(s, 6 H), 1.21 (s, 12 H), 3.64 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 21.99 (q), 24.04 (q, double intensity), 44.08 (s), 49.28 (s, double intensity), 51.47 (q), 178.16 (s); mass spectrum (70 eV), m/z (relative intensity) 213 ($M^+ - OCH_3$, 8), 185 (15), 143 (36), 111 (11), 102 (75), 83 (63), 73 (100), 55 (18), 41 (35). Anal. Calcd for $C_{13}H_{24}O_4$ (244.3): C, 63.91; H, 9.90. Found: C, 63.97; H, 10.11.

Partial Oxidation of 4. Compound **4** (0.81 g, 4.0 mmol), $NaIO_4$ (12.8 g, 60 mmol), $RuO_2 \cdot xH_2O$ (20 mg, 0.12 mmol), acetonitrile (16 mL), CCl_4 (12 mL), and 24 mL of water were stirred at ambient temperature for 26 h. After adding 50 mL of water the mixture was extracted with five 25-mL portions of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and filtered, and CH_2Cl_2 was evaporated under reduced pressure. The residue was dissolved in ether and filtered. The filtrate was extracted with aqueous sodium bicarbonate solution, and the two layers were worked up separately.

The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.264 g of a neutral product. According to GC analysis (4 m column 20% GE SE 30 on Chromosorb W AW DMCS 80-100 mesh, 220 °C column temperature), this product contained **10** (t_R 5.55 min, 30%), **4** (t_R 6.87 min, 5.5%), and **5** (t_R 7.77 min, 59%). Compound **10** (47 mg) was isolated from this mixture by medium-pressure liquid chromatography (RP 18, methanol/water, 95:5). **3,3,4,4,5,5-Hexamethylcyclopentane-1,2-dione (10)**:[15] IR (neat) 2966, 2872, 1750, 1738, 1475, 1459, 1454, 1382, 1276, 1145, 1099, 1060, 1032, 984 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 6 H), 1.20 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 20.69 (q), 21.88 (q, double intensity), 39.85 (s), 48.44 (s, double intensity), 208.95 (s); mass spectrum (70 eV), m/z (relative intensity) 182 (M^+, 14), 84 (100), 70 (21), 69 (47), 57 (11), 55 (9), 43 (16), 42 (9), 41 (27).

(15) Crandall, J. K.; Paulson, D. R. *J. Org. Chem.* **1968** *33*, 3291.

The sodium bicarbonate washings were stirred with charcoal, filtered, acidified with hydrochloric acid, and extracted with ether. The ether extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to give a mixture of carboxylic acids. Esterification was carried out by adding 2 mL of methanol and 15 mL of an ethereal solution of CH_2N_2.[14] The yellow solution was left under the hood overnight and concentrated under reduced pressure to yield 0.335 g of a mixture of methyl esters. GC analysis (230 °C column temperature, other conditions see above) indicated the following composition of the mixture: **7** (t_R 7.1 min, 6%), **11** (t_R 11.5 min, 67%), and two unidentified compounds with retention times of 15.6 and 19.1 min. Compound **11** (154 mg) was isolated from this mixture by medium-pressure liquid chromatography (RP 18, methanol/water, 85:15). **1,5-Bis(methoxycarbonyl)-2,2,3,3,4,4-hexamethyl-6-oxabicyclo[3.1.0]hexane (11)**: viscous oil; bp 145 °C (bath)/0.7 mbar; IR (neat) 2945, 1740, 1439, 1380, 1303, 1278, 1240, 1208, 1125, 1061, 1045, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 0.98 (s, 3 H), 1.09 (s, 6 H), 1.26 (s, 6 H), 3.75 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 20.94 (q, double intensity), 21.57 (q), 23.71 (q, double intensity), 26.75 (q), 44.79 (s, double intensity), 45.83 (s), 52.25 (q), 74.86 (s), 166.54 (s); mass spectrum (70 eV), m/z (relative intensity) 284 (M^+, 17), 269 (29), 241 (24), 225 (25), 193 (44), 165 (60), 155 (100). Anal. Calcd for $C_{15}H_{24}O_5$ (284.4): C, 63.36; H, 8.51. Found: C, 62.90; H, 8.56.

