An Access to *erythro*-Diols via Sharpless's Asymmetric Dihydroxylation Reaction

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Received December 22, 1993 (Revised Manuscript Received February 28, 1994•)

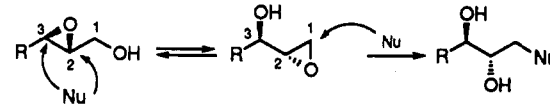
A method has been developed to access *erythro*-2,3-diols via Sharpless's asymmetric dihydroxylation reaction. Thus, a TBDMS-protected (*E*)-allylic alcohol is dihydroxylated and the resulting *threo*-2,3-diol is converted to the cyclic sulfate. Upon desilylation, this compound undergoes a Payne-type rearrangement. Nucleophilic epoxide-opening then provides an *erythro*-2,3-diol. The conversions from the cyclic sulfate to the diol product are performed in a single reaction vessel. Due to the irreversible nature of the Payne-type rearrangement, this process is easy to perform and completely regioselective independent of the substrate structures. Also, being performed in THF, the process is compatible with a variety of nucleophiles, including thiolates, $^-N_3$, ^-OAc, ^-CN, halides as well as carbon nucleophiles and hydride.

Sharpless's asymmetric epoxidation (AE) reaction is now generally recognized as one of the most important discoveries made in the 1980's in organic chemistry.[1] One of the reasons for this reaction's wide acceptance is that the product epoxy alcohols are very useful synthetic intermediates.[2] Asymmetric epoxidations followed by regioselective epoxide ring-opening reactions have provided numerous syntheses of enantiomerically pure compounds.[3]

There are three potential reactive sites in a 2,3-epoxy alcohol for nucleophilic substitution (Scheme 1). The less-obvious electrophilicity at the C-1 of an *unactivated* 2,3-epoxy alcohol is revealed by Payne rearrangement under aqueous alkaline conditions.[4] While of limited preparative value *per se* due to its reversible nature, the Payne rearrangement has been exploited to its full synthetic potential by being coupled with a regioselective, in situ nucleophilic trapping in a process called the Payne rearrangement–opening reaction.[3a] This process has been widely used to produce enantiomerically pure vicinal diol products, culminating in the synthesis of eight L-hexoses.[5]

As for the synthesis of enantiomerically pure vicinal diols, Sharpless's more recent asymmetric dihydroxylation (AD) reaction would seem to offer some advantages over the AE strategy.[6] The AD process produces vicinal diols directly, thus obviating further transformations and is not limited to allylic alcohol substrates as is the AE process. Indeed, a protected D-threitol **2** is obtained in high chemical

Scheme 1



yield and enantiomeric purity by a single-step AD reaction of 1,4-bis-*O*-protected (*E*)-2-butenediol **1** using AD-mix-β (eq 1).[7]

A fundamental weakness of the AD strategy, however, is revealed when an *erythro*-diol is desired. While this stereoisomer is easily prepared employing the AE strategy via *trans*-2,3-epoxy alcohol followed by an epoxide ring-opening, it is not directly accessible employing the AD strategy as it would be formally prepared from a (*Z*)-olefin, which is not a good substrate for the AD reaction (eq 2).[7] Despite continuous efforts from the Sharpless group and others, the AD of (*Z*)-olefins is still not stereoselective enough to be synthetically useful, the highest enantioselectivity so far observed being ca. 80% ee with dissimilarly disubstituted (*Z*)-olefins.[8]

Our interest in the synthesis of carbohydrates and related polyhydroxylated compounds led us to seek an indirect access to *erythro*-diols via the AD strategy, and an efficient method was thus found converting the threitol derivative **2** into an erythritol compound.[7] Reported in this paper is the full scope of the process.[9]

• Abstract published in *Advance ACS Abstracts,* April 1, 1994.

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(2) (a) Smith, J. G. *Synthesis* **1984**, 629. (b) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7. (c) Pfenninger, A. *Synthesis* **1986**, 89.

(3) (a) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687. (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696. (c) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67. (d) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803.

(4) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(5) (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245, and references cited therein. (b) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.

(6) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübb, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. (c) Sharpless, K. B.; Amberg, W.; Bennani, Y.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (d) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (e) Arrington, M. P.; Bennani, Y. L.; Göbel, T.; Walsh, P.; Zhao, S.-H.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *46*, 7375. (f) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463. (g) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317.

