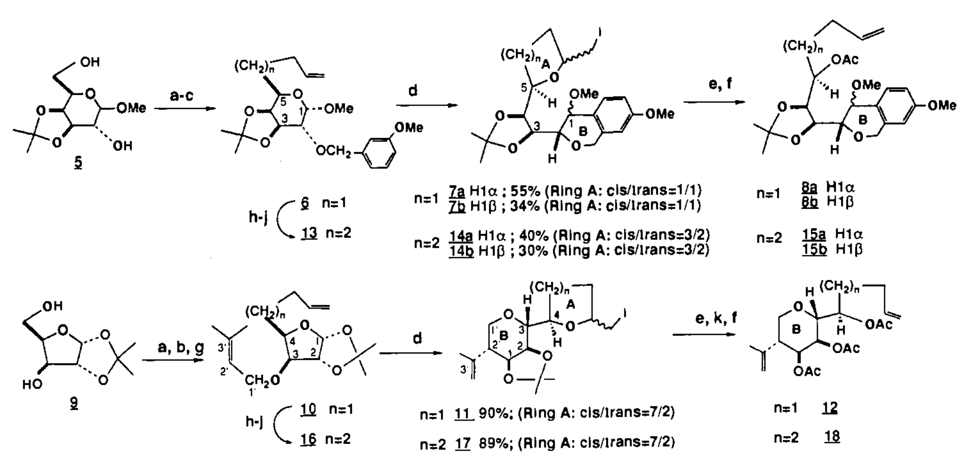
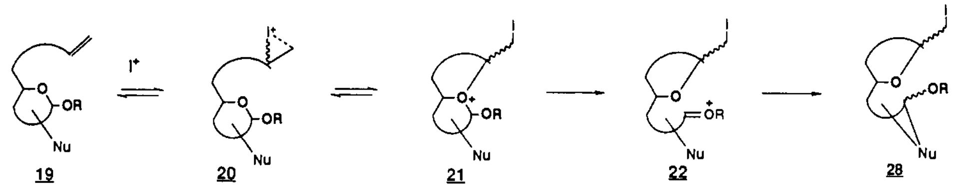
Scheme II[a]



[a] Reagents: (a) PhH, Ph_3P, I_2, imidazole; (b) allyltributyltin, AIBN, PhH, 80 °C; (c) NaH, 3-$MeOC_6H_4CH_2Cl$, Bu_4NI, DMF; (d) $I(coll)_2ClO_4$, CH_2Cl_2; (e) Zn, EtOH, reflux; (f) Ac_2O, DMAP, EtOAc; (g) $(Me)_2C{=}CHCH_2Br$, NaH, Bu_4NI, DMF; (h) 9-BBN, THF, then Na_2O_2; (i) Swern's oxidation; (j) $Ph_3P{=}CH_2$, THF; (k) MeOH, HCl.

Scheme III



and furanoside substrates. Since these test compounds are very sterically crowded and conformationally restricted, this reaction should be equally successful for simpler systems, where the transition state for this step is expected to be less highly strained. It should also be noted that products arising from direct electrophilic attack on the nucleophilic residues were not observed in any of these cases. Since these nucleophiles are very electron rich, electrophile–nucleophile compatibility problems are not anticipated for less electron rich nucleophiles.

The relative reactivities observed for the different substrates are interesting from a mechanistic standpoint. Since the intramolecular trapping of **3** is expected to be fast, the higher reactivities for the more strained furanoside compared to the pyranoside substrates in both RO5 (**10**, <10 min vs **6**, ~45 min) and RO6 (**16**, ~45 min vs **13**, ~16 h) initiated reactions suggest that the slow step in the overall transformation **1** → **3** is the cleavage process (**2** → **3**), rather than the participation reaction (**1** → **2**). In view of this observation and the proven reversibility of oxonium ion formation in the related halocyclization reaction of alkoxyalkene derivatives,[15,18] a mechanism in which all steps leading to the formation of the bicyclic oxonium ion intermediate **21** are reversible, followed by a slow, irreversible fragmentation step, is postulated (Scheme III).

