combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed at reduced presure. The residue was flash chromatographed (5% MeOH-CH_2Cl_2) and rechromatographed (50% acetone-CH_2Cl_2) to afford 179 mg (32%) of **7f** as a deep purple, crystalline solid: mp >280 °C; δ ^{1}H NMR 8.22-8.15 (m, 6 H, H-4′, H-5′, H-8), 7.65-7.48 (m, 10 H, H-5, H-6, H-6′, H-7′, H-8′), 7.34 (m, 2 H, H-3′), 6.47 (d, $J_{1',3'}$ = 2.6, 2 H, H-1′), 3.16 (m, 4 H, H-4), 2.96 (s, 6 H, NMe_2), 2.78 (m, 2 H, H-2), 2.30 (m, 2 H, H-3), 1.42 (s, 18 H, 17-tBu); MS, *m/e* (FD) 945 (M^+, 100); *m/e* calcd for $C_{65}H_{61}N_5$ 911.49267, measured 945.49539.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2-chloro-7-*tert*-butylacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (7g). Tetralone **4g** (40 mg, 0.10 mmol) and 80 mg (0.13 mmol) of benzylidene **5g** were combined in a 5-mL flask, and 2.0 mL of 70% perchloric acid was added. The mixture was stirred at 90-95 °C under nitrogen for 2 h. After cooling of the mixture slightly, 15 mL of ethanol was added, and the mixture was heated at 80 °C for 1.5 h. The solvent was removed at reduced pressure, and the residue was treated with ammonia-saturated methanol until basic. The resulting mixture was stirred overnight and concentrated to a crude solid, which was triturated with CH_2Cl_2. The organic extracts were flash chromatographed (30% EtOAc-petroleum ether) to afford 165 mg (36%) of **7g** as a cream-colored solid: mp >280 °C; ^{1}H NMR δ 8.53* (d, $J_{1,3}$ = 1.1, 1 H, H-1), 8.48* (d, $J_{1,3}$ = 1.2, 1 H, H-1), 8.08-8.01 (m, 4 H, H-4′, H-5′), 7.71-7.27 (m, 12 H, H-1′, H-3, H-3′, H-4, H-6′, H-8′), 7.55 (d, $J_{16,18}$ = 1.0, 1 H, H-18), 7.15 (d, $J_{16,18}$ = 1.0, 2 H, H-16), 3.01 (m, 4 H, H-6), 2.89 (m, 4 H, H-5), 1.42 (s, 18 H, 17-tBu), 1.05* (s, 9 H, 7′-tBu), 0.94* (s, 9 H, 7′-tBu); MS, *m/e* (FD) 1006 (M^+, 100); *m/e* calcd for $C_{69}H_{65}N_3Cl_2$ 1005.45552, measured 1005.45651.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2-*tert*-butylacridin-9-yl)dibenz[*c*,*h*]acridine (1b). To a solution of 185 mg (0.20 mmol) of **7b** in 6 mL of chlorobenzene was added 134 mg (0.59 mmol) of DDQ. The dark mixture was heated to reflux under a nitrogen atmosphere for 8 h. The mixture was partitioned between 100 mL of saturated aqueous sodium bicarbonate solution and 100 mL of chloroform. The aqueous layer was washed once with 75 mL of chloroform, and the combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed at reduced pressure. ^{1}H NMR of the residue showed ca. 50% conversion. The material was redissolved in chlorobenzene and 100 mg (0.4 mmol) of DDQ was added. The mixture was refluxed for 4 h and worked up as described above. Flash chromatography (20% EtOAc-petroleum ether) afforded 138 mg (75%) of **1b** as an amber, crystalline solid: mp 225 °C, dec; ^{1}H NMR δ 9.70* (s, 1 H, H-1), 9.69* (s, 1 H, H-1), 8.17 (m, 2 H, H-5′), 8.13 (m, 2 H, H-4′), 7.87 (d, $J_{5,6}$ = 9.2, 2 H, H-6), 7.8-7.6 (m, 11 H, H-1′, H-3, H-4, H-6′, H-8′, H-18), 7.78 (d, $J_{5,6}$ = 9.2, 2 H, H-5), 7.75 (d, $J_{3',4'}$ = 8.1, 2 H, H-3′), 7.41 (s, 2 H, H-16), 7.19* (t, $J_{6',7'}$ = 7.5, $J_{7',8'}$ = 7.5, 1 H, H-7′), 7.15* (t, $J_{6',7'}$ = 7.5, $J_{7',8'}$ = 7.5, 1 H, H-7′), 1.47* (s, 4.5 H, 16-tBu), 1.465* (s, 9 H, 16-tBu), 1.455* (s, 4.5 H, 16-tBu), 1.11* (s, 9 H, 2-tBu), 0.97 (s, 9 H, 2-tBu); MS, *m/e* (70 EV, EI) 933 (M^+, 100); *m/e* calcd for $C_{69}H_{63}N_3$ 933.50216, measured 933.50370.

7-(3,5-Di-*tert*-butylphenyl)-2,12-bis(2-chloro-7-*tert*-butylacridin-9-yl)dibenz[*c*,*h*]acridine (1g). By the procedure for **1b**, 7.5 mg (51%) of **1g** was obtained as a brown solid: ^{1}H NMR δ 9.75 (s, 2 H, H-1), 8.14 (d, $J_{5',6'}$ = 7.6, 2 H, H-5′), 8.12 (d, $J_{3',4'}$ = 6.8, 2 H, H-4′), 7.90 (d, $J_{5,6}$ = 9.4, 2 H, H-6), 7.81 (d, $J_{5,6}$ = 9.4, 2 H, H-5), 7.72 (m, 12 H, H-1′, H-3′, H-6′, H-8′, H-3, H-4), 7.58 (s, 1 H, H-18), 7.42 (d, $J_{16,18}$ = 1.7, 2 H, H-16), 1.47 (s, 18 H, 17-tBu), 1.08* (s, 9 H, 7′-tBu), 0.98* (s, 9 H, 7′-tBu).

7-(3,5-Di-*tert*-butylphenyl)-2-(2-*tert*-butylacridinyl-9-yl)-12-(2,5-dimethoxyacridin-9-yl)-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (8). Tetralone **4e** (106 mg, 0.28 mmol) and 200 mg (0.35 mmol) of benzylidene **5b** were combined with 0.4 mL of boron trifluoride etherate, and the mixture was heated to 110 °C for 2.5 h. The homogeneous, maroon solution was transferred to a larger flask with 10 mL of CH_2Cl_2, and 20 mL of ammonia-saturated methanol was added. The clear brown solution was stirred at room temperature overnight and the solvent removed under reduced pressure. The residue was partitioned between 70 mL of CH_2Cl_2 and 100 mL of a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc to 5% MeOH-CH_2Cl_2) to afford 143.5 mg (55%) of **8** as an amber, crystalline solid: mp 255 °C dec; ^{1}H NMR δ 8.51 (s, 1 H, H-13), 8.48 (s, 1 H, H-1), 8.24-8.12 (m, 3 H, H-4′, H-4″, H-5″), 7.77-7.56 (m, 4 H, H-1″, H-3″, H-6″, H-8″), 7.52 (s, 1 H, H-18), 7.41-7.15 (m, 6 H, H-3′, H-8′, H-3, H-4, H-10, H-11), 7.13 (s, 2 H, H-16), 7.12-6.73 (m, 4 H, H-1′, H-6′, H-7′, H-7″), 4.15* (s, 1.5 H, 5′-OMe), 4.13* (s, 1.5 H, 5′-OMe), 3.51* (s, 1.5 H, 2′-OMe), 3.44* (s, 1.5 H, 2′-OMe), 1.42 (s, 18 H, 17-tBu), 1.10* (s, 4.5 H, 2″-tBu), 1.05* (s, 4.5 H, 2″-tBu); MS, *m/e* (70 eV, EI) 941 (M^+, 100); *m/e* calcd for $C_{67}H_{63}N_3O_2$ 941.49120, measured 941.49263.

Acknowledgment. We thank Prof. R. Foster for helpful correspondence. Funding from the Research Corporation, American Cancer Society (Junior Faculty Award to S.C.Z.), the National Institutes of Health (Grant No. GM38010-01), and the National Science Foundation (PYI Award) is gratefully acknowledged.

(Dialkoxymethyl)lithiums: Generation, Stability, and Synthetic Transformations

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Abstract: (Dialkoxymethyl)lithium reagents, $(RO)_2CHLi$, can be generated simply and efficiently and employed as synthetically useful one-carbon nucleophiles. Reductive lithiation of phenylthio-substituted precursors, $(RO)_2CHSPh$, at −95 °C or transmetalation of tri-*n*-butylstannyl compounds, $(RO)_2CHSn(n\text{-}Bu)_3$, at −110 to −111 °C afforded the acyclic species $(MeO)_2CHLi$ (**4**) and $(EtO)_2CHLi$ (**5**). The cyclic reagents, 2-lithio-1,3-dioxolane (**6**) and 2-lithio-1,3-dioxane (**7**), were similarly prepared at −78 °C by reductive lithiation or transmetalation. Reactions of (dialkoxymethyl)lithiums with electrophiles, including aldehydes, ketones, 2-cyclohexen-1-one (1,2- or 1,4-addition as desired), dimethyl sulfate, primary alkyl bromides, epoxides, oxetane, and $n\text{-}Bu_3SnCl$, afforded structurally diverse, functionalized acetals. In these experiments, which emphasized transformations of lithiodioxane **7**, yields of products generally exceeded 90%. The thermal stability of each reagent was investigated at several temperatures. The acyclic compounds **4** and **5** decompose rapidly even at −95 °C, whereas lithiodioxolane **6** and dioxane derivative **7** are relatively stable at −78 and −45 °C, respectively. These striking differences in solution lifetimes can be rationalized in terms of alternative decomposition pathways and steric and stereoelectronic factors. The primary products of thermal decomposition of **7** can be ascribed to formation of a reactive carbene or carbenoid via α-elimination. Equilibration experiments established that (dialkoxymethyl)lithium **7** is more stable thermodynamically than the α-monoalkoxy species [(benzyloxy)methyl]lithium, in accord with previous ab initio calculations.

α-Heterosubstituted organometallics serve as versatile, effective reagents for the preparation of organic structures.[1] Whereas α-alkoxy organolithiums[2] (**1**) and bis(α-alkylthio) organolithium compounds[3,4] (**2**) have been widely employed in synthesis, no viable

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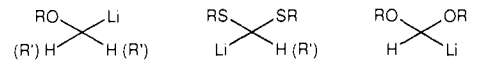

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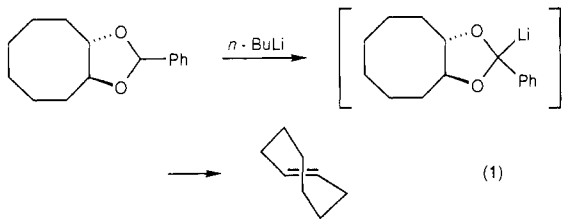
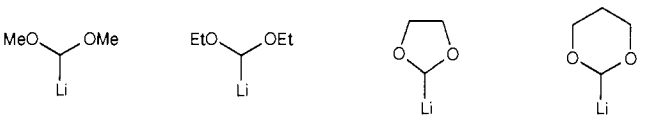
procedures for generation of simple (dialkoxymethyl)lithium reagents (**3**) have previously been devised.[5,6] Inspired by intensive interest in the development of acyl anion equivalents,[7] several early efforts to prepare (dialkoxymethyl)lithiums were undertaken without success.[8] The suggestion that these species might be too unstable for use as one-carbon nucleophiles was reinforced by an essentially contemporaneous discovery, the facile fragmentation of aryl dioxolanes initiated by C(2) metalation (e.g., eq 1).[9,10]



(1)

These unpromising precedents notwithstanding, the elusive (dialkoxymethyl)lithiums have remained attractive as reagents for synthesis. Expectations of considerable synthetic utility rest upon the ease and familiarity of acetal hydrolysis to aldehydes,[11,12] as well as the recent development of important transformations of acetals to numerous other functionalities.[13] Suitable (dialkoxymethyl)lithium derivatives might also be advantageously employed in the synthesis of strained or otherwise inaccessible acetals (e.g., via intramolecular alkylation). These considerations led us to initiate further studies of these novel reagents. The plausibility of this venture was substantiated by previous ab initio calculations, which indicated that dialkoxymethyl carbanions actually should be more stable thermodynamically (i.e., less basic) than the corresponding monoalkoxy species.[14] However, these minimal basis set computations could not address the possibility that (dialkoxymethyl)lithiums might suffer exceedingly rapid decomposition, as suggested by the aforementioned experimental studies.

Herein we report the efficient generation of four prototypical (dialkoxymethyl)lithium compounds, (dimethoxymethyl)- and (diethoxymethyl)lithium (**4** and **5**), 2-lithio-1,3-dioxolane (**6**), and



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2-lithio-1,3-dioxane (**7**), via two complementary approaches of considerable generality. Reactions of these species with diverse electrophilic partners are described, together with studies of their thermal and thermodynamic stability and modes of decomposition.

Generation of (Dialkoxymethyl)lithiums. We have prepared (dialkoxymethyl)lithium reagents by reductive lithiation of phenylthio precursors, $(RO)_2(PhS)CH$, and by transmetalation of tributylstannyl compounds, $(RO)_2(n\text{-}Bu_3Sn)CH$. Analogous methods were employed previously for the generation of α-monoalkoxy organolithiums.[2,15] Haloacetals, $(RO)_2CHX$, probably could also be converted efficiently to (dialkoxymethyl)lithiums.[16]

(1) For reviews, see: (a) Krief, A. *Tetrahedron* **1980**, *36*, 2531–2640. (b) Stowell, J. C. *Carbanions in Organic Synthesis*; John Wiley & Sons: New York, 1979; Chapter 4. (c) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275–316. (d) Ahlbrecht, H. *Chimia* **1977**, *31*, 391–403. (e) Seebach, D.; Geiss, K.-H. In *New Applications of Organometallic Reagents in Organic Synthesis*; Seyferth, D., Ed.; Elsevier: Amsterdam, 1976; pp 1–92. (f) Peterson, D. J. *Organomet. Chem. Rev. A* **1972**, *7*, 295–358.

(2) See, for example: (a) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131, and references cited therein. (b) Still, W. C. *Ibid.* **1978**, *100*, 1481–1487. (c) Still, W. C.; Sreekumar, C. *Ibid.* **1980**, *102*, 1201–1202. (d) Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *Ibid.* **1984**, *106*, 3376–3377. (e) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. **1988**, *110*, 842–853. (f) Review: Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; pp 165–172.

(3) The most prominent members of this class are the 2-lithio-1,3-dithianes and related species; several acyclic reagents have been prepared as well. See ref 7, and literature cited therein. See also ref 15.

(4) A few α-alkoxy-α-(alkyl- or arylthio) organolithiums are also known; for leading references, see: (a) 2-Lithio-1,3-oxathiane: Fuji, K.; Ueda, M.; Sumi, K.; Kajiwara, K.; Fujita, E.; Iwashita, T.; Miura, I. *J. Org. Chem.* **1985**, *50*, 657–661. (b) Chiral 2-lithio-1,3-oxathiane derivatives: Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484–489, and references cited therein. (c) [Methoxy(phenylthio)methyl]lithium: Hackett, S.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.* **1986**, 75–76.