(7) Ko, S. Y.; Malik, M. *Tetrahedron Lett.* **1993**, *34*, 4675.

(8) (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568. (b) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron Lett.* **1992**, *33*, 4021. (c) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-V.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991.

(9) This work has been presented in part at the Seventh IUPAC Symposium on Organometallic Chemistry directed toward Organic Synthesis (OMCOS 7), September, 1993, Kobe.

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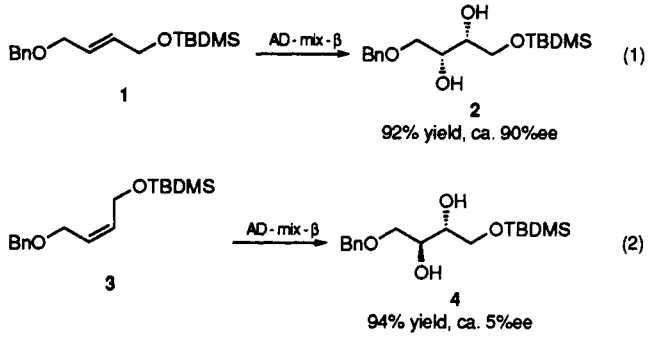
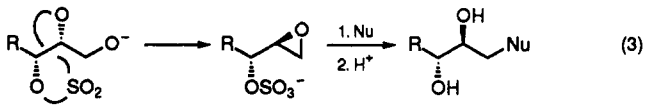


Results and Discussion

Conversion of **2** to an *erythro*-diol requires a *regioselective* epimerization of one of the carbinol carbons, not an easy task given that the two hydroxyl groups are in a very similar steric and electronic environment. Vicinal diol cyclic sulfates have been said to be "like epoxides, only more reactive".[10] It was therefore envisaged that 2,3-cyclic sulfate 1-ols would undergo a Payne-type rearrangement, and a nucleophilic trapping of the resulting epoxides would form, after hydrolysis, 2,3-diols in which the C-2 chirality center would have been epimerized (eq 3).

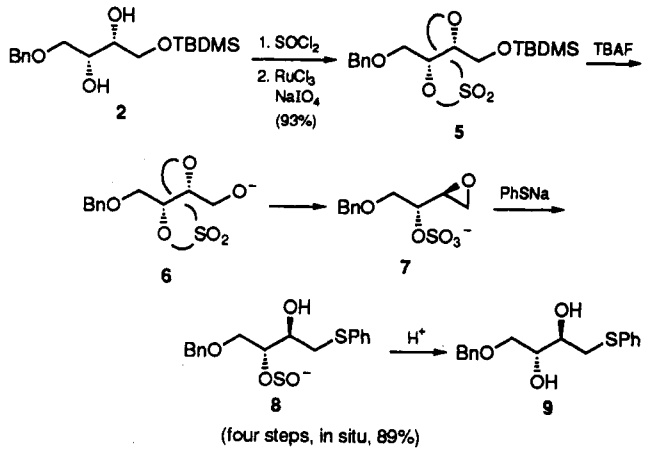


Thus, the *threo*-diol **2** was converted to the cyclic sulfate **5** following a known procedure (Scheme 2).[10a] Upon deprotection of the TBDMS group using F^- (tetrabutylammonium fluoride) in THF, the rearrangement took place in situ, as judged by TLC.[11] Benzenethiolate nucleophile was then added, and the epoxide-opening product was hydrolyzed[12] to yield (2*R*,3*R*)-1-(benzyloxy)-4-(phenylthio)-2,3-butanediol (**9**), an *erythro*-diol product. The four-step sequence from the cyclic sulfate **5** to the final product **9** was performed in a single reaction vessel.

