tilted toward the micelle surface so that the ester group is radially aligned (Figure 2b) and hence more accessible to hydroxide ions.

Experimental Section

Materials. 2-(Octanoyloxy)benzoic acid (**2**), mp 83.5–85 °C (EtOH) (lit.[15] mp 81 °C), was prepared by the acylation of salicylic acid (octanoyl chloride/pyridine in benzene, 2 h at room temperature).

5-1′-Octylsalicylic acid, mp 71–72 °C (lit.[16] mp 72–73 °C), was prepared[16] from methyl salicylate by acylation (octanoyl chloride, $AlCl_3$, CS_2), hydrolysis (OH^-/H_2O), and Clemmensen reduction (ZnHg, HCl). Acetylation (Ac_2O/H^+) gave compound **3**, mp 91–92 °C; found C, 70.0; H, 8.0; $C_{17}H_{24}O_4$ requires C, 69.9; H, 8.2.

2-(Acetyloxy)benzoic acid (**1**) was prepared by the acetylation (Ac_2O/H^+) of salicylic acid.[5] Cetyltrimethylammonium bromide was purified by the method of Mukerjee and Mysels.[17] Distilled water was further purified by using a Millipore system.

Solutions of CTAOH were prepared as described previously.[18]

Kinetic Studies. Stock solutions of substrates (0.01 M in dioxan), CTAB (0.02 M in water), and sodium hydroxide were prepared. Borate buffers (pH 8–10) were prepared from sodium tetraborate solution by the addition of the required amounts of either 0.1 M HCl or 0.1 M NaOH.[19] Phosphate buffers (pH 6–8) were prepared from Analar potassium dihydrogen phosphate by adding the required volume of 0.1 M NaOH.[19] The pH of the solutions was measured at room temperature with a combination electrode and a Radiometer pHM 80 portable pH meter. It has previously been shown[20] that the pH of phosphate buffer varies by less than 0.1 pH unit between 23 and 56 °C. The pH of borate buffer is 0.2 pH unit lower at 56 °C than at 23 °C.

The rate measurements were carried out as described previously,[21] following the absorbance at 297 nm for compound **2** and 303 nm for compound **3**.

NMR spectra of aspirin (8 mM) in D_2O and in the presence of CTAB (10 mM) were determined on a JEOL 200-MHz spectrometer.

Viscoelasticity was detected by either swirling the solution and visually observing the recoil of air bubbles trapped in the solution after swirling was stopped[9] or by the absence of a vortex in a rapidly stirred solution. Solutions for these tests were prepared by using equal amounts of CTAOH and substrate (e.g., salicylic acid) to produce a CTA salicylate solution (12 mM).[9]

Solvent Isotope Studies. All the stock solutions (buffers, CTAB) were prepared in D_2O (Australian Atomic Energy Commission) and the substrates were dissolved in dioxane. The reaction mixtures were prepared as for the normal (H_2O) measurements, except that all dilutions were done with D_2O.

Acknowledgment. We gratefully acknowledge the assistance of Aldo Lentini in obtaining the NMR spectra.

Registry No. **1**, 50-78-2; **2**, 70424-62-3; **3**, 95772-48-8; CTAOH, 505-86-2; CTAb, 57-09-0; salicylic acid, 69-72-7; octanoyl chloride, 111-64-8; methyl salicylate, 119-36-8; 5-(1-octyl)salicylic acid, 28488-49-5.

Supplementary Material Available: Observed second-order rate constants for the hydrolysis of compounds **1–3** at pH 12 in water and in the presence of micelles of CTAB (1–28 mM) (Table S1), observed first-order rate constants for the hydrolysis of compounds **2** and **3** in the pH range 6–13 in water and in 2 mM CTAB (Table S2), and ^1H NMR spectra of the aromatic region of substrate **1**: (a) in D_2O; (b) in CTAB (10 mM) (Figure S1) (3 pages). Ordering information is given on any current masthead page.

