Table I. Reductions of Alkyl Halides by Sodium Borohydride Catalyzed by Polyether Phase-Transfer Catalysts and Tri-*n*-Butyltin Chloride[a]

substrate	catalyst	$10^5 k_{obsd}$ (s^{-1})	$10^5 k_{obsd}$ (s^{-1} $M_{cat.}^{-1}$)
1-bromooctane	1	0.0[b]	0[b]
	1	0.1	25[c]
	1	1.2	300
	2	0.0[b]	0[b]
	2	0.15	54
1-bromodecane	1	0.75	200
	2	0.12	48
1-bromododecane	1	1.1[d]	275[d]
	1	2.1[d]	263[d]
	1	3.2[d]	267[d]
	2	0.13[e]	48[e]
	2	0.30[e]	53[e]
	3	0.8	60
1-bromonaphthalene	2	3.2	45
bromocyclohexane	2	0.2	72
chlorocyclohexane	3	0.12	35
1-chlorooctane	3	0.10	30
benzyl chloride	2	0.9	225
1-bromooctadecane	1	4.0	60

[a] Reactions were typically run at 110 °C using toluene suspensions containing a 12-fold excess of sodium borohydride that were 4 mM in crown catalyst (5% catalyst), 8 mM in tri-*n*-butyltin chloride. An excess of tri-*n*-butyltin chloride was used in all reactions in this table unless otherwise noted. Reactions were analyzed by GC. In all examples in this table, the starting organic halide was completely consumed. GC yields of hydrocarbons were consistently 95% or better. Reaction rates were measured by using the procedures described in ref 2. [b] No phase-transfer catalyst was used. [c] No tri-*n*-butyltin chloride was added to the reaction. [d] The amount of crown ether used in these reactions was varied from 0.004 to 0.012 M. [e] The concentration of the oligomeric crown ether was varied from 0.0024 to 0.0057 M.

first procedure uses a less reactive hydride source, it requires the use of an alcoholic solvent to prepare a solution of the hydride reagent.[8] The procedure described in this communication extends this procedure by avoiding the need to dissolve the penultimate hydride source.

Kinetic studies using varying concentrations of tri-*n*-butyltin chloride and crown ether 1 showed that mequiv ratios of $1/R_3SnCl$ of less than 1 led to lower overall reaction rates. However, if at least 1 mequiv of tin chloride were used per mequiv of crown catalyst, further changes in the amount of the tin halide did not affect the reaction rate. So long as a slight excess of tin halide was present, the reaction rate was linearly dependent on the concentration of 1 as expected.

Crown ethers 1 and 2 and the poly(ethylene glycol) derivative were all effective as cocatalysts in reaction 1. However, reactions using equivalent concentrations of 2 or 3 were slower than reactions using 1 as catalyst. We previously noted similar, lower rates for phase-transfer-catalyzed reactions using such polyethylene-bound crown ethers. Nonetheless, 2 or 3 could be used if higher amounts of the polyether catalyst were added to compensate for the lower rate.[10] The need to use larger amounts of 2 or 3 over 1 is compensated for by the fact that 2 can be recovered and reused in subsequent reactions and by the fact that 3 is less expensive than 1.

The preparation of octadecane from 1-bromooctadecane is a representative procedure for this reaction. To a dry, 250-mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser were added 5 g (125 mmol) of $NaBH_4$, 6.4 g (20 mmol) of 1-bromooctadecane, 5 g of 2 (1.8 mequiv), and 125 mL of dry toluene. Heating this heterogeneous mixture to 110 °C dissolved the oligomeric crown ether. Addition of 0.7 g (2.1 mmol) of tri-*n*-butyltin chloride at this point initiated the reaction. After 36 h, GC analysis showed that the reaction was complete and the reaction mixture was cooled to 25 °C. After filtration to remove the oligomeric crown ether and excess $NaBH_4$, the solvent was removed. The product isolated in this manner was purified by distillation to yield 4.0 g (80% yield) of octadecane. The oligomeric crown ether was recovered and reused following previously described procedures.[2] Identical procedures were effective in reactions using 3. Reactions using 1 could be carried out on a similar time scale using less catalyst or in shorter times using 10% catalyst as in this procedure.