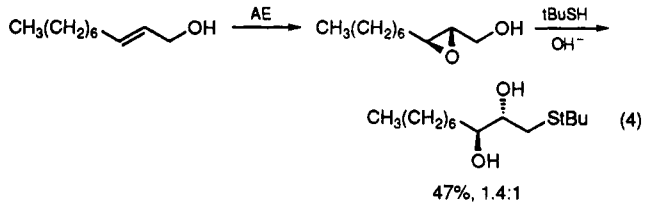
The entire process is obviously reminiscent of the Payne rearrangement–opening of an epoxy alcohol.[3a] Starting from an (*E*)-allylic alcohol, both processes produce the same *erythro*-2,3-diol. A major difference is, however, that the Payne rearrangement is a reversible process while the rearrangement in Scheme 2 is not, as there is a huge pK_a difference between the alkoxide (**6**) and the sulfate (**7**) anions. Although the reversible nature of the Payne rearrangement has been fully utilized in the Payne rearrangement–opening process by adding the nucleophile *slowly* to the equilibrating mixture of epoxy alcohols and thus performing the rearrangement and the epoxide-opening in situ, it is also a source of poor regioselectivity with some substrates (*vide infra*). The irreversible nature of the cyclic sulfate rearrangement, on the other hand, offers several advantages.

As mentioned above, the Si-deprotection is immediately followed by the rearrangement (*cf. vide infra*), producing the epoxy sulfate intermediate in a quantitative yield. The nucleophile is then added *after* the desilylation/rearrangement is complete. Therefore, there is no need for a slow addition of the nucleophile.

Scheme 2



In addition, the irreversibility renders the process completely regioselective, independent of the structures of the substrates (Table 1). Thus, the substrates having a branching at the C-4 (entry 2) and an aryl or alkyl substituent at the C-3 (entries 3 and 4) all produced the desired *erythro*-2,3-diols in high yields.[14] In contrast, the Payne rearrangement–opening of epoxy alcohols is regioselective only when the competitive C-3 opening is suppressed. Typical examples of "good" substrates for the Payne rearrangement–opening process are epoxy alcohols corresponding to entries 1 and 2. On the other hand, 3-alkyl-substituted 2,3-epoxy alcohols are poor substrates, producing a high proportion of unwanted regioisomers. Compare, for example, the entry 4 with a corresponding Payne rearrangement–opening reaction reported in the literature (eq 4).[3a] Although the cyclic



sulfate rearrangement–opening process requires additional steps—four operations (silylation; AD; cyclic sulfate formation; desilylation/opening) from the allylic alcohol starting material to the final *erythro*-2,3-diol product, compared to two for the Payne rearrangement–opening process—they are all very efficient transformations, and the overall yield is much higher than in the case of the corresponding Payne rearrangement–opening process. 3-Aryl-substituted 2,3-epoxy alcohols are probably even poorer substrates in the Payne rearrangement–opening process.

Another drawback in the Payne rearrangement–opening process is that it is performed in aqueous alkaline solution at high temperature. These reaction conditions preclude the use of many synthetically useful nucleophiles.[15] The most common nucleophiles used in this process are thiolates. In contrast, the cyclic sulfate rearrangement–

(10) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Lohray, B. B. *Synthesis* **1992**, 1035.

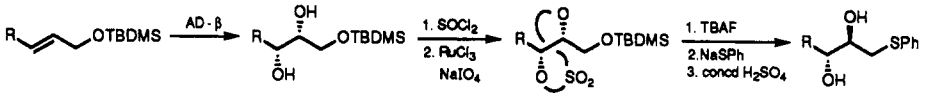
(11) (a) Only base-line material was observed on TLC. (b) The formation of **7** at this point was recently confirmed by NMR.

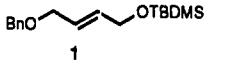
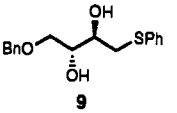
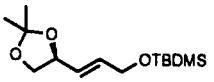
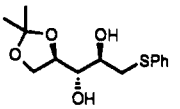
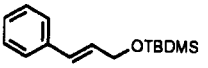
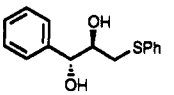
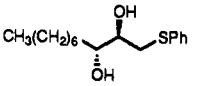
(12) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655.

(13) The low yield from this reaction was probably due to a partial deprotection of the acetonide group during the acidic hydrolysis. *cf.* A selective procedure has been reported for the hydrolysis of sulfate anions in the presence of ketal protecting groups. See ref 12.

(14) The position of the nucleophilic attack has been confirmed by MS ($^+CH_2Nu$ fragments) and/or NMR of the peracetylated products.

