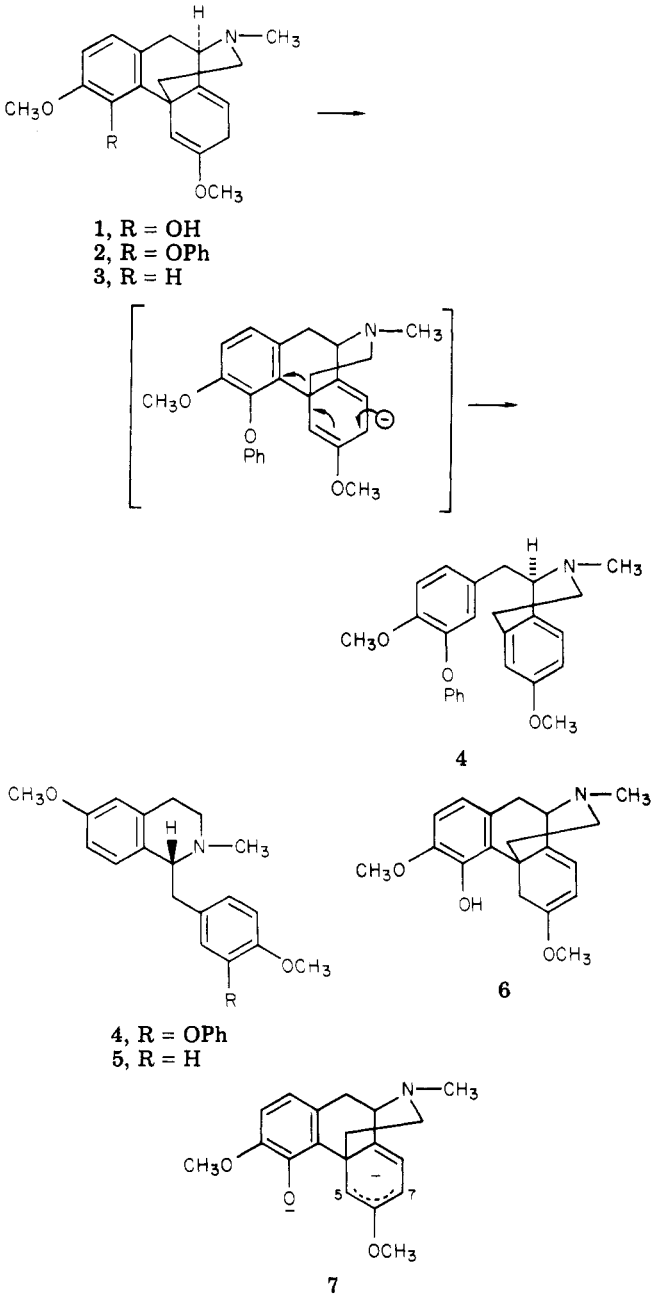
Communications

Conversion of a Morphine Alkaloid to Its Benzylisoquinoline Precursor: A Unique Case of Carbon-Carbon Cleavage

Summary: A morphine derivative **2** is converted to its isoquinoline precursor **4** with KNH_2/NH_3.

Sir: A key step in the biosynthesis of morphine alkaloids involves the transformation of a benzylisoquinoline precursor into the morphine skeleton utilizing an oxidative coupling reaction. This biosynthetic pathway is well established mainly due to the elegant work of Barton and co-workers.[1] Based on the same principle, Schwartz and Mami[2] have recently published an elegant synthesis of morphine from derivatives of reticuline. The Grewe synthesis[3] provides an additional example of the utilization of benzylisoquinoline precursors for the formation of various morphinans which have gained importance as analgesics. We wish to report that during the course of our work on morphine derivatives[4] we have found that a morphine derivative (**2**) is converted into its benzylisoquinoline precursor (**4**). As far as we are aware this reaction has been observed for the first time and provides a unique example of carbon–carbon cleavage in this class of compounds.[5]

