

$\text{CsO}_2\text{CC}_2\text{H}_5$ (DMF, 60 °C)^{14,15} followed by reduction (LiAlH_4 , THF, reflux) afforded (–)-trachelanthamidine (**1**) ($[\alpha]^{25}_{\text{D}} -14.1^\circ$ (c 3.6, $\text{C}_2\text{H}_5\text{OH}$), lit.¹⁶ -13.5° (c 2, $\text{C}_2\text{H}_5\text{OH}$)] in 80% yield after chromatography.

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(13) Representative experimental procedure is as follows: An oven-dried 100-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, nitrogen inlet, serum cap, and reflux condenser, was thoroughly flushed with nitrogen. To the flask was added **14** (1.325 g, 5 mmol), benzene (50 mL), iodoethane (2.73 g, 17.5 mmol), and Bu_3Sn_2 (1.595 g, 2.75 mmol). The resulting solution was stirred and irradiated with a 275-W sunlamp for 20 min whereupon GC and TLC indicated the consumption of **14**. The benzene was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel to provide **15a** and **b** (**15a**/**15b** = 30) (0.77 g, 58%), mp 48–49 °C; $[\alpha]^{25}_{\text{D}} -23.9^\circ$ (c 1.13, $\text{C}_2\text{H}_5\text{OH}$).

(14) Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, 52, 4230.

(15) In addition, ca. 5% of the corresponding alkene was formed by a competing elimination reaction.

(16) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 909.

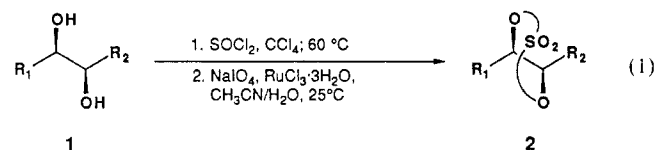
Vicinal Diol Cyclic Sulfates: Like Epoxides Only More Reactive

Yun Gao and K. Barry Sharpless*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

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Epoxides play a unique role in organic synthesis: they simultaneously activate and protect adjacent functionalized carbon atoms for nucleophilic attack, and they are usually superior to equivalent acyclic synthons because their cyclic nature renders competing elimination processes stereoelectronically unfavorable.¹ The same fortunate properties are shared by another class of vicinally substituted electrophiles—the 1,2-cyclic sulfates.²



However, these diol cyclic sulfates **2** are not found in the repertoire of main line organic synthesis. This deficit is apparently due to lack of a good method for their preparation. Our recent discovery of a catalytic process for the asymmetric dihydroxylation of olefins provided incentive to find uses for the chiral diol products.³ We report here on a facile process for conversion of diols **1** to cyclic sulfates **2** and on the versatile electrophilic behavior of this overlooked functional group.

(1) Having the crucial insight that stereoelectronic factors would disfavor eliminations in small rings has enabled Seebach to develop ingenious synthetic methods which depend on such eliminations not occurring, see: Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, 70, 1194 and references cited therein.

(2) For reviews, see: (a) Breslow, D. S.; Skolnik, H. *Multi-Sulfur and Sulfur and Oxygen Five- and Six-Membered Heterocycles, Part One*; Wiley-Interscience: New York, 1966; p 17. (b) Fisher, G. W.; Zimmermann, T. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 6, p 851. (c) Tillett, J. G. *Phosphorus and Sulfur* **1976**, 1, 341.

(3) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, 110, 1968. (b) For additional examples of substrate scope see the Aldrich advertisement on the back of *J. Org. Chem.* **1988**, 53(12), June 10 issue.

Table I. One-Pot Synthesis of Cyclic Sulfates **2**^a

entry	cyclic sulfate 2	R ₁	R ₂	yield ^b (%)	mp (°C)
1	2a	CO ₂ i-Pr	CO ₂ i-Pr	90–93 ^c	
2	2b	CO ₂ Et	CO ₂ Et	69 ^c	75–76
3	2c	CO ₂ Me	CO ₂ Me	63 ^c	70–71
4	2d	n-C ₈ H ₁₇	H	92	
5	2e	c-C ₆ H ₁₁	H	97 ^d	75–76
6	2f	n-C ₄ H ₉	n-C ₄ H ₉	89	
7	2g	n-C ₁₅ H ₃₁	CO ₂ Me	90–95	45–46
8	2h	c-C ₆ H ₁₁	CO ₂ Et	95–97	
9	2i	H	CO ₂ c-C ₆ H ₁₁	88	55–57
10	2j	H	CONHCH ₂ Ph	64	95–97

^a Reactions were performed as described in ref 8. ^b Isolated yields. ^c (2*R*,3*R*)-(+)-Tartrates were used. ^d Prepared by Dr. B. B. Lohray.