(5) Numerous (dialkoxyalkyl)lithiums stabilized by conjugating substituents have been reported: (a) Lithiated acetals of aryl aldehydes: Meyers, A. I.; Campbell, A. L. *Tetrahedron Lett.* **1979**, 4155–4158. Meyers, A. I.; Campbell, A. L.; Abatjoglou, A. G.; Eliel, E. L. *Ibid.* **1979**, 4159–4162. Campbell, A. L.; Khanna, I. K. *Ibid.* **1986**, *27*, 3963–3966. (b) Lithium enolate of methyl dimethoxyacetate: Huet, F.; Pellet, M.; Conia, J. M. *Synthesis* **1979**, 33–34. (c) Lithiated 2-alkynyl-1,3-dioxanes: Kruithof, K. J. H.; Schmitz, R. F.; Klumpp, G. W. *Tetrahedron* **1983**, *39*, 3073–3081. *J. Chem. Soc., Chem. Commun.* **1983**, 239. (d) Lithiated acrolein dimethyl and diethyl acetals: Seyferth, D.; Mammarella, R. E.; Klein, H. A. *J. Organomet. Chem.* **1980**, *194*, 1–7. The latter species were generated by metalation of the acrolein acetals, whereas attempted metalation of 2-vinyl-1,3-dioxane, under different conditions, furnished S_N' products: Bailey, W. F.; Zartun, D. L. *J. Chem. Soc., Chem. Commun.* **1984**, 34–35.

(6) (Dialkoxymethyl)metallics containing mercury, tin, iron, germanium, and bismuth have previously been reported. Transition-metal complexes of 1,1-dialkoxyalkenes have also been formulated as (dialkoxymethyl)metallic species; many compounds of this type are known.

(7) Numerous acyl anion equivalents have been described; for reviews, see: (a) Ager, D. J. In *Umpoled Synthons*; Hase, T. A., Ed.; Wiley-Interscience: New York, 1987; Chapter 2. (b) Hase, T. A.; Koskimies, J. K. *Aldrichimica Acta* **1981**, *14*, 73–77. *Ibid.* **1982**, *15*, 35–41.

(8) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639–649, and references cited therein. Other early studies are unpublished. See also ref 22.

(9) For early reports describing this process, see: Berlin, K. D.; Rathore, B. S.; Peterson, M. *J. Org. Chem.* **1965**, *30*, 226–228, and references cited therein. Subsequently the fragmentation was employed in syntheses of strained *trans*-cycloalkenes and other olefins: Connell, A. C.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1983**, 989–994, and references cited therein.

(10) An alternative mode of *n*-BuLi-induced dioxolane fragmentation involves deprotonation at C(4); see, for example: Klemer, A.; Rodemeyer, G. *Chem. Ber.* **1974**, *107*, 2612–2614.

(11) For examples, see: Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; Chapter 4.

(12) It is noteworthy that acetals and ketals ordinarily undergo acidic hydrolysis more readily than the corresponding 1,3-dithianes. Indeed, selective acetal hydrolyses have been effected in the presence of dithianes; see, for example: Narasaka, K.; Yamazaki, S.; Ukaji, Y. *Chem. Lett.* **1985**, 1177–1178. Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499–502. Dithianes can also be cleaved in the presence of acetals and ketals by using procedures described in ref 11.

(13) Johnson et al. have pioneered the use of chiral acetals in asymmetric variants of many of these processes. For review and discussion of the properties and reactions of acetals in the context of asymmetric synthesis, see: Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods 1986*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; pp 125–259. For leading references, see also: (a) Stereoselective aldol-type condensations with silyl enol ethers and α-silyl ketones: Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249. Silverman, I. R.; Edington, C.; Elliott, J. D.; Johnson, W. S. *J. Org. Chem.* **1987**, *52*, 180–183. (b) Reactions with organometallic reagents: Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075–3078, 3079–3082, 3083–3086. Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Ibid.* **1984**, *25*, 3947–3950. (c) Initiation of polyolefin cyclizations: Johnson, W. S.; Elliott, J. D.; Hanson, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. (d) Addition of allylsilanes: Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941–942. *Ibid.* **1978**, 499–502. Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951–3954. (e) Addition of alkynylsilanes: Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904–2905. (f) Reduction to ethers: Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979**, 4679–4680. (g) Cyanation: Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Ibid.* **1984**, *25*, 591–594.

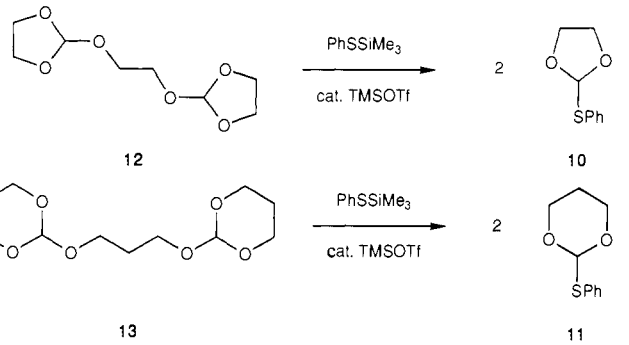
(14) (a) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498–7505. (b) For a more recent theoretical study of the structures and stabilities of α-(mono)heterosubstituted organolithiums, see: Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *Ibid.* **1984**, *106*, 6467–6475. (c) See also: Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *Ibid.* **1986**, *108*, 8171–8175. (d) For a recent experimental investigation of the stabilities of α-monoalkoxy organolithiums, see ref 2e.

(15) Transmetalation of tri-*n*-butylstannyl precursors has also been employed in the preparation of lithiodithianes: Seebach, D.; Willert, I.; Beck, A. K.; Groebel, B. T. *Helv. Chim. Acta* **1978**, *61*, 2510–2523.

(16) The requisite haloacetals are not well-known. However, several α-monoalkoxy organolithiums have been generated by metal–halogen exchange; see: Gadwood, R. C.; Rubino, M. R.; Nagarajan, S. C.; Michel, S. T. *J. Org. Chem.* **1985**, *50*, 3255–3260, and references cited therein.

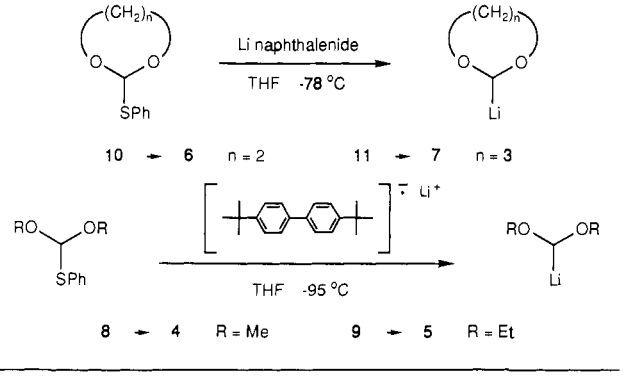
The phenylthio precursors of **4** and **5**, $(MeO)_2(PhS)CH$ (**8**) and $(EtO)_2(PhS)CH$ (**9**), were readily obtained in 80–85 and 55–60% yields, respectively, by reaction of trimethyl or triethyl

orthoformate with $PhSSiMe_3$[17] and trimethylsilyl triflate (TMSOTf) catalyst.[18] The precursors of **6** and **7**, 2-(phenylthio)-1,3-dioxolane and -dioxane (**10** and **11**, respectively), could likewise be prepared from the 2-methoxy or 2-ethoxy derivatives of 1,3-dioxolane and 1,3-dioxane. However, samples of **10** and **11** generated in this fashion invariably contained small amounts of **8** or **9**, which were not easily removed by distillation. To circumvent this difficulty we employed the novel diorthoesters **12** and **13**, readily obtained in ca. 60% yields by transacetalization of triethyl orthoformate with ethylene glycol or 1,3-propanediol and *p*-TsOH catalyst. Treatment of **12** or **13** with $PhSSiMe_3$ and



TMSOTf smoothly furnished pure **10** or **11**, respectively, in 50–60% yields.[19] Thus, one can readily prepare the phenylthio precursors of (dialkoxymethyl)lithiums **4–7** in quantity, via procedures optimized with emphasis on product purity.

The cyclic (dialkoxymethyl)lithiums **6** and **7** could be generated rapidly and cleanly by reaction of the phenylthio compounds **10** and **11** with lithium naphthalenide in THF at −78 °C for 20 min.[20] Attempted preparation of the acyclic species **4** and **5** under these conditions led to extensive decomposition of the desired organolithiums. However, **4** and **5** were efficiently formed by reduction of precursors **8** and **9** with a more reactive radical anion, prepared from lithium metal and 4,4′-di-*tert*-butylbiphenyl,[21] for 1 min at −95 °C.



(17) Prepared by reaction of thiophenol with hexamethyldisilazane; cf. Glass, R. S. *J. Organomet. Chem.* **1973**, *61*, 83–90.

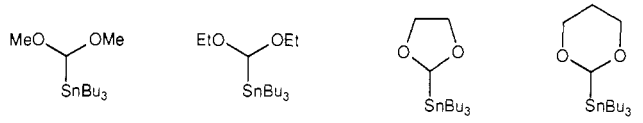
(18) These transformations are related to the well-known ketalization procedure employing alkyl trimethylsilyl ethers and trimethylsilyl triflate catalyst: Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358. For applications of thiosilanes in protection of carbonyl groups, see: Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009–5017.

(19) Significant byproducts of the preparations of **10** and **11** are 2-(phenylthio)ethyl formate and 3-(phenylthio)propyl formate, respectively.

(20) The phenoxy analogue of **11** was not reduced under these conditions.

(21) This reagent is highly effective for the preparation of organolithium compounds from halides: Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930, and references cited therein. We employed a modified preparation of 4,4′-di-*tert*-butylbiphenyl as described in the Experimental Section.

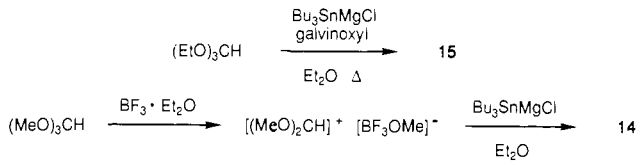
We have also prepared **4–7** by transmetalation of the corresponding tri-*n*-butylstannyl precursors **14–17**. In a previous study,



14 15 16 17

14 and **15** were obtained in low yield via reaction of the corresponding trialkyl orthoformates with (tri-*n*-butylstannyl)magnesium chloride, whereas treatment of diethyl phenyl orthoformate with the stannyl Grignard reportedly furnished **15** in 77% yield.[22] Via the latter method we prepared **15** in GC yields approaching 80%, but careful purification resulted in isolated yields less than 50%.[23] Similarly, the reaction of (tri-*n*-butylstannyl)magnesium chloride with dimethyl phenyl orthoformate gave **14** in 33–40% yields after purification; this mixed orthoester was less accessible than the diethyl homologue.[24] The reported preparation of **15** from triethyl orthoformate afforded crude product of higher purity, but the yields were indeed exceedingly low (ca. 10%).

In attempting to develop improved preparations of **14** and **15**, we employed an efficacious procedure for the galvinoxyl-mediated metalation of tri-*n*-butylstannane by isopropylmagnesium chloride.[25] We were delighted to find that galvinoxyl also promoted the coupling of (tri-*n*-butylstannyl)magnesium chloride with triethyl orthoformate, affording very pure stannane **15** in ca. 60% yield via a one-flask procedure. In contrast, similar reactions of trimethyl orthoformate furnished **14** in only 10–14% yields. The predominant formation of hexabutylditin suggested that the product **14** underwent transmetalation by the stannyl Grignard, with concomitant generation of the unstable organometallic $(MeO)_2CHMgCl$. Subsequent experiments verified that **14** was rapidly destroyed upon exposure to (tri-*n*-butylstannyl)magnesium chloride. However, this difficulty was easily surmounted by using the highly electrophilic dimethoxy carbenium ion, $[(MeO)_2CH]^+[BF_3OMe]^-$, generated in situ by treatment of trimethyl orthoformate with boron trifluoride etherate.[26] Addition of the stannyl Grignard then furnished **14** in 60–65% yields.[27,28]



(22) (a) Quintard, J.-P.; Elissondo, B.; Pereyre, M. *J. Organomet. Chem.* **1981**, *212*, C31–C34. This brief report did not explicitly mention (diethoxymethyl)lithium, and we were unaware of this previous work until our own study was well underway. (b) See also: Pereyre, M.; Elissondo, B.; Quintard, J.-P. In *Selectivity—A Goal for Synthetic Efficiency*; Bartmann, B., Trost, B. M., Eds.; Verlag Chemie: Weinheim, 1984; pp 191–212. (c) For a large-scale preparation of **15** from diethyl phenyl orthoformate, see: Quintard, J.-P.; Elissondo, B.; Mouko-Mpegna, D. *J. Organomet. Chem.* **1983**, *251*, 175–187.

(23) The crude product also contained $(EtO)(PhO)CHSnBu_3$ and $(PhO)_2CHSnBu_3$, among other impurities. Disproportionation products were likewise formed in the preparation of **14** from dimethyl phenyl orthoformate.

(24) We prepared dimethyl phenyl orthoformate and diethyl phenyl orthoformate in 75–85% yields by reaction of trimethyl and triethyl orthoformate with phenol and *p*-toluenesulfonic acid catalyst; methanol and ethanol were removed by codistillation with pentane and cyclohexane, respectively. The former process required reaction times of several days; the use of cyclohexane for separation of methanol led to unwanted removal of trimethyl orthoformate from the reaction mixture. Related procedures were recently described: Barbot, F.; Poncini, L.; Randrianoelina, B.; Miginiac, P. *J. Chem. Res. (M)* **1981**, 4016–4035.

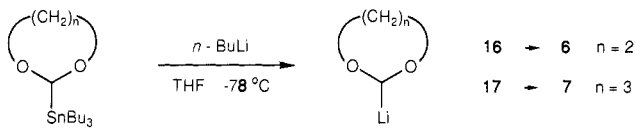
(25) Albert, H.-J.; Neumann, W. P. *Synthesis* **1980**, 942–943. Another method, involving photolysis of a mixture of isopropylmagnesium chloride and tri-*n*-butylstannane, gave somewhat variable results; see: Quintard, J.-P.; Elissondo, B.; Jousseaume, B. *Ibid.* **1984**, 495–498.

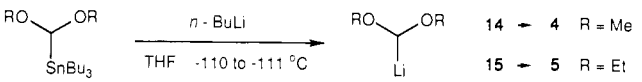
(26) Generation of carbenium ions in this fashion followed by reaction with organolithium compounds furnishes the corresponding acetals: Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717–742, and references cited therein.

(27) (Aminomethyl)tri-*n*-butylstannanes have likewise been prepared by addition of (tri-*n*-butylstannyl)magnesium chloride to iminium salts.[22b]

Transacetalization of either **14** or **15** with ethylene glycol or 1,3-propanediol and *p*-TsOH catalyst afforded **16** or **17** in 95–98% yields. An efficient alternative approach involved reductive lithiation of **10** or **11** as described above, followed by reaction with *n*-Bu_3SnCl.