In summary, this methodology illustrates the way in which neighboring group participation mechanisms may be used to effect regiospecific cleavage of acetal bonds under mild, nonacidic, reaction conditions, leading to oxonium ions which may be then subjected to known chemistry. Specifically, by using monosaccharides as the acetal templates, highly substituted oxocarbenium ions are accessible, and their trapping by strategically located internal carbon nucleophiles constitutes a novel approach to bis-cyclic ether frameworks containing several stereogenic centers. Our current investigations are probing stereochemical aspects and also the use of other combinations of electrophilic and nucleophilic residues, particularly aimed at effecting efficient medium ring formation.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Supplementary Material Available: Listing of experimental and spectral details for the cyclization precursors and products (4 pages). Ordering information is given on any current masthead page.

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(18) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III *J. Org. Chem.* **1987**, *52*, 4191.

Synthesis and Characterization of an Aluminosilsesquioxane Framework That Violates Loewenstein's Rule

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Received August 10, 1992

According to "Loewenstein's rule"[1-4] the distribution of aluminum atoms in aluminosilicates is not entirely random:

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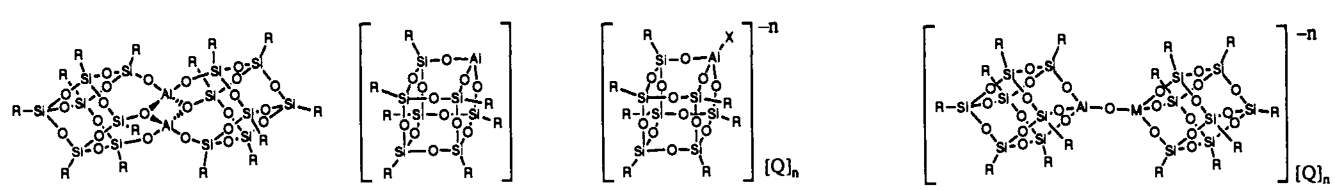
(1) Loewenstein, W. *Am. Mineral.* **1954**, *39*, 92–96.

(2) For selected reviews with discussions of Si/Al ordering in aluminosilicates, see: (a) Fyfe, C. A.; Feng, T.; Grondey, H.; Kokotailo, G. T.; Gies, H. *Chem. Rev.* **1991**, *91*, 1525–43. (b) Klinowski, J. C. *Chem. Rev.* **1991**, *91*, 1459–79. (c) Engelhardt, G.; Michel, D. *High Resolution Solid-State NMR of Silicates and Zeolites*; Wiley: New York, 1987. (d) Thomas, J. M.; Catlow, C. R. A. *Prog. Inorg. Chem.* **1987**, *35*, 1–49. (e) Klinowski, J. *Prog. NMR Spectrosc.* **1984**, *16*, 237–309. (f) Liebau, F. *Structural Chemistry of Silicates*; Springer-Verlag: Heidelberg, 1985. (g) Barrer, R. M. *Hydrothermal Chemistry of Zeolites*; Academic Press: New York, 1982. (h) Barrer, R. M. *Zeolites and Clay Minerals as Sorbents and Molecular Sieves*; Academic Press: New York, 1978. (i) Breck, D. W. *Zeolite Molecular Sieves: Structure, Chemistry and Use*; Wiley: London, 1974.

(3) Other discussions of Si/Al ordering: (a) Earley, C. W. *Inorg. Chem.* **1992**, *31*, 1250–5. (b) Klinowski, J.; Ramdas, S.; Thomas, J. M.; Fyfe, C. A.; Hartman, J. S. *J. Chem. Soc., Faraday Trans. 2* **1982**, *78*, 1025–50. (c) Barron, P. F.; Slade, P.; Frost, R. L. *J. Phys. Chem.* **1985**, *89*, 3880–5. (d) Lipsicas, M.; Raythatha, R. H.; Pinnavaia, T. J.; Johnson, I. D.; Giese, R. F.; Costanzo, P. M.; Robert, J.-L. *Nature* **1984**, *309*, 604–6. (e) Melchior, M. T.; Vaughan, D. E. W.; Jacobson, A. J. *J. Am. Chem. Soc.* **1982**, *104*, 4859–64.



1 R = c-C_6H_{11}

2

3 X = OH n = 1 Q = Me_4Sb^+
4 O 2 Me_4Sb^+/Me_4P^+
5 $OSbMe_4$ 1 Me_4P^+

6 M = Al n = 2 Q = Me_4Sb^+/Me_4P^+
7 Si 1 Me_4Sb^+

Figure 1.