(10) The amount of catalyst was increased from 5% to 10% in preparative runs using the oligomeric catalyst to shorten reaction times. Reactions with increased amounts of polyether catalyst did not require a concomitant increase in the amount of tin reagent.

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David E. Bergbreiter,* J. R. Blanton
Department of Chemistry
Texas A&M University
College Station, Texas 77843
Received October 20, 1986

Total Synthesis of *dl*-Morphine[1]

Summary: The synthesis of racemic morphine from 2-allylcyclohexane-1,3-dione and isovanillin is described.

Sir: As the cornerstone strategy in our approach to the morphine ring system we desired to effect the intramolecular conjugate addition of the aryloxy anion 1 to the β-substituted vinyl sulfone terminus, thereby providing incipient α-sulfonyl anion 2 which would suffer further intramolecular alkylation providing tetracyclic sulfone 3 in a single operation (Scheme I).

Treatment of isovanillin (4) as outlined in Scheme II afforded dibromophenol 5 in 40% overall yield on large scale. Reaction of 2-allylcyclohexane-1,3-dione (6)[3] with oxalyl chloride[4] (to give 7) followed by addition–elimination with sodium benzenesulfinate provided β-sulfonyl enone 8 (74% overall). Conversion of 8 to its silyl enol ether[5] followed by MCPBA oxidation[6] afforded the α-silyloxy ketone 9. Reduction[7] of 9 provided cis alcohol 10 (62% overall from 8). Mitsunobu coupling[8] of phenol 5 with alcohol 10 produced *trans*-silyloxy aryl ether 11 which was desilylated[9] to give alcohol *t*-12 (80% for the two steps). Jones oxidation[10] of *t*-12 followed by DIBAL-H reduction[11] afforded epimeric alcohol *c*-12 (90% yield).

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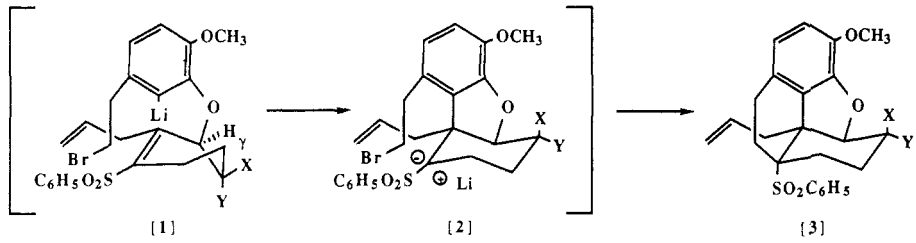
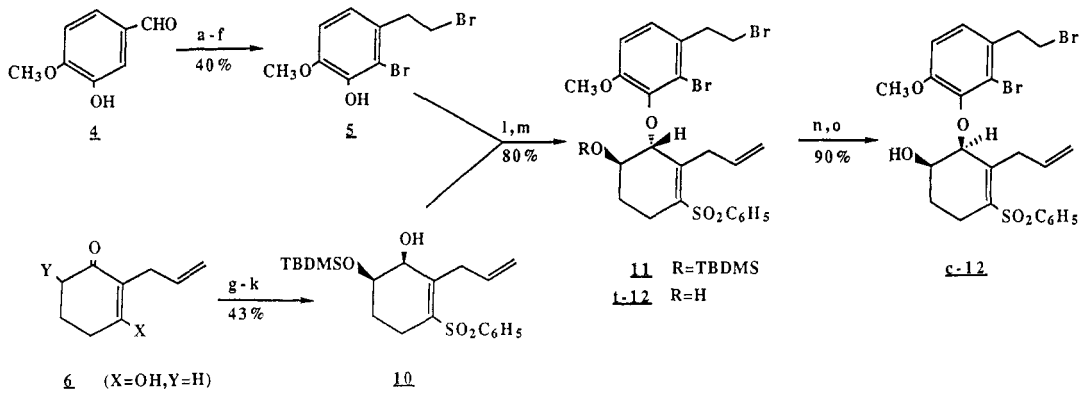
Scheme I



