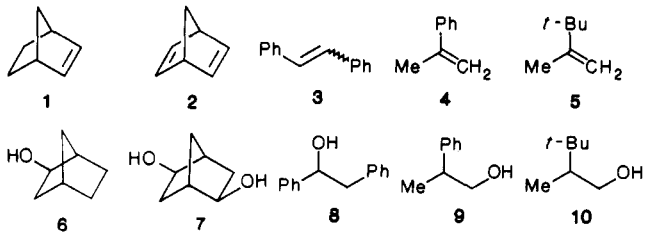
Table I. Enantioselective Hydroboration Experiments[a]



entry (substrate)	T, °C	catalyst[b]/ solvent	product	ee,[c] %	absolute configuration
1 (1)	40	A/C_6H_6	6[d]	23	1*R*,2*R*
2 (1)	5	A/C_6H_6	6	31	1*R*,2*R*
3 (1)	5	B/C_6H_6	6	43	1*R*,2*R*
4 (1)	−5	A/THF	6	46	1*R*,2*R*
5 (1)	−25	A/THF	6	57	1*R*,2*R*
6 (1)	−25	B/THF	6	64	1*R*,2*R*
7 (1)	−40	A/THF	6	55	1*R*,2*R*
8 (2)	−25	A/THF	7	76	1*S*,2*R*[d]
9 (*E*-(3))	20	A/C_6H_6	8	7	*S*
10 (*E*-(3))	5	A/C_6H_6	8	~0	
11 (*Z*-(3))	5	A/C_6H_6	8	17	*S*
12 (*Z*-(3))	−25	A/THF	8	19	*S*
13 (4)	−5	A/THF	9	27	*R*
14 (5)	−5	A/THF	10	69	*R*

[a] See note 13 for a typical experimental procedure. [b] A, in situ $[Rh(COD)Cl]_2$·2DIOP; B, in situ [Rh(COD)Cl]·2BINAP. [c] Determined by ^1H NMR analysis of Mosher's ester derivatives[14] and ^1H NMR experiments with $Eu(hfc)_3$, to within ±5%. [d] By inference from entries 1–7 only.

have shown[6] that stoichiometric amounts of catecholborane and Wilkinson's catalyst react to give a hydride complex $[RhClH(BO_2C_6H_4)(PPh_3)_2]$;[12] this reacts with alkenes to give hydroboration products. Thus the catalyzed reaction may proceed via oxidative addition of catecholborane to the rhodium(I) center, insertion of the alkene into the rhodium–hydride bond so formed, and reductive elimination of alkyl and boronate ligands.

Existing methods for asymmetric hydroboration are excellent for many applications[1-5] but are not generally applicable to all alkenes[3] and are sometimes limited by the cost/availability of the borane reagents.[5] Clearly the evolution of methods for chiral induction in hydroboration methodology is not complete. The results presented here provide an interesting perspective in the development of new asymmetric hydroboration techniques.[16]

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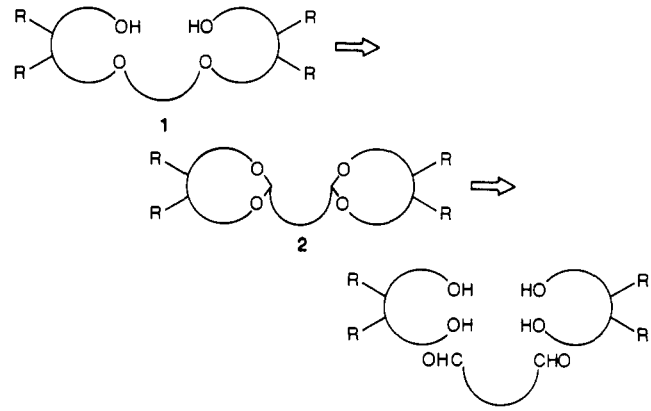
A Convenient Synthesis of Substituted Polyether Diols

