Cascade Cyclizations of Cyclic Sulfates: An Enantioselective Alternative to Polyepoxide Cyclizations in the Synthesis of Poly(tetrahydrofurans)

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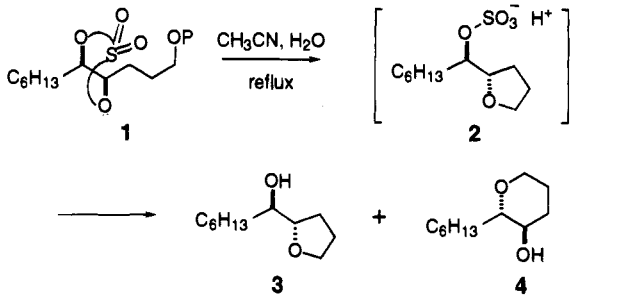
Polyepoxide cascade cyclizations[2] form the basis of an appealing strategy for the synthesis of oligo(tetrahydrofurans) common to many polyether ionophore natural products. Unfortunately, the diastereomerically pure polyepoxide precursors for these cyclizations are not easily accessible. Several optically pure polyepoxides have been prepared using the Sharpless asymmetric epoxidation, either in a stepwise fashion[3] or through a two-directional chain synthesis approach.[4] An alternative strategy based on face-selective epoxidation of macrocyclic polyenes has been used in synthesis of monensin-like fragments[5] and was recently used as a key step in the synthesis of emericid.[6] The most desirable approach, direct enantioselective epoxidation of a linear polyene, has not been achieved. Sharpless' recent demonstration of a related polyene oxidation in his enantioselective dihydroxylation of squalene[7] shows that this type of direct enantioselective oxidation is possible, but no cascade cyclization has been reported using these optically pure polyols.[8] We report the first examples of cascade cyclizations using cyclic sulfates derived from optically pure polyols.

While searching for an epoxide equivalent that would favor a 6-*endo-tet* cyclization over the normally preferred 5-*exo-tet* cyclization, we investigated the solvolysis of the cyclic sulfates **1a−e**. These substrates all favored a 5-*exo-tet* cyclization, but led unexpectedly to the free alcohol **3** rather than the expected sulfate esters **2a−e** as shown in Table 1. The 5-*exo-tet* selectivity was lowered to 3:1 in the case of the methyl ether **1e**, but the ratio was never reversed.[9] To clarify the mechanism of the reaction, the benzyl ether of 1-decanol was added to a cyclization reaction of benzyl ether **1a** and was recovered unchanged, showing that the benzyl ether itself cyclizes rather than hydrolyzing to the corresponding alcohol before cyclization.[10] In analogous reactions, the MOM, *tert*-butyldimethylsilyl (TBS), and *tert*-butyl ethers of 1-decanol were all partially hydrolyzed under the reaction conditions. The most interesting feature of these reactions is that alcohol **3** was isolated directly from the reaction instead of the expected sulfate ester **2**. The sulfate ester was presumably hydrolyzed by acid produced in the course of the reaction in an autocatalytic process.[11] When the reaction was buffered with pyridine, the cyclization still took place with all ethers, but the sulfate ester **2** was isolated rather than the free alcohol. The unexpected *in situ* hydrolysis leaves the alcohol free to participate in further reactions, suggesting the possibility of a polysulfate cascade cyclization. The cascade cyclization reaction was reduced to practice as described below.

Table 1. Cyclization and *in Situ* Hydrolysis of Sulfate Ethers **1**[a]

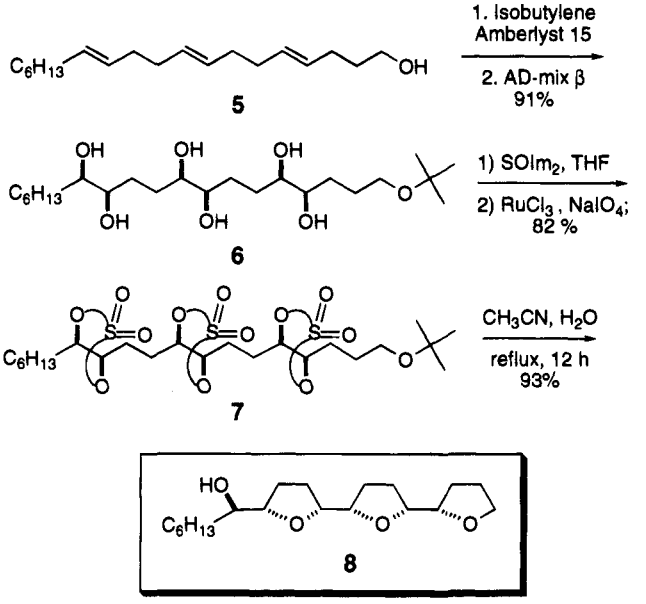


1 **2** **3** **4**

sulfate	P	3/4	% yield (3 + 4)
1a	Bn	>50[b]	97[e]
1b	MOM	32[c]	90
1c	TBS	10[c]	98
1d	*tert*-butyl	32[c,d]	91
1e[f]	Me	3[c]	18

