow solid which was filtered through 2 in. of silica gel with ethyl acetate-hexane (1:3). No further purification was attempted to avoid enantiomer enrichment. The naphthamide thus obtained was injected as a concentrated ethyl acetate solution onto a J. T. Baker Column (see General Methods section) with 5% isopropyl alcohol-hexane as the eluent at 3.0 mL/min. The separations were base line for the racemic naphthamides, prepared in the same way from *tert*-butyl formamides,⁴ and >98% ee for the product from 16a, 16b (Figure 1).

(10) Private communication from Dr. Arnold Brosi, National Institutes of Health. Dr. Brosi has prepared 9, mp (oxalate salt, mp 183 °C) and performed elemental analysis which were in accordance with the calculated values.

(11) Schnider, O.; Brosi, A.; Vogler, K. *Helv. Chim. Acta* 1954, 37, 710.

(12) Schnider, O.; Grussner, A. *Helv. Chim. Acta* 1949, 32, 321.

(*S*)-*N*-Methyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (19a). A solution of 0.094 g (0.36 mmol) of the (*S*)-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (16a) in 2 mL of ethyl formate was heated at 40 °C for 15 h. The reaction mixture was concentrated in vacuo, and the crude formamide was dissolved in 5 mL of diethyl ether to which 0.035 g (0.92 mmol) of lithium aluminum hydride was added. After 2 h of stirring at room temperature, the reaction was quenched successively with 5 drops of water, 3 drops of 20% aqueous KOH solution, and 5 drops of water. The solution was filtered and concentrated, and the crude product was subjected to bulb-to-bulb distillation (0.05 mmHg; 110 °C), which afforded 0.088 g (89%) of the product as a colorless oil: ¹H NMR (CDCl₃) δ 1.75 (1 OH, m), 2.36 (3 H, s), 2.50 (1 H, m), 2.77 (2 H, m), 2.90 (2 H, m), 3.77 (3 H, s), 6.80 (2 H, d, *J* = 8.7 Hz), 7.16 (2 H, d, *J* = 8.6 Hz); ¹³C NMR (CDCl₃) δ 22.9, 23.2, 28.1, 28.2, 30.1, 35.7, 42.8, 47.3, 55.0, 66.2, 113.2, 127.0, 129.1, 129.8, 132.9, 157.3; [α]_D²⁵ -76.9° (c 2.9, ether), lit.¹¹ [α]_D²⁵ -78.9° (c 3.0, ether).

Dextrorphan [(+)-3-Hydroxy-17-methylmorphinan] (4a). A solution of 0.139 g (0.51 mmol) of 19a in 1 mL of phosphoric acid was heated¹² at 135–140 °C for 65 h under argon. The mixture was poured over ice and neutralized with concentrated ammonium hydroxide. Extraction with benzene-ether, drying (K₂CO₃), and concentration in vacuo gave a crude product which was purified via radial chromatography; silica gel, 1 mm thickness, eluted with hexane-triethylamine-ethyl acetate (60:15:25), to give 0.060 g (45%), mp 188–190 °C; [α]_D²⁴ +54.0° (c 3.0, ethanol). An authentic sample¹³ showed [α]_D²⁵ +56.3° (c 3.0, ethanol), mp 191–193 °C.

(13) We thank Dr. John Scott, Hoffmann-LaRoche for a sample. Previous preparation of (+)-4a has been described: Schnider, O.; Grüssner, A. *Helv. Chim. Acta* 1951, 34, 2211.

(*S*)-1-Benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (16b). In a manner analogous to the preparation of 16a, 16b was obtained in 82% yield and HPLC analysis of its naphthamide showed that the enantiomeric excess was 99 ± 1%. The product 16b was obtained as an oil, via bulb-to-bulb distillation (135 °C, 0.05 mmHg): ¹H NMR (CDCl₃) δ 1.7 (5 H, m), 1.9 (6 H, m), 2.8 (3 H, m), 3.2 (2 H, m), 7.3 (5 H, br s).

(*S*)-*N*-Methyl-1-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (19b). In a manner analogous to 19a, 19b was methylated in 82% yield to give an oil, purified by bulb-to-bulb distillation (135 °C, 0.05 mmHg): ¹H NMR (CDCl₃) δ 1.58 (4 H, m), 1.87 (6 H, m), 2.35 (3 H, s), 2.57 (1 H, t, *J* = 5 Hz), 2.84 (4 H, m), 7.23 (5 H, m); [α]_D²⁴ +9.9° (c 2.87, ethanol).

Morphinan 4b. In a manner similar to the formation of 4a, the octahydroisoquinoline 19b was heated in phosphoric acid to give 4b in 57% yield. The product was purified with radial chromatography using conditions identical with that employed for 4a: ¹H NMR (CDCl₃) δ 1.34 (7 H, m), 1.70 (3 H, m), 2.05 (1 H, d of t, *J* = 2.5, 12.2 Hz), 2.39 (3 H, s), 2.40 (2 H, m), 2.63 (1 H, dd, *J* = 5.6, 18.3 Hz), 2.80 (1 H, br m), 3.03 (1 H, d, *J* = 18.3 Hz), 7.15 (3 H, m), 7.24 (1 H, d, *J* = 7.6 Hz); [α]_D²⁴ +56.9° (c 1.50, ethanol). reported for the (–)-antipode, [α]_D²⁵ -56° (ethanol), mp 33–34 °C.¹⁴ 4b was obtained as an oil, which did not crystallize.

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Synthesis of Vinyl Selenides or Sulfides and Ketene Selenoacetals or Thioacetals by Nickel(II) Vinylation of Sodium Benzeneselenolate or Benzenethiolate

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The substitution of a bromine atom on a double bond by benzeneselenolate or benzenethiolate anions is catalyzed by the bis(bipyridine)nickel(II) bromide complex. Various alkenyl selenides or sulfides and seleno- or thioacetals are prepared in good to excellent yields.

A number of useful functional group transformations can be achieved with vinyl selenides or sulfides. Owing to their ability to stabilize carbanionic intermediates for further functionalization and/or the easy removal of the metalloid, they have been widely used in organic synthesis. As a matter of fact, their preparations have held attention these past years, and several methods have been proposed. The preparations of vinyl selenides generally imply multiple steps procedures involving addition of electrophilic selenium on triple or double bonds followed by elimination reactions¹ or Wittig-type reactions with α-selenated ylides.^{1f,2} Other possible preparations are the reaction of

phosphorus tetraiodide or triiodide with selenoacetals or seleno esters,^{1f} the reduction of phenylselenoalkynes,^{1d} the reaction of alkynyl trialkyl borates,^{1e} alkenylboranes, and alkenyl mercurials,^{1d} selenyl halides, or diaryl selenides, the addition of selenic acids^{1f,3} and selenols⁴ on alkynes, and the syn elimination of selenoacetals monoselenoxides.⁵ Vinyl sulfides are obtained by Wittig reaction⁶ or addition of a thiolate on a triple bond.⁷ Ketene thioacetals are prepared by Wittig,⁸ Wittig–Horner,⁹ and Peterson¹⁰ re-

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