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Registry No. **1**, 934-53-2; **2**, 563-79-1; **3**, 594-57-0; **4**, 91324-94-6; **5**, 115942-54-6; **6**, 115942-55-7; **7**, 115942-56-8; **9**, 115942-57-9; **10**, 16980-19-1; **11**, 115942-58-0.

Communications

Radical Cyclizations in Conformationally Restrained Systems. Generation of the *cis,cis*-Hexahydrophenanthro(4,5-*bcd*)furan Tetracycle of Morphine

Summary: Tandem radical cyclization converts an appropriately substituted phenyl cyclohexenyl ether **1** to the cis,cis tetracyclic morphine model **2b** and its epimer **2a**. The stereochemical relationships in each isomer were determined by analysis of ^1H NMR decoupling and NOE experiments.

Sir: Radical reactions have generally been perceived as lacking in stereochemical predictability.[2] The requirement for stereoselectivity in the addition of a radical to an olefin may be simply stated (only one face of each prochiral center, either radical or olefinic carbon, can be available for reaction) but it is not easily fulfilled. Notable exceptions are those radical cyclizations leading to 5,5- or 5,6-cis-fused ring systems[2,3] in which reactive centers are subject to the conformational constraint of the short tether. Striking successes in the application of this methodology and its tandem variant for the synthesis of quinane[4] and indane[5] natural products have been reported.

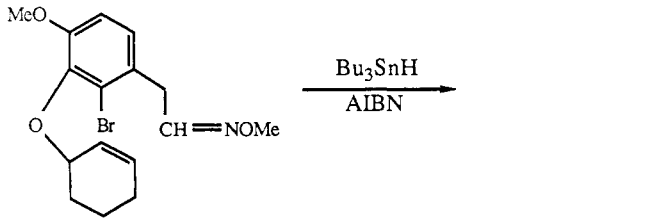
The use of radical cyclizations for the preparation of ring systems other than 5,5- or 5,6-cis fused has not been extensive.[6] Formation of larger rings may suffer from competitive side reactions[7] as well as uncertain stereochemical results. It seems plausible, however, that radicals generated with the proper spatial orientation in conformation-

(1) NSF Visiting Professorship for Women Recipient, 1987-1988; Guggenheim Fellow, 1988-1989.
(2) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883.
(3) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829.
(4) Curran, D. P.; Kuo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106 and references therein.
(5) Hart, D. J.; Huang, H.-C. *J. Am. Chem. Soc.* **1988**, *110*, 1634; *Tetrahedron Lett.* **1985**, *26*, 3749.
(6) Radical cyclizations that afford decalins have been reported; however, the stereochemical results are not of general predictive value as the substrates or conditions were special. (a) Cyclizations leading to *trans*-decalins in which one or more of the closures is reversible: Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386. (b) A cyclization leading to a *trans*-decalin in which copper salts are present: Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett.* **1968**, 1837. (c) A cyclization of a bridgehead radical: Buchi, G.; Wuest, H. *J. Org. Chem.* **1979**, *44*, 546. (d) Cyclization of 2-(3-butenyl)cyclohexenyl radical in which trace amounts of *cis*- and *trans*-decalin result from endo closure: Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811. (e) Cyclization of 4-(cyclohex-1-enyl)butyl and 2-methylenecyclohexylpropyl radical in which the stereochemistry of ring fusion is determined by the quenching of a 9-decalyl radical: Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem.* **1972**, *25*, 1081. See also ref d. (f) Reductive cyclization of a steroidal 2-(4-pentynyl)cyclohexanone which leads to a *cis*-decalin system: Pradhan, S. K.; Radhakrishnan, T. V.; Subramanian, R. *J. Org. Chem.* **1976**, *41*, 1943. (g) Cyclization of 4-(2,4-cyclohexadienyl)butyl radicals which affords *cis*-octalin systems: Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.
(7) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 593.

0022-3263/88/1953-4628$01.50/0

ally constrained systems would be subject to neither of these limitations.