"whenever two (MO_4; M = Al or Si) tetrahedra are linked by one oxygen bridge, the center of only one of these can be occupied by aluminum; the other center must be occupied by silicon...".[1] As generally (and sometimes liberally) interpreted this so-called "aluminum avoidance rule" is frequently used to dismiss the possibility that $[O_3AlOAlO_3]^{2-}$ groups play any role in the chemistry of aluminosilicates and zeolites.[4] In this communication we describe the synthesis and characterization of an interesting doubly anionic aluminosilsesquioxane which violates Loewenstein's rule. The implications of this result for the chemistry of zeolites are briefly discussed.

As reported earlier,[5] dimer **1** is an excellent latent source of **2**; it reacts with a variety of neutral and anionic Lewis bases to afford stable adducts. The reaction of **1** with Me_4SbOH (C_6H_6, 25 °C, 4 h)[6] affords a quantitative (NMR) yield of **3**, which can be isolated as poorly diffracting colorless crystals (65%) by allowing hexane or acetonitrile to diffuse slowly into a benzene solution of **3**. Four-coordinate Al complexes containing anionic $[O_3AlOH]$ moieties with nonbridging hydroxyl groups are quite rare,[7] but combustion analysis, multinuclear NMR spectra, and a solution molecular weight determination for **3** provide a compelling case for its assignment as an anionic aluminosilsesquioxane with four-coordinate Me_4Sb^+ ions.[8]

The hydroxyl group of **3** is poorly acidic, but it can be readily deprotonated by Me_3PCH_2 (C_6D_6, 25 °C, 3 h),[9] which is one of the few strong bases that does not initiate the polymerization of silsesquioxane frameworks; subsequent reaction of the intermediate dianion (i.e., **4**) with Me_4Sb^+ affords **5**.[10] The reaction of **5** with 0.5 equiv of **1** (C_6D_6, 80 °C, 15 min) affords an 80% NMR yield of **6**, which can be isolated (20%) as large benzene-solvated crystals by slow evaporation of the solvent. Analytical and NMR spectral data[11] for **6** strongly supported its formulation as a dianionic aluminosilsesquioxane with discrete Me_4Sb^+ and Me_4P^+ ions; this structure was confirmed by a preliminary single-crystal X-ray diffraction study.[12]

Large numbers of $[O_3AlOAlO_3]^{2-}$ groups are formed when network aluminates are assembled from corner-sharing $[AlO_{4/2}]^-$ groups,[13] yet a notion persists among many in the field that $[O_3AlOAlO_3]^{2-}$ groups are too unstable to form in aluminosilicates. Our synthesis of **6** clearly provides no alternative to the formation of $[O_3AlOAlO_3]^{2-}$ groups. Nevertheless, the dissociation of dimer **1** by **5** still requires that the energy of the newly formed Al–OAl bond be comparable to the sum of bond energies for both the Sb–O bond in **5** and a dative Al–O bond in **1**. In light of the observation that **1** is only dissociated by good donor ligands[5] and the fact that **4** is more strongly attracted to **2** than a positively charged $[Me_4Sb]^+$ ion, the new Al–O bond must be quite strong. In fact, replacement of the electron-donating cyclohexyl groups in **6** by electron-withdrawing oxygen atoms (e.g., an extended silicate lattice) would be expected to produce an even stronger Al–O–Al linkage. Despite plenty of folklore to the contrary—including the original arguments presented by Loewenstein—the formation of $[O_3AlOAlO_3]^{2-}$ groups appears to be quite favorable.

From a practical standpoint, Loewenstein's aluminum avoidance rule provides a convenient guide for predicting and rationalizing the structures of Al distributions in aluminosilicates. At the molecular level, however, the thermal stability of $[O_3AlOAlO_3]^{2-}$ groups leads to the expectation that all aluminosilicates prepared under hydrothermal conditions should contain some $[O_3AlOAlO_3]^{2-}$ groups. The enthalpic preference for aluminum avoidance may limit the number of these groups in an aluminosilicate—perhaps beyond the detection limits of current analytical techniques—but the entropically driven tendency to randomize placement of Al and Si in available $[MO_{4/2}]$ lattice sites should prevent complete isolation of individual $[AlO_4]^-$ sites. For most purposes, small numbers of $[O_3AlOAlO_3]^{2-}$ groups will be of no practical significance, but in catalysis—where exceedingly small concentrations of highly active sites can be responsible for all of the observed chemistry—the rigorous extrapolation of Loewenstein's simple rule to the molecular level is not reasonable. Like all empirical "rules", the aluminum avoidance rule named in honor of Walter Loewenstein should not be too literally interpreted.