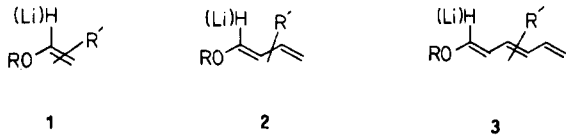
(15) Kaufmann, H. P. *Z. Angew. Chem.* **1927**, *40*, 69.
(16) Coburn, P. A.; Batista, A. J.; Evans, R. T.; Genko, R. J. *J. Med. Chem.* **1981**, *24*, 1245.
(17) Mukerjee, P.; Mysels, K. J. *J. Am. Chem. Soc.* **1955**, *77*, 2937.
(18) Bunton, C. A.; Gan, L. H.; Moffat, J. R.; Romsted, L. S.; Savelli, G. *J. Phys. Chem.* **1981**, *85*, 4118.
(19) *Handbook of Chemistry and Physics*, 57th ed.; The Chemical Rubber Company: Cleveland, OH 1976–77; p D134.
(20) Broxton, T. J. *Aust. J. Chem.* **1984**, *37*, 977.
(21) Broxton, T. J.; Wright, S. *J. Org. Chem.* **1986**, *51*, 2965.

Communications

Stereoselective Synthesis and α-Lithiation of 1-Alkoxy Polyenes

Summary: 4-Alkyl-1,4-dialkoxy-*cis*-2-butenes undergo a regio- and stereoselective base-catalyzed 1,4-elimination to yield all-trans 1-alkoxy dienes and trienes. These dienes and trienes are successfully lithiated α to oxygen when the alkoxy substituent is OCH_2OCH_3 (O-MOM).

Sir: While the α-lithiation of simple enol ethers **1** has enjoyed extensive use in organic synthesis,[1] the corresponding lithiations of dienyl ethers **2** has received less attention[2] and the α-lithiation of trienyl ethers **3** is unknown. In the course of our studies on the directed β-lithiation of certain methoxymethyl (R = CH_2OCH_3 (MOM)) enol ethers,[3] we noted that the MOM group facilitated the α-lithiation of the parent enol ether **1** (R = CH_2OCH_3, R′ = H).[4,5] In an effort to exploit the directing influence of the MOM group, we sought to explore the α-metalation of substituted 1-alkoxy dienes **2** (R = MOM, R′ = alkyl) and alkoxy trienes **3** (R = MOM, R′ = alkyl). In this paper we wish to report the successful deprotonation of these systems, one of which is dependent on the presence of the MOM group, as well as an efficient, ste-

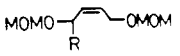
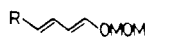
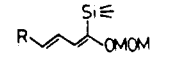
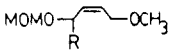
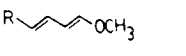
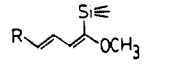


1 **2** **3**

(1) For some recent reviews, see: (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997. (b) Gschwend, H. W.; Rodriquez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(2) (a) Baldwin, J. E.; Hofle, G.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125. (b) Everhardus, R. H.; Grafing, R.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 69. (c) Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **1980**, *102*, 1577.
(3) (a) McDougal, P. G.; Rico, J. G. *Tetrahedron Lett.* **1984**, *25*, 5977. (b) McDougal, P. G.; Rico, J. G.; Vanderveer, D. G. *J. Org. Chem.* **1986**, *51*, 4492.
(4) Another acetal, the THP group, has been used to direct the α-lithiation of a simple enol ether, see: Hartmann, J.; Stahle, M.; Schlosser, M. *Synthesis* **1974**, 888.
(5) The MOM group has found use in directing the metalations of arenes, see: Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031. It is thought that the additional oxygen of the MOM acetal **1** (R = CH_2OCH_3) aids in the prior complexation of the alkylithium base.