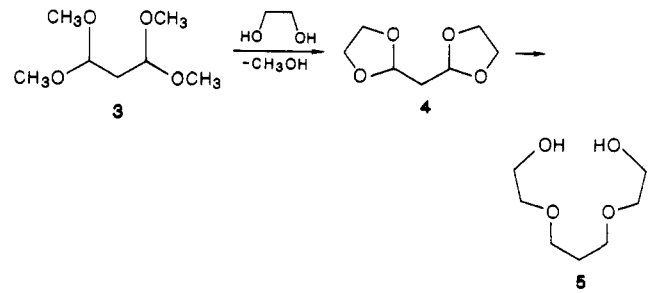
Summary: Alkyl-substituted polyether diols (or polythioether diols), which are potential precursors to substituted crown ethers, are produced in high yield by the selective reductive cleavage of C–O bonds in bis(cyclic acetals) [or bis(cyclic hemithioacetals)] by borane or monochloroborane.

Sir: Crown ethers bearing alkyl, aryl, and functional group substituents have been used in a variety of applications including enzyme mimics, receptor site models, and selective ionophores.[1-3] Our interest in the synthesis of highly substituted crown ethers prompted the development of methodology for the preparation of alkyl-substituted polyether diols 1 useful as acyclic precursors to these.

Our approach is conceptually simple: substituted polyether diols 1 would result from the reductive cleavage of one C–O bond in each 1,3-dioxolane (or 1,3-dioxane) ring in bis(acetals) 2. These could, in turn, be prepared from a dialdehyde (or its synthetic equivalent) and 2 equiv of an appropriately substituted 1,2- or 1,3-diol. This is the first report of the generation of diether diols by such an approach.



To test the feasibility of this approach, we first attempted to selectively reduce 4[4] to 3,7-dioxa-1,9-nonanediol (5) with $LiAlH_4/AlCl_3$ mixtures in diethyl ether solvent.[5a] However, only an 8–11% yield of diether diol 5 was obtained and no starting material was recovered. Manipulation of reaction conditions and isolation procedures failed to significantly increase yields.

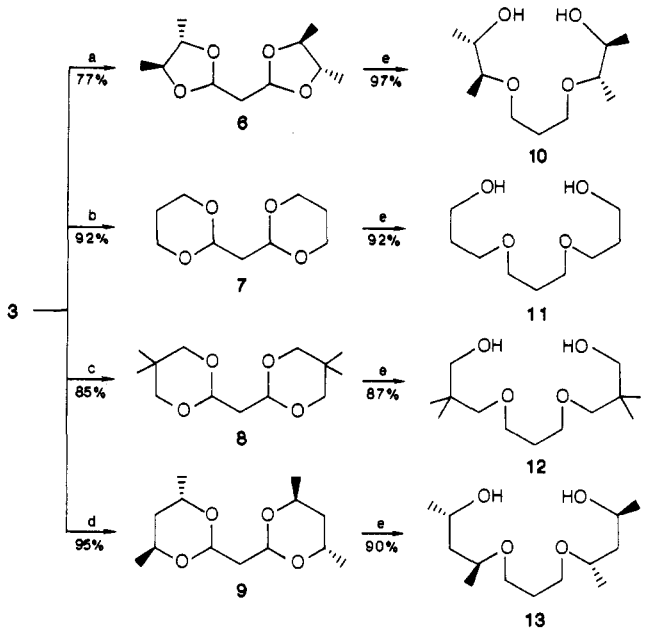


This procedure, which required an aqueous workup to remove the aluminum salts, was unacceptable since most of the product was not recovered, possibly due to its great

(1) Gokel, G. W.; Korzenniowski, S. H. *Macrocyclic Polyether Synthesis*; Springer Verlag: New York, 1982.
(2) Voegtle, F.; Weber, E. *Host-Guest Chemistry/Macrocycles*; Springer Verlag: New York, 1985.
(3) Izatt, R. M.; Christiansen, J. J., Eds. *Synthesis of Macrocycles: The Design of Selective Complexing Agents*; Wiley-Interscience: New York, 1987.
(4) Bis(acetals) **4**, **7**, **14a**, and **16a** have been previously prepared: Chastrette, F.; Hassambay, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1976**, 601. We synthesized malonaldehyde bis(acetals) **4–9** by the toluenesulfonic acid catalyzed reaction of malonaldehyde bis(dimethyl acetal) and the appropriate diol in toluene solution. The reaction was driven to completion by distillation of the methanol–toluene azeotrope to give products in considerably higher yields than by procedures previously reported.