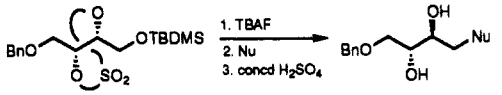
Table 1. Rearrangement-Opening of the Cyclic Sulfates with PhS^-



entry	olefin	AD, % yield (stereoselectivity)	cyclic sulfate, % yield	*erythro*-diol product, % yield
1	 **1**	92 (90% ee)	93	 **9** 89
2	 **10**	96 (60:1)	100	 **11** 52[a]
3	 **12**	89 (>95% ee)	100	 **13** 82
4	 **14**	92 (>95% ee)	93	 **15** 86

[a] See ref 13.

Table 2 Rearrangement-Opening of the Cyclic Sulfate 5 with Hetero Nucleophiles



5 **9, 16–19**

entry	Nu	% yield	product
1	^-SPh	89	**9**
2	$^-N_3$	81	**16**
3	^-OAc	64[a]	**17**
4	^-CN	70	**18**
5	^-I	85	**19**

[a] The product was isolated after peracetylation (see ref 23).

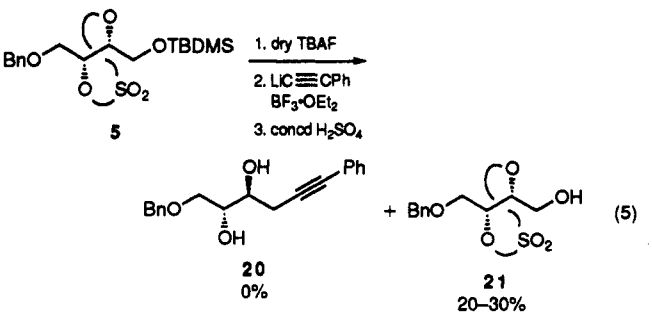
opening process is performed in THF, therefore a wide variety of nucleophiles can be used.

Heteroatom nucleophiles successfully tried in this process are listed in Table 2. In addition to benzenethiolate, $^-N_3$, ^-OAc, ^-CN and halides[16] all opened the epoxide intermediate **7** to give the corresponding *erythro*-2,3-diol products **16–19**.[14]

A great advantage of the cyclic sulfate rearrangement–opening process is with carbon nucleophiles and hydride, which are out of the question under the Payne rearrangement conditions.[15] Initial results with these nucleophiles were, however, discouraging.

Tetrabutylammonium fluoride (TBAF) obtained from commercial sources exists as the trihydrate. In order to maintain the anhydrous conditions required for the reactions with carbon nucleophiles, the commercial TBAF was first dried in a THF solution using molecular sieves.[17]

The desilylation of **5** was then performed using this THF solution of dry TBAF (the molecular sieves were not added to the reaction mixture), and as before, TLC revealed only a base-line material, evidencing the formation of the epoxy sulfate anion intermediate **7**. The reaction mixture was then treated with lithium phenylacetylide in the presence of $BF_3{\cdot}OEt_2$. The product obtained after acidic hydrolysis (concd. sulfuric acid), however, was not the desired *erythro*-2,3-diol **20** but the simple desilylation product **21** in 20–30% yield (eq 5). The isolation of **21** was completely



5 **20** 0% **21** 20–30% (5)

unexpected as the rearrangement from **6** to **7** had been thought to be spontaneous. From careful control experiments, it is now believed that the *rearrangement (**6**→**7**) is indeed spontaneous when commercial TBAF·3H₂O is used in the desilylation step; however, when dry TBAF is used under anhydrous reaction conditions, the reaction stops after the desilylation and does not proceed further to the rearrangement product* (Scheme 3).[18] In fact, the desilylated product **21** could be isolated in a better yield (ca. 50%) when the anhydrous reaction was quenched by

(15) Apparent Payne rearrangement–opening reactions have been reported under aprotic conditions using carbon nucleophiles. See; (a) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc. Chem. Commun.* **1988**, 356. (b) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1375. (c) Yamaguchi, M.; Hirao, I. *J. Chem. Soc., Chem. Commun.* **1984**, 202.

(16) (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (b) In addition to iodide, bromide and chloride are also effective nucleophiles in this process.

(17) (a) Katritzky, A. R.; Sengupta, S. *Tetrahedron Lett.* **1987**, *28*, 5419. (b) Azeotropically dried TBAF has been also used.