Rapid transmetalations of the cyclic tri-*n*-butylstannyl precursors **16** and **17**, effected by reaction with *n*-BuLi in THF at −78 °C for 10–20 min, cleanly generated the (dialkoxymethyl)lithiums **6** and **7**. In contrast, the preparation of (dimethoxymethyl)- and (diethoxymethyl)lithiums (**4** and **5**) by transmetalation required more stringent conditions, as in the analogous reductive lithiation studies. After considerable experimentation, we found that the acyclic species could be generated simply by treatment of **14** or **15** with 1 equiv of *n*-BuLi in THF at −110 to −111 °C for 8–12 min. Careful control of the cold bath temperature proved to be critical. Slight warming caused only modest decomposition of **4** and **5**, but at bath temperatures below −111 °C, precipitation of **14** or **15** led to variable and significantly lower yields. The requisite temperature range was readily maintained by using a slush bath prepared from liquid nitrogen and a mixture of THF and ether (12:1). Contrary to a previous report,[22] we could not efficiently prepare **5** by transmetalation of **15** at −78 °C (vide infra).





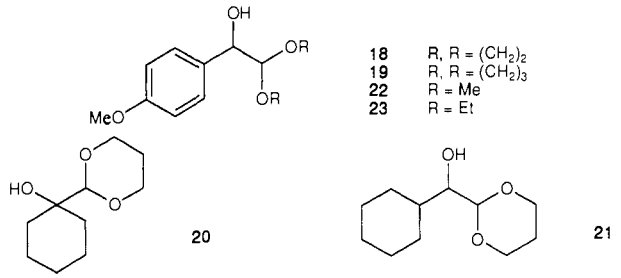
Whereas the transmetalations of the cyclic stannanes **16** and **17** readily proceeded to completion, solutions of **4** or **5** generated from **14** or **15** always contained small quantities of unreacted *n*-BuLi. Neither prolonged reaction times nor the use of excess **15** obviated this difficulty. The persistence of *n*-BuLi may reflect incomplete reactions rather than unfavorable transmetalation equilibria (vide infra); we note also that the transmetalation of **17**, which is rapid and quantitative at −78 °C, proceeded only to 90% of completion under the conditions employed for generation of **5**.

We have not yet undertaken detailed NMR study of the solution structures of any (dialkoxymethyl)lithium species.[29] The structural assignments rest upon expectations for the methods of synthesis employed, and upon the transformations effected with the reagents. ^{119}Sn NMR analysis at −60 °C did confirm that reaction of **17** with *n*-butyllithium in THF afforded tetra-*n*-butylstannane; there was no evidence for formation of a stable ate complex.[30]

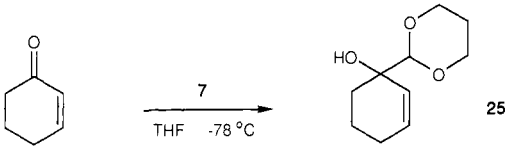
Reactions of (Dialkoxymethyl)lithiums with Electrophiles. The reactions of **4**–**7** with representative, structurally diverse electrophiles have been investigated, with emphasis on transformations of lithiodioxane **7**. Reagent **7** allowed the efficient generation of a wide range of functionalized acetals. Although not yet extensively explored, the reactivity of **6** is presumably similar in scope, based upon the satisfactory thermal stability of the reagent. In contrast, **4** and **5**, as well as other acyclic species, appear to be useful primarily for addition to aldehydes and ketones and other highly reactive electrophiles.

In preparative applications of (dialkoxymethyl)lithium chemistry, the nucleophilicity of the byproduct lithium thiophenoxide and the inconvenience of separating the products from recovered arene reagents constitute drawbacks of reductive lithiation, vis-ã-vis the transmetalation route. The latter method of (dialkoxymethyl)lithium generation appears to be limited only by the presence of small amounts of *n*-BuLi in solutions of **4** and **5**.

All four reagents reacted cleanly with carbonyl compounds, affording the expected addition products in excellent yields. Thus, the reactions of **6** and **7** (1.15 equiv), prepared in THF from **10** and **11**, respectively, with *p*-anisaldehyde afforded the carbinols **18** and **19** in 90 and 100% yields.[31] Enolization did not appreciably complicate the additions, as reaction of **7** (1.2 equiv, prepared from **11**) with cyclohexanone furnished alcohol **20** in 97% yield, and addition to cyclohexanecarboxaldehyde gave **21** in 92% yield. The acyclic compounds **4** and **5** (1.3 equiv), generated by reductive lithiation of **8** and **9** at −95 °C for 1 min, also added efficiently to *p*-anisaldehyde, affording carbinols **22** and **23** in 90 and 95% yields, respectively. Similarly, formation of **4** and **5** by transmetalation of **14** and **15** at −110 to −111 °C, followed by reaction with excess *p*-anisaldehyde, gave **22** and **23** in 87 and 91% yields,[32] together with *p*-anisyl-*n*-butylcarbinol (**24**) in 3 and 6% yields. Preparation of **7** by transmetalation of **17** and addition to *p*-anisaldehyde at −78 °C furnished **19** quantitatively.



The addition of 2-cyclohexen-1-one to a solution of **7** generated by reductive lithiation afforded approximately equal amounts of the desired 1,2-addition product **25** and 3-(phenylthio)cyclohexanone. Formation of the latter byproduct was readily obviated by employing the tri-*n*-butylstannyl precursor **17** for the preparation of **7** (1.1 equiv), whereupon reaction with 2-cyclohexen-1-one in THF at −78 °C gave **25** in 97% yield.



We also explored the use of various organocopper reagents derived from **7** for conjugate addition to α,β-unsaturated carbonyl compounds.[33] Attempted generation of the cuprate (from 2.4 equiv of **7**, prepared in THF by transmetalation, and 1.2 equiv of cuprous iodide–tri-*n*-butylphosphine complex[34]) and reaction with 2-cyclohexen-1-one afforded the 1,4-addition product **26** in

(28) Unwanted transmetalation of **15** by the stannyl Grignard was less troublesome. Accordingly, we did not investigate the formation of **15** via the corresponding diethoxy carbenium ion.

(29) Measurement of ^{13}C, ^{6}Li couplings, in particular, provides detailed information about aggregation of organolithium compounds in solution; for a review, see: Fraenkel, G.; Hsu, H.; Su, B. M. In *Lithium. Current Applications in Science, Medicine, and Technology*; Bach, R. O., Ed.; Wiley-Interscience: New York, 1985; Chapter 19.

(30) Previous studies have established that transmetalations of α-alkoxystannanes likewise afford discrete organolithium products, rather than stable stannylate species (ref 2e). However, lithium pentaalkyl(aryl) tin complexes were recently observed in other systems: Reich, H. J.; Phillips, N. H. *Pure Appl. Chem.* **1987**, *59*, 1021–1026, and references cited therein. The available evidence indicates that these complexes are less reactive than the corresponding organolithium compounds toward electrophiles.

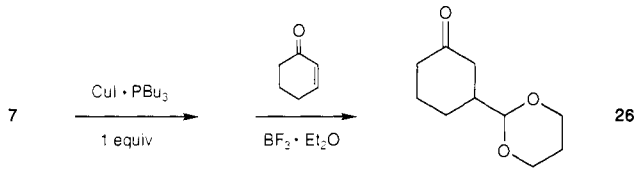
(31) The formation of α-hydroxy acetals via novel SmI_2-promoted coupling of 1,3-dioxolane with carbonyl compounds was recently reported: Matsukawa, M.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 5877–5878.

(32) In these experiments, *n*-BuLi and **14** or **15** were employed as the limiting reagents to facilitate optimization of the transmetalation procedures. The use of **4** and **5** in slight excess with respect to the electrophile would presumably furnish the carbinols in higher yields.

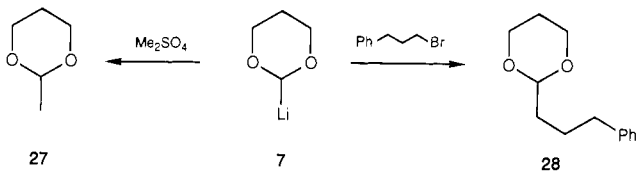
(33) Conjugate addition reactions of cuprates and organocopper reagents derived from α-monoalkoxy organolithiums have recently been reported: (a) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930–4939. (b) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron Lett.* **1987**, *28*, 3911–3914. A cuprate prepared from 2-lithio-1,3-dithiane has also been described: (c) Trost, B. M.; Weber, L.; Strege, P.; Fullerton, T. J.; Dietsche, T. J. *Ibid.* **1978**, *100*, 3426–3435.

(34) Preparation: Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9–12.

only 25% yield. In contrast, excellent results were obtained by using the organocopper species formed by treatment of **7** (ca. 2 equiv) with an equimolar quantity of CuI·P(*n*-Bu)$_3$ in THF at −78 °C.[35] Addition of 2-cyclohexen-1-one followed by 2 equiv of boron trifluoride etherate furnished **26** in 92% yield.[36,37] 1,4-Addition to methyl crotonate did not occur under these conditions, however.



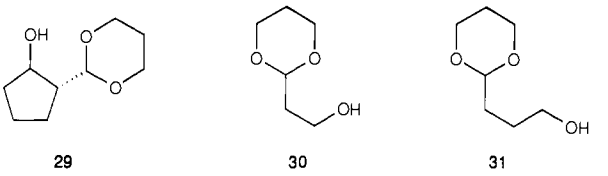
In contrast with the behavior of simple alkyllithiums, lithiodioxane **7** also undergoes efficient alkylation upon exposure to suitable alkylating agents.[38] Thus, generation of **7** in THF at −78 °C, by either reductive lithiation or transmetalation, followed by addition of excess dimethyl sulfate and gradual warming to ambient temperature, afforded 2-methyl-1,3-dioxane (**27**) in ca. 95% yield (determined by GC). Reaction with methyl iodide



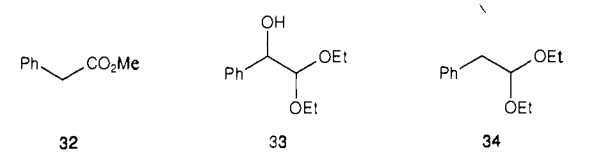
was less effective. Alkylation with primary alkyl bromides also proceeded efficiently; for example, transmetalation of **17** and reaction with 1-bromo-3-phenylpropane (1.2 equiv) in THF–HMPA (−78 → 0 °C) furnished dioxane **28** in 93% yield. Under similar conditions, alkylation with the corresponding iodide afforded **28** in only 41% yield. Reaction of the bromide with **7** generated by reductive lithiation gave **28** in 81% yield. The use of phenylthio compounds as precursors generally resulted in reaction of 1 equiv of the alkylating agent with the byproduct PhSLi.

Attempted alkylation with benzyl bromide, in the presence or absence of HMPA, furnished the desired phenylacetaldehyde acetal in less than 10% yield from **7**, formed by transmetalation.[39] The major product, 1,2-diphenylethane, was isolated in 70–80% yields.[40] Further, exposure of **7**, generated by transmetalation, to secondary alkyl bromides afforded primarily elimination products; reactions with secondary iodides were similarly unsuccessful. Efforts to employ the aforementioned organocopper species derived from **7** in coupling with secondary halides also failed. The possible involvement of single-electron transfer in certain alkylation reactions of **7** is under investigation.

Addition of (dialkoxymethyl)lithiums to epoxides and oxetane furnished other synthetically valuable species. For example, reaction of cyclopentene oxide with **7** (prepared by transmetalation) and boron trifluoride etherate (3 equiv each) in THF at −78 °C afforded carbinol **29** in 82% yield.[41] Similar transformations of ethylene oxide and oxetane gave alcohols **30** and **31** in 62 and 82% yields, respectively.



As noted above, the preparation of (diethoxymethyl)lithium (**5**) at −78 °C, via transmetalation of the tri-*n*-butylstannyl precursor **15** with *n*-BuLi, was outlined previously.[22] In the earlier study, addition of **5** to benzaldehyde produced methyl phenylacetate (**32**), rather than the expected carbinol **33**, in 60% yield.



Reaction of **5** with benzyl bromide reportedly gave phenylacetaldehyde diethyl acetal (**34**) in 78% yield. 1,4-Addition to 2-cyclohexen-1-one in the presence of cuprous iodide was also described (43% yield).

In the course of experiments culminating in the efficient generation of **5** from **15** at −110 to −111 °C, we made numerous attempts to effect this transmetalation at −78 °C, under the conditions described earlier[22,42b] and variations thereof. We found that **5** rapidly decomposed at this temperature, despite careful purification of the precursor **15**, and reactions with electrophiles afforded the desired products very inefficiently. For example, efforts to prepare carbinol **23** at −78 °C furnished the alcohol in less than 10% yield, whereas we obtained **23** in greater than 90% yield at −110 to −111 °C. After generation of **5** by transmetalation at −110 to −111 °C, warming to −78 °C likewise led to extensive decomposition (vide infra). Treatment of **5** with benzyl bromide afforded predominantly 1,2-diphenylethane, in accord with our efforts to alkylate the lithiodioxane **7** with this halide. We cannot account for the discrepancies between our results and those published earlier;[42] however, we believe that the transmetalation procedure described herein will prove to be reliable.

Thermal and Thermodynamic Stabilities and Modes of Decomposition of (Dialkoxymethyl)lithiums. The preparative investigations described herein revealed that the acyclic compounds

(35) In consequence of the limited thermal stability of our organolithium compounds, we employed the soluble phosphine complex of cuprous iodide to facilitate generation of the organocopper reagent at low temperature. Conjugate additions have previously been effected by RCu·phosphine complexes alone: see, for example: Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348–3349. However, we were unable to prepare **26** in this fashion. The role of phosphine, if any, in our 1,4-addition reactions is not known.

(36) For a review of conjugate additions and other reactions of "RCu·BF$_3$" reagents and related species, see: Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947–959.

(37) In analogous published procedures,[36] "RCu·BF$_3$" reagents ordinarily have been generated prior to addition of the unsaturated carbonyl compound. We obtained none of the desired product when this order of addition was employed; apparently the organocopper reagent decomposed rapidly in the presence of BF$_3$·Et$_2$O. This observation is, of course, consistent with the possibility that the Lewis acid interacts advantageously with the enone rather than the organocopper species (cf. ref 41a). For related findings, see: Reference 33a. Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 3595–3596.

(38) Other α-heterosubstituted organolithiums, including (α-alkoxyalkyl)lithiums[2] and lithiodithianes,[3] also couple readily with halides, whereas simple alkyllithiums generally do not (ref 1b, p 50).

(39) This transformation was attempted under various conditions, including those successfully employed for the formation of **28**.

(40) In the reaction of (methoxymethyl)lithium with benzyl bromide, 1,2-diphenylethane comprises 50% of the product in the presence of HMPA and 90% in its absence: Duchene, A.; Mouko-Mpegna, D.; Quintard, J.-P. *Bull. Soc. Chim. Fr.* **1985**, 787–793.