Treatment of 1.25 g (4 mmol) of dihydrothebaine-ϕ 4-phenyl ether (**2**)[6] with excess KNH_2/NH_3 (prepared by the addition of 0.65 g of K to NH_3 containing a few crystals of $Fe(NO_3)_3 \cdot 9H_2O$)[7] and quenching the reaction with solid NH_4Cl after stirring for 1.5 h gave 0.96 g (77%) of an amber oil: NMR ($CDCl_3$) δ 7.47–6.5 (m, 11 H, aromatic), 3.8 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 2.46 (s, 3 H, NCH_3), 3.25–2.6 (m, 7 H); IR (neat) 1610 cm^{-1}; TLC single spot R_f 0.3 (silica gel, 10% MeOH/$CHCl_3$). Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.6. Found: C, 76.93; H, 6.93; N, 3.54. These data are consistent with those expected of structure **4**. The structure was confirmed by its conversion to the known benzylisoquinoline derivative **5**.[8] Thus the cleavage of the phenyl ether was achieved by the addition of a solution of **4** in dry toluene to liquid NH_3 and subsequent treatment with small pieces of Na until the dark blue color persisted for 1.25 h. The reaction was quenched (solid NH_4Cl), NH_3 was evaporated, and to the residue was added ether and water. The ether layer was separated and extracted with 5% NaOH to give **5** as an oil (83%) which was purified by chromatography (Florisil, 2–10% MeOH/$CHCl_3$). Compound **5** crystallized as needles:[9] $[\alpha]_D$ −107° (95% EtOH); mp 61–62 °C (dilute EtOH) [lit. $[\alpha]_D$ −130.5° (95% EtOH), mp 64–65 °C];[8] NMR ($CDCl_3$) δ 7.23–6.62 (m, 7 H, aromatic), 3.75 (s, 6 H, OCH_3), 2.48 (s, 3 H, NCH_3), 3.27–2.35 (m, 7 H); TLC single



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(4) R. K. Razdan, D. E. Portlock, H. C. Dalzell, and C. Malmberg, *J. Org. Chem.*, **43**, 3604 (1978).

(5) Transformation of morphine alkaloids involving carbon–carbon cleavage, such as the formation of neodihydrothebaine and morphothebaine, are known. For a detailed discussion, see, for example, K. W. Bentley, *The Alkaloids*, 13, Chapter 1 (1971).

(6) Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, **15**, 154 (1961).

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(9) Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.54; H, 7.80; N, 4.70.

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spot R_f 0.64 (silica gel, 10% MeOH/$CHCl_3$); mass spectrum m/e (% base peak) 297 (0.34, M^+.), 176 (base), 161 (21), 132 (16), 121 (11), consistent with the fragmentation pattern of known benzylisoquinoline derivatives:[10] formed a hydrochloride,[11] mp 184–186 °C.

This carbon–carbon cleavage (**2** → **4**) did not take place when either compound **1** or **3** was subjected to the same KNH_2/NH_3 conditions. In the case of dihydrothebaine-ϕ (**1**), as previously reported by us,[4] a 1:1 mixture of **1** and **6** was obtained, presumably by protonation of the dianion **7** at both C_5 and C_7, whereas in the case of compound **3** a deep red coloration (anion) was observed but on quenching only unchanged **3** was recovered. It is quite likely that the absence of cleavage in this system may be due to the lack of an *o*-phenoxy substituent to stabilize the anion on the aromatic ring. Further work along these lines is in progress.

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Registry No. **1**, 6878-93-9; **2**, 71435-24-0; **3**, 1092-95-1; **4**, 71435-25-1; **5**, 71484-72-5; **5** hydrochloride, 71484-73-6; **6**, 63944-52-5.

Supplementary Material Available: Experimental section describing the preparation of compounds **4** and **5** (1 page). Ordering information is given on any current masthead page.

(10) H. Budzikiewicz, C. Djerassi, and D. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. I, Holden-Day, San Francisco, Calif., 1964, p 173.

(11) Anal. Calcd for $C_{19}H_{24}NO_2Cl$: N, 4.19. Found: N, 3.80.

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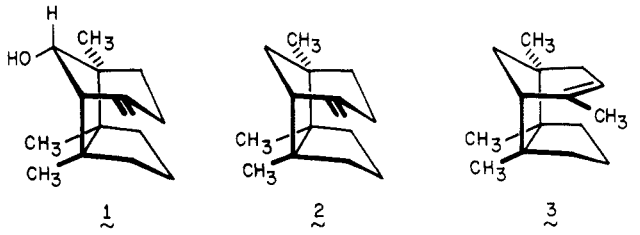
Vinylsilane Mediated Stereoselective Total Synthesis of (±)-Gymnomitrol

Summary: An efficient and stereoselective synthesis of (±)-gymnomitrol was achieved by tandem conjugate addition–methylation of a vinylsilane reagent to 1,5-dimethyl-2-methylenebicyclo[3.3.0]octan-3-one, followed by epoxidation, hydrolysis, cyclization, and introduction of the exocyclic methylene carbon.