[1] [2] [3]

Scheme II[a]



4 5 11 R=TBDMS t-12 R=H c-12

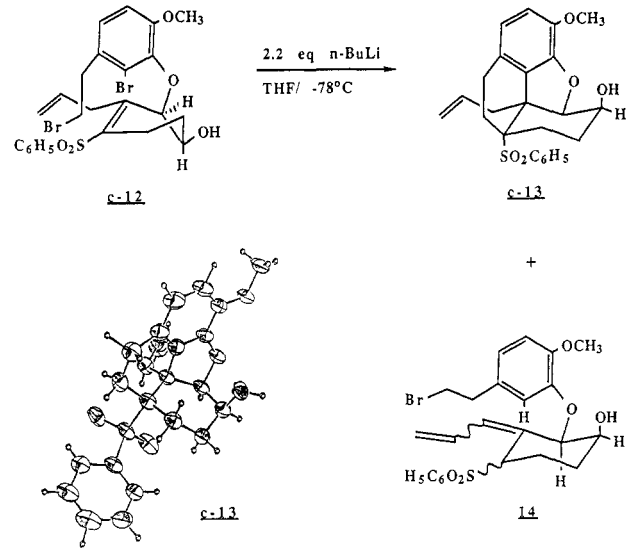
6 (X=OH,Y=H) 10
7 (X=Cl,Y=H)
8 (X=$SO_2C_6H_5$,Y=H)
9 (X=$SO_2C_6H_5$,Y=OTBDMS)

[a] (a) Br_2/HOAc/NaOAc, 2 h, 25 °C (70%);[2] (b) H_3COCH_2Cl/NaH/DMF, 18 h, 25 °C (80%); (c) $(C_6H_5)_3P^+CH_3I^-$/5 N NaOH/C_6H_6, 12 h, 25 °C (86%); (d) $(Sia)_2BH$/THF, 1 h, 0 °C, then H_2O_2/NaOH, 1 h, 0 °C (95%); (e) TsOH/CH_3OH, 4 h, 25 °C (93%); (f) CBr_4/$(C_6H_5)_3P$/CH_3CN, 1 h, 25 °C (92%); (g) $(COCl)_2$/$CHCl_3$, 1 h, 61 °C (82%); (h) $C_6H_5SO_2^-Na^+$/cat. n-$Bu_4N^+HSO_4^-$/C_6H_6, 40 h, 60 °C (90%); (i) TBDMSOTf/$(Et)_3N$/CH_2Cl_2, 1 h, 25 °C; (j) MCPBA/CH_2Cl_2, 2 h, −78→25 °C (62% from 8); (k) $CeCl_3$/$NaBH_4$/CH_3OH/CH_2Cl_2, 0.5 h, −20→0 °C (95%); (l) n-Bu_3P/DEAD/THF, 0.5 h, 25 °C (85%); (m) 48% HF/CH_3CN, 4 h, 25 °C (95%); (n) $(CrO_3$/aq. $H_2SO_4)$/$(CH_3)_2CO$, 3 h, 0 °C; (o) DIBAL-H/THF, 1 h, −78→25 °C (90% from t-12).

Treatment of alcohol t-12 with 2.2 equiv of n-butyllithium in THF at −78 °C followed by warming and quenching with aqueous ammonium chloride provided an inseparable mixture of at least three compounds.[12-14] Similar treatment of the isomeric alcohol c-12 provided far more spectacular results. Tetracyclic sulfone c-13 was isolated as a beautiful crystalline material from this reaction (45%); chromatography of the mother liquors afforded an additional 15% of c-13 as well as 10% of alcohol 14. Verification of the structure of c-13 was provided by X-ray crystallography (Scheme III).[15]