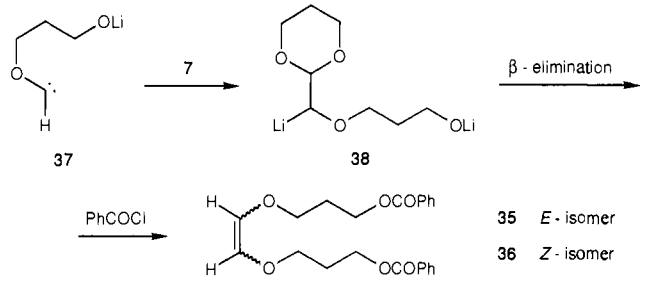
(41) BF$_3$-promoted addition of organolithium compounds to epoxides and oxetanes has been previously described: (a) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693–3694, and references cited therein. (b) See also: Reference 36. Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075–3078.

(42) (a) The authors of the previous report[22] have suggested[42b] that trace impurities in **15** may critically influence the rate of decomposition of **5** and, accordingly, that the method of preparation of **15** might be crucial. The organotin precursor employed in the published[22] transmetalation experiments was synthesized in low yield by reaction of (tri-*n*-butylstannyl)magnesium chloride with triethyl orthoformate, rather than via the more efficient diethyl phenyl orthoformate procedure.[42b] We prepared **15** by both of these routes, as well as by the galvinoxyl-mediated process described herein. After careful purifications, all three preparations gave **15** admixed with the same detectable contaminants (capillary GC analysis). For transmetalation studies at −78 °C, a sample obtained via the published triethyl orthoformate reaction was purified to 99.2% homogeneity by distillation followed by two flash chromatographies; the diethyl phenyl orthoformate route afforded material of 99.9% purity after three distillations. Neither sample efficiently furnished **5** at −78 °C. We note, however, that negative results such as these cannot exclude the possibility that some samples of **15** could be successfully transmetalated at this temperature. Material synthesized by any of these routes can be employed for transmetalation at −110 to −111 °C. (b) Pereyre, M., personal communication.

4 and **5** decomposed much more rapidly than the cyclic reagents **6** and **7**. As noted earlier, attempted generation of **4** and **5** by reductive lithiation with lithium naphthalenide at −78 °C, followed by trapping with *p*-anisaldehyde, furnished at most low yields of products. Efficient generation of **5** at −95 °C followed by warming to −78 °C also resulted in rapid decomposition. Even at −95 °C, the decomposition of **5** was relatively fast. Preparation of **5** (1.1 equiv) by reductive lithiation for 1 min and reaction with *p*-anisaldehyde furnished **23** in 91% yield, but the yield diminished to 42% when the solution of **5** was stirred for 30 min at −95 °C prior to addition of the aldehyde.

The thermal stabilities of **4**–**7** were further explored with samples prepared by transmetalation. After reaction of tri-*n*-butylstannyl precursor **16** or **17** with *n*-BuLi in THF at −78 °C, for 20 or 30 min, respectively, a solution was stirred at a constant higher temperature for 30 min, and the remaining organolithium compound was then trapped by reaction with *p*-anisaldehyde. The yields of alcohols thus obtained are indicative of the thermal stabilities of **6** and **7** when prepared in this manner. Lithiodioxane **7** afforded alcohol **19** in 95, 58, and 2% yields after warming to −45, −20, and 0 °C, respectively. Analogous reactions of **6** furnished carbinol **18** in 91, 86, 65, and 25% yields after 30-min periods at −78, −70, −60, and −50 °C, respectively. Thus, 2-lithiodioxane is significantly longer lived in solution than 2-lithiodioxolane. Similar experiments were carried out with **4** and **5**, prepared by transmetalation of **14** and **15** at −110 to −111 °C. *p*-Anisaldehyde trapping of **4** afforded carbinol **22** in 89, 43, and 20% yields after 30-min periods at −110 to −111, −95, and −78 °C, respectively. Under the same conditions, **5** furnished alcohol **23** in 92, 61, and 17% yields. Hence, both acyclic reagents decompose much more rapidly than either of the cyclic species. Further experiments established that the solution lifetimes of **6** and **7** are insensitive to small amounts of excess *n*-BuLi.

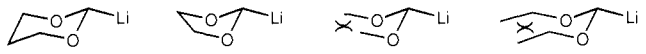
To elucidate the factors responsible for these striking variations in thermal stability, we first identified the major products of thermal decomposition of **7**, prepared by transmetalation. Warming a THF solution of **7** to room temperature for 2 h, followed by reaction with benzoyl chloride at 0 °C for 30 min, afforded equal amounts of the *E* and *Z* dibenzoates **35** and **36** in 54% combined yield.[43] Their formation probably involves the generation of carbene intermediate **37** or a related carbenoid by α-elimination.[44] Reaction of this species with **7** would afford the



organolithium **38**,[45,46] followed by internal β-elimination of lithium alkoxide to furnish the dialkoxide precursors of **35** and **36**. In situ benzoylation of the dialkoxides facilitated product isolation. The decomposition of **7** also produced 1,3-dioxane, presumably via deprotonation of the solvent, in 22% yield (determined by GC). Relatively minor amounts of several other products, including the dibenzoate of 1,3-propanediol, were also detected.[47]

The enhanced thermal stability of the cyclic species **6** and **7**, vis-à-vis **4** and **5**, may reflect, in part, the reversibility of α-elimination of LiOR in the former cases. This process is likely to be essentially irreversible in the decomposition of **4** and **5**. Presumably **6** can also decompose via fragmentation to lithium formate and ethylene, analogous to the facile dioxolane fragmentations reported earlier (e.g., eq 1).[9] This pathway may account for the relative stabilities of **6** and **7**, as the dioxane derivative cannot decompose in this fashion. Wittig rearrangement could play a significant role in the decomposition of **4** and **5**, and the latter species can also suffer internal β-elimination, affording ethylene, lithium ethoxide, and formaldehyde. α-Elimination, internal β-elimination, and Wittig rearrangement likewise are the major modes of decomposition of many α-monoalkoxy organolithium compounds.[48]

Steric and stereoelectronic factors undoubtedly influence the conformations and energies of (dialkoxymethyl)lithiums, and thermodynamic stabilities may in turn affect the relative rates of decomposition of **4**–**7**. Thus, **7** and **6** should adopt the stereoelectronically preferred chair and envelope conformations **39**



39 40 41 42

and **40**, respectively.[49] The analogous conformations of **4** and **5** (i.e., **41** and **42**) are destabilized by repulsions involving the methyl and ethyl hydrogens. Unfavorable eclipsing interactions in **40** may contribute to the kinetic, and probably also thermodynamic, instability of **6** relative to **7**.

Previous ab initio calculations[14] at the STO-3G level indicated that (dialkoxymethyl)lithiums should be more stable thermodynamically than (α-alkoxymethyl)lithiums.[50,51] This is indeed the case. [(Benzyloxy)methyl]lithium (**43**) was generated by treatment of $PhCH_2OCH_2Sn(n\text{-}Bu)_3$ (**44**) with *n*-BuLi[2b] and allowed

(43) Similar transformations of metalated thioacetals have been observed previously.[47a]

(44) α-Alkoxy carbenes or carbenoids have been generated from chloromethyl and dichloromethyl ethers via α-elimination pathways: Olofson, R. A.; Lotts, K. D.; Barber, G. N. *Tetrahedron Lett.* **1976**, 3779–3782, and references cited therein.

(45) Formation of formal carbene dimers often involves reactions of carbenes or carbenoids with carbene precursor species, rather than carbene dimerization; see, for example: Wentrup, C. *Reactive Molecules*; John Wiley & Sons: New York, 1984; p 184.

(46) Alternatively, **38** might arise via direct combination of two molecules of **7**, involving C–O bond cleavage assisted by the second RLi moiety and subsequent or concurrent C–C bond formation (cf. ref 47).

(47) (a) Decomposition reactions of dimetalated hydroxy bis(phenylthio) acetals furnish carbenoid-derived products: Ritter, R. H.; Cohen, T. *J. Am. Chem. Soc.* **1986**, *108*, 3718–3725, and references cited therein. In several cases, 2-(phenylthio)cyclopentanols were generated efficiently; these structures are formally accessible via α-elimination of LiSPh and insertion of the resulting carbenoid into an alkoxide α-C–H bond. A similar insertion of **37** would furnish 3-(benzoyloxy)tetrahydrofuran, after trapping with benzoyl chloride. Although small amounts of the latter material may have been formed in our experiments, this insertion clearly is not a significant pathway for the decomposition of **7**. However, by analogy with the detailed mechanistic proposals of Cohen, wherein the decomposition of a metalated thioacetal is induced or facilitated by a proximate alkoxide moiety, preferential formation of 3-(benzoyloxy)tetrahydrofuran would not in fact be expected. (b) See also: Harada, T.; Yamaura, Y.; Oku, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1715–1719, and references cited therein. (c) A carbenoid decomposition induced by *t*-BuLi was recently postulated: Rachon, J.; Goedken, V.; Walborsky, H. M. *J. Am. Chem. Soc.* **1986**, *108*, 7435–7436.

(48) See, for example: Maercker, A.; Demuth, W. *Justus Liebigs Ann. Chem.* **1977**, 1909–1937.

(49) Mixing of the σ_{C-Li} bonding orbital and the σ^*_{C-O} antibonding orbitals stabilizes chair conformer **39**. This conformation also minimizes destabilizing overlap of the filled oxygen nonbonding orbitals and the σ_{C-Li} bonding orbital.[14] Experimental support for this conformational preference can be found in metalation studies of 1,3-dioxanes bearing conjugating C(2) substituents.[5a] Substituted 1,3-dioxolane rings typically are highly flexible: Fuchs, B. *Top. Stereochem.* **1978**, *10*, 63–65, and references cited therein. However, the envelope conformer (**40**) of **6** will be favored by the same stereoelectronic effects operative in **39**.

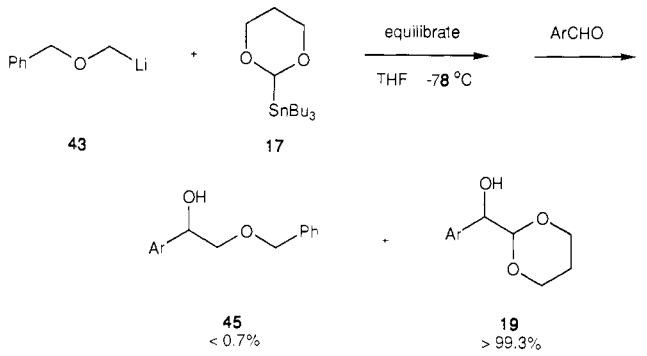
(50) The energies of the model compounds in eq 2 were calculated.[14a]

equatorial $HOCH_2Li + (HO)_2CH_2 \rightarrow HOCH_3 +$ equatorial $(HO)_2CHLi$ (2)

For species related by isodesmic processes such as eq 2, STO-3G calculations can afford useful estimates of relative thermodynamic stabilities. For general discussion and evaluation of minimal basis set calculations, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986; Chapter 6.

(51) In the gas phase, 5,5-dimethyl-1,3-dioxane is ca. 18–27 kcal mol^{-1} less acidic than 5,5-dimethyl-1,3-dithiane: Bartmess, J. E.; Hays, R. L.; Khatri, H. N.; Misra, R. N.; Wilson, S. R. *J. Am. Chem. Soc.* **1981**, *103*, 4746–4751. The p*K* of 1,3-dithiane in THF is 34.8; Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Chem. Soc., Chem. Commun.* **1983**, 620–621; the p*K* of 1,3-dioxane is unknown but certainly higher. The earlier STO-3G calculations[14a] indicated that in the gas phase $(HO)_2CH_2$ should be 12 kcal mol^{-1} less acidic at carbon than $(HS)_2CH_2$ (cf. ref 50).

to react with 2-tri-*n*-butylstannyl-1,3-dioxane (**17**) in THF at −78 °C for 0.5 h. Trapping of the resulting mixture of **43** and lithiodioxane **7** with *p*-anisaldehyde then furnished carbinols **19** and **45** in a ratio of 99.3:0.7.[52] The analogous reaction of preformed



7 with **44** afforded **19** admixed with at most 0.1% of **45**. The presumed close correspondence of the ratios of organolithium compounds with the proportions of carbinol products was confirmed by a competition experiment, wherein reaction of an equimolar mixture of **7** and **43** with a limited amount of *p*-anisaldehyde afforded comparable amounts of alcohols **19** and **45** (ratio 1.21:1). Thus, the formation of **7** from **43** by tin–lithium exchange is exothermic by ca. 4 kcal mol^{-1}.[53,54,14]

The effects of aggregation[55] and possible lithium bridging[56] on the relative stabilities of **4–7**, and of α-alkoxy organolithiums, are as yet unknown.

Experimental Section

Materials. Lithium wire (ca. 0.01% sodium) was purchased from Aldrich Chemical Co. *p*-Anisaldehyde was purchased from Aldrich and purified by a published procedure.[57] 4,4′-Di-*tert*-butylbiphenyl was prepared by Friedel–Crafts alkylation of biphenyl.[58] After an initial recrystallization from 95% ethanol, traces of colored impurities were removed by sublimation, followed by a second recrystallization. Tri-*n*-butylstannane was prepared by reaction of bis(tri-*n*-butyltin) oxide with polymethylhydrosiloxane.[59] Ethylene oxide in ether was purchased from Alfa Products. Other commercially available reagents and solvents were purified by standard procedures or used as received.

Dimethoxy(phenylthio)methane (8). In a 500-mL flask, a mixture of 1.71 g (7.70 mmol, 1.50 mL) of trimethylsilyl trifluoromethanesulfonate and 53.1 g (500 mmol, 54.7 mL) of trimethyl orthoformate was stirred at 5 °C, and 86.5 g (475 mmol) of (phenylthio)trimethylsilane[17] was introduced dropwise through an addition funnel. After the addition was complete, the reaction mixture was warmed to ambient temperature and stirred for 1 h. A short-path distillation apparatus was fitted, and volatile side products were removed at a bath temperature of 95 °C and atmospheric pressure. The residue was diluted with 100 mL of THF and allowed to react with tetra-*n*-butylammonium fluoride (20 mL of a 1 M THF solution) at ambient temperature for 1 h.[60] The mixture then was added to 300 mL of ice-cold 10% aqueous sodium hydroxide solution and extracted with three 300-mL portions of ether. The combined organic extracts were washed with 300 mL of water and dried over sodium sulfate. Filtration and solvent evaporation followed by fractional distillation gave 73.2 g of **8** (83% yield) as a clear, colorless liquid: bp 68–70 °C (0.02 mmHg); ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 6 H), 5.76 (s, 1 H), 7.24–7.36 (m, 3 H), 7.49 (dd, J = 7.9, 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 52.74, 111.59, 127.19, 128.60, 132.43, 132.46; IR (neat) 3100 (w), 3030 (w), 1600 (m), 1495 (m), 1455 (m), 1295 (m), 1200 (s), 1080 (br s), 760 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 184 (1, M$^+$), 153 (26), 124 (18), 110 (35), 109 (43), 91 (12), 75 (100), 65 (22), 47 (47); Anal. ($C_9H_{12}O_2S$) C, H, S.