0022-3263/88/1953-5179$01.50/0

Scheme I[a]



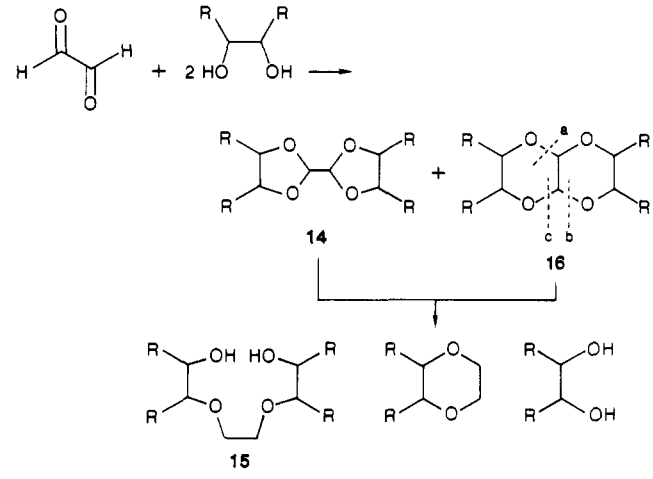
[a] (a) (*S,S*)-2,3-Butanediol; (b) 1,3-propanediol; (c) 2,2-dimethyl-1,3-propanediol; (d) (*S,S*)-2,4-pentanediol; (e) BH_3·THF or BH_2Cl·SMe_2.

water solubility and/or its being intractably associated with the aluminum salts.

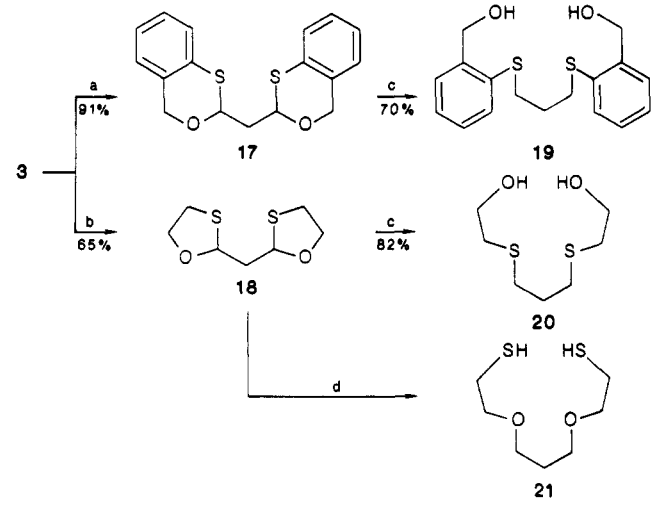
Reduction was finally achieved in high yield with 2.5 equiv of borane–tetrahydrofuran (BH_3·THF) complex in refluxing THF. A modification of the procedure used by Fleming and Bolker to reduce monoacetals allowed us to easily produce and isolate **5** in good yields.[5b] The reaction was monitored by thin layer chromatography, and after the disappearance of starting material **4** (48 h), instead of an aqueous workup, the intermediate borate esters and remaining hydride were decomposed with excess methanol. Removal of the THF, methanol, and volatile trimethylborate at reduced pressure gave a 98% yield of essentially pure **5**, which could be made analytically pure by chromatography.[6] The use of the more electrophilic monochloroborane[5c] afforded the identical product in under 12 h. We used commercial (Aldrich) monochloroborane–dimethyl sulfide complex and ran the reactions in diethyl ether solvent at room temperature. THF solvent, particularly at reflux temperatures, is attacked by monochloroborane to produce, after workup, 4-chlorobutanol. This result is consistent with the observation that cyclic ethers are cleaved by haloboranes.[7]

In this same way we prepared bis(acetals) **6**–**9**[4,8] and reduced them in good yield to the alkyl-substituted diether diols **10**–**13** (Scheme I).[8] These bis(acetals) have either a symmetry plane (**4**, **7**, and **8**) or a C_2 axis (**6** and **9**), and consequently reduction is unambiguous as cleavage of either geminal C–O bond produces the same diether diol. When chiral diols [e.g., (*S,S*)-2,3-butanediol or (*S,S*)-2,4-pentanediol] are used to prepare the bis(1,3-heterocycles) **6** and **9**, the product diether diols **10** and **13** retain that chirality, as expected, as bonds to the chiral centers are

Scheme II



Scheme III[a]



[a] (a) *o*-Mercaptobenzyl alcohol; (b) mercaptoethanol; (c) BH_3·THF or BH_2Cl·SMe_2; (d) Bu_3SnH.