Catalytic osmylation of c-13[16] followed by lead tetraacetate cleavage of the resulting diols afforded aldehyde 15 in 85% overall yield. Reaction of 15 with methylamine hydrochloride and sodium cyanoborohydride[17] in methanol followed by acylation of the resultant secondary amine with (trimethylsilyl)ethoxy chloroformate (TEOC-Cl)[18] provided urethane 16 in 85% yield for the two-step process. Swern oxidation[19] of the secondary alcohol followed by treatment of the resulting ketone with trimethyl orthoformate in acidic methanol afforded enol ether 17 after a workup involving treatment with TEOC-Cl to reacylate a small amount of amine resulting from competing ure-

Scheme III



c-12 c-13 c-13 14

(12) Inspection of the 50-MHz carbon NMR of this mixture suggests that these products result from deprotonation at both the γ[13] and the γ' position of t-12 to produce a pair of delocalized sulfonyl anions which afford the observed product mixture by quenching at the α position to the sulfone moiety. Inspection of the crude product mixture fails to reveal the presence of any of the desired tetracyclic alcohol t-13, an authentic sample of which was prepared from c-13 by oxidation and reduction.

(13) Presumably the γ-deprotonation is occurring via an intramolecular process (see: Hamann, P. R.; Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1984**, *49*, 3865.

(14) A large number of additional substrates were examined in this cyclization reaction and these results will be discussed in detail in the full paper.

(15) Single-crystal X-ray analysis by P. E. Fanwick, Purdue University, Department of Chemistry, West Lafayette, IN 47907.

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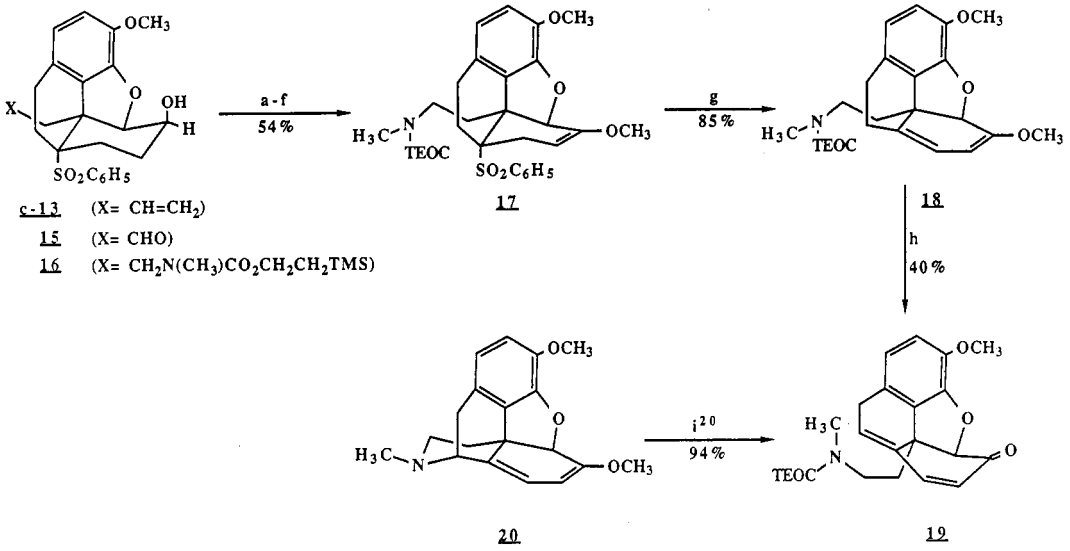
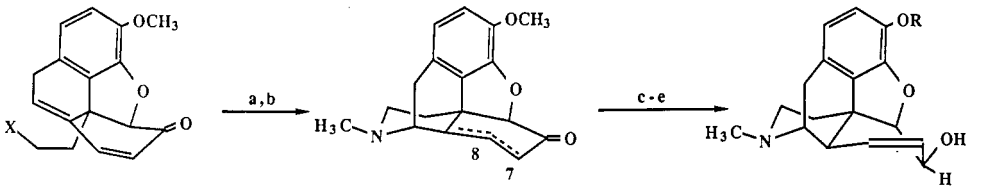
Scheme IV[a]