A full account of our work in this area, including our efforts to measure equilibrium constants for the hydrolysis of **6** and **7**,[5b] as well as relative acidities and basicities for aluminosilsesquioxanes **3**, **6**, and **7**, will appear in due course.[14]

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(4) For an excellent commentary, see ref 2c, pp 219–222.

(5) (a) Feher, F. J.; Budzichowski, T. A.; Weller, K. J. *J. Am. Chem. Soc.* **1989**, *111*, 7288–9. (b) Feher, F. J.; Weller, K. J. *Organometallics* **1990**, *9*, 2638–40.

(6) Schmidbaur, H.; Arnold, H.-S.; Beinhofer, E. *Chem. Ber.* **1964**, *97*, 449.

(7) A search of the Cambridge Crystallographic Database revealed one example: $(Me_4N)_4(Si_4Al_4O_{12}(OH)_8)\cdot 24H_2O$: Smolin, Yu. I.; Shepelev, Yu. F.; Ershov, A. S.; Hoebbel, D. *Dokl. Akad. Nauk SSSR* **1987**, *297*, 1377–80.

(8) Selected data[15] for **3**: $^{13}C\{^1H\}$ NMR (125.03 MHz, C_6D_6, 25 °C) δ 25.65, 24.61, 24.24, (3:3:1 for *C*H), 4.72 (for Sb*Me*$_4$); ^{17}O NMR (67 MHz, C_6D_6, 25 °C) δ 44 ($w_{1/2}$ 1400 Hz for Al*O*H).

(9) (a) Schmidbaur, H. *Chem. Ber.* **1968**, *101*, 595–603. (b) Koster, R.; Simic, D.; Grassberger, M. A. *Liebigs Ann. Chem.* **1970**, *739*, 211–9. (c) Koster, R.; Simic, D.; Grassberger, M. A. *Inorg. Synth.* **1978**, *18*, 138–39.

(10) Selected data[15] for **5**: $^{13}C\{^1H\}$ NMR (125.03 MHz, C_6D_6, 25 °C) δ 26.16, 24.74, 24.31, (3:3:1 for *C*H), 14.21 (for Sb*Me*$_4$), 9.83 (d, J_{CP} = 54 Hz for P*Me*$_4$); $^{31}P\{^1H\}$ NMR (202 MHz, C_6D_6, 25 °C) δ 22.41 vs 85% H_3PO_4 (0.0 ppm); ^{17}O NMR (67 MHz, C_6D_6, 25 °C) δ 145 ($w_{1/2}$ 1400 Hz for Al*O*SbMe$_4$).

(11) Selected data[15] for **6**: $^{13}C\{^1H\}$ NMR (125.03 MHz, C_6D_6, 25 °C) δ 26.61, 24.87, 24.24, (3:3:1 for *C*H), 1.68 (for Sb*Me*$_4$), 10.32 (d, J_{CP} = 56 Hz for P*Me*$_4$); $^{31}P\{^1H\}$ NMR (202 MHz, C_6D_6, 25 °C) δ 22.88 vs 85% H_3PO_4 (0.0 ppm); ^{17}O NMR (67 MHz, C_6D_6, 25 °C) δ 27 ($w_{1/2}$ = 2900 Hz for Al*O*Al).

(12) (a) Weakly diffracting crystals of **6** were eventually obtained from benzene. The molecule crystallizes (with six molecules of benzene) as isolated cations and anions in the space group *C*2/*c*. The bridging oxygen is located on a 2-fold axis of rotational symmetry, which generates the Al/Si/O framework from a single $[AlSi_7O_{12}]$ cage. The Me_4Sb^+ and Me_4P^+ ions, as well as three of the seven independent cyclohexyl rings, are disordered; the current R_F is ~14%. The poor quality of the X-ray structure does not permit a meaningful discussion of metrical data, but the solution is good enough to definitively establish Al/Si/O connectivity. (b) Full details regarding the X-ray structure of **6** are provided in the supplementary material.

