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.

Acknowledgment. We thank Professors R. E. Lyle, R. A. Raphael and John C. Sheehan for helpful discussions and Miles Laboratories, Elkhart, Indiana, for financial support.

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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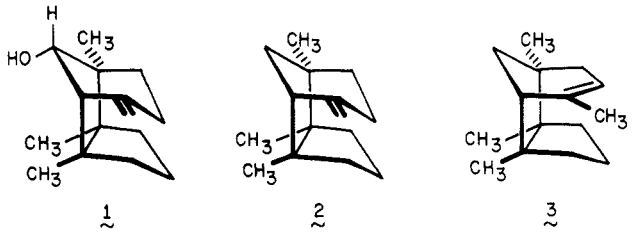
Vinylsilane Mediated Stereoselective Total Synthesis of (±)-Gymnomitrol

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

(1) Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *J. Chem. Soc., Chem. Commun.* **1970**, 1320–1321; *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2487–2493.

(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]

(3) (a) Nozaki, H.; Matsuo, A.; Nakayama, M.; Kushi, Y.; Kamijo, N.; Hayashi, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 568–574. (b) Matsuo, A.; Uto, S.; Nakayama, M.; Hayashi, S. *Z. Naturforsch. C* **1976**, *31*, 401–402. (c) Matsuo, A.; Nozaki, H.; Nakayama, M.; Kushi, Y.; Hayashi, S.; Kamijo, N. *Tetrahedron Lett.* **1975**, 241–244. (d) Matsuo, A.; Maeda, T.; Nakayama, M.; Hayashi, S. *Ibid.* **1973**, 4131–4134.

(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.

(5) Paquette, L. A. *Fortschr. Chem. Forsch.* **1979**, *79*, 41–165.

(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.

(8) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, 4885–4887.

(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.

(13) Chan, T. H.; Mychajlowskij, W.; Ong, B. S.; Harpp, D. N. *J. Org. Chem.* **1978**, *43*, 1526–1532.

(14) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775–1781.

(15) House, H. O.; Chu, C. Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460–1469. For more recent applications, see: Alexakis, A.; Chapdelaine, M. J.; Posner, G. H.; Runquist, A. A. *Tetrahedron Lett.* **1978**, 4205–4208. Marfat, A.; Helquist, P. *Ibid.* **1978**, 4217–4220.

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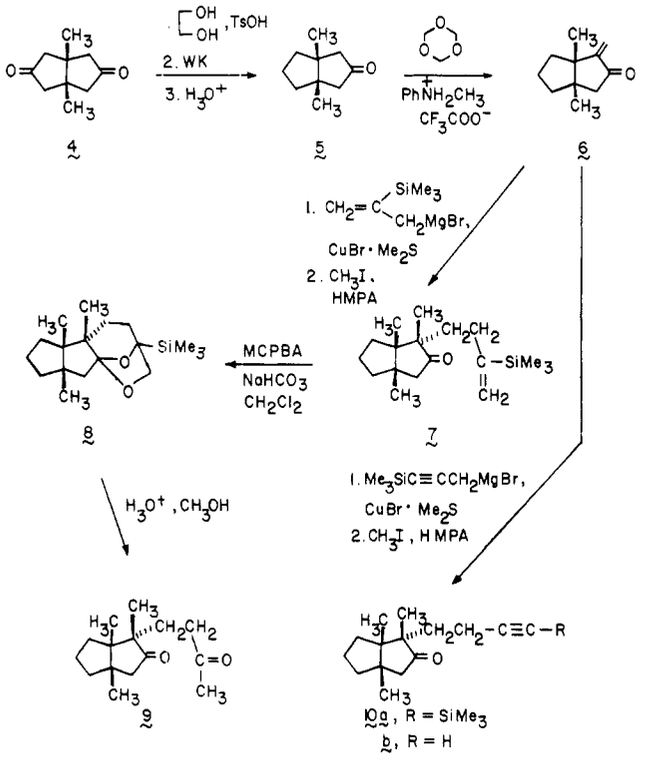
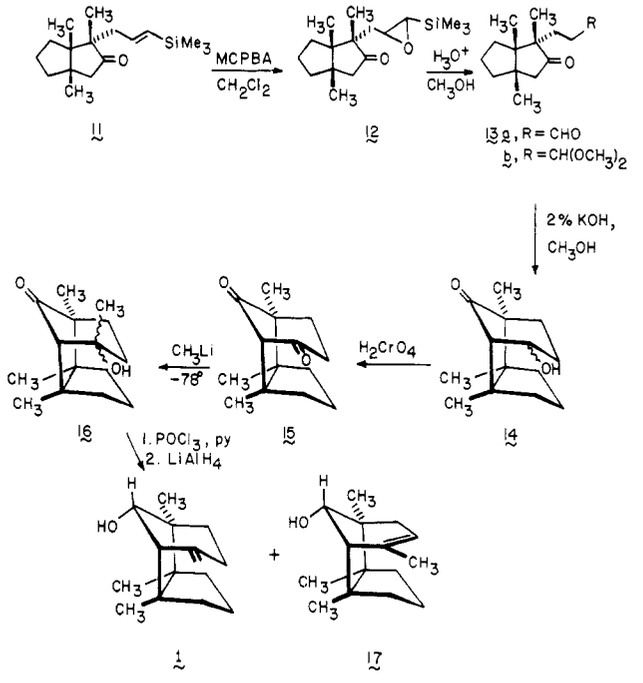
Scheme I