0022-3263/87/1952-4817$01.50/0

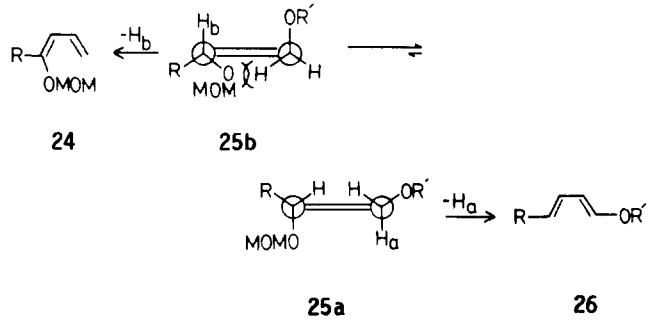
Table I. Preparation and Deprotonation of 1-Alkoxy Polyenes

entry	allylic ethers	alkoxy polyenes % yield[a] (% 1*E*,3*E* isomer)[b]	silylated alkoxy polyenes % yield[a] (% 1*Z*,3*E* isomer)[d]
			
1	**4**, R = H	**11**, R = H, 73% (1*E* = 75%)	**18**, R = H, 80% (1*Z* = 90%)
2	**5**, R = CH_3	**12**, R = CH_3, 52% (90%)	**19**, R = CH_3, 84% (*d*)
3	**6**, R = *i*-Pr	**13**, R = *i*-Pr, 69% (90%)	**20**, R = *i*-Pr, 77% (90%)
4	**7**, R = *i*-Bu	**14**, R = *i*-Bu, 70% (95%)	not performed
5	**8**, R = (*E*)-CH=CHCH$_3$	**15**, R = (*E*)-CH=CHCH$_3$, 80% (*c*)	**21**, R = (*E*)-CH=CHCH$_3$, 68% (*e*)
			
6	**9**, R = CH_3	**16**, R = CH_3, 58% (84%)	**22**, R = CH_3, 76% (*d*)
7	**10**, R = (*E*)-CH=CHCH$_3$	**17**, R = (*E*)-CH=CHCH$_3$, 80% (*c*)	**23**, R = (*E*)-CH=CHCH$_3$, 0%

[a] All yields are for isolated (usually distilled) material. [b] The signal for the proton α to the oxygen easily distinguished the 1*E* isomers (δ 6.4–6.6; J = 11.5–12.5 Hz) from the 1*Z* isomers (δ 5.90–6.10; J = 5.5–6.5 Hz). In certain instances all the isomers could be identified by ^{1}H NMR and their exact ratio confirmed by capillary GLC. For **12**, 90% 1*E*,3*E*, 7% 1*Z*,3*E*, 3% 1*E*,3*Z*; for **13**, 90% 1*E*,3*E*, 10% 1*Z*,3*E*; for **16**, 84% 1*E*,3*E*, 8% 1*Z*,3*E*, 8% 1*E*,3*Z*. No attempts were made to further purify the major stereoisomer. [c] The exact isomer ratio for the trienes is difficult to assay due to the proliferation of olefin protons. Clearly one isomer with a 1*E* configuration (H-1, δ 6.50, J = 12 Hz) is the major product (greater than 80%). [d] See ref 21. For entries 2 and 6 the exact geometrical assignment was not possible, although both products are composed of one major isomer (>90%). [e] See ref 22.

reoselective synthesis of the requisite dienes and trienes.