(13) (a) Depmeier, W. *Acta Crystallogr.* **1984**, *C40*, 226–31. (b) Sahl, K. *Z. Kristallogr.* **1980**, *152*, 13–21. (c) Gebert, W. *Z. Kristallogr.* **1972**, *135*, 437–52. (d) Saalfeld, H.; Depmeier, W. *Krist. Tech.* **1972**, *7*, 229–33. (e) Ponomarev, V. I.; Kheiker, D. M.; Belov, N. V. *Kristallografiya* **1970**, *15*, 918–21. (f) Perrotta, A. J.; Smith, J. V. *Bull. Soc. Fr. Mineral. Cristallogr.* **1968**, *91*, 85–7. (g) Johannson, G. *Acta Chem. Scand.* **1966**, *20*, 505–15. (h) Halsted, P. E.; Moore, A. E. *J. Appl. Chem.* **1962**, *12*, 413–7.

(14) Feher, F. J.; Weller, K. J.; Ziller, J. W. Manuscript in preparation.

(15) Complete descriptions of experimental procedures, including combustion analyses and ^1H, ^{13}C, ^{17}O, ^{29}Si, and ^{31}P NMR data, are provided in the supplementary material.

9688 *J. Am. Chem. Soc.* **1992**, *114*, 9688-9689

Acknowledgment. These studies were supported by the National Science Foundation (CHE-9011593). Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Funds for the purchase of the X-ray diffraction equipment were made available from NSF Grant CHE-85-14495. F.J.F. gratefully acknowledges financial support from an Alfred P. Sloan Foundation Research Fellowship. The early creative input of Dr. Theodore A. Budzichowski is gratefully acknowledged.

Supplementary Material Available: Listings of experimental procedures and characterization data for **3**, **5**, and **6** and X-ray crystal data for **6** including experimental procedures, tables of crystal data, atomic coordinates, thermal parameters, bond lengths, and bond angles, and ORTEP figures (25 pages); table of calculated and observed structure factors for **6** (30 pages). Ordering information is given on any current masthead page.

Convergent Synthesis of (±)-Dihydroisocodeine in 11 Steps by the Tandem Radical Cyclization Strategy. A Formal Total Synthesis of (±)-Morphine[†,‡]

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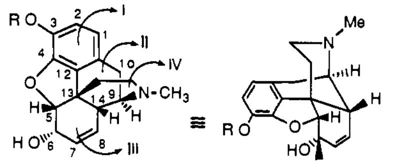
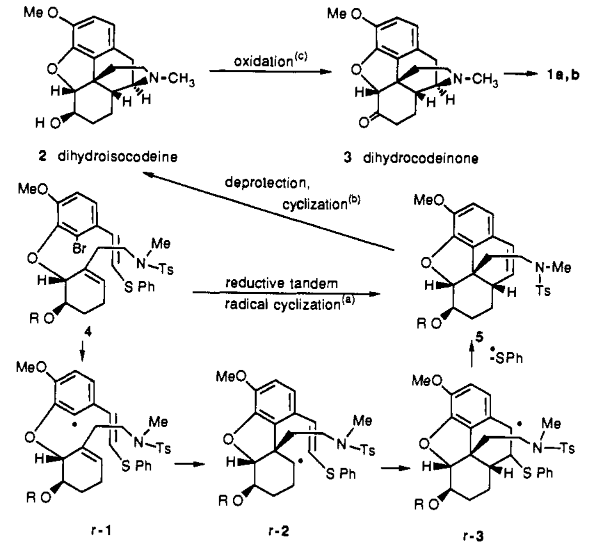
Received August 13, 1992

Morphine (**1a**) and its derivatives and analogs continue to hold the fascination of chemists and neuroscientists.[1] For the synthetic chemist, this small molecule offers an interesting challenge.[2] Its intrinsic complexity arises from the presence of five contiguous chiral centers, four of which define the ring junctions. The problem of establishing these chiral centers is especially difficult because the C-13 center is quaternary and bears an aryl substituent.[3,4]