Scheme II



crude product delivered the stereochemically homogeneous vinylsilane **7** in 40% yield. Stereochemical assignment to **7**, which was originally inferred from the close similarity of its methyl signals (δ 1.11, 1.03, and 0.95 in $CDCl_3$, $\Delta\delta$ = 0.16)[16] and later substantiated chemically (see below), conforms to the anticipated[5] kinetically favored alkylation of the intermediate enolate anion from the exo direction which, in this instance, is syn to the angular methyl substituents.

Peracid treatment of **7** under buffered conditions ($NaHCO_3$, CH_2Cl_2) led not to the epoxysilane, but to cyclic ketal **8** (99%),[17] hydrolysis of which with dilute sulfuric acid in methanol provided diketone **9** ($\Delta\delta_{CH_3}$ = 0.21) in 97.5% yield. Numerous attempts to effect the cyclization of **9** under a wide variety of acidic[18] and alkaline conditions[19] proved unsuccessful. We believe this lack of reactivity to be a reflection of the enormous steric strain which must necessarily develop within the concave underside of the molecule.

Along similar lines, conditions were not found to cause the acetylenic ketone **10b** to enter into ene reaction, despite prior demonstration by Conia and his co-workers of the broad applicability of this process as an efficient method of thermal cyclization.[20]

In an effort to minimize the apparent steric congestion, we next made recourse to the Grignard reagent from [(*E*)-2-bromovinyl]trimethylsilane.[21] Under conditions of the copper-catalyzed 1,4-addition–methylation procedure described above, **11** was obtained as a colorless oil in 66% yield ($\Delta\delta_{CH_3}$ = 0.21). Epoxidation of **11** led to silyl epoxide **12** (74%), which was directly hydrolyzed in 20% sulfuric acid–methanol (1:1, reflux, 24 h) (Scheme II). Preparative layer chromatography of the resultant mixture on silica gel gave two fractions consisting of **13a**/**13b** (45:55, 74%) and **14** (22%). Hydrolysis of the acetal/aldehyde mixture in HOAc/H_2O (1:1) led to isolation of pure **13a** (74%, $\Delta\delta_{CH_3}$ = 0.20). When subjected to 2% KOH in methanol (room temperature, 2.5 days), the keto aldehyde underwent partial cyclization to **14** (43% conversion, 61% based on recovered **13a**).

With the availability of **14**, introduction of the final carbon atom could be readily accomplished by sequential oxidation with Jones' reagent (89%) and regioselective reaction with methyllithium (1 equiv) at −78 °C (70%). The IR and ^1H NMR spectra of diketone **15** proved to be in excellent agreement with those reported for the optically active ozonolysis product of gymnomitrone.[1,22] In addition, ketol **16** proved to be stereochemically homogeneous. The dehydration of **16** with phosphorous oxychloride in pyridine (reflux, 2 h) gave an approximate 1:1 mixture of gymnomitrone and its double bond isomer (70%), which without purification was reduced with lithium aluminum hydride (THF, 0 °C). Preparative layer chromatography on silver nitrate impregnated silica gel led to the isolation of (±)-gymnomitrol (**1**, 45%), the spectral (IR, ^1H NMR) features of which were superimposable upon those of the authentic natural product.[1,22]

Acknowledgment. We would like to thank Professor J. D. Connolly (University of Glasgow) for generously providing the comparison spectra. Partial financial support was provided by the National Cancer Institute (CA-12115) and Eli Lilly and Company.