The ring strain energy (~5–6 kcal/mol)⁴ of 1,2-cyclic sulfates is most often cited as the reason for the very poor yields in attempted direct preparations from the diol and SO_2Cl_2 or related SO_2X_2 species.⁵ However, cyclic sulfites form readily from 1,2-diols, and hence permanganate oxidation of the sulfite has been the favored route to cyclic sulfates.² Even so, the permanganate approach often gives poor yields and impure products. In 1981 Denmark (1,3-cyclic sulfites) and in 1983 Lowe (1,2-cyclic sulfites) reported that the oxidation step was much cleaner when effected by a stoichiometric quantity of RuO_4 ,⁶ but this procedure is too expensive for preparative work. We now report that our catalytic RuO_4 system⁷ is highly active for this same transformation. The oxidations are complete in less than 1 h with as little as 1 part in 1500 of the ruthenium catalyst. A general procedure for the conversion of diols to cyclic sulfates was developed (Table I). The simplicity of this one-pot procedure is exemplified by the details given for the case of diisopropyl tartrate in ref 8. Pure cyclic sulfates are obtained by simple extraction and filtration of the crude product through a pad of silica gel.⁹

Most of the 30 cyclic sulfates we have prepared by this method are new compounds.¹⁰ Many are from complex synthetic intermediates, such as sugar derivatives, and their novelty is not surprising. However, the entries in Table I, all previously unknown, were selected for their simplicity to reveal just how little the chemistry of this functional group has been developed.

Although there are a number of studies of the reactivity of cyclic sulfate compounds,^{2b,11} there are only a few reported applications

(4) Kaiser, E. T.; Panar, M.; Westheimer, F. H. *J. Am. Chem. Soc.* **1963**, 85, 602.

(5) (a) Tewson, T. J. *J. Org. Chem.* **1983**, 48, 3507 and references cited therein. (b) Tewson, T. J.; Soderlind, M. J. *Carbohydr. Chem.* **1985**, 4, 529.

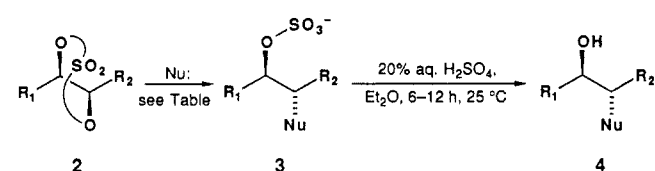
(6) Denmark, S. E. *J. Org. Chem.* **1981**, 46, 3144. Lowe, G.; Salamone, S. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1392.

(7) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, 46, 3936.

(8) Preparation of **2a**: A 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser and topped with a CaCl_2 drying tube connected to an HCl trap, a stopper, and a rubber septum was charged with (+)-diisopropyl tartrate (11.72 g, 50 mmol) and CCl_4 (50 mL). Thionyl chloride (4.4 mL, 60 mmol) was added via a syringe to the flask, and the resulting solution was refluxed for 30 min. [These intermediate cyclic sulfites, especially if water soluble, can undergo partial hydrolysis during the following oxidation. To suppress this hydrolysis one expels most of the HCl formed in the first step by refluxing, as done here, or by performing the oxidation rapidly (<5 min) by using up to 1 mol % ruthenium catalyst. Refluxing is needed, in most cases, only for acid removal; sulfite formation is rapid even at room temperature. Alternatively, the HCl can be scavenged by Et_3N or pyridine (0 °C, <10 min), but this necessitates isolation of the sulfite before oxidation to the sulfate.] The solution was then cooled with an ice–water bath and diluted with CH_3CN (50 mL). $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (8 mg, 0.03 mmol) and NaIO_4 (16 g, 75 mmol) were added followed by water (75 mL). The resulting orange mixture was stirred at room temperature for 60 min. The mixture was then diluted with ether (400 mL), and the two phases were separated. The organic layer was washed with water (20 mL), saturated aqueous NaHCO_3 (2 × 20 mL), and brine (20 mL). After drying over MgSO_4 , the solution was filtered through a small pad of silica gel to remove the brown color. The filtrate was then concentrated to afford **2a** as an analytically pure colorless liquid (13.6 g, 92%); $[\alpha]^{25}_{\text{D}} -71.43^\circ$ (c 4.41, CHCl_3).