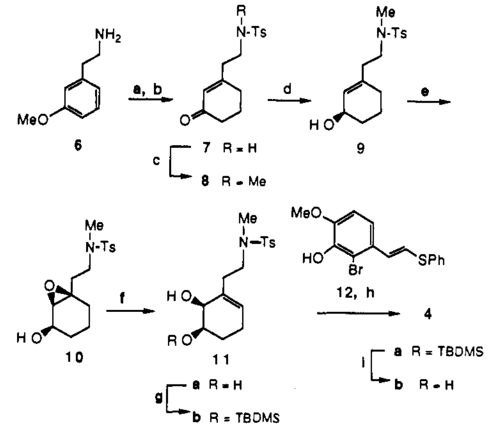
1a R = H morphine
1b R = Me codeine

Scheme I. Strategy for the Synthesis of the Morphine Alkaloids[a]



[a] (a) Bu$_3$SnH, AIBN, C$_6$H$_6$, 130 °C, 35 h, 35% of **5** (R = H) from **4b** (R = H). (b) Li, *t*-BuOH, NH$_3$, THF, −78 °C, 10 min, 85%. (c) (COCl)$_2$, DMSO, 0 °C to room temperature, 2.5 h, 83%.

Scheme II[a]



[a] (a) Li/NH$_3$, *t*-BuOH, −68 °C, 97%. (b) TsCl, NEt$_3$, THF, then 1 N HCl, 81%. (c) MeI, K$_2$CO$_3$, acetone, 96%. (d) NaBH$_4$, CeCl$_3$, MeOH, 0 °C, 97%. (e) *m*-CPBA, CH$_2$Cl$_2$, 0 °C, 92%. (f) Ti(O*i*Pr)$_4$, C$_6$H$_6$, 70 °C, 85%. (g) TBDMSOTf, *i*-Pr$_2$NEt, −78 °C, 82%. (h) PBu$_3$, DEAD, THF, 0 °C, 83%. (i) 10% HF, CH$_3$CN, 98%.

Our approach to the construction of the morphine ring system is based on a tandem cyclization of an ortho allyloxy aryl radical.[5] We are now pleased to report the short (11 steps from commercial materials), convergent, and stereospecific synthesis of (±)-dihydroisocodeine (**2**).[6] Oxidation to dihydrocodeinone (**3**) completes the formal total synthesis of (±)-morphine (Scheme I).

By analogy to transformations in our model studies,[5b,c] we predicted that aryl ether **4** would undergo tandem closure to tetracyclic styrene **5** via an intramolecular tandem cyclization. We expected the C-12 aryl radical (**r-1**), derived from substrate **4**, to attack the nearer but more substituted end of the cyclohexene double bond, generating the 5-membered dihydrofuran ring and establishing the desired cis fusion between this ring and ring III. Radical **r-2** was expected to add to the β-carbon of the styrene double bond to give radical **r-3**, a resonance-stabilized radical which is not especially strained. This second closure would form the 6-membered ring II, completing the desired tetracyclic carbon skeleton and establishing the cis fusion between rings II and III. Finally, elimination of the phenylthio group from the styryl radical would give the key intermediate **5**.

In order to achieve the morphine ring system, the final critical bond connection, that from C-9 to the nitrogen, would have to

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[†] Dedicated to Professor Gilbert Stork.

[‡] This work was described at the 204th National Meeting of the American Chemical Society, Washington, DC, August 1992.

(1) A review entitled "Medicinal Chemistry of Central Analgetics" by D. Lednicer includes a concise history of morphine and a discussion of the development of structural analogs; see: Lednicer, D. *Central Analgetics*; John Wiley & Sons, Inc.: New York, 1982; pp 137-213.

(2) For a recent formal total synthesis and many references to much of the previous work on this problem, see: Tius, M. A.; Kerr, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 5959. In addition, see: Magnus, P.; Coldham, I. *J. Am. Chem. Soc.* **1991**, *113*, 672.

(3) (a) Rieke, R. D.; Schulte, L. D.; Dawson, B. T.; Yang, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 8388. (b) Lee, E.; Shin, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112*, 260 and references therein.

(4) (a) The intramolecular Heck reaction has been shown to be an efficient method for the generation of a quaternary center which bears an aryl group; see: Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) The use of this methodology for the preparation of dihydrothebainone was recently reported by Overman at the 9th International Conference on Organic Synthesis, Montreal, Quebec, Canada, July 1992.

(5) (a) Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833. (b) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628. (c) Parker, K. A.; Fokas, D. Submitted for publication.

(6) For (−)-dihydroisocodeine, see: Makleit, S.; Bognăr, R. *Acta Chim. Acad. Sci. Hung.* **1969**, *59*, 387 and references therein.

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