(5) Several reagents effect reductive cleave C–O bonds in acyclic acetals to form ethers or alkoxy alcohols from cyclic acetals: (a) $LiAlH_4$–Lewis acids: Eliel, E.; Badding, V. G.; Rerick, M. N. *J. Am. Chem. Soc.* **1962**, *84*, 2371. Joniak, D.; Kosikova, B.; Kosakova, L. *Collect. Czech. Chem. Commun.* **1978**, *43*, 769. Ishikawa, H.; Mukaiyama, T. *Bull. Soc. Chem. Jpn.* **1978**, *51*, 2059. (b) BH_3·THF: Fleming, B.; Bolker, H. I. *Can. J. Chem.* **1974**, *52*, 889; *Can. J. Chem.* **1977**, *53*, 2818. (c) BH_2Cl: Bonner, T. G.; Lewis, D.; Rutter, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1807. (d) H_2 over catalysts: Fleming, B.; Bolker, H. I. *Can. J. Chem.* **1976**, *54*, 685. Howard, W. L.; Brown, J. H. *J. Org. Chem.* **1961**, *26*, 1026. (e) $NaBH_4$·HCl: Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978**, 1357. Kloosterman, M.; Kuyl-Yeheskiely, E.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 291. (f) $NaBH_4$·CF_3COOH: Nutaitis, C. f.; Gribble, G. W. *Org. Prep. Proc. Int.* **1985**, *17*, 11. (g) $Zn(BH_4)_2$·$SiMe_3Cl$: Kotsuki, H.; Ushio, Y.; Yoshimura, N.; Ochi, M. *J. Org. Chem.* **1987**, *52*, 2594. (h) R_3SiH: Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, 4679. Olah, G. A.; Yamato, T.; Iyer, P. S.; Surya Prakash, G. K. *J. Org. Chem.* **1986**, *51*, 2826. Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 3659. (i) Diisobutylaluminum hydride: Schill, G.; Doejer, G.; Longemann, E.; Vetter, W. *Chem. Ber.* **1980**, *113*, 3697. (j) $AlBr_2H$: Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581. (k) $Al(CH_3)_3$: Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. (l) PhCu·BF_3 or $(CH_3)_2CuLi$·BF_3: Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075, 3079. (m) $TiCl_4$ and organosilanes: Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 3947, 3951. Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904. Elliot, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. Elliot, J. D.; Choi, V. M. F.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. (n) CH_3TiCl_3: Mori, A.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 4421. (o) Me_3SiI: Bryant, J. D.; Keyzer, G. E.; Barrio, J. R. *J. Org. Chem.* **1979**, *44*, 3733.

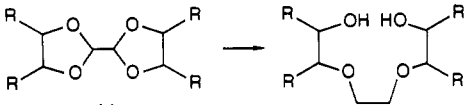
(6) We found that this was very conveniently done on Harrison Research Chromatotron (Palo Alto, CA), a centifugally accelerated, radial, thin layer chromatograph.

(7) Guindon, Y.; Therien, M.; Girard, Y.; Yoakim, C. *J. Org. Chem.* **1987**, *52*, 1680.

(8) All new compounds exhibited nuclear magnetic resonance and infrared spectra consistent with the assigned structure and analyzed for the appropriate molecular formula by either combustion or high resolution mass spectrometry.

not broken in the reduction process.

It was anticipated that reduction of a 2,2′-bi-1,3-dioxolane of type **14** would produce substituted triethylene glycols **15**, which we required as precursors to substituted 18-crown-6 derivatives.