(18) (a) This has been confirmed by performing the reactions in THF-d_8 and observing the reaction mixture directly by NMR. (b) The base-line material observed on TLC was probably an artefact, i.e., the rearrangement must have taken place during the TLC sample preparation or even on the TLC plate.

Scheme 3

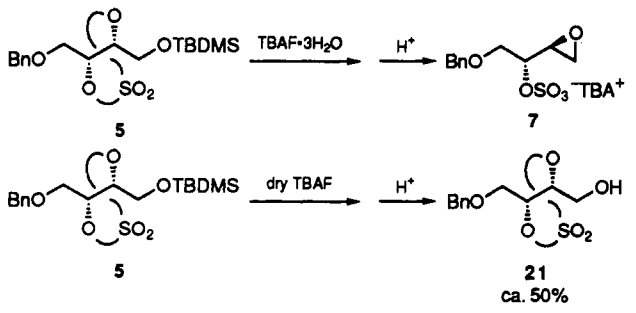
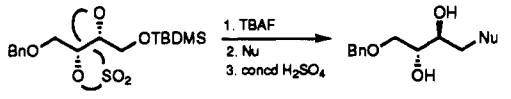


Table 3 Rearrangement-Opening of the Cyclic Sulfate 5 with Carbon Nucleophiles



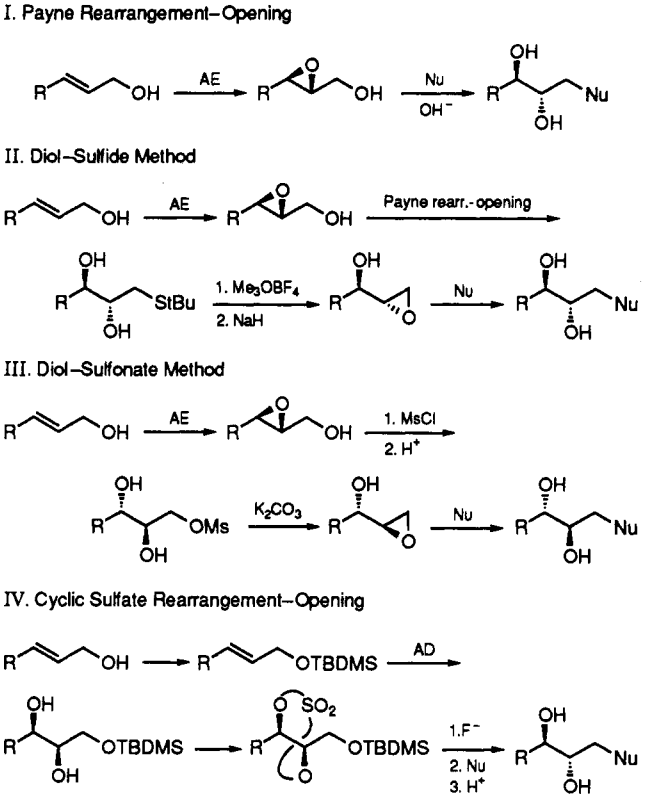
entry	Nu	conditions	% yield	product
1	LiC≡CPh	A	84	**20**
2	LiC≡CPh	B	72	**20**
3	Bu_2CuLi	A	70	**22**
4	Bu_2CuLi	B	73	**22**
5	Bu_2CuLi	C	13	**22**
6	LAH	A	84	**23**

milder acid hydrolysis. The exact roles of water in the rearrangement step are at present unknown, but it is difficult to imagine that even the huge pK_a difference between the alkoxide and sulfate anions is not enough to drive the rearrangement forward.