In this context we report the reductive closure of phenoxycyclohexene 1 to the bridged hydrophenanthrenes **2a** and **2b**; this appears to be the first tandem radical cyclization initiated by an aryl radical and the first radical cyclization to form a bridged hydrophenanthrene structure. Several features of the second cyclization step are especially noteworthy: the efficient formation of a six-membered ring, the trapping of the cyclohexyl radical with the *O*-methyloxime group,[8] and the clean generation of the *cis*-decalin system[6] (see discussion below). This cyclization is viewed by us as a model for the eventual synthesis of morphine (**3**)[9-11] and a prototype of a general approach to the synthesis of convex polycyclic molecules.[12]



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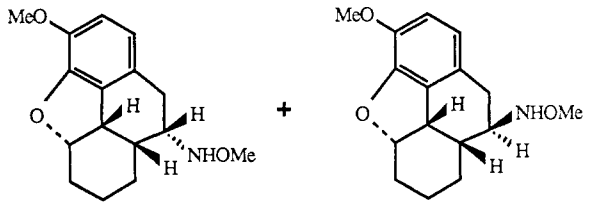
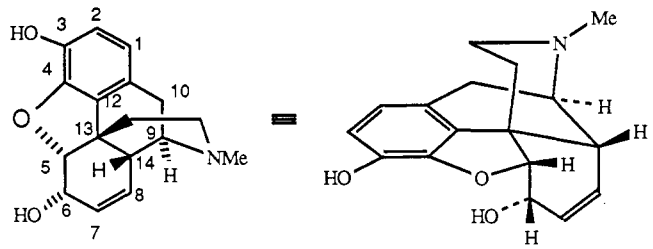
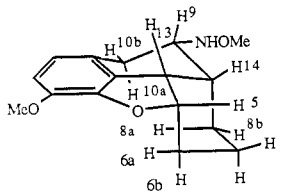


2a **2b**

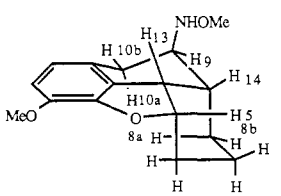


3, Morphine

Cyclization of the *O*-methyloxime **1**[13,14] was effected by heating 47 mg (0.13 mmol) of the substrate with 77 mg (0.26 mmol) of Bu_3SnH and 2.3 (0.013 mmol) of AIBN in 4 mL of benzene (140 °C, 1.5 days). Chromatotron separation of the components of the product mixture (eluent 1:3 EtOAc/hexane) resulted in the isolation of 15 mg (40%) of methoxyamine isomer I and 11 mg (31%) of methoxyamine isomer II.



2a (I)



2b (II)

	δ (ppm)			δ (ppm)	
H-5	4.99	q (J≈8Hz)	H-5	5.02	q (J≈8Hz)
H-13	3.43	m	H-13	3.53	m
H-14	2.51	m	H-14	2.44	m
H-9	3.48	m	H-9	3.42	m
H-8a	0.81	q (J≈12Hz)	H-8a	0.89	q (J≈12Hz)
H-10a	2.30	dd (J_{gem}=16.4Hz, J_{vic}=11.4Hz)	H-10a	2.75	dd (J_{gem}=18.0Hz, J_{vic}=5.3Hz)
H-10b	2.90	dd (J_{gem}=16.4Hz, J_{vic}=6.1Hz)	H-10b	2.64	d (J_{gem}=18.0Hz, J_{vic}≈0Hz)
H-6a	1.99	m	H-6a	1.99	m

Figure 1. ^{1}H NMR absorptions.

Assignments of the cis,cis-tetracyclic structures to products I and II were based on their proton NMR spectra;[13] for characteristic signals and correlation with structures **2a** and **2b**, see Figure 1.

The cis relationship of the C-5 and C-13 protons was suggested by the chemical shifts of the C-5 protons at 4.99 ppm for I and 5.02 ppm for II.[15] Closure of radical **4** to the cis-fused intermediate radical **5** had been predicted by examination of models and by comparison with the behavior of a closely related system in the literature.[16,17] Closure in the second step to give the cis fusion between rings B and C of the morphine skeleton (**5** → **6**) had also been predicted by examination of molecular models (see below); however, no related system had been tested by experiment.

Although innumerable morphine analogues have been prepared, the tetracyclic ring system of **2a** and **2b** is relatively rare.[18] Completion of the stereochemical assignments required extensive decoupling experiments. The cis relationship of H-13 and H-14 was established for each

(8) (a) An intramolecular trapping of a radical by an *O*-alkyloxime was reported by Corey in 1983: Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (b) A recent report on radical cyclizations terminated by oxime ethers indicates a precipitous decline in yields when the reaction involves formation of a six-membered ring: Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (c) Intermolecular trapping with *O*-benzylformaldoxime has been reported: Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631.