[a] Standard reaction conditions: A 0.1 M solution of **1** in CH_3CN containing 50−100 equiv of H_2O was refluxed under a N_2 atmosphere for approximately 12 h until the starting material was no longer observed (TLC). [b] GC ratios of corresponding acetates. [c] Determined by ^1H NMR integration. [d] Reaction carried out on a 2.0 g scale. [e] Yield is for cyclization and acetylation. None of **4** was isolated. [f] In addition to **3** and **4**, 81% of 4-methoxyundecane-1,5-diol was isolated from the reaction of **1e**.

Scheme 1



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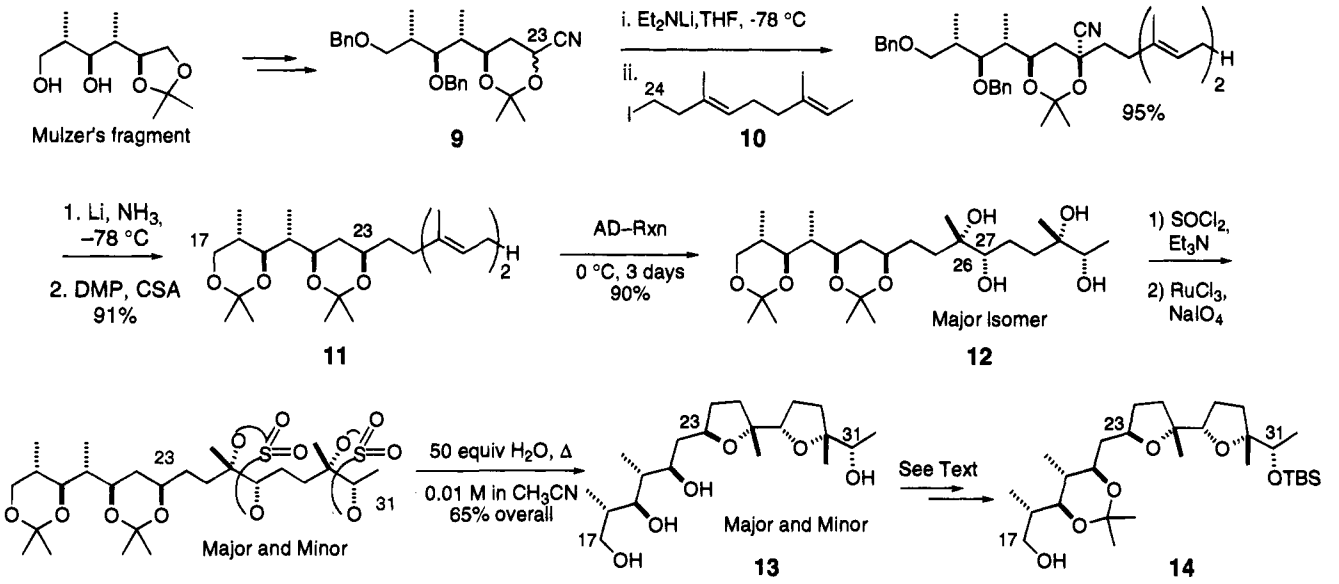
(9) The major product, *anti*-4-methoxyundecane-1,5-diol, resulted from nucleophilic opening of the cyclic oxonium ion intermediate by water.

(10) For other examples in which benzyl ethers participate in cyclizations, see: (a) Dehmlow, H.; Mulzer, J.; Seilz, C.; Strecker, A. R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, *33*, 3607. (b) Mead, K. T.; Yang, H. L. *J. Org. Chem.* **1990**, *55*, 2991. (c) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(11) The hydrolyses of similar sulfate esters are described in the following reference: Kalanter, T. H.; Sharpless, K. B. *Acta Chem. Scand.* **1993**, *47*, 307.