While the unexpected water effects brought a temporary set-back in the reactions with organometallic nucleophiles, the situation was certainly not as serious as that in the Payne rearrangement–opening process, since there are only 3 equiv of water (from TBAF·$3H_2O$) present in the reaction mixture. Two sets of reaction conditions have been devised to circumvent this problem (Table 3). Thus, after the desilylation/rearrangement is performed with commercial TBAF·$3H_2O$, the reaction mixture, the epoxy sulfate intermediate, is treated with an excess (ca. 10 equiv) of carbon nucleophile (conditions A). Under these conditions, a lithium acetylide, a cuprate, and $LiAlH_4$ have been successfully used to give the desired *erythro*-2,3-diols (**20, 22, 23**) in high yields (entries 1, 3, and 6). Alternatively, when one wishes to avoid the use of excess organometallic nucleophile, the reaction mixture after the desilylation/rearrangement with TBAF·$3H_2O$ is concentrated with the aid of dichloromethane. The resulting material, the *dry* epoxy sulfate intermediate, is then redissolved in anhydrous THF and the epoxide ring-opening reaction is carried out under anhydrous conditions with only a slight excess (ca. 1.5–2 equiv) of carbon nucleophile (conditions B). The same acetylide and cuprate nucleophiles used under these conditions produced the corresponding *erythro*-2,3-diols in yields comparable to those obtained under conditions A (entries 2 and 4). An attempt to dry the desilylation/rearrangement reaction mixture using molecular sieves (conditions C) was not successful (entry 5).

Starting from an (*E*)-allylic alcohol, one now has several different ways of making an *erythro*-2,3-diol in high enantiomeric purity (Scheme 4). The Payne rearrangement–opening process following an AE offers the shortest route, but its usefulness is rather limited to certain types of structure, e.g., a thio-substitution at the C-1 and an

Scheme 4. From (*E*)-Allylic Alcohols to *erythro*-2,3-Diols



oxy-substitution at the C-4. Following an AE, two other methods have been reported in the literature.[3a] The so-called "diol–sulfide method" and "diol-sulfonate method" both employ the *isolated* 1,2-epoxy 3-ol,[19] which is synthesized in several steps, and the epoxide ring-opening reaction is carried out in a separate operation. A wide variety of the C-1 substituents (i.e., the nucleophiles) are therefore possible in these processes, and the ring-opening reaction itself is of course completely regioselective. However, each process has its respective limitation in regioselectivity along the routes leading to the 1,2-epoxy 3-ol intermediate.[20]

In contrast, the cyclic sulfate rearrangement-opening process described in this paper is executed in four very efficient steps from the starting (*E*)-allylic alcohol to the final *erythro*-2,3-diol product. It is also completely regioselective and compatible with a variety of substituents at the C-1. This process, therefore, compares very favorably with any other process following an AE reaction. With easy accesses to *erythro*- as well as *threo*-diols now, the synthetic utility of the AD process will be further expanded.

Experimental Section

General. Allylic alcohols were prepared following literature procedures, or purchased. The TBDMS protections were performed on the allylic alcohols using TBDMS-Cl, triethylamine, and a catalytic amount of DMAP in dichloromethane, as described in the synthesis of **1** for a representative procedure. The AD reactions were carried out following the literature procedure using

(19) The diol–sulfide method and diol–sulfonate method each produces, starting from the same epoxy alcohol, 1,2-epoxy 3-ol of the opposite enantiomer. See Scheme 4.

(20) In the diol–sulfonate method, the minor regioisomer (the C-2 opening product) may be the opposite enantiomer of the major C-3 opening product.

AD-mix-β, which was purchased from Aldrich. A representative procedure was given for the synthesis of **2**. The enantiomeric purities of the diol products were measured by NMR analysis of the corresponding bis-Mosher esters.[21] The cyclic sulfates were prepared following a two-step literature procedure[10a] and used directly for the rearrangement–opening reactions after little purification.

(*E*)-1-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-2-butene (1). To a solution of (*E*)-4-(benzyloxy)-2-buten-1-ol[3a] (0.57 g, 3.2 mmol) in dichloromethane (15 mL) were added in succession triethylamine (0.89 mL, 6.4 mmol), DMAP (a catalytic amount), and TBDMS-Cl (0.72 g, 4.8 mmol). The mixture was stirred at rt for 3 h. The solvent was removed and the residue was redissolved in EtOAc. It was washed with 10% aqueous citric acid and brine. The organic phase was dried (Na_2SO_4). The concentrated crude product was purified on a silica column (hexane–EtOAc 15:1) to yield the product **1** (0.94 g, 100%): ^{1}H NMR ($CDCl_3$) δ 7.35–7.28 (5H, m), 5.83–5.77 (2H, m), 4.50 (2H, s), 4.20–4.15 (2H, m), 4.04–3.97 (2H, m), 0.88 (9H, s), 0.05 (6H, s); IR 2955 (s), 2930 (s), 2855 (s), 1473 (m), 1361 (m) cm^{-1}.