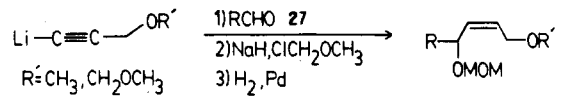
Even though 1-alkoxy dienes have played a major role in the development of the Diels–Alder reaction, the stereoselective synthesis of such compounds can be troublesome.[6] In an effort to develop a stereoselective synthesis of 4-substituted 1-alkoxy dienes, we studied the 1,4-elimination of the *cis*-allylic ethers **4–10** (see Table I). In accord with the literature precedent,[7] the parent cis olefin **4** suffered base-catalyzed 1,4-elimination using LDA[8] to yield the (*E*)-diene **11** as the major isomer (see Table I, entry 1). More significantly, the substituted cis olefins **5–10** all underwent clean 1,4-elimination[8] with complete regioselectivity[9] (note the absence of products related to diene **24**) and higher stereoselectivity than the parent olefin **4** (see Table I). Both the regioselectivity and the stereoselectivity can be rationalized by considering the conformation (see **25a** and **25b**) needed for a syn-1,4-elimination.[10] The cis relationship of the two allylic



24 **25b**

25a **26**

carbons forces the compound to adopt conformation **25a** in which both allylic carbons point their smallest substituent (i.e., hydrogen) toward each other, thereby yielding, upon elimination, the (*E*,*E*)-diene **26** as the major product. Elimination initiated by removal of H_b would place either the R or more likely the OMOM group in a sterically conjested position. This unfavorable interaction coupled with the decreased kinetic acidity of H_b accounts for both the observed regioselectivity and stereoselectivity. The relationship of conformational preference and regioselectivity is more obvious in the production of the trienyl ethers **15** and **17**. In these examples the increased acidity of H_b due to its bis-allylic nature (**25a,b**, R = vinyl) does not destroy the regioselectivity of elimination, presumably because a suitable conformation for elimination still cannot be attained. The requisite cis olefins **4–10** are all available in three steps from the generalized aldehyde **27**. The observed selectivity of the 1,4-elimination allows



4-10

for an efficient synthesis of terminally substituted 1-alkoxy polyenes which is amenable to large-scale production. Furthermore, this route offers a viable alternative to Wittig-type chemistry[11] for the construction of 1-alkoxy polyenes.[12,13]

The paucity of data on the α-metalation of 1-alkoxy polyenes may be in part due to the poor yields (~30%) initially reported for 1-methoxybutadiene.[2a] Since that time, efficient α-lithiation of 1-methoxybutadiene has been achieved,[2b,c] yet only one substituted 1-alkoxy diene has ever been α-metalated.[2c] We are pleased to report that all of the polyenes in Table I, except for the methoxy triene

(6) For some recent syntheses, see: (a) Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.* **1986**, *51*, 3400. (b) Van Hulsen, E.; Hoppe, D. *Tetrahedron Lett.* **1985**, *26*, 411. (c) Luengo, J. I.; Koreeda, M. *Tetrahedron Lett.* **1984**, *25*, 4881.

(7) Everhardus, R. H.; Peterse, A.; Vermeer, P.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 90.

(8) Elimination is most conveniently carried out with LDA in THF at −78 °C (2 h). Added potassium *tert*-butoxide (Margot, C.; Schlosser, M. *Tetrahedron Lett.* **1985**, *26*, 1035) had no effect on yields or stereoselectivity.

(9) There is some precedent for the regioselectivity in the elimination of propargyl diethers to cumulenes, see: Mantione, R.; Alves, A.; Montijn, P. P.; Wildschut, G. A.; Bos, H. J. T.; Brandsma, L. *Recueil* **1970**, *89*, 97.

(10) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 1992.

(11) The Wittig reaction of alkoxy-substituted phosphorus ylides usually give low yields and/or poor stereoselectivity (see ref 11a for a compilation of references). There has been one report of a highly stereoselective synthesis of 1-alkoxy polyenes via Wittig chemistry (ref 11b). (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 448. (b) Vo-Quang, Y.; Carniato, D.; Vo-Quang, L.; LeGoffic F. *J. Chem. Soc., Chem. Commun.* **1983**, 1505.

(12) There has been renewed interest in the synthesis of 1-alkoxy polyenes due to the isolation of the potent mutagen fecapentaene. The most stereoselective synthesis of this alkoxy pentaene is via a non-Wittig-type 1,4-reductive elimination, see: Pfaendler, H. R.; Maier, F. K.; Klar, S. *J. Am. Chem. Soc.* **1986**, *108*, 1338.