[a] (a) cat. OsO_4/NMO/aq. $(CH_3)_2CO$, 9 h, 25 °C; (b) $Pb(OAc)_4/CHCl_3$, 0.1 h, 25 °C (85% from *c*-**13**); (c) $H_3CNH_2 \cdot HCl/CH_3OH/NaBH_3CN$, 24 h, 25 °C; (d) $(CH_3)_3SiCH_2CH_2OCOCl/CH_2Cl_2$/aq. $NaHCO_3$, 0.2 h, 25 °C (85% from **15**); (e) $Me_2SO/TFAA/CH_2Cl_2$, then $(Et)_3N$, 1 h, −78→−20 °C (95%); (f) $(CH_3O)_3CH/CH_3OH$/PTSA, 1 h, 65 °C, then (d) (80%); (g) $(CH_3)_3CO^-K^+$/THF, 3 h, 25 °C (85%); (h) DDQ/PTSA/$CHCl_3/H_2O$, 3 h, 25 °C (40%); (i) $(CH_3)_3SiCH_2CH_2OCOCl$/EtOAc/aq. $NaHCO_3$, 0.5 h, 25 °C (94%).

Scheme V[a]



[a] (a) CF_3CO_2H, 5 min, 25 °C (90%); (b) $CHCl_3$/aq. $NaHCO_3$, 0.3 h, 25 °C (60%); (c) $HCl/(Et)_2O/CH_2Cl_2$, 0.5 h, 25 °C, then 0.2 N NaOH/$CHCl_3$ (95%); (d) $NaBH_4/CH_3OH$, 0.5 h, 25 °C (95%); (e) $BBr_3/CHCl_3$, 0.5 h, 25 °C.

thane cleavage (75% from **16**). Reaction of **17** with potassium *tert*-butoxide in THF at room temperature smoothyl afforded dienyl ether **18** (85%). Oxidation of this material with DDQ[20] provided the reacemic TEOC-dienone **19** (40%) which was identical in all respects (except rotation) with an authentic sample prepared from natural thebaine **20** (Scheme IV).[21]

Culmination of the total synthesis involved the application of established processes to the racemic substrates (Scheme V).[21] Reaction of **19** with trifluoroacetic acid produced dienone-ammonium salt **21** which upon neutralization spontaneously underwent an intramolecular 1,6-Michael addition to the dienone. The resulting mixture of codeinone **22** and neopinone **23** (63% from **19**) was isomerized to codeinone **22** by the method of Rapoport employing the 8-chlorodihydrocodeinone intermediate.[22] Sodium borohydride[23] reduction of *rac*-**22** afforded racemic codeine **24** which was identical with natural codeine[24] by 470-MHz ^1H NMR and ^{13}C NMR. O-Demethylation by the method of Rice[24] provided racemic morphine **25**, identical with natural morphine[24] by TLC, 200-MHz ^1H NMR, and ^{13}C NMR (50% from **22**, **23**). Thus, the overall yield of morphine **25** from 2-allylcyclohexane-1,3-dione **6** and isovanillin **4** was 1.1%.

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Registry No. **4**, 2973-58-2; **5**, 105728-94-7; **6**, 32774-70-2; **7**, 50314-05-1; **8**, 105728-95-8; (±)-**9**, 105728-96-9; (±)-**10**, 105728-97-0; (±)-**11**, 105728-98-1; (±)-**c-12**, 105728-99-2; (±)-**t-12**, 105729-00-8; (±)-**c-13**, 105729-01-9; (±)-**15**, 105729-02-0; (±)-**16**, 105729-03-1; (±)-**17**, 105729-04-2; (±)-**18**, 105729-05-3; (±)-**19**, 105816-46-4; **20**, 115-37-7; (±)-**21**, 105816-48-6; (±)-**22**, 105815-00-7; (±)-**23**, 105762-42-3; (±)-**24**, 70982-46-6; (±)-**25**, 70982-47-7.

Supplementary Material Available: Tables of atomic coordinates, bond distances, bond angles, and crystal and collection parameter data (12 pages). Ordering information is given on any current masthead page.

J. E. Toth, P. L. Fuchs*

Department of Chemistry
Purdue University
West Lafayette, Indiana 47907

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