14 **15**

However the reaction of glyoxal with 1,2-diols gave a mixture of the desired 2,2′-bi-1,3-dioxolane **14** and the tetraoxadecalin isomers **16** (Scheme II).[4,9] The reaction of ethylene glycol and glyoxal produced a 70:30 mixture of **14a** (R = H) to **16a** (R = H).[10] Reduction of this mixture with either BH_3 or BH_2Cl was complicated by the presence of **16**: the bidioxolane **14a** reduced cleanly to triethylene glycol (confirmed by the reduction of a pure sample of **14a** obtained by fractional recrystallization). However the tetraoxadecalin **16** can yield triethylene glycol if bonds labeled a and b are cleaved but also dioxane and ethylene glycol if bonds a and c are reduced. The latter appears to be the more favored mode. The reaction of (*S*,*S*)-2,3-butanediol with glyoxal gave a 1:1 mixture of **14b** (R = CH_3) and **16b** (R = CH_3).[10] We were unable to separate this mixture, and reduction of the mixture with monochloroborane gave only a 30% yield of (*S*,*S*,*S*,*S*)-3,8-dimethyl-2,9-decanediol after chromatography on silica gel.[11] We are currently developing alternative procedures for the preparation of substituted triethylene glycols of type **15**.

We also found that bis(hemithioacetals) **17** and **18**, prepared from **3** and the appropriate mercapto alcohol, were reduced to the dithioether diols **19** (OH stretch at 3336 cm^{-1})[8] and **20**[12] in good yields (Scheme III). Under no circumstances did we see the cleavage of a C–S bond in these reductions.[13] This procedure is complementary to other work in our laboratories wherein the C–S bond in these systems is reduced by tributyltin hydride (TBTH) to the isomeric diether dimercaptan **21** (SH stretch at 2550 cm^{-1}).[14] The hemithioacetal carbons in **17** and **18** are chiral, so these compounds are produced as mixtures of diastereomers. Destruction of the chiral centers by reduction produced the products **19** and **20**, each as a single compound.

In conclusion, the selective reduction of bis(cyclic acetals) by borane (or monochloroborane) is a viable way to produce diether diols bearing several substituents. Reduction of bis(hemithioacetals) produces dithioether diols. The procedure is conceptually and experimentally simple and provides the essentially pure products in high yield. We are presently elaborating these diether diols, and dithioether diols, into substituted crown ether compounds and/or to crowns bearing both oxygen and sulfur donor atoms.

Acknowledgment. We thank the National Institutes of Health [NIGMS-MARC (GM 08228) and MBRS-DRR (S06 RR-08101)] for support of this work.

Registry No. **3**, 102-52-3; **4**, 4405-17-8; **5**, 67439-82-1; **6**, 116261-28-0; **7**, 30963-84-9; **8**, 30859-70-2; **9**, 116185-04-7; **10**, 116185-05-8; **11**, 4161-32-4; **12**, 116185-06-9; **13**, 116210-21-0; **14a**, 6705-89-1; **14b**, 116261-29-1; **15a**, 112-27-6; **16a**, 4362-05-4; **16b**, 38737-48-3; **17** (isomer 1), 116185-08-1; **17** (isomer 2), 116210-22-1; **18** (isomer 1), 116185-09-2; **18** (isomer 2), 116185-10-5; **19**, 76124-47-5; **20**, 16260-48-3; **21**, 88458-55-3; $HO(CH_2)_2OH$, 463-57-0; OHCCHO, 107-22-2; (2*S*,3*S*)-2,3-butanediol, 19132-06-0; (*S*,*S*,*S*,*S*)-3,8-dimethyl-2,8-decanediol, 116185-07-0; 1,3-propanediol, 504-63-2; 2,2-dimethyl-1,3-propanediol, 126-30-7; (*S*,*S*)-2,4-pentanediol, 72345-23-4; *o*-mercaptobenzyl alcohol, 4521-31-7; 2-mercaptoethanol, 60-24-2.

Supplementary Material Available: Experimental procedures for compounds **6** and **10**; combustion analyses, complete ^1H NMR spectra, and selected IR data for compounds **6**, **8**–**10**, **12**, **13**, **17**, and **19** and for the mixture **14b** and **16b** (2 pages). Ordering information is given on any current masthead page.