Diethoxy(phenylthio)methane (9). The procedure described above for the preparation of **8** was employed, substituting 74.1 g (500 mmol, 83.1 mL) of triethyl orthoformate for trimethyl orthoformate. In this experiment, 100 mL of the tetra-*n*-butylammonium fluoride solution was used.[60] Workup and distillation as before furnished 58.2 g of **9** (58% yield) as a clear, colorless liquid: bp 77–80 °C (0.02 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 6.5 Hz, 6 H), 3.62–3.90 (A_2B_2, 4 H), 5.90 (s, 1 H), 7.24–7.36 (m, 3 H), 7.50 (dd, J = 7.5, 1.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.61, 61.49, 109.77, 127.07, 128.55, 132.42, 133.04; IR (neat) 3100 (m), 1600 (m), 1485 (s), 1445 (s), 1270 (s), 1100 (br s), 745 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 167 (46), 139 (46), 110 (60), 109 (58), 103 (100), 77 (38), 75 (80), 65 (41); Anal. ($C_{11}H_{16}O_2S$) C, H, S.

1,2-Bis(1,3-dioxolan-2-yloxy)ethane (12). A 2-L flask fitted with a fractional distillation apparatus was charged with 500 mL of cyclohexane, 163 g (1.10 mol, 183 mL) of triethyl orthoformate, 96.2 g (1.55 mmol, 86.3 mL) of ethylene glycol, and 0.90 g (4.70 mmol) of *p*-toluenesulfonic acid monohydrate. After the resultant mixture was stirred at ambient temperature for 1 h, the ethanol–cyclohexane azeotrope was distilled during ca. 5 h, at a bath temperature of 100 °C and atmospheric pressure. Additional cyclohexane was added as needed. Following addition of 5 g of potassium carbonate, fractional distillation of the resulting concentrated solution afforded 65.9 g of **12** (62% yield) as a colorless, viscous liquid: bp 96–97 °C (0.02 mmHg); ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 4 H), 3.86–4.10 (A_2B_2, 8 H), 5.80 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 62.31, 62.97, 114.31; IR (neat) 1480 (m), 1160–950 (br s) cm^{-1}; mass spectrum (70 eV), m/z 73 (100); Anal. ($C_8H_{14}O_6$) C, H.

2-(Phenylthio)-1,3-dioxolane (10). To a solution of 40.4 g (200 mmol, 33.7 mL) of **12** and 78.4 g (430 mmol, 81.2 mL) of (phenylthio)trimethylsilane[17] was added dropwise 1.7 g (7.7 mmol, 1.5 mL) of trimethylsilyl trifluoromethanesulfonate. The reaction mixture was stirred at ambient temperature for 0.5 h. Volatile side products were removed by vacuum distillation at 0.1 mmHg and a bath temperature of 95 °C. Further distillation at 0.005 mmHg and a bath temperature of 100 °C gave 45.0 g of impure material, which was allowed to react with 150 mL of a 0.3 M solution of tetra-*n*-butylammonium fluoride in THF at 0 °C for 3 h.[60] The mixture then was added to 200 mL of 10% aqueous sodium hydroxide solution and extracted with three 200-mL portions of ether. The combined organic layers were dried over sodium sulfate, filtered, and evaporated. Fractional distillation gave 34.6 g (48% yield) of **10** as a clear, colorless liquid: bp 92–94 °C (0.005 mmHg); ^{1}H NMR ($CDCl_3$) δ 3.90–4.20 (A_2B_2, 4 H), 6.62 (s, 1 H), 7.22–7.40 (m, 3 H), 7.61 (dd, J = 10.0, 2.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 64.00, 111.92, 127.58, 128.69, 132.17, 133.24; IR (neat) 3050 (w), 1480 (s), 1440 (s), 1100 (s), 1080 (s), 1025 (s), 940 (s), 750 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 182 (1.8, M$^+$), 110 (41), 73 (100); Anal. ($C_9H_{10}O_2S$) C, H, S.

1,3-Bis(1,3-dioxan-2-yloxy)propane (13). The general procedure described above for the preparation of **12** was employed for the reaction of 121.5 g (0.82 mol, 138 mL) of triethyl orthoformate, 88.3 g (1.16 mol, 84 mL) of 1,3-propanediol, 400 mL of cyclohexane, and 1.0 g (5.3 mmol) of *p*-toluenesulfonic acid monohydrate. Workup and fractional distillation as before furnished 78.1 g of **13** (58% yield) as a viscous, colorless liquid: bp 106–108 °C (0.01 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.6–1.8 (m, 4 H), 1.91 (pentet, J = 6.4 Hz, 2 H), 3.64–3.84 (m, 8 H), 4.08–4.20 (m, 4 H), 5.24 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.58, 29.52, 61.82, 61.99, 109.67; IR (neat) 1380 (br s), 1250 (s), 1200 (s), 1180–1000 (br s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 87 (100); Anal. ($C_{11}H_{20}O_6$) C, H.

2-(Phenylthio)-1,3-dioxane (11). The procedure described above for the preparation of **10** was employed for the reaction of 65.0 g (0.262 mol,

(52) When **17** and **43** were allowed to react for 2 **h** prior to trapping, **19** and **45** were formed in a ratio of 99.6:0.4.

(53) (a) An obvious conceptual limitation of these equilibrations involves the use of organotin compounds as surrogates for the carbon acids of interest. The latter species unfortunately do not undergo the requisite proton-transfer reactions at temperatures compatible with survival of the derived organolithiums. In accord with earlier interpretations,[54] we believe that these tin-mediated equilibria do reveal the relative stabilities of the respective organolithium species. We assume that in each equilibrium the free energy difference is larger for the pair of organolithiums than for the more covalent organotins[53b] and, further, that the latter correlate more closely in energy with the respective C–H compounds. (b) For discussion of the predominantly ionic character of carbon–lithium bonds, see: Streitwieser, A., Jr. *Acc. Chem. Res.* **1984**, *17*, 353–357, and references cited therein.

(54) Equilibration studies involving various α-monoalkoxy organolithiums and the respective tri-*n*-butylstannyl precursors are described in ref 2b,d,e.

(55) The enthalpies of aggregation of several organolithiums bearing γ- and ε-methoxy substituents were recently reported: Guerink, P. J. A.; Klumpp, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 538–539.

(56) Ab initio calculations indicate that $LiCH_2OH$ is significantly stabilized by Li–O bridging.[14b] However, we are unaware of any experimental studies that address the importance of bridged structures for α-alkoxy organolithium compounds.

(57) Perrin, D. D.; Armarego, W. C. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Oxford, 1980; p 109.

(58) Horne, D. A. *J. Chem. Educ.* **1983**, *60*, 246.

(59) Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81–94.

(60) Fluoride treatment presumably effects desilylation of unreacted $PhSSiMe_3$ and other silylated materials, facilitating isolation of the desired product in pure form.

57 mL) of **13**, 102.9 g (0.564 mol, 107 mL) of (phenylthio)trimethylsilane,[17] and 2.0 g (9.0 mmol, 1.8 mL) of trimethylsilyl trifluoromethanesulfonate. Volatile byproducts were removed by simple distillation at aspirator pressure and a bath temperature of 100–110 °C. Further distillation at 0.01 mmHg and 120 °C bath temperature gave 65.1 g of impure product. After reaction with tetra-*n*-butylammonium fluoride (100 mL of a 0.4 M THF solution, 1 h at ambient temperature)[60] and workup as before, simple distillation through a Claisen head gave 57.2 g of **11** (58% yield) as a clear, colorless liquid: bp 78–81 °C (0.01 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.66–1.80 (m, 1 H), 1.90–2.08 (m, 1 H), 3.84–3.96 (m, 2 H), 4.32–4.44 (m, 2 H), 6.28 (s, 1 H), 7.26–7.38 (m, 3 H), 7.52 (dd, J = 7.9, 1.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.92, 62.32, 107.02, 127.19, 128.60, 132.45, 132.52; IR (neat) 3050 (w), 1580 (m), 1475 (s), 1245 (s), 1145 (s), 1105 (br s), 1055 (s), 1030 (s), 1015 (s), 765 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 196 (12, M^+), 110 (52), 109 (51), 87 (100), 65 (37), 59 (59); Anal. ($C_{10}H_{12}O_2S$) C, H, S.

(Dimethoxymethyl)tri-*n*-butylstannane (14). In a 500-mL flask under argon, a solution of boron trifluoride etherate (5 mL) in 25 mL of ether was stirred at −78 °C, and a solution of trimethyl orthoformate (20 mL, distilled from sodium and benzophenone) in 160 mL of ether was added dropwise over 45 min via a cannula. The solution then was stirred 15 min further at −78 °C. In a 100-mL flask fitted with a reflux condenser, galvinoxyl (0.2 g, ca. 0.5 mmol) was added to 20 mL of a 2 M ethereal solution of isopropylmagnesium chloride. After the mixture was cooled to −8 °C (ice/acetone bath), neat tributyltin hydride (10.8 mL, 40 mmol) was added dropwise to the stirred solution over 15–20 min. The cooling bath was removed, and the mixture was stirred for 1 h. The solution then was transferred by cannula to the flask containing the dimethoxycarbenium tetrafluoroborate solution at −78 °C. The resulting mixture was stirred for 2 h at −78 °C and then warmed slowly to −60 °C over ca. 1 h. After quenching with 50 mL of aqueous pH 7 buffer, the reaction mixture was filtered through a sintered glass funnel and the solid residue washed with two 50-mL portions of ether. The layers were separated and the aqueous phase further extracted with two 100-mL portions of ether. The combined organic layers were dried over potassium carbonate, filtered, and concentrated. The crude product was chromatographed on 250 g of silica, packed by using 1% triethylamine/pentane. The byproducts hexabutylditin and tetrabutyltin were eluted with pentane, and further elution with 20% benzene/pentane then furnished 9.2 g of **14** (63% yield) as a clear, colorless liquid. After an earlier preparation from dimethyl phenyl orthoformate, **14** was distilled and characterized: bp 94–98 °C (0.28–0.30 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.1 Hz, 9 H), 0.94 (t, J = 7.8 Hz, J_{Sn-H} = 45.8 Hz, 6 H), 1.32 (br sextet, J = 6.9 Hz, 6 H), 1.50 (br pentet, J = 7.4 Hz, 6 H), 3.33 (s, 6 H), 5.05 (J_{Sn-H} = 31.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.58 (J_{Sn-C} = 310, 296 Hz[61]), 13.57, 27.30 (J_{Sn-C} = 53.1 Hz), 29.02 (J_{Sn-C} = 20.8 Hz), 56.22 (J_{Sn-C} = 34.9 Hz), 111.17 (J_{Sn-C} ≈ 470, 450 Hz); IR (neat) 1465 (m), 1090 (s), 1040 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 291 (3.7), 287 (2.6), 287 (1.5), 235 (4), 233 (3), 231 (2), 178 (10), 177 (8), 175 (5), 75 (100); Anal. ($C_{15}H_{34}O_2Sn$) C, H.

(Diethoxymethyl)tri-*n*-butylstannane (15). A 500-mL, three-necked flask fitted with a reflux condenser and addition funnel was cooled to 0 °C and charged with galvinoxyl (0.75 g) and isopropylmagnesium chloride (65 mL of a 1.94 M solution in ether). Neat tributyltin hydride (34 mL, 0.126 mol) then was added dropwise over 1 h to the stirred solution. After removal of the cold bath and stirring 1 h further, the solution was heated to reflux. Triethyl orthoformate (150 mL, distilled from sodium and benzophenone) was added dropwise over 1 h to the refluxing solution. The mixture was heated at reflux overnight, and the internal temperature gradually increased to ca. 55 °C. The mixture was diluted with 200 mL of pentane and filtered. After evaporation of solvent and excess orthoformate, careful distillation through a 15-cm Vigreaux column packed with glass helices gave 29.2 g of **15** (59% yield) as a clear, colorless oil, 97.5% pure by capillary GC analysis: bp 94–96 °C (0.015 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.89 (q, J = 7.4 Hz, 9 H), 0.91 (t, J = 7.4 Hz, J_{Sn-H} = 49.0 Hz, 6 H), 1.19 (t, J = 7.0 Hz, 6 H), 1.31 (sextet, J = 7.4 Hz, 6 H), 1.52 (br pentet, J = 7.4 Hz, 6 H), 3.51 (A_2B_2, 4 H), 5.18 (J_{Sn-H} = 31.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.71 (J_{Sn-C} = 308, 294 Hz[61]), 13.50, 15.32, 27.26 (J_{Sn-C} = 51.6 Hz), 29.04 (J_{Sn-C} = 20.8 Hz), 64.57 (J_{Sn-C} = 34.6 Hz), 108.44 (J_{Sn-C} ≈ 505, 485 Hz); IR (neat) 1480 (m), 1260 (m), 1090 (s), 1055 (s), 1005 (m) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 365 (2.6), 363 (2.6), 361 (1.3), 291 (13), 289 (10), 287 (5), 235 (18), 233 (12), 231 (8), 179 (36), 177 (39), 175 (22), 121 (22), 119 (16), 117 (9), 103 (100), 75 (68), 57 (62); Anal. ($C_{17}H_{38}O_2Sn$) C, H.

(1,3-Dioxolan-2-yl)tri-*n*-butylstannane (16). To a solution of 3.52 g (9.64 mmol) of **14** in 60 mL of benzene were added 4.45 g (71.7 mmol, 4.0 mL) of ethylene glycol and 200 mg (1.05 mmol) of *p*-toluenesulfonic acid monohydrate. As the mixture refluxed for 4 h, 60 mL of benzene was introduced through an addition funnel, and 60 mL of methanol–benzene azeotrope was collected with a Dean–Stark apparatus. The resulting mixture was poured into 100 mL of saturated aqueous sodium bicarbonate solution and extracted with four 50-mL portions of dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography on 20 g of silica gel, using benzene/hexanes mixtures (1:10, then 1:1) for elution, gave 3.41 g of **16** (97% yield) as a colorless oil: R_f 0.27 using 50% benzene/hexanes for development; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 9 H), 1.00 (t, J = 8.0 Hz, J_{Sn-H} = 52.0 Hz, 6 H), 1.33 (sextet, J = 7.6 Hz, 6 H), 1.56 (br pentet, J = 7.6 Hz, 6 H), 3.63 (A_2B_2, 2 H), 3.85 (A_2B_2, 2 H), 4.98 (J_{Sn-H} = 103, 99.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.88 (J_{Sn-C} = 325, 310 Hz[61]), 13.45, 27.17 (J_{Sn-C} = 51.6 Hz), 28.92 (J_{Sn-C} = 21.2 Hz), 65.11 (J_{Sn-C} = 32.3 Hz), 106.41 (J_{Sn-C} = 442, 422 Hz); IR (neat) 1470 (m), 1070 (s), 945 (m), 920 (m) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 363 (0.4), 361 (0.3), 359 (0.2) ($M^+ - 1$), 291 (13), 289 (8), 287 (5), 235 (16), 233 (12), 231 (8), 179 (40), 177 (41), 175 (16), 121 (28), 119 (21), 117 (13), 73 (100), 45 (55); Anal. ($C_{15}H_{32}O_2Sn$) C, H.