(9) 3,3-Dimethyldihydrobenzofurans are formed cleanly by cyclization of *O*-methallyloxy aryl radicals so long as additional aryl substituents do not promote neophyl rearrangement of the intermediate radical: Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833.

(10) A leading reference for other approaches to morphine synthesis is: Schultz, A. G.; Shannon, P. J. *J. Org. Chem.* **1985**, *50*, 4421. See also ref 9 and literature cited therein.

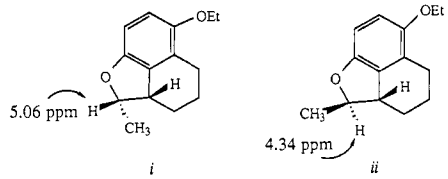
(11) A tandem anion-initiated cyclization (intramolecular conjugate addition/intramolecular alkylation) approach to morphine has been completed; see: Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473.

(12) The general problem of preparing convex systems has been discussed; see, for example: Eaton, P. E. *Tetrahedron* **1979**, *35*, 2189.

(13) Details are contained in the supplementary material.

(14) All new compounds exhibited IR and NMR spectra consistent with the structures assigned. Each afforded a molecular ion in the high-resolution mass spectrum.

(15) The models relevant for comparison here are *cis*- and *trans*-tetrahydronaphthofurans i and ii; see: Crow, W. D.; Engkaninan-Low, U.; Pang, Y. T. *Aust. J. Chem.* **1984**, *37*, 1915.

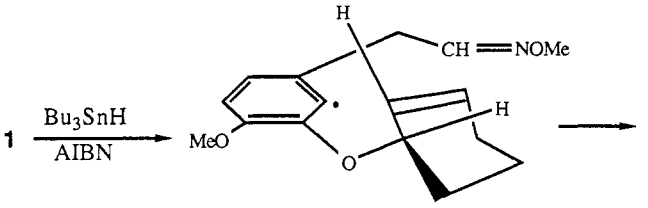


i *ii*

(16) Beckwith, A. L. J.; O'Shea, D. M.; Roberts, D. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1445.

(17) Formation of a five-membered ring by attack of an exocyclic radical on a preexisting cycloalkene double bond generally gives cis-fused systems: for specific examples, see the following. (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (c) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (d) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (e) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (f) An apparent exception to this tendency is seen in the cyclooctadienylpropyl radicals: Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708.

(18) Horaguchi, T.; Abe, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2437 and references therein.



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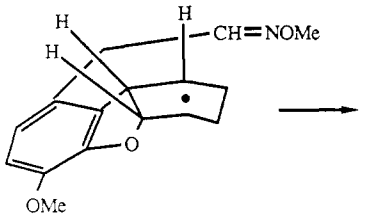
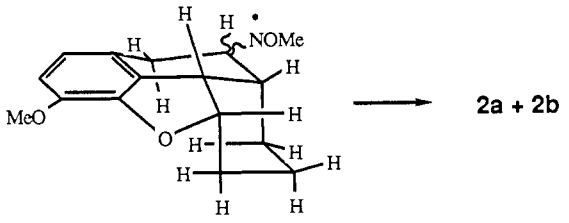


5A



6

isomer by the following procedure. First, H-13, H-14, and H-9 were identified by chemical shift and coupling constant data and by a sequence of decoupling experiments.[13] Then the H-14 signal was examined during irradiation of H-9. Thus, for isomer I, irradiation of the signal at 3.50 ppm resulted in the collapse of the multiplet at 2.51 ppm to a doublet of doublets of doublets with one large coupling constant ($J_{8a,14}$ = 12.6 Hz) and two smaller coupling constants ($J_{13,14}$, $J_{8b,14}$ = 4.9, 4.5 Hz). If the B,C ring fusion had been trans, this signal would have shown splitting with two large (diaxial) coupling constants; therefore, isomer I must have a cis,cis ring fusion. Likewise, for isomer II, irradiation of the multiplet at 3.42 ppm resulted in collapse of the multiplet at 2.44 ppm to a doublet of triplets ($J_{8a,14}$ = 12.6, and $J_{13,14}$ = $J_{8b,14}$ = 5.3 Hz); therefore, isomer II also has the cis,cis ring fusion.