Registry No. **1**, 71564-38-0; **4**, 21170-10-5; **5**, 32139-03-0; **6**, 71519-43-2; **7**, 71519-44-3; **8**, 71519-45-4; **9**, 71519-46-5; **10b**, 71519-47-6; **11**, 71519-48-7; **12**, 71519-49-8; **13a**, 71519-50-1; **13b**, 71519-51-2; **14**, 71519-52-3; **15**, 71605-98-6; **16**, 71519-53-4; **17**, 71564-39-1; 2-(trimethylsilyl)-2-propenyl, 762-72-1; $Me_3SiC{\equiv}CCH_2Br$, 38002-45-8;

(16) In our experience, the ^1H NMR spectra (in $CDCl_3$ solution) of *exo*-2,*cis*-1,5-trimethylbicyclo[3.3.0]octan-3-ones are characterized by a more narrow triad of methyl singlets ($\Delta\delta$ ~0.2) than their endo-2,cis-1,5 isomers ($\Delta\delta$ ~0.4).

(17) This phenomenon has been previously recognized and attributed to efficient ketone carbonyl participation: Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682–3684.

(18) See, for example: Marshall, J. A.; Schaeffer, D. J. *J. Org. Chem.* **1965**, *30*, 3642–3646.

(19) See, for example: Julia, S. *Bull. Soc. Chim. Fr.* **1954**, 780–789.

(20) Conia, J. M.; LePerchec, P. *Synthesis* **1975**, 1–19.

(21) Mironov, V. F.; Petrov, A. D.; Maksimova, N. G. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1959**, 1954–1960.

(22) The spectra of authentic **1** and **15** were kindly provided by Professor J. D. Connolly.

[(*E*)-2-bromovinyl]trimethylsilane, 41309-43-7.

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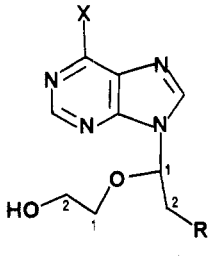
Acyclic Nucleoside Analogues: Synthesis of Open-Ring Riboside or Deoxyriboside Analogues Lacking C(3′) or the C(3′)–C(4′) Bond

Summary: 2-Alkyl-1,3-dioxolanes were treated with trimethylsilyl iodide to generate iodoalkyl (trimethylsilyloxy)ethyl ethers which were used to provide acyclic nucleoside analogues lacking C(3′) or the C(3′)–C(4′) bond.

Sir: Several reports have appeared recently describing the very potent antiviral activity of nucleoside analogues in which the cyclic sugar component has been replaced by an acyclic side chain.[1-4] 9-(2,3-Dihydroxypropyl)adenine (DHPA) inhibits replication of a number of DNA and RNA viruses,[1,2] while 9-[(2-hydroxyethoxy)methyl]guanine (acycloguanosine) demonstrates selective inhibition toward *Herpes simplex* virus type I.[3,4] Interestingly, DHPA includes the C(1′)–C(2′)–C(3′) portion of a ribofuranosyl moiety, whereas acycloguanosine contains the C(1′)–O–C(4′)–C(5′) part of the natural nucleoside. In view of the biological activity which has accompanied the substitution of a sugar segment for a ribose in a nucleoside, we considered it desirable to synthesize acyclic nucleosides which incorporated both types of side chain. We describe herein efficient syntheses of (*R,S*)-9-[1-(2-hydroxyethoxy)-ethyl]adenine (**1a**), (*R,S*)-9-[1-(2-hydroxyethoxy)-2-hydroxyethyl]adenine (**1b**), and (*R,S*)-9-[1-(2-hydroxyethoxy)-3-hydroxypropyl]adenine (**1c**) as examples of a very general and simple synthetic methodology suitable for the formation of a wide range of acyclic nucleoside analogues.