(9) This filtration removes a brown or dark green ruthenium species.

(10) The cyclic sulfates not included here will be described in the planned full account.

Table II. Reactions of Cyclic Sulfates **2** with Nucleophiles

entry	cyclic sulfate 2	product 4	Nu:	reaction conditions ^a	yield ^b (%)
1	2a	4a	H ⁻	NaBH ₃ CN, 2.0 eq.; pH 4-5, THF, 65 °C, 5 h	55
2	2a	4b	N ₃ ⁻	NaN ₃ , 2.0 eq.; acetone/H ₂ O, 0-25 °C, 1 h	81
3	2b	4c	N ₃ ⁻	NaN ₃ , 2.0 eq.; acetone/H ₂ O, 0-25 °C, 1 h	82
4	2a	4d	F ⁻	Et ₄ NF·2H ₂ O, 1.5 eq.; acetone, 25 °C, 6 h	90
5	2a	4e	PhCO ₂ ⁻	PhCO ₂ NH ₄ , 2.0 eq.; acetone, 25 °C, 12 h	95
6	2a	4f	NO ₃ ⁻	Bu ₄ NNO ₃ , 1.5 eq.; acetone, 25 °C, 12 h	96
7	2a	4g	SCN ⁻	NH ₄ SCN, 2.0 eq.; acetone, 25 °C, 5 h	87
8	2a	4h	PhCH ₂ ⁻	PhCH ₂ MgCl, 1.5 eq.; Li ₂ CuCl ₄ , 1% eq.; THF, -78 °C, 2 h	73
9	2g	4i	H ⁻	NaBH ₄ , 1.0 eq.; DMAC, 25 °C, 15 min	90
10	2g	4j	N ₃ ⁻	NaN ₃ , 2.0 eq.; acetone/H ₂ O, 25 °C, 1 h	92
11	2g	4k	PhCO ₂ ⁻	PhCO ₂ NH ₄ , 2.0 eq.; acetone, 25 °C, 48 h	83
12	2g	4l	SCN ⁻	NH ₄ SCN, 2.0 eq.; acetone, 25 °C, 20 h	90
13	2g	4m	F ⁻	Bu ₄ NF, 2.0 eq.; acetone, 25 °C, 40 min	63

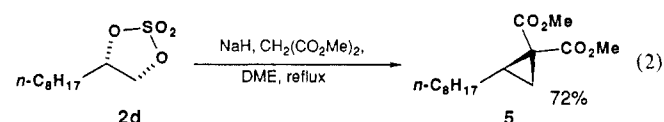
^a General procedure: the cyclic sulfate **2** (1.0 equiv) was dissolved in a solvent (ca. 0.1-0.5 M), and the nucleophile (1.5-2.0 equiv) was added at room temperature or 0 °C. The resulting solution or suspension was then stirred at room temperature until no cyclic sulfate **2** remained (TLC.) The solution was then concentrated, and the residue was stirred with 20% aqueous H₂SO₄ and ether (ca. 5 mL of each phase/mmol substrate) for 6-12 h. Following extraction with ether or CH₂Cl₂, the combined organic phases were washed with water and brine and dried over MgSO₄. After concentration, the crude product was purified by chromatography on silica gel to give compound **4**.

^b Isolated yields.

of cyclic sulfates as electrophiles in organic synthesis: the parent substance, ethylene glycol cyclic sulfate, has been used for hydroxy-ethylating polymers,¹² and a few uses have been described for carbohydrate transformations.⁵ We offer the following preliminary examples of their electrophilic reactivity in support of our belief that cyclic sulfates might eventually rival epoxides in importance as synthetic intermediates.

Among chiral 1,2-diols the tartrate derivatives are by far the most available, and the use of tartaric acid for generating chiral synthons has been richly developed.¹³ The entries in Table II (entries 1-8) reveal how the new tartrate cyclic sulfate derivatives provide an important extension of this methodology. Available in one step from the tartrate diesters, the cyclic sulfates make substitutions at the central carbon atoms either easier or, in some cases, possible for the first time. For example, this is now the best route to the popular azide-opening products **4b** and **4c** and the fluoro derivative **4d** is a new compound.