(13) In considering the synthesis of more highly conjugated alkoxy polyenes, one should be aware of the demonstrated mutagenicity of simple alkoxy tetraenes and pentaenes, see: Gupta, I.; Suzuki, K.; Bruce, W. R.; Krepinsky, J. J.; Yates, P. *Science (Washington, D.C.)* **1984**, *225*, 521.

17, undergo clean α-lithiation as evidenced by the production of the silyl polyenes 18–22.[20] For the alkoxy dienes 11–14 and 16 metalation was achieved with *sec*-butyllithium in THF (–78 °C, 1.5 h). No products arising from either allylic deprotonation[14] or addition of the alkyllithium base[2b,c] to the dienyl system were isolated.[15] Hence, the α-metalation of 1-alkoxy dienes is indeed a general reaction.[21] Noteworthy is the observation that the MOM-substituted diene 12 undergoes metalation faster than the methoxy diene 16.[16] While both these dienes ultimately gave satisfactory yields of α-silylated dienes, the observed rate acceleration of the MOM group is essential in the deprotonation of the trienyl systems.

Treatment of the MOM-substituted triene 15 (entry 5) with *sec*-butyllithium resulted in addition of the alkyllithium base to the trienyl system.[17] After considerable experimentation, it was found that *n*-butyllithium (1.5 equiv) in DME containing TMEDA (1.0 equiv) cleanly deprotonated the MOM triene 15 (–78 °C, 2 h).[18] The resulting silylated triene 21 was isolated as a single isomer, presumably with the 1*Z*,3*E*,5*E* configuration.[22] Extension of these metalation conditions, as well as numerous other deprotonation recipes to the methoxy triene 17, have failed to yield any products resulting from α-lithiation. Therefore, the MOM group is a necessary feature for the successful deprotonation of 1-alkoxy trienes.[18] Furthermore, α-deprotonation of triene 15 represents the first example of vinyl deprotonation on a conjugated triene.

In conclusion, the combination of an efficient, stereoselective synthesis of 1-alkoxy polyenes coupled with the successful α-lithiation of these systems allows for the rapid construction of highly functionalized polyene systems of well-defined configuration. Particularly exciting is the synthesis and metalation of the alkoxy trienes, as the chemistry of these materials is virtually unexplored.[19] Besides exploring the chemistry of these new materials, we are evaluating the use of other highly active chelators to control the lithiation reactions of nonaromatic systems.

Acknowledgment. We gratefully acknowledge the financial support from the National Science Foundation (CHE-8612735). Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of the research.

(14) For an example of an alkoxy diene which gives only allylic deprotonation, see: Oakes, F. T.; Yang, F.-A.; Sebastian, J. F. *J. Org. Chem.* **1982**, *47*, 3094.

(15) Products resulting from the metalation and silylation of both the (*E*)- and (*Z*)-dienyl ethers (geometry about the enol ether double bond) can be detected by both ^{1}H NMR (300 MHz) and capillary GLC. However, the silylated products are generally enriched in the isomer resulting from the metalation of the (*E*,*E*)-diene. The selective destruction of (*Z*)-dienyl ethers during the metalation reaction has previously been noted (ref 2c).

(16) Initially this was obvious from comparing the time necessary for complete deprotonation at –78 °C (1.5 h for 12 vs 8 h for 16). More substantial data was obtained by reacting 1 mole equiv of *sec*-BuLi with a mixture containing 1 mole equiv of both the methoxy diene 16 and the OMOM diene 12 (2 h, –78 °C). After silylation, the reacting mixture was analyzed by capillary GLC against an internal standard (decane) and found to contain 75% unreacted methoxy diene 16 and 25% unreacted OMOM diene 12.