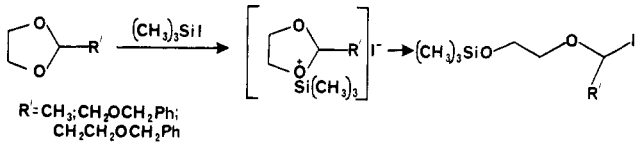


1a X = NH_2; R = H
b X = NH_2; R = OH
c X = NH_2; R = CH_2OH

2a X = Cl; R = H
b X = Cl; R = OCH_2Ph
c X = Cl; R = CH_2OCH_2Ph

3b X = NH_2; R = OCH_2Ph
c X = NH_2; R = CH_2OCH_2Ph

Scheme I



Recently we reported that 1,3-dioxolane and 1,3-oxathiolane could be treated with trimethylsilyl iodide at low temperature to generate efficiently iodomethyl (trimethylsilyloxy)ethyl ether or thioether, respectively.[5] We have now extended the scope of this reaction to include the ring opening of various 2-substituted dioxolanes with trimethylsilyl iodide to provide acyclic sugar analogues which are lacking only C(3′) or the C(3′)–C(4′) bond (Scheme I). This result is interesting when one considers the dealkylation which normally accompanies the reaction of acetals with trimethylsilyl iodide.[6] Although Jung et al. observed the formation of iodomethyl methyl ether upon treatment of methylal with trimethylsilyl iodide at room temperature, the authors suggest this is a result of the totally unhindered methylene center in the acetal.[7] Our reaction conditions avoid a dealkylation and are sufficiently mild that a benzyloxy group, normally sensitive at room temperature to trimethylsilyl iodide,[8] can function as a latent hydroxyl group on the generated acyclic sugar moiety. Furthermore, the use of substituted cyclic acetals as precursors for acyclic riboside analogues is attractive in that the requisite dioxolanes are readily available.[9] In a typical reaction, trimethylsilyl iodide (Aldrich or PCR, 0.16 mL, 1.1 mmol) in cyclohexene (0.5 mL) was added to 2-(benzyloxymethyl)-1,3-dioxolane[10] (215 mg, 1.1 mmol) in cyclohexene (0.5 mL) at −78 °C. After 15 min this alkylating reaction mixture was added to the sodium salt of 6-chloropurine (1 mmol, generated with NaH) in dry DMF at −63 °C. The mixture was warmed to 25 °C over 2 h and after the addition of aqueous 10% KF and 10% $NaHCO_3$, the solvent was evaporated and the residue extracted ($CHCl_3$). Concentration of the organic layer followed by chromatography on neutral alumina ($CHCl_3$) afforded analytically pure (*R,S*)-9-[2-benzyloxy-1-(2-hydroxyethoxy)ethyl]-6-chloropurine (**2b**): yield 65%; NMR ($CDCl_3$) δ 3.5–3.9 (m, 4, OCH_2CH_2O), 3.96 (d, J = 6 Hz, 2, OCH_2), 4.55 (s, 2, CH_2Ph), 6.03 (t, J = 6 Hz, 1, NCHO), 7.28 (s, 5, ArH), 8.32 (s, 1, purine CH), 8.71 (s, 1, purine CH).[11] Similarly obtained in 50–70% yield were

(1) De Clercq, E.; Descamps, J.; DeSommer, P.; Holý, A. *Science* **1978**, *200*, 563.
(2) De Clercq, E.; Holý, A. *J. Med. Chem.* **1979**, *22*, 510.
(3) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716.
(4) Fyfe, J. A.; Keller, P. M.; Furman, P. A.; Miller, R. L.; Elion, G. B. *J. Biol. Chem.* **1978**, *253*, 8721.

(5) Keyser, G. E.; Bryant, J. D.; Barrio, J. R. *Tetrahedron Lett.* **1979**, 3263. 1-[2-(Trimethylsilyloxy)ethoxy]ethyl iodide (R = CH_3, Scheme I) shows ^{1}H NMR [($CDCl_3$) δ 0.15 (s, 9, $Si(CH_3)_3$), 2.27 (d, J = 6 Hz, 3, CH_3), 3.61 (s, 4, OCH_2CH_2O), 6.12 (q, J = 6 Hz, 1, ICHO)] which is in agreement with iodoalkyl ethers previously reported (Jung, M. E.; Mossman, A. B.; Lyster, M. A. *J. Org. Chem.* **1978**, *43*, 3698) and not in agreement with the expected ^{1}H NMR spectra of alkyloxonium ions like the intermediate shown in Scheme I. Similarly consistent ^{1}H NMR were also obtained with other trimethylsilyl iodide–2-substituted-1,3-dioxolane reaction products. See also ^{1}H NMR of **1a–c**, **2a–c**, **3b**, and **3c** for comparison. Unfortunately various attempts to isolate the iodomethyl (trimethylsilyloxy)ethyl ethers were unsuccessful, similar to the reports of Jung et al. (vide supra) for aldehyde iodohydrin trimethylsilyl ethers. However, the solutions of the iodoalkyl ethers were stable at low temperatures and could be used directly in further reactions.
(6) Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *4175*.
(7) Jung, M. E.; Mazurek, M. A.; Lim, R. M. *Synthesis* **1978**, 588.
(8) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.
(9) 2-Methyl-1,3-dioxolane can be purchased from Eastman Chemical Co.; 2-(bromomethyl)-1,3-dioxolane and 2-(2-bromoethyl)-1,3-dioxolane are available from Tridom/Fluka A. G.
(10) The 2-(benzyloxyalkyl)-1,3-dioxolanes were prepared by reaction of the corresponding 2-(bromoalkyl)-1,3-dioxolanes with sodium benzylate in toluene, followed by fractional distillation.

0022-3263/79/1944-3733$01.00/0