(1,3-Dioxan-2-yl)tri-*n*-butylstannane (17). a. From 15. To a solution of 19.5 g (49.6 mmol) of **15** in 250 mL of benzene were added 4.4 mL (71.0 mmol) of 1,3-propanediol and 1 g (5.8 mmol) of anhydrous *p*-toluenesulfonic acid. After stirring for 1 h, the solution was heated to reflux and 200 mL of the ethanol–benzene azeotrope was collected with a Dean–Stark apparatus. An additional 100 mL of benzene was added and a further 100 mL of azeotrope was distilled. The last step was repeated, and the resulting mixture then was poured into 50 mL of aqueous pH 7 buffer and extracted with three 100-mL portions of ether. The combined extracts were dried over potassium carbonate, filtered and concentrated. Distillation through a 10-cm Vigreux column gave 19.1 g of **17** (98% yield) as a clear, colorless oil, 98.8% pure by capillary GC analysis: bp 98–100 °C (0.02 mmHg); R_f 0.36 with 2.5% ethyl acetate/hexanes for development; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.9 Hz, 9 H), 0.95 (t, J = 7.9 Hz, J_{Sn-H} = 57.8 Hz, 6 H), 0.8–1.00 (m, 1 H), 1.34 (sextet, J = 7.9 Hz, 6 H), 1.54 (br pentet, J = 7.9 Hz, 6 H), 2.21 (qt, J = 12.7, 4.8 Hz, 1 H), 3.62 (br t, J = 12.7 Hz, 2 H), 4.06 (br dd, J = 10.5, 4.8 Hz, 2 H), 5.24 (J_{Sn-H} = 34.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.82 (J_{Sn-C} = 327, 313 Hz[61]), 13.59, 27.24 (J_{Sn-C} = 52.0 Hz), 27.44, 28.96 (J_{Sn-C} = 21.0 Hz), 68.98 (J_{Sn-C} = 35.7 Hz), 108.16 (J_{Sn-C} ≈ 495, 475 Hz); IR (neat) 1460 (m), 1100 (s), 975 (m) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 377 (0.15, $M^+ - 1$), 291 (2), 235 (3), 179 (9), 121 (6), 87 (100), 59 (13); Anal. ($C_{16}H_{34}O_2Sn$) C, H.

(1,3-Dioxan-2-yl)tri-*n*-butylstannane (17). b. From 11. Lithium wire (3.76 mmol, 0.58 cm, cut into four pieces) was added to a solution of 256 mg (2.0 mmol) of naphthalene in 10 mL of THF. The mixture was stirred at ambient temperature for 3 h and then cooled to −78 °C. After addition of **11** (1.0 mmol, 0.17 mL) in one portion, the mixture was stirred for 20 min at −78 °C. To the resulting dark brown solution was added 651 mg of chlorotri-*n*-butylstannane (2.0 mmol, 0.54 mL). The reaction mixture was stirred at −78 °C for 0.5 h and then was slowly warmed to −10 °C over 1 h. The mixture was poured into 20 mL of saturated aqueous ammonium chloride solution and extracted with three 20-mL portions of ether. The organic extracts were dried over sodium sulfate, filtered, and concentrated. Flash chromatography using 2% ethyl acetate/hexanes as eluant furnished 330 mg of **17** (88% yield). For spectroscopic data, see the previous preparation.

Generation of 4 by Reductive Lithiation. Reaction with *p*-Anisaldehyde. To a mixture of 1.066 g of 4,4′-di-*tert*-butylbiphenyl (4.00 mmol) and 31.1 mg of lithium wire (4.48 mmol), cut into six pieces, was added 10 mL of THF. The mixture was vigorously stirred at 0 °C for 4 h. The resulting deep blue solution was diluted with 10 mL of THF and cooled to −95 °C,[62] and 311 mg of **8** (1.69 mmol) was added all at once. The reaction mixture was vigorously stirred at −95 °C for 1 min, immediately followed by addition, via a cannula, of a solution of 176 mg of *p*-anisaldehyde (1.30 mmol) in 1.5 mL of THF, precooled to −95 °C. After stirring at −95 °C for 10 min, the reaction was quenched by rapid addition of 1 mL of methanol. The mixture was added to 40 mL of pH 7 phosphate buffer and extracted with three 20-mL portions of chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. Flash chromatography using ethyl acetate/

(61) $J(^{119}Sn, ^{13}C)$ = 1.046 $J(^{117}Sn, ^{13}C)$: Mann, B. E.; Taylor, B. F. *^{13}C NMR Data for Organometallic Compounds*; Academic: New York, 1981; pp 17–18. For small values of J, the ^{117}Sn, ^{13}C and ^{119}Sn, ^{13}C satellites are coincident.

(62) Slush baths: −110 to −111 °C, liquid nitrogen–THF/ether (12:1); −95 °C, liquid nitrogen–methanol. The THF/ether bath temperatures were determined by using a digital thermometer; this device gave correct values for liquid nitrogen slushes prepared with pure ether (−116.5 °C) and isooctane (−107.5 °C).

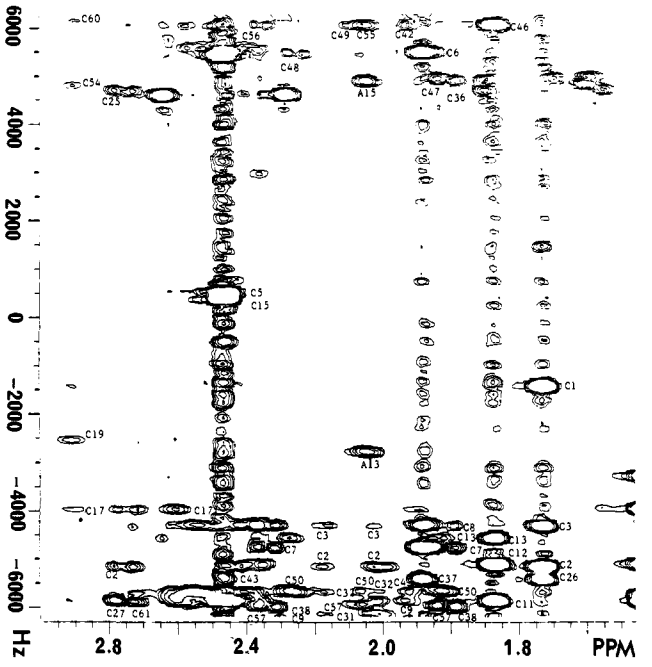


Figure 5. Expanded region of Figure 4 displaying the multiple-bond ^1H–^{13}C correlations of the methylene protons. The lowest contour level in this figure is 2.5 times lower than that of Figure 4.

The assignment of the carbonyl resonances was difficult since the protons that show connectivity to them are in a very crowded region (Figure 5). The only protons that show connectivity to these carbonyl carbons are methylene protons. Although the proton assignments for some methylene groups (i.e., C30, C31, C55, and C56) were not determined unambiguously, they have been assigned to a specific side chain and would show connectivity to a particular carbonyl in any case. In this way, all the carbonyl carbons were assigned.

Verification of the proton and ^{13}C assignments of C30 and C31 can be made from the HMBC spectrum (Figure 5). C30H', which was assigned from the COSY spectrum, shows a correlation to C31, confirming the ^{13}C assignments made from the HMQC spectrum. Another proton resonance at 2.03 ppm also shows a correlation to C31, thus assigning this resonance to C30H''.

The proton and ^{13}C assignments of C55 and C56 can also be made from the HMBC spectrum by comparing the intensity of their correlations to C57, which was assigned from the correlation between this carbonyl carbon and Pr1H_2. In Figure 5, three correlations to C57 can be seen. Two are of greater intensity than the third. The less intense one can be assigned to C56H'' in the following way: One would expect protons on the same carbon to show correlations of similar intensity to a given carbon. For example, in Figure 5 both C37 methylene protons show correlations of similar intensity to C38. It can also be seen in Figure 5 that the two C49 methylene protons show correlations with similar intensities to C50, while C48H'' shows a correlation to C50 with a different (weaker) intensity. The proton signal (C56H'') with the weaker correlation to C57 also shows a correlation to a carbon that has been unambiguously assigned to C55 from a correlation to C54H_3. This carbon signal (C55) cannot possibly be assigned to C56 because C54H_3 is too many bonds away from C56 to show any correlation in the HMBC spectrum. Therefore, the proton signal that shows weaker correlation to C57 must be C56H''. The other two proton signals that show a stronger correlation to C57 were then assigned to C55H' and C55H''. The remaining methylene proton in this side chain (identified from the HOHAHA spectrum; see above), C56H', is buried under the noise from C35H_3/C53H_3 in the HMBC spectrum. The ^{13}C shift of C56 was determined from the correlation of this carbon to C55H'.

Assignment of the ^{13}C chemical shifts of C42 and C49, which was impossible from the HMQC spectrum (Figure 3), is readily done from the HMBC spectrum (Figure 5). C41H'' shows a correlation to C42. C48H'' and C13H both show correlations to C49. These resonances and those of C55 and C56 were most easily assigned by comparing the relative positions of C42, C46, C49, C55, and C56 in the HMBC spectrum. These resonances occur in a very crowded region of the ^{13}C spectrum and exact chemical shifts cannot be determined precisely. The HMBC spectrum shows that correlations for C42 and C49 (from C41H'' and C48H'', respectively) have the same ^{13}C chemical shift and are upfield of a correlation from C47H_3 to C46 (whose exact ^{13}C chemical shift was determined from an INEPT experiment; see above), assigning them to the peak at 34.0 ppm in the one-dimensional ^{13}C spectrum. The correlation from C54H_3 to C55 is downfield of the correlation to C46 and upfield of the correlation to C56 (Figures 4 and 5), assigning the peaks at 34.3 and 35.0 ppm to C55 and C56, respectively, and completing the ^{13}C assignments.

The ^1H and ^{13}C assignments of AdoCbi$^+$ are now complete. The corresponding ^1H and ^{13}C resonances of AdoCbi$^+$ and coenzyme B_{12} at pH 2.1 and 7.0 are shown in Table II.

Discussion

The absence of signals for the dimethylbenzimidazole nucleotide in the ^1H NMR spectrum of AdoCbi$^+$ confirms the finding[5] that the dimethylbenzimidazole nucleotide loop has been chemically removed. The ^1H and ^{13}C resonances whose chemical shifts show the greatest difference when comparing AdoCbi$^+$ to protonated, base-off coenzyme B_{12} are those of Pr2. This is consistent with cleavage occurring at the O–P bond, leaving Pr2 adjacent to a hydroxyl group in AdoCbi$^+$ instead of a phosphate group as it is in coenzyme B_{12}. There is no evidence for cleavage at a second site or for isomerization at any site in the cobinamide since the ^1H and ^{13}C chemical shifts of Pr1, which is only one bond removed from Pr2, hardly differ when comparing AdoCbi$^+$ to protonated, base-off coenzyme B_{12}. The small differences in shifts for other carbons in this part of the base-off species (Pr3 and C55) suggest some difference in the f side chain conformation results from cleavage of the nucleotide loop.

The sugar on the adenosyl moiety appears to have the same major conformation in both AdoCbi$^+$ and coenzyme B_{12} as judged by ^1H NOE data. The evidence for very similar conformations of the adenosyl moiety in AdoCbi$^+$ and coenzyme B_{12} is the NOE cross peaks A11H–C54H_3, A11H–C46H_3, A14H–C19H, and A15H'–C19H, which are found for AdoCbi$^+$ and both base-on and protonated, base-off coenzyme B_{12}. However, in AdoCbi$^+$ there is no NOE between A14H and C46H_3, an NOE that was used as evidence for an equilibrium between two conformations of the adenosyl moiety in both base-on and protonated, base-off coenzyme B_{12}.[13b]

Most of the adenine carbons of AdoCbi$^+$ have ^{13}C NMR chemical shifts that are closer to those found for base-on coenzyme B_{12} than the protonated, base-off form. The greatest shift differences are the A2 and A6 signals, probably due to the protonation of N1, which occurs at pH 2.1, conditions necessary to form base-off coenzyme B_{12}. Since N1 of adenosine has a pK_a of 3.6,[25] this nitrogen would be protonated at pH 2.1 (protonated, base-off coenzyme B_{12}) but not at pH 7.0 (base-on coenzyme B_{12}). The ^{13}C NMR shifts of A2 and A6 in AdoCbi$^+$ are much closer to those of coenzyme B_{12} in the base-on form than the protonated, base-off form, most likely due to the fact that at pH 4.8 N1 of the adenosyl moiety has not been protonated.

Except for the differences noted above, the ^1H and ^{13}C chemical shifts of AdoCbi$^+$ are generally closer to those of the benzimidazole-protonated, base-off form than the base-on form of the coenzyme, which is expected since AdoCbi$^+$ is serving as a "base-off" analogue for coenzyme B_{12}. The A15 ^{13}C resonances of both AdoCbi$^+$ and protonated, base-off coenzyme B_{12} are shifted substantially upfield in comparison to base-on coenzyme B_{12} by 5.7 and 5.0 ppm, respectively, indicating that whatever is in the trans axial position in protonated, base-off coenzyme B_{12} is also

(25) Martin, R. B. *Acc. Chem. Res.* **1985**, *18*, 32–38.

Generation of 7 by Reductive Lithiation. Reaction with Cyclohexanecarboxaldehyde. Using 186 mg (1.66 mmol, 0.20 mL) of cyclohexanecarboxaldehyde, the reaction, workup, and chromatographic purification were carried out as described for addition to cyclohexanone, affording 310 mg of **21** (92% yield) as a colorless solid: R_f 0.39 using 40% ethyl acetate/hexanes for development; mp 31–32 °C; ^{1}H NMR ($CDCl_3$) δ 1.00–1.96 (m, 12 H), 2.10 (qt, J = 13.6, 4.8 Hz, 1 H), 2.18 (d, J = 2.5 Hz, 1 H, O*H*), 3.31 (td, J = 4.4, 2.5 Hz, 1 H), 3.80 (br t-like, 2 H), 4.08–4.22 (m, 2 H), 4.54 (d, J = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.74, 25.97, 26.21, 26.37, 27.36, 29.31, 38.65, 66.72, 66.79, 76.26, 100.95; IR (neat) 3480 (br s), 1450 (s), 1240 (s), 1150 (s), 1085 (s), 1025 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 201 (2, $M^+ - 1$), 95 (8), 87 (100), 59 (19); Anal. ($C_{11}H_{20}O_3$) C, H.

Generation of 7 by Transmetalation. 1,2-Addition to 2-Cyclohexen-1-one. A solution of 418 mg (1.11 mmol) of **17** in 5 mL of THF was cooled to −78 °C, and *n*-butyllithium in hexanes (0.66 mL of a 1.67 M solution, 1.10 mmol) was added dropwise. After the resultant mixture was stirred at −78 °C for 20 min, 98 mg (1.02 mmol, 99 μL) of 2-cyclohexen-1-one was added. The resulting mixture was stirred for 70 min at −78 °C, followed by addition of 0.2 mL of methanol and 15 mL of pH 7 phosphate buffer. After extraction with three 15-mL portions of chloroform, the organic solution was dried over sodium sulfate, filtered, and concentrated. Purification by gravity column chromatography on 30 g of silica gel, using mixtures of ethyl acetate/hexanes as eluant (1:10, then 1:5, then 1:1), afforded 181 mg of **25** (97% yield) as a colorless oil: R_f 0.15 using 30% ethyl acetate/hexanes for development; ^{1}H NMR δ 1.38 (br d, J = 13.6 Hz, 1 H), 1.6–1.85 (m, 4 H), 1.9–2.2 (m, 3 H), 2.44 (1 H, O*H*), 3.80 (br t, J = 11.6 Hz, 2 H), 4.18 (br dd, J = 11.6, 4.9 Hz, 2 H), 4.40 (s, 1 H), 5.71 (br d, J = 10.2 Hz, 1 H), 5.98 (ddd, J = 10.2, 4.0, 2.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.02, 25.11, 25.69, 30.54, 66.91, 66.94, 70.13, 104.57, 127.69, 131.98; IR (neat) 3500 (br s), 3040 (w), 1155 (s), 1110 (s), 1030 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 97 (19), 87 (100), 59 (42); Anal. ($C_{10}H_{16}O_3$) C, H.