Sir: The sesquiterpenic alcohol gymnomitrol, isolated almost a decade ago by Connolly et al. from *Gymnomitrion obtusum* (Lindb) Pears,[1] has been assigned the unusual tricyclic structure **1** on the basis of sound chemical and spectroscopic evidence.[1] Additional support for this formulation can be derived from more recent X-ray crystal structure analysis of a derivative of the two closely related hydrocarbons **2** and **3**[2-4] with which it co-occurs. Our



1 **2** **3**

interest in **1** as a synthetic target stems from its diquinane nature[5] which is further embellished by incorporation of one cyclopentane ring into a stereochemically well-defined bicyclo[3.2.1]octane framework. While it is most likely that **1** is elaborated in nature by cyclization of a bazzanenyl cation,[1,6] a variety of alternative highly stereoselective approaches to **1** appear entirely feasible.[7] We now report a very direct total synthesis of (±)-gymnomitrol which takes advantage of the chemical versatility of vinylsilane functionality.

In our retrosynthetic analysis, proper rapid elaboration of the three contiguous quaternary carbons with their all-cis methyl substitution plan was underscored, since subsequent incorporation of the remaining stereochemical features appeared straightforward. The ready availability of diketone **4**[8] and its facile conversion to the known[9] monoketone **5** proved to be nicely suited to our requirements. Thus, **4** can be efficiently monoketalized (0.63 molar equiv of ethylene glycol, *p*-TsOH, benzene, reflux, 95% based on diketone consumption) and the latter intermediate reduced to **5** (mp 159–160 °C, sealed tube) under Wolff–Kishner conditions on a large scale without difficulty (82%).

Methylenation of **5** was achieved by heating with *s*-trioxane and *N*-methylanilinium trifluoroacetate in dioxane solution (50% conversion, 90% based on recovered **5**) in an adaptation of Gras' recent findings.[10] Initially, our intent was to perform conjugate additions to **6**[11] in a manner which would lead to incorporation of the remaining carbon atoms. To this end, **6** was treated first with 2-(trimethylsilyl)-2-propenylmagnesium bromide[12] and the $CuBr{\cdot}Me_2S$ complex,[15] followed by methyl iodide in HMPA (Scheme I). Chromatographic purification of the

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(2) Hydrocarbon **2** has been variously called gymnomitrene,[1] β-pompene,[3] and β-barbatene,[4] whereas **3** is known as isogymnomitrene,[1] α-pompene,[3] and α-barbatene.[4]

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(4) (a) Andersen, N. H.; Tseng, C. W.; Moore, A.; Ohta, Y. *Tetrahedron* **1978**, *34*, 47–52. (b) Andersen, N. H.; Costin, C. R.; Kramer, M., Jr.; Ohta, Y.; Huneck, S. *Phytochemistry* **1973**, *12*, 2709–2716. (c) Andersen, N. H.; Huneck, S. *Ibid.* **1973**, *12*, 1818–1819.

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(6) Matsuo, A.; Hayashi, S. *J. Chem. Soc., Chem. Commun.* **1977**, 566–568.

(7) We are presently aware of the successful completion of three independent alternative syntheses of (±)-gymnomitrol: Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, in press. Büchi, G.; Chu, P.-S. *Ibid.* **1979**, *101*, in press. Welch, S. C.; Chayabunjonglard, S. *Ibid.* **1979**, *101*, in press. Approximate copublication in this manner was arrived at by prior agreement.

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(9) Borden, W. T.; Ravindranathan, T. *J. Org. Chem.* **1971**, *36*, 4125–4127.

(10) Gras, J.-L. *Tetrahedron Lett.* **1978**, 2111–2114.

(11) All compounds described in this report have been characterized by IR, ^1H NMR, and high-resolution mass spectrometry. Additionally, satisfactory combustion analyses were obtained for the following compounds: **7**, **8**, **9**, **10b**, and **11**.

(12) Prepared by reaction of 2-(trimethylsilyl)-2-propen-1-ol[13] with triphenylphosphine dibromide in dichloromethane (2 days, room temperature, 86%) and exposure of the bromide to activated magnesium powder[14] in ether.

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