Note that in all cyclic sulfate openings the first formed product is the β -sulfate **3**, which is hydrolyzed to the β -hydroxy compound **4** by treatment with a two-phase mixture of ether and 20% sulfuric acid at 25 °C for 6-12 h with stirring.¹⁴ It is in this sense that cyclic sulfates are synthetically equivalent to epoxides. However, unlike the β -hydroxyl group generated in epoxide openings, the corresponding β -sulfate moiety is still a leaving group and can serve as such in certain situations. For example, the simple cyclic sulfate **2d** affords the cyclopropane **5** as a consequence of such a process when treated with malonate anion (eq 2). Primary amines proceed via a similar sequence to the corresponding aziridines.¹⁵ These double displacement scenarios suggest a variety of useful transformations not available to epoxides.



We are finding that α,β -unsaturated esters are good substrates for the catalytic asymmetric dihydroxylation process.^{3b} This fact increases the importance of substitution processes involving the corresponding cyclic sulfates (entries 7-10, Table I). Cyclic sulfate **2g** (entry 7, Table I) reacts readily with a wide variety of nucleophiles with apparent complete selectivity for attack at C-2, the α -position (Table II, entries 9-13).¹⁶ The carbonyl group must be responsible for the increased reactivity of the α -position,¹⁷ but interestingly, the corresponding epoxide derivatives (glycidic esters) show no clear preference for C-2 versus C-3 opening. Though not shown in Table II, even an unsubstituted case, the cyclic sulfate of cyclohexyl glycerate **2i** (entry 9, Table I), was found to react with azide, benzoate, chloride, and fluoride, either predominantly or exclusively at C-2. In control experiments, the epoxide analogues of **2i** were recovered unchanged under the conditions employed for opening **2i**. By contrast, under different conditions, the ethyl ester of the corresponding epoxide reacts with azide only at C-3.¹⁸ From a synthetic point of view, noteworthy entries in Table II are those involving hydride and azide (i.e., entries 9 and 10); they lead to β -hydroxy esters and α -amino- β -hydroxy esters, respectively.

Given the vast chemistry associated with synthetic applications of epoxides, exploration of the chemistry of 1,2-cyclic sulfates, their hitherto neglected cousins, should prove fruitful. Initially, the simple realization that cyclic sulfates are like epoxides, but generally much more reactive, should give synthetic chemists many ideas of where they might be useful.

Acknowledgment. Financial support was provided by the National Science Foundation (CHE-8303355) and Eli Lilly & Co.

Supplementary Material Available: Experimental details for the preparation of all the cyclic sulfates in Table I (3 pages). Ordering information is given on any current masthead page.

(14) (a) Note that these sulfates **3** may be useful in their own right, see: Andersen, K. K. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, p 367. (b) **Note Added in Proof:** Sulfates **3** can be rapidly hydrolyzed to alcohols **4** by using a catalytic amount of sulfuric acid in moist dioxane at room temperature (Goren, M. B.; Kochansky, M. E. *J. Org. Chem.* **1973**, *38*, 3510 and references therein). Alcohols which have acid-sensitive groups such as an acetonide were thus obtained with this mild hydrolysis procedure (Kim, B. M.; Sharpless, K. B., unpublished results).

(15) Lohray, B. B.; Gao, Y.; Sharpless, K. B., unpublished results. In this case there are two stages: the first involves opening in CH₂Cl₂ or THF to the zwitterionic salt of the amino alcohol sulfate, and the second involves closure to the aziridine (achieved by treating it with LiAlH₄ in THF at room temperature or by heating the salt with aqueous base).

(16) Although not included here, compounds **2h** and **2i** also react with the same nucleophiles with complete C-2 selectivity.

(17) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 381 and references cited therein.

(18) Nakajima, Y.; Kinishi, R.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2025.

(11) Tomalia, D. A.; Falk, J. C. *J. Heterocycl. Chem.* **1972**, *9*, 891.

(12) Sorm, M.; Nespurek, S. *European Polymer J.* **1978**, *14*, 977.

(13) For an excellent review, see: Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, E., Ed.; Otto Salle Verlag: Frankfurt, 1980; p 91.