Generation of 7 by Transmetalation. 1,4-Addition to 2-Cyclohexen-1-one. In a 5-mL flask, 455 mg (1.11 mmol) of tetrakis[iodo(tri-*n*-butylphosphine)copper(I)][34] was dissolved in 3 mL of dry THF and the solution was cooled to −78 °C. In a second flask, a solution of 419 mg (1.11 mmol) of **17** in 10 mL of THF was cooled to −78 °C and treated dropwise with *n*-butyllithium in hexanes (0.73 mL of a 1.67 M solution, 1.22 mmol). After stirring for 20 min, the cold solution of the copper complex was transferred via a cannula into the solution of **7**, and the mixture was stirred at −78 °C for 40 min. To the resulting yellow solution were added 2-cyclohexen-1-one (48 mg, 0.50 mmol, 48 μL) and, after stirring for 5 min, boron trifluoride etherate (135 μL, 1.10 mmol). The resulting mixture was stirred for 15 min at −78 °C, and 10 mL of 10% aqueous ammonium hydroxide solution (buffered to pH 8 with ammonium chloride) then was introduced at −78 °C. The mixture was poured into 40 mL of brine and extracted with five 40-mL portions of ethyl acetate. After drying over sodium sulfate, filtration, and evaporation of solvent, the product was purified by gravity column chromatography on 10 g of silica gel, using ethyl acetate/hexanes mixtures as eluant (1:10, then 1:1), furnishing 84 mg of **26** (92% yield) as a colorless oil: R_f 0.35 using 30% ethyl acetate/hexanes for development; ^{1}H NMR ($CDCl_3$) δ 1.35 (br d, J = 14.0 Hz, 1 H), 1.5–1.8 (m, 2 H), 1.85–2.2 (m, 4 H), 2.2–2.5 (m, 4 H), 3.75 (br t, J = 10.5 Hz, 2 H), 4.11 (br dd, J = 10.5, 4.7 Hz, 2 H), 4.39 (d, J = 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.55, 25.34, 25.81, 41.34, 42.07, 42.94, 66.78, 66.81, 103.20, 210.86; IR (neat) 1715 (s), 1150 (s), 1010 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 183 (1.5, $M^+ - 1$), 87 (100), 71 (26), 59 (16); Anal. ($C_{10}H_{16}O_3$) C, H.

Generation of 7 by Transmetalation. Reaction with Dimethyl Sulfate. A solution of 377 mg of **17** (1.0 mmol, 0.35 mL) in 4 mL of THF was cooled to −78 °C and *n*-butyllithium in hexanes (0.7 mL of a 1.55 M solution, 1.1 mmol) was added dropwise. After the mixture was stirred for 20 min at −78 °C, 277 mg of dimethyl sulfate (2.2 mmol, 0.2 mL) was added. The reaction mixture was stirred at −78 °C for 4 h and then was warmed to ambient temperature over 1 h. Capillary GC analysis of the resulting solution, using *n*-octane as internal standard, established that **27** had been formed in 94% yield:[64] mass spectrum (70 eV), m/z (rel intens) 101 ($M^+ - 1$, 21), 87 (100), 59 (20), 43 (79); mass spectrum (CI, isobutane), m/z (rel intens) 103 (MH^+, 100).

Generation of 7 by Reductive Lithiation. Reaction with Dimethyl Sulfate. A solution of lithium naphthalenide in 10 mL of THF was prepared as described for reaction of **7** with *p*-anisaldehyde and was cooled to −78 °C. Following the addition of 372 mg of **11** (1.9 mmol, 0.32 mL) the mixture was stirred at −78 °C for 20 min and 757 mg of dimethyl sulfate (6.0 mmol, 0.55 mL) was introduced. The reaction was stirred at −78 °C for 0.5 h and at −40 °C for 3 h and then was allowed to warm to ambient temperature over 1 h. Capillary GC analysis of the resulting mixture, using *n*-octane as internal standard, revealed that **27** had been formed in 95% yield.[64]

Generation of 7 by Reductive Lithiation. Reaction with 1-Bromo-3-phenylpropane. A solution of **7** was prepared by reductive lithiation as described for the reaction with *p*-anisaldehyde, and HMPA (2 mL) and 1-bromo-3-phenylpropane (1.97 g, 9.87 mmol, 1.5 mL) were added. The reaction mixture was stirred at −78 °C for 0.5 h and at −40 °C for 3 h and then was allowed to warm to −10 °C over 1 h. The mixture was poured into 20 mL of saturated aqueous ammonium chloride solution and extracted with three 20-mL portions of ether. The organic extracts were dried over sodium sulfate, filtered, and concentrated. Flash chromatography using 5% ethyl acetate/hexanes as eluant furnished 336 mg of **28** (81% yield) as a colorless liquid: R_f 0.29 using 10% ethyl acetate/hexane for development; ^{1}H NMR ($CDCl_3$) δ 1.32 (br d, J = 12.4 Hz, 1 H), 1.52–1.82 (m, 4 H), 2.06 (qt, J = 12.4, 4.8 Hz, 1 H), 2.61 (t, J = 7.3 Hz, 2 H), 3.73 (ddd, J = 12.4, 11.0, 2.2 Hz, 2 H), 4.08 (dd, J = 11.0, 4.8 Hz, 2 H), 4.50 (t, J = 4.9 Hz, 1 H), 7.10–7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 25.41, 25.60, 34.56, 35.47, 66.44, 101.86, 125.38, 127.93, 128.11, 141.99; IR (neat) 3100 (w), 3050 (w), 1500 (m), 1450 (m), 1400 (m), 1240 (m), 1150 (s), 750 (s), 700 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 205 (12, $M^+ - 1$), 130 (57), 104 (100), 87 (70); Anal. ($C_{13}H_{18}O_2$) C, H.

Generation of 7 by Transmetalation. Reaction with 1-Bromo-3-phenylpropane. A solution of 1.27 g of **17** (3.36 mmol) in 10 mL of THF was cooled to −78 °C, and *n*-butyllithium in hexanes (2.2 mL of a 1.55 M solution) was added. After the mixture was stirred for 20 min at −78 °C, HMPA (1.5 mL) and 1-bromo-3-phenylpropane (786 mg, 3.95 mmol) were introduced. The mixture was stirred at −78 °C for 0.5 h, at −40 °C for 5 h, and at ambient temperature overnight. Workup and flash chromatography as described for the preparation of **28** from **11** gave 640 mg of **28** (93% yield). For spectroscopic data, see the previous preparation.

Generation of 7 by Transmetalation. Reaction with Cyclopentene Oxide. A solution of 569 mg (1.51 mmol) of **17** in 10 mL of THF was cooled to −78 °C, and a solution of *n*-butyllithium in hexanes (1.67 M, 1.0 mL, 1.67 mmol) was added dropwise. After the mixture was stirred for 10 min, 42 mg of cyclopentene oxide (0.50 mmol, 44 μL) was added, followed after 5 min by 213 mg (1.50 mmol, 185 μL) of boron trifluoride etherate. The resulting mixture was stirred for 2 h at −78 °C, and then 10 mL of 10% aqueous ammonium hydroxide solution (buffered to pH 8 with ammonium chloride) was added at this temperature. The mixture was poured into 40 mL of saturated brine containing some solid sodium chloride and then was extracted with five 40-mL portions of ethyl acetate. Concentration of the combined extracts and purification by gravity column chromatography on 10 g of silica gel, using ethyl acetate/hexanes (1:5, then 1:0) for elution, gave 71 mg of alcohol **29** (82% yield) as a colorless oil: R_f 0.32 using 50% ethyl acetate/hexanes for development; ^{1}H NMR ($CDCl_3$) δ 1.3–2.2 (m, 9 H), 2.7 (1 H, O*H*), 3.77 (m, 12 sharp peaks, 2 H), 4.10 (m, 3 H), 4.49 (d, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.71, 25.31, 25.81, 33.75, 51.90, 66.76, 74.81, 104.78; IR (neat) 3450 (br s), 1155 (s), 1110 (s), 1010 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 171 (4, $M^+ - 1$), 155 (30), 87 (100), 69 (56), 57 (53); Anal. ($C_9H_{16}O_3$) C, H.

Generation of 7 by Transmetalation. Reaction with Ethylene Oxide. The detailed procedure described for the addition of **7** to cyclopentene oxide was employed. Reaction with ethylene oxide (0.36 mL of a 1.4 M solution in diethyl ether, 0.50 mmol), followed by purification via gravity column chromatography on 10 g of silica gel, using ethyl acetate/hexanes (1:5, then 1:0) as eluant, afforded 40 mg of **30** (62% yield) as a colorless oil: R_f 0.38 using ethyl acetate for development; ^{1}H NMR ($CDCl_3$) δ 1.37 (br d, J = 13.4 Hz, 1 H), 1.89 (dt, J = 5.3, 4.8 Hz, 2 H), 2.11 (dtt, J = 13.7, 12.6, 5.2 Hz, 1 H), 2.66 (1 H, O*H*), 3.76 (t, J = 5.3 Hz, 2 H), 3.8 (m, br t-like, 2 H), 4.12 (br dd, J = 10.5, 5.2 Hz, 2 H), 4.76 (t, J = 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.65, 37.25, 58.43, 66.75, 101.54; IR (neat) 3440 (br s), 1155 (s), 1060 (br s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 131 (10, $M^+ - 1$), 115 (22), 87 (100), 59 (45); Anal. ($C_6H_{12}O_3$) C, H.

Generation of 7 by Transmetalation. Reaction with Oxetane. The detailed procedure described for the addition of **7** to cyclopentene oxide was employed. Reaction with oxetane (30 mg, 0.51 mmol, 33 μL) followed by purification via gravity column chromatography on 10 g of silica gel, using ethyl acetate/hexanes (1:5, then 1:0) as eluant, afforded 61 mg of **31** (82% yield) as a colorless oil: R_f 0.38 using ethyl acetate for development; ^{1}H NMR ($CDCl_3$) δ 1.36 (br d, J = 13.4 Hz, 1 H), 1.71 (m, 4 H), 2.08 (dtt, J = 13.4, 12.1, 5.0 Hz, 1 H), 3.63 (t, J = 6.3 Hz, 2 H), 3.78 (br t, J = 12.1 Hz, 2 H), 4.11 (br dd, J = 10.5, 5.0 Hz, 2 H), 4.58 (t, J = 4.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.62, 26.92, 31.77,

(64) The highly volatile product was identified by GC/MS comparison with an authentic sample: Ronderstvedt, Tr. C. S. *J. Org. Chem.* **1961**, *26*, 2247–2253.

62.38, 66.72, 102.00; IR (neat) 3450 (br s), 1155 (s), 1095 (br s), 1005 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 145 (8, $M^+ - 1$), 87 (100), 71 (26), 59 (20); Anal. ($C_7H_{14}O_3$) C, H.

Thermal Stability of (Dimethoxymethyl)lithium. General procedure: a solution of **14** (230 mg, 0.63 mmol) in 1.7 mL of THF was cooled to −110 to −111 °C,[62] and *n*-butyllithium in hexanes (0.39 mL of a 1.6 M solution) was added dropwise over 1 min.[63] After the resultant mixture was stirred for 8 min at this temperature, the flask was transferred to another bath which was maintained at the desired higher temperature. The reaction mixture was stirred for 30 min, and a solution of *p*-anisaldehyde (126 mg, 0.92 mmol) in 0.5 mL of THF was added. After stirring 10 min further, the reaction was quenched by addition of 1 mL of methanol, and hexadecane (71 mg) was introduced as a GC internal standard.

Control reaction at −110 to −111 °C: generation of **4** according to the general procedure, followed immediately by reaction with *p*-anisaldehyde, gave **22** in 90% GC yield, together with **24** in 3.3% yield and 1.5% of unreacted **14**.

Stability at −110 to −111 °C: generation of **4** according to the general procedure, stirring 30 min further at −110 to −111 °C, and reaction with *p*-anisaldehyde gave **22** (89% GC yield), **24** (3% yield), and unreacted **14** (0.5%).

Stability at −95 °C:[62] generation of **4** according to the general procedure, stirring 30 min further at −95 °C, and reaction with *p*-anisaldehyde gave **22** (43% GC yield) and **24** (2% yield); **14** was not detected.

Stability at −78 °C: generation of **4** according to the general procedure, stirring 30 min further at −78 °C, and reaction with *p*-anisaldehyde gave **22** (20% GC yield) and **24** (4% yield); **14** was not detected.

Thermal Stability of (Diethoxymethyl)lithium. General procedure: a solution of **15** (275 mg, 0.70 mmol) in 1.9 mL of THF was cooled to −110 to −111 °C,[62] and *n*-butyllithium in hexanes (0.43 mL of a 1.6 M solution) was added dropwise over 1 min.[63] After the resultant mixture was stirred for 12 min at this temperature, the flask was transferred to another bath which was maintained at the desired higher temperature. The reaction mixture was stirred for 30 min, and a solution of *p*-anisaldehyde (140 mg, 1.03 mmol) in 0.55 mL of THF was added. After stirring 10 min further, the reaction was quenched by addition of 1 mL of methanol, and hexadecane (61 mg) was introduced as a GC internal standard.

Control reaction at −110 to −111 °C: generation of **5** according to the general procedure, followed immediately by reaction with *p*-anisaldehyde, gave **23** in 92% GC yield, together with **24** in 6% yield and 4% of unreacted **15**.

Stability at −110 to −111 °C: generation of **5** according to the general procedure, stirring 30 min further at −110 to −111 °C, and reaction with *p*-anisaldehyde gave **23** (92% GC yield), **24** (4% yield), and unreacted **15** (1.5%).

Stability at −95 °C:[62] generation of **5** according to the general procedure, stirring 30 min further at −95 °C, and reaction with *p*-anisaldehyde gave **23** (61% GC yield) and **24** (1% yield); **15** was not detected.

Stability at −78 °C: generation of **5** according to the general procedure, stirring 30 min further at −78 °C, and reaction with *p*-anisaldehyde gave **23** (17% GC yield) and **24** (0.3% yield); **15** was not detected.

Thermal Stability of 2-Lithio-1,3-dioxolane. General procedure: a solution of **16** (ca. 0.50 mmol) in 5 mL of THF was cooled to −78 °C and a solution of *n*-butyllithium in hexanes (1.1 equiv) was added dropwise. After the mixture was stirred for 20 min at −78 °C, the flask was transferred to another bath which was maintained at the required higher temperature. The reaction was stirred for 30 min further, *p*-anisaldehyde (1.1 equiv) was added, and the resulting mixture was stirred for 30 min. The reaction then was quenched by addition of 5 mL of 10% aqueous ammonium hydroxide solution (buffered to pH 8 with ammonium chloride), poured into 30 mL of water, and extracted with five 30-mL portions of chloroform. The combined extracts were dried over sodium sulfate, filtered, and concentrated. Purification by gravity column chromatography on 5 g of silica gel, using ethyl acetate/hexanes mixtures as eluant (1:3, then 1:1), gave alcohol **18** as a colorless oil.