(17) Increasing the conjugation of a polyene system both lowers its reduction potential (ref 17a) and lowers the energy of the LUMO (ref 17b). It is therefore not surprising that the trienes, relative to the dienes, are more prone to addition relative to deprotonation. (a) Bredas, J. L.; Silbey, R.; Boudreaux, D. S.; Chance, R. R. *J. Am. Chem. Soc.* **1983**, *105*, 6555. (b) Ann, N. T.; Canadell, E.; Eisenstein, O. *Tetrahedron* **1978**, *34*, 2283.

(18) It has been observed independently (ref 2b) that *n*-BuLi is less prone to add to heterosubstituted dienes than either *t*-BuLi or *sec*-BuLi. For triene 12, employment of *n*-BuLi in THF still yielded only addition products. We had previously found (ref 3b) that DME facilitated the deprotonation process, but in this case the TMEDA additive was also necessary (*t*-BuOK as additive gave only addition products).

(19) The few reactions reported to date all involve 1-siloxy trienes, see: (a) Chan, T. H.; Stossel, D. *J. Org. Chem.* **1986**, *51*, 2423. (b) Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841.

(20) The anion from diene 12 also reacts with aldehydes (CH_3CHO, 65%) and ketones (cyclohexanone, 40%). We have not yet been able to effect conjugate addition to cyclohexenone with any of a variety of cuprate reagents.

(21) The stereochemistry of the silylated dienes is more difficult to assign. In accord with the literature precedent (ref 2c), we have used the proton signal at C-2 to assign stereochemistry about the enol ether bond. For compounds which possess the 1*Z* configuration (the major isomers) H-2 resonates downfield (δ 6.1, J = 11.0 Hz) relative to H-2 in the 1*E* isomers (δ 5.7, J = 11.0 Hz). In most compounds, the stereochemistry about the Δ^3 olefin is clearly indicated by a $J_{3,4}$ value of 14.5–15.5 Hz. We have not detected any silylated compounds which have a *Z* configuration about the Δ^3 olefin. The assignment of the 1*Z*,3*E* configuration to all the major isomers is consistent with the idea that deprotonation and silylation occur without isomerization about the double bonds.

(22) For the triene 21 the 400-MHz ^{1}H NMR clearly indicates that one isomer is present. Unfortunately an exact assignment of olefin geometry is impossible due to the overlap of the vinyl proton signals. Hence, the geometry is assigned on the assumption that the major isomer of the starting triene 15 has undergone deprotonation and silylation with retention of olefin geometry.

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Preferred Conformation of C-Glycosides. 1. Conformational Similarity of Glycosides and Corresponding C-Glycosides

Summary: The conformational preference of α(axial)-C-glucosides 3–12 and β(equatorial)-C-glucosides 15–21 was studied by ^{1}H NMR spectroscopy. Axial and equatorial C-glycosides exist predominantly in the conformation **2A** and **14A**, respectively. This conformational preference is parallel to that of corresponding glycosides.

Sir: In connection with structural and synthetic studies on the marine natural product palytoxin,[1-3] we became interested in comparing the conformational preference of glycosides to that of corresponding C-glycosides, since major parts of the palytoxin structure could be viewed as C-oligosaccharides. Regarding the O–R bond at the anomeric center, α(axial)-glycosides are known to prefer

(1) For the gross structure of palytoxin, see: (a) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781 and references cited therein. (b) Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491 and references cited therein. For the structures of minor constituents, see: Uemura, D.; Hirata, Y.; Iwashita, T.; Naoki, H. *Tetrahedron* **1985**, *41*, 1007.

(2) For the stereochemistry assignment primarily based on organic synthesis, see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369 and preceding papers. For the stereochemistry assignment primarily based on spectroscopic methods, see: Moore, R. E.; Bartolini, G.; Barchi, J.; Bothner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776.

(3) For synthetic studies on palytoxin, see: (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644 and references cited therein. (b) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774.

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