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(9) Sprung, M. M.; Guenther, F. O. *J. Am. Chem. Soc.* **1951**, *73*, 1884.
(10) The composition of the bidioxolane and tetraoxadecalin mixture was determined by ^1H NMR. E. Caspi, Th. A. Wittstruck, and D. M. Piatak (*J. Am. Chem. Soc.* **1962**, *27*, 3183) have found that the chemical shift of the methine protons in **14a** and **16a** depends on the ring size of the heterocycle. In bidioxolane **14a** they absorb at δ = 4.85 ppm; those on the tetraoxadecalin **16a** at δ = 4.65 ppm. We found that this trend toward lower field for the dioxolane acetal methine protons relative to the dioxane acetal methine protons was consistent with the shifts (in $CDCl_3$) observed in unambiguous compounds: **4** (4.95 ppm) and **7** (4.45 ppm); **6** (5.15 ppm) and **9** (4.85 ppm). Extending this, we assigned the absorbance at 4.85 ppm to the acetal methine protons in tetramethylbidioxolane **14b** and the resonance at 4.65 to those on tetramethyltetraoxadecalin **16b**.
(11) There is evidence that perchlorate salts selectively complex bis(dioxolanes) in preference to the isomeric tetraoxadecalins. We are currently pursuing this as a means of purifying **14b**: Chastrette, F.; Hassambay, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1976**, *607*, 613.
(12) Rosen, W.; Busch, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 4694.
(13) A TLC comparison (with authentic samples of **20** and **21**) showed that the crude reaction product exhibited only the one spot by TLC, which corresponded to the dithioether diol **20**. Also, no S–H stretch was observed in the infrared.
(14) Alexis, C. P.; Uribe, J.; Gutierrez, C. G., unpublished results.

Facile Synthesis of 2,6-Dialkylphenols by Cross-Aromatization of Cyclohexanones with Aldehydes Catalyzed by Zirconocene Complexes

Summary: 2,6-Dialkylphenols, which are difficult to prepare by conventional methods, have been conveniently synthesized in one step via zirconocene-catalyzed cross-aromatization of cyclohexanones with aldehydes.

Sir: Although phenol derivatives are versatile compounds from the pharmaceutical and industrial points of view, there is no practical method available to prepare 2,6-dialkylphenols except for 2,6-dimethyl- or 2,6-di-*tert*-butylphenol derivatives.[1] Direct alkylation of phenols with olefins,[2] alcohols,[3] or alkyl halides[4] generally results in mixtures of mono- and polysubstituted phenols alkylated preferentially at the para position. 2,6-Dibenzylphenol has been synthesized by $IrCl(CO)(PPh_3)_2$-catalyzed isoaromatization of 2,6-dibenzylidenecyclohexanone,[5] derived

(1) (a) Fullerton, T. J.; Ahern, S. P. *Tetrahedron Lett.* **1976**, 139. (b) Nishinaga, A.; Tominaga, H.; Matsuura, T. *Tetrahedron Lett.* **1980**, *21*, 1261. (c) Nishinaga, A.; Tominaga, H.; Tarumi, Y.; Matsuura, T. *Tetrahedron Lett.* **1980**, *21*, 2833.
(2) (a) Dewar, M. J. S.; Puttnam, N. A. *J. Chem. Soc.* **1959**, 4080 and 4090. (b) Kozlova, L. N.; Romadane, I. *Chem. Abstr.* **1971**, *74*, 64007*t*. (c) Navruzov, Kh.; Kuchukarov, A. B.; Sarankina, S. A.; Kurbanov, F. K.; Babaeva, Kh. Z. *Chem. Abstr.* **1974**, *80*, 108097*c*.
(3) (a) Kutz, W. M.; Corson, B. B. *J. Am. Chem. Soc.* **1946**, *68*, 1477. (b) Ismailov, R. G.; Alimardanov, R. S.; Mustafaev, E. Kh. *Chem. Abstr.* **1971**, *74*, 53211*d*. (c) Kheifits, L. A.; Podberezina, A. S.; Kaznacheev, Yu. D. *Chem. Abstr.* **1974**, *81*, 91133*g*.
(4) (a) Alul, H. R. and McEwan, G. J. *J. Org. Chem.* **1972**, *37*, 3323. (b) Alul, H. R.; McEwan, G. J. *J. Org. Chem.* **1972**, *37*, 4157.

0022-3263/88/1953-5181$01.50/0