The one-proton absorption in the 0.8–0.9-ppm region of each isomer was of particular interest; this seemed most probably to correspond to H-8a, strongly shielded by the ring current effect of the benzene ring.[19] This multiplet resembles a quartet with J = 12.6 Hz in the undecoupled spectrum. Irradiation of H-14 reduces this signal to an apparent triplet ($J \simeq 12$ Hz), confirming the vicinal trans-diaxial relationship of the high-field proton and H-14 in each isomer.

Identification of 0.8–0.9-ppm absorption with H-8a served as the basis of a solution to the remaining structural problem—the determination of which isomer was **2a** (the stereochemical analogue of the morphine alkaloids)[20] and which was **2b**. Observation of a nuclear Overhauser effect between H-8a and the benzylic (C-10) proton at 2.3 ppm in isomer I implied that the 2.3-ppm signal corresponds to an axial H-10a on a chairlike B ring.[21] The appearance of H-10a as a doublet of doublets with two large coupling constants shows that the adjacent H-9 is trans to H-10a and axial; therefore, isomer I is **2a**.[22] Similarly, an NOE was observed between H-8a in isomer II and the benzylic proton at 2.75 ppm.[23] In isomer II, the H-10a appears as a doublet of doublets and H-10b appears as a simple doublet (because the dihedral angle between H-10b and H-9 is approximately 90°).[22] Therefore, H-10a is axial and H-9 is equatorial and cis to H-10a; this confirms the assignment of isomer II as **2b**.

The closure of intermediate radical **5** to cis,cis-fused products may be rationalized by inspection of models. Only the conformation shown (**5A**)[13] seems capable of significant overlap between the radical center and the oxime π-system without the concomitant introduction of considerable strain.

It is noteworthy that radical **5** cyclizes to radical **6** rather than undergoing rearrangement by hydrogen-atom abstraction from the benzylic (C-10) methylene. It is possible that the transition state for this hydrogen migration is too strained to compete with intramolecular addition to the oxime functional groups.

Additional studies of the stereoselectivity of radical cyclizations in simple and complex systems are under way.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. CHE-8306687, continued as 8705647) and the Petroleum Research Fund, administered by the American Chemical Society (Grant No. 17787-AC1). NMR spectra were acquired with a Bruker WM250 spectrometer, purchased with funds from the National Science Foundation and from Montedison, SPA (Milan, Italy), and with a Bruker AM400WB spectrometer, purchased with funds from the National Science Foundation. The Kratos mass spectrometer was purchased with funds from the Division of Research Resources of the National Institutes of Health. We thank Professor R. G. Lawler for his helpful comments on the manuscript and Dr. George Chang for assistance with the Macromodel Program.

Supplementary Material Available: Scheme for the preparation of 1, NMR data and MM2 energies for **2a** and **2b**, and reactive conformations of radical **5** (9 pages). Ordering information is given on any current masthead page.

(19) A high-field absorption has been assigned to the similarly situated axial hydrogens in a *cis,cis*-decahydropyrene derivative; see: Sato, T.; Nishiyama, K.; Morita, A.; Iitaka, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2366.

(20) Data (400 MHz) for other morphine alkaloids are tabulated in Chazin and Colebrook: Chazin, W. J.; Colebrook, L. D. *J. Org. Chem.* **1986**, *51*, 1243. The 400-MHz spectrum of codeine is shown in this reference.

(21) NOE difference spectrum: during irradiation of the 0.8-ppm signal in isomer I, the doublet of doublets at 2.3 ppm was enhanced (1.5%); during irradiation at 2.3 ppm, the 0.8-ppm multiplet was enhanced (2.3%).

(22) MM2 calculations on the desmethoxy primary amines corresponding to **2a** and **2b** indicate that a chairlike B ring is favored for each. Coupling constants calculated by the MM2 program (B-ring chair and B-ring boat) are shown in the supplementary material. Although assignment of stereochemistry to **2a** and **2b** does not require the comparison of measured and calculated coupling constants, the correlation between these two sets of numbers was particularly satisfying.

(23) NOE difference spectrum: when the 0.8-ppm signal in isomer II was irradiated, the signals for both benzylic protons were enhanced (1.6%, 1.6%). Although one might have anticipated enhancement of only the H-10a signal, it is reasonable to assume that H-10b is being enhanced through intensity borrowing. Indeed, irradiation of the 2.65-ppm signal gave no NOE for the 0.8-ppm signal; irradiation of the 2.75-ppm signal gave a 0.8% NOE for the 0.8-ppm signal.

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