(2*R*,3*R*)-1-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-butane-2,3-diol (2) (Asymmetric Dihydroxylation of 1). A 250-mL round-bottomed flask, equipped with a magnetic stirrer, was charged with *tert*-BuOH (40 mL), water (40 mL), and AD-mix-β (Aldrich, 11.02 g). The mixture was stirred at rt and methanesulfonamide (0.75 g, 7.86 mmol) was added. The reaction flask was placed in a cooling bath (ice, 0–5 °C) and the olefin **1** (2.30 g, 7.86 mmol) was added, washing the container with *t*-BuOH (4 mL). The mixture was stirred overnight in a cold room maintained at ca. 5 °C.

With stirring, sodium sulfite (11.8 g) was added to the cold reaction mixture. It was allowed to warm to rt. After stirring for 1 h, EtOAc (100 mL) was added and the phases were separated. The aqueous phase was further extracted with EtOAc (3 × 60 mL). The combined organic phases were dried (Na_2SO_4). The concentrated crude product was purified on a silica column (hexane–EtOAc 2:1) to yield the product **2** (2.40 g, 92%, 90% ee): $[\alpha]_D$ −5.90° (*c* 1.82, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.38–7.31 (5H, m), 4.58 (2H, s), 3.96–3.88 (1H, m), 3.75 (3H, s), 3.66–3.58 (2H, m), 2.90 (1H, br), 2.75 (1H, br), 0.88 (9H, s), 0.08 (6H, s); IR 3427 (b), 2954 (s), 2929 (s), 2882 (s), 1472 (m), 1463 (m) cm^{-1}.

(2*R*,3*S*,4*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1,2-*O*-isopropylidenepentane-1,2,3,4-tetrol. The AD reaction was performed with the olefin **10**[5b] to afford the title compound in 96% yield: $[\alpha]_D$ −9.5° (*c* 0.665, EtOH); ^{1}H NMR ($CDCl_3$) δ 4.17–4.08 (2H, m), 4.03–3.98 (1H, m), 3.84–3.76 (3H, m), 3.63–3.60 (1H, m), 2.94 (1H, br), 2.68 (1H, br), 1.41 (3H, s), 1.36 (3H, s), 0.91 (9H, s), 0.10 (6H, s); IR 3448 (b), 2988 (s), 2955 (s), 2932 (s), 2859 (s), 1473 (s) cm^{-1}; MS 307 (MH^+).

(1*R*,2*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylpropane-1,2-diol. The AD reaction was performed with the olefin **12** to afford the title compound in 89% yield (>95% ee): $[\alpha]_D$ −12.9° (*c* 0.99, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.38–7.29 (5H, m), 4.71 (1H, d, J = 5.8 Hz), 3.74–3.66 (1H, m), 3.62–3.51 (2H, m), 3.23 (1H, br), 2.75 (1H, br), 0.94 (9H, s), 0.05 (6H, s); IR 3415 (b), 2955 (s), 2929 (s), 2884 (s), 1472 (m), 1463 (m) cm^{-1}; MS 283 (MH^+).

(2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]decane-2,3-diol. The AD reaction was performed with the olefin **14** to afford the title compound in 92% yield (>95% ee): $[\alpha]_D$ 1.66° (*c* 2.225, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.82–3.61 (3H, m), 3.51–3.45 (1H, m), 2.77–2.60 (2H, b), 1.45–1.33 (4H, m), 1.27–1.13 (8H, m), 0.85–0.75 (12H, m), 0.05 (6H, s); IR 3413 (b), 2955 (s), 2928 (s), 2857 (s), 1472 (s), 1464 (s) cm^{-1}; MS 325 (MH^+).

(2*R*,3*R*)-1-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-butane-2,3-diol Cyclic Sulfate (5). The diol **2** (0.71 g, 2.2 mmol) was dissolved in dichloromethane (25 mL), and triethylamine (0.7 mL, 5.1 mmol) was added. The mixture was cooled in an ice bath, and thionyl chloride (0.2 mL, 2.8 mmol) was added. The mixture was stirred for 10 min. The reaction was quenched by adding water (15 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated.