Control reaction at −78 °C: generation of **6** (0.51 mmol) followed immediately by reaction with *p*-anisaldehyde gave 102 mg of **18** (94% yield).

Stability at −78 °C: generation of **6** (0.50 mmol) according to the general procedure, stirring 30 min further at −78 °C, and reaction with *p*-anisaldehyde gave 96 mg of **18** (91% yield).

Stability at −70 °C: generation of **6** (0.50 mmol) according to the general procedure, stirring 30 min further at −70 °C, and reaction with *p*-anisaldehyde gave 90 mg of **18** (86% yield).

Stability at −60 °C: generation of **6** (0.52 mmol) according to the general procedure, stirring 30 min further at −60 °C, and reaction with *p*-anisaldehyde gave 71 mg of **18** (65% yield).

Stability at −50 °C: generation of **6** (0.50 mmol) according to the general procedure, stirring 30 min further at −50 °C, and reaction with *p*-anisaldehyde gave 27 mg of **18** (25% yield).

Thermal Stability of 2-Lithio-1,3-dioxane. General procedure: A solution of 377 mg of **17** (0.35 mL, 1.0 mmol) in 4 mL of THF was cooled to −78 °C, and a solution of *n*-butyllithium in hexanes (0.64 mL, 1.55 M, 1.0 mmol) was added. After the mixture was stirred for 30 min at −78 °C, the flask was transferred to another bath which was maintained at the required higher termperature. The solution was stirred 30 min further, *p*-anisaldehyde (0.12 mL, 1.0 mmol) was added and the resulting mixture was stirred for 2 min. The reaction then was quenched by addition of 0.3 mL of methanol, poured into 20 mL of pH 7 phosphate buffer, and extracted with four 30-mL portions of dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and concentrated. Purification by flash column chromatography on silica gel, using 25% ethyl acetate/hexanes for elution, gave alcohol **19** as a colorless oil.

Stability at −45 °C: generation of **7** according to the general procedure, stirring at −45 °C for 30 min, and reaction with *p*-anisaldehyde gave 232 mg of **19** (95% yield).

Stability at −20 °C: generation of **7** according to the general procedure, stirring at −20 °C for 30 min, and reaction with *p*-anisaldehyde gave 131 mg of **19** (58% yield).

Stability at 0 °C: **7** was generated according to the general procedure. After stirring at 0 °C for 15 min rather than 30 min, reaction with *p*-anisaldehyde gave 6 mg of **19** (2% yield).

Thermal Decomposition of 7. A solution of 193 mg (0.51 mmol) of **17** in 5 mL of THF was cooled to −78 °C, and a solution of *n*-butyllithium in hexanes (1.67 M, 0.34 mL, 0.55 mmol) was added dropwise. After the mixture was stirred for 20 min at −78 °C, the flask was transferred to a water bath maintained at ambient temperature and the solution was stirred for 2 h. The resulting mixture was cooled to 0 °C, and benzoyl chloride (73 mg, 0.52 mmol, 60 μL) was added. After stirring for an additional 30 min, the mixture was quenched with 5 mL of 10% aqueous ammonium hydroxide solution (buffered to pH 8 with ammonium chloride) and poured into 30 mL of water. The mixture was extracted with three 30-mL portions of dichloromethane. After addition of 20.0 μL of toluene as an internal standard, capillary GC analysis showed that 1,3-dioxane was formed in 22% yield. The extracts were then dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography on 8 g of silica gel, using 10% ethyl acetate/hexanes as eluant, gave 26 mg of (*E*)-dibenzoate **35** (27% yield) as a colorless solid and 26 mg of (*Z*)-dibenzoate **36** (27% yield) as a colorless oil. For **35**: R_f 0.34 using 20% ethyl acetate/hexanes for development; mp 49–50 °C, needles (hexanes); ^1H NMR ($CDCl_3$)[65] δ 2.08 (pentet, J = 6.3 Hz, 4 H), 3.73 (t, J = 6.3 Hz, 4 H), 4.42 (t, J = 6.3 Hz, 4 H), 6.30 (s, 2 H), 7.44 (br t, J = 8.3 Hz, 4 H), 7.55 (tt, J = 8.3, 0.9 Hz, 2 H), 8.03 (br dd, J = 7.5, 0.9 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 28.89, 61.71, 68.02, 128.29, 129.52, 130.42, 132.81, 134.51, 166.40; IR (CCl_4) 3070 (w), 3045 (w), 1730 (s), 1280 (s), 1175 (m), 1115 (m), 715 (m) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 384 (0.1, M^+), 163 (87), 105 (100), 77 (30); Anal. ($C_{22}H_{24}O_6$) C, H. For **36**: R_f 0.25 using 20% ethyl acetate/hexanes for development; ^1H NMR ($CDCl_3$)[65] δ 2.13 (pentet, J = 6.3 Hz, 4 H), 3.92 (t, J = 6.3 Hz, 4 H), 4.44 (t, J = 6.3 Hz, 4 H), 5.37 (s, 2 H), 7.41 (br t, J = 7.6 Hz, 4 H), 7.54 (tt, J = 7.7, 0.9 Hz, 2 H), 8.02 (br dd, J = 7.5, 0.9 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 29.15, 61.64, 69.32, 128.24, 128.96, 129.49, 130.39, 132.75, 166.34; IR (neat) 3070 (w), 1720 (s), 1285 (s), 1120 (s), 725 (s) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 384 (0.1, M^+), 163 (98), 105 (100), 77 (25); Anal. ($C_{22}H_{24}O_6$) C, H.

Generation of 43 by Transmetalation. Reaction with *p*-Anisaldehyde. For preparation of an authentic sample of carbinol **45**, a solution of 452 mg (1.1 mmol) of **44**[2b] in 4.5 mL of THF was cooled to −78 °C, and *n*-butyllithium (0.64 mL of a 1.6 M solution in hexanes, 1.0 mmol) was added dropwise. The resulting clear, light yellow solution was stirred at −78 °C for 30 min, and 150 mg of *p*-anisaldehyde (1.1 mmol, 0.13 mL) was added dropwise. After the mixture was stirred 0.5 h further, the reaction was quenched at −78 °C by addition of 1 mL of methanol. After removal of solvent, the concentrate was partitioned between 20 mL of methylene chloride and 20 mL of saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with three 5-mL portions of methylene chloride, and the combined organic solutions were dried over sodium sulfate, filtered, and concentrated. Flash chromatography using 28% ethyl acetate/hexanes as eluant, followed by short-path distillation [bp 124 °C (0.2 mmHg)], afforded 243 mg of **45** (94% yield) as an off-white solid: mp 48–50 °C; R_f 0.24 using 28% ethyl acetate/hexanes for development; ^1H NMR ($CDCl_3$) δ 2.84 (br s, 1 H, OH), 3.49 (dd, J = 9.8, 9.0 Hz, 1 H) 3.59 (dd, J = 9.8, 3.5 Hz, 1 H), 3.79 (s, 3 H), 4.59 (d, J = 12.1 Hz, 1 H), 4.60 (d, J = 12.1 Hz, 1 H), 4.88 (dd, J = 9.0,

(65) The *E* and *Z* isomers were assigned by analogy with the reported ^1H NMR resonances of (*E*)- and (*Z*)-1,2-dimethoxyethenes: Jones, G., II; Santhanam, M.; Chiang, S.-H. *J. Am. Chem. Soc.* **1980**, *102*, 6088–6095.

3.5 Hz, 1 H), 6.89 (br d, J = 8.8 Hz, 2 H), 7.3-7.5 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 55.02, 72.16, 73.10, 75.66, 113.55, 127.24, 127.59, 128.23, 132.41, 137.67, 158.98; IR (KBr) 3500 (m), 3350 (m), 1610 (s), 1515 (s), 1245 (s), 1120 (br s), 1075 (br s), 1025 (br s), 830 (s), 740 (s), 700 (m) cm^{-1}; mass spectrum (70 eV), m/z (rel intens) 258 (2, M$^+$), 137 (100), 109 (29), 91 (35), 77 (20); Anal. ($C_{16}H_{18}O_3$) C, H.

Equilibration of [(Benzyloxy)methyl]lithium (43) and 2-Lithio-1,3-dioxane (7). A solution of 185 mg of **44**[2b] (0.485 mmol) in 1 mL of THF was cooled to -78 °C, and n-butyllithium (0.28 mL of a 1.6 M solution in hexanes, 0.44 mmol) was added dropwise. The resulting clear, pale yellow solution was stirred at -78 °C for 20 min, and a solution of **17** (183 mg, 0.485 mmol) in 1 mL of THF was added via a cannula, followed by rinsing with two 1-mL portions of THF. After the mixture was stirred 30 min further, 84 mg of p-anisaldehyde (0.62 mmol, 80 μL) was added dropwise. The resulting solution was stirred for an additional 30 min, and then the reaction was quenched at -78 °C by addition of 2 mL of methanol. Capillary GC analysis revealed that carbinols **19** and **45** were formed in a ratio of 99.3:0.7, corrected for product response factors. Workup as described for the preparation of **45**, followed by flash chromatography using 45% ethyl acetate/hexanes as eluant, gave 92 mg of **19** (93% yield).

Relative Rates of Addition of 43 and 7 to p-Anisaldehyde. A solution of 127 mg (0.31 mmol) of **44** and 116 mg (0.31 mmol) of **17** in 3 mL of THF was cooled to -78 °C, and n-butyllithium (0.39 mL of a 1.6 M solution in hexanes, 0.62 mmol) was added dropwise. The resulting pale yellow solution was stirred for 30 min, and p-anisaldehyde (37 μL, 0.31 mmol) was added all at once. After stirring 30 min further, the reaction was quenched at -78 °C by addition of 2 mL of methanol. Quantitative capillary GC analysis, using octadecane as internal standard, indicated that carbinols **19** and **45** were formed in a ratio of 1.21:1 (52 and 43% yields, respectively). p-Anisyl-n-butylcarbinol (**24**) was also formed in 3% yield.

Acknowledgment. We thank the National Institutes of Health, the American Heart Association, and the Colorado Heart Association for generous financial support.

Registry No. 4, 118418-15-8; **5**, 118418-16-9; **6**, 118418-17-0; **7**, 118418-18-1; **8**, 118418-19-2; **9**, 25604-67-5; **10**, 19798-66-4; **11**, 118418-20-5; **12**, 4544-19-8; **13**, 81381-75-1; **14**, 79411-59-9; **15**, 79411-58-8; **16**, 118418-21-6; **17**, 118418-22-7; **18**, 118418-23-8; **19**, 63457-96-5; **20**, 63458-00-4; **21**, 118418-24-9; **22**, 118418-25-0; **23**, 118418-26-1; **24**, 19523-03-6; **25**, 118418-27-2; **26**, 118418-28-3; **27**, 626-68-6; **28**, 64181-30-2; **29**, 118418-29-4; **30**, 5465-07-6; **31**, 99423-28-6; **35**, 118418-30-7; **36**, 118418-31-8; **43**, 71316-95-5; **44**, 66222-28-4; **45**, 838-66-4; p-anisaldehyde, 123-11-5; 4,4'-di-*tert*-butylbiphenyl, 1625-91-8; ethylene oxide, 75-21-8; trimethylsilyl trifluoromethanesulfonate, 27607-77-8; trimethyl orthoformate, 149-73-5; (phenylthio)-trimethylsilane, 4551-15-9; ethylene glycol, 107-21-1; triethyl orthoformate, 122-51-0; 1,3-propanediol, 504-63-2; galvinoxyl, 2370-18-5; isopropylmagnesium chloride, 1068-55-9; tributyltin hydride, 688-73-3; cyclohexanone, 108-94-1; cyclohexanecarboxaldehyde, 2043-61-0; dimethyl sulfate, 77-78-1; 1-bromo-3-phenylpropane, 637-59-2; cyclopentene oxide, 285-67-6; oxetane, 503-30-0; 2-cyclohexen-1-one, 930-68-7; tetrakis[iodo(tri-n-butylphosphine)copper(I)], 59245-99-7; chloro-tri-n-butylstannane, 1461-22-9.

Redox Glycosidation: A New Strategy for Disaccharide Synthesis‡

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Abstract: A new procedure for the preparation of disaccharides via redox glycosidation is described. The crucial anomeric C-O bond is established by acylation not alkylation as in traditional Koenigs-Knorr chemistry. Tebbe methylenylation followed by cyclization unravels the protected nonreducing or reducing disaccharides. Thus, for example, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) was coupled with 5-[(*tert*-butyldiphenylsilyl)oxy]pentanoyl chloride (**5**). The resultant α-ester **2** was methylenylated with the Tebbe reagent, desilylated, and cyclized with iodine to produce the pyranosylmethyl iodide **4** in good yield. The redox glycosidation protocol was extended to a range of reducing and nonreducing disaccharide systems.

The efficient construction of oligosaccharides in a stereocontrolled manner remains a challenging area for synthetic organic chemistry. Such compounds are of considerable interest in consequence of their diverse, vital roles in many biological processes.[1] Classically, oligosaccharides are assembled with iterative Koenigs-Knorr[2] reactions to sequentially construct the glycosidic bonds. There are now many variations on this theme in which a protected glycosyl halide or related electrophile is condensed with a partially protected second sugar unit.[3] All these existing methods employ an alkylation strategy to elaborate the crucial glycosidic C-O bonds. In oligosaccharide synthesis it is essential that the glycosidation methods used are high yielding. Additionally, the reactions should proceed rapidly and readily control the α versus β diastereoselectivity at each iteration irrespective of ring substituents. However, in spite of extensive studies on variants of Koenigs-Knorr chemistry spanning nearly 100 years, oligosaccharide synthesis cannot yet be considered simple routine.[4]

Herein we describe model studies on a new procedure for the preparation of disaccharides via redox glycosidation. In this process the two units are linked via an ester bond; subsequent reductive unravelling reveals the disaccharide entity. Thus in the process of crucial anomeric C-O bond is established via acylation,

‡Dedicated to Professor Sir Derek H. R. Barton on the occasion of his 70th birthday.

(1) For examples, see: Kennedy, J. F.; White, C. A. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 5, p 755. Schaner, R. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 131.

(2) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243.

(3) For examples of recent developments in glycosidation chemistry, see: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. Nicolaou, K. C.; Ladduwahetty, J. L. R.; Chuchulowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466. Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189. Nicolaou, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1153.

(4) In contrast to oligosaccharide chemistry, syntheses of oligonucleotides and polypeptides are now highly sophisticated. For examples, see: Letsinger, R. L. Chemical Synthesis of Oligodeoxyribonucleotides: A Simplified Procedure. In *Genetic Engineering: Principles and Methods*; Setlow, J. K., Hollaender, A., Eds.; Plenum Press: New York, 1983; Vol. 5, pp 191-209. Merrifield, B. *Science* **1986**, *232*, 341.

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