0002-7863/95/1517-12873$09.00/0

Scheme 2



The cascade cyclization was investigated using alcohol **5**, which was prepared by iterative Johnson ortho-ester Claisen rearrangements. The cyclization sequence is illustrated in Scheme 1. Formation of the *tert*-butyl ether and Sharpless asymmetric dihydroxylation gave hexaol **6** as a single isomer in good yield. The tris(sulfate) **7** was prepared by a modification of the Sharpless procedure[12] using thionyl bis(imidazole).[13] Refluxing **7** (0.01 M) in acetonitrile with 50 equiv of H_2O for 12 h gave the tris(tetrahydrofuran) **8** as a single isomer in 93% yield.[14] This remarkably efficient cyclization apparently proceeded by a series of cyclizations and *in situ* sulfate hydrolyses and was almost completely free of side reactions.

The cascade cyclization was further tested in the construction of the C17−C32 fragment of ionomycin, Scheme 2.[15] Cyanohydrin acetonide **9** was prepared from mannitol by way of Mulzer's polypropionate fragment.[16] The 3,7-dimethyl-9-iodo-2,6-nonadiene (**10**) was prepared from geraniol[16] and then coupled with the anion of cyanohydrin **9** in 95% yield. Reductive decyanation set the configuration at C23 and cleaved the benzyl ethers.[17] Reprotection as a bis(acetonide) gave diene **11**. Sharpless asymmetric dihydroxylation of **11** using the $(DHQ)_2$-DP-PHAL ligand gave tetraol **12** as a 2.5:1 mixture of isomers at C26−C27 positions in 90% yield.[18,19] The isomers were carried through the cyclization reaction as a mixture and were separated after acetonide formation in the correlation sequence. Preparation of the disulfate of **12** and cyclization gave bis(tetrahydrofuran) **13** (along with the minor isomer) in 65% yield. Reprotection[20] and separation of the major and minor isomers arising from the dihydroxylation reaction gave bis(tetrahydrofuran) **14**, which showed NMR spectra identical with those of the C17−C32 fragment of ionomycin previously used by both Hanessian and Evans in their total syntheses.[15,21] The cyanohydrin coupling, Sharpless asymmetric dihydroxylation, and disulfate cyclization sequence provides a very direct route to the C17−C32 fragment of ionomycin and demonstrates the utility of polysulfate cascade cyclizations in the synthesis of poly(tetrahydrofuran) natural products.

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Supporting Information Available: Experimental procedure for the cyclization of **7**, characterizations for **6**−**8**, **11**, and **14**, schemes and characterization for the preparation of **9** and **10**, and comparison of the naturally derived and synthetic **14** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) Reviews: (a) Lohray, B. B. *Synthesis* **1992**, 1035. (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(13) Denmark, S. E. *J. Org. Chem.* **1981**, *46*, 3144.

(14) Compound **8** was a single isomer by ^1H and ^{13}C NMR. A minor isomer, isolated in 0.7% yield, was identified as a threo isomer, which presumably arises from a *cis*-alkene impurity. For ^1H NMR chemical shift analysis of poly(tetrahydrofurans), see the following: Hoye, T. R.; Zhuang, Z. *J. Org. Chem* **1988**, *53*, 5583. We thank Professor Hoye for helpful discussions.

(15) To date there have been two total syntheses of ionomycin. The C17−C32 fragment shown in Scheme 2 was the enantiomer of an intermediate used in both syntheses: (a) Hanessian, S.; Cook, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276. (b) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

(16) Schemes for the preparation of cyanohydrin **9** and iodide **10** are given in the supporting information.

(17) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550.

(18) Ratio of tetraol epimers at C26,C27 with other ligands (*SS*:*RR*): $(DHQ)_2$-PHAL (1:1); $(DHQ)_2$-AQN (1:2); $(DHQ)_2$-PYR (1:1.5). Ratios were determined from the ^1H NMR spectra of the tetraol **12**.

(19) We are grateful to Professor K. Barry Sharpless for helpful discussions and for providing us with the $(DHQ)_2$-DP-PHAL and the $(DHQ)_2$-AQN ligands: Becker, H.; King, S. B.; Taniguchi, M.; Banhessche, K.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940.

(20) Reprotection sequence: (i) pivaloyl chloride, DMAP; (ii) 2,2-dimethoxypropane, acetone, PPTs separate major and minor isomers; (iii) TBSOTf, lutidine; (iv) DIBAL-H.

(21) We would like to thank Professors Evans and Hanessian for providing NMR spectra of their ionomycin intermediates. The reported rotation for *ent*-**14** prepared by Hanessian's group was $[\alpha]^{24}_D$ −20.9° (c = 0.6, $CHCl_3$), while the rotation observed for our synthetic **14** was $[\alpha]^{24}_D$ +20° (c = 1.0, $CHCl_3$).