The cyclic sulfite thus obtained was dissolved in CCl_4–MeCN–water (2:2:3, 21 mL), and $RuCl_3 \cdot 3H_2O$ (25 mg, 0.12 mmol) was added followed by $NaIO_4$ (0.90 g, 4.2 mmol). The mixture was stirred at 0 °C for 1 h. It was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with water and with brine. After drying ($MgSO_4$), the organic solution was filtered through a short column of silica. The filtrate was concentrated to yield the pure cyclic sulfate **5** (0.846 g, 93%): ^{1}H NMR ($CDCl_3$) δ 7.48–7.22 (5H, m), 5.04–4.96 (1H, m), 4.88–4.78 (1H, m), 4.66, 4.57 (2H, AB, J = 12 Hz), 4.00–3.88 (2H, m), 3.80 (2H, d, J = 4.4 Hz), 0.89 (9H, s), 0.09 (3H, s), 0.07 (3H, s).

(2*R*,3*R*)-1-(Benzyloxy)-4-(phenylthio)-2,3-butanediol (9). The cyclic sulfate **5** (0.47 g, 1.1 mmol) was dissolved in THF (10 mL) and tetrabutylammonium fluoride (trihydrate, 0.36 g, 1.15 mmol) was added. The mixture was stirred at rt under nitrogen. TLC taken after 10 min (SiO_2, hexane–EtOAc 2:1) indicated the complete disappearance of the starting material and the presence of base-line material. After 30 min, a THF solution of PhSNa (prepared from PhSH [0.15 mL, 1.5 mmol] and NaH [60%, 60 mg, 1.5 mmol] in THF [5mL]) was added *via* syringe. The mixture was stirred for 2 h at rt. Concentrated sulfuric acid (0.055 mL, 2 mmol) was then added. Stirring for 30 min at rt was followed by an extractive workup (EtOAc–$NaHCO_3$). The combined organic phases were dried (Na_2SO_4). The concentrated crude product was purified on a silica column (hexane–EtOAc 3:2) to yield the sulfide diol product **9** (0.30 g, 89% yield): mp 108–109 °C (lit.[5b] 107–108 °C); $[\alpha]_D$ −47.1° (*c* 0.655, EtOH, lit.[5b] $[\alpha]_D$ +40.3° for the enantiomer); ^{1}H NMR ($CDCl_3$) δ 7.41–7.20 (10H, m), 4.55 (2H, s), 3.83–3.58 (4H, m), 3.33, 3.00 (2H, ABX, J = 14, 8.3, 3.7 Hz), 2.72 (1H, d, J = 4.2 Hz), 2.53 (1H, d, J = 4.9 Hz); IR 3350, 3249, 1582, 1482 cm^{-1}; MS 305 (MH^+). Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62. Found: C, 67.0; H, 6.6.

A small amount of the product **9** was peracetylated (Ac_2O–pyridine 1:2, 60 °C, 1 h) to afford (2*R*,3*R*)-1-(benzyloxy)-4-(phenylthio)butane-2,3-diol diacetate: ^{1}H NMR ($CDCl_3$) δ 7.42–7.15 (10H, m), 5.37–5.25 (2H, m), 4.54, 4.45 (2H, AB, J = 14 Hz), 3.70–3.52 (2H, m), 3.29, 3.12 (2H, ABX, J = 15, 7, 4 Hz), 2.05 (3H, s), 1.89 (3H, s).

(2*R*,3*S*,4*R*)-5-(Phenylthio)-1,2-*O*-isopropylidenepentane-1,2,3,4-tetrol (11). (2*R*,3*S*,4*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1,2-*O*-isopropylidenepentane-1,2,3,4-tetrol was converted to the corresponding cyclic sulfate as described above in quantitative yield. The cyclic sulfate was then treated with TBAF·3H_2O followed by PhSNa as described above for the synthesis of **9**. The concd H_2SO_4 hydrolysis took 2 h. The title product was isolated in 52% yield after column chromatography (hexane–EtOAc 1:1): mp 120–122 °C (lit.[22] 124–5 °C); $[\alpha]_D$ −36.4° (*c* 0.555, EtOH, lit.[22] $[\alpha]_D$ −38.0°); ^{1}H NMR ($CDCl_3$) δ 7.43–7.21 (5H, m), 4.22 (1H, dd, J = 12, 6.2 Hz), 4.08 (1H, dd, J = 8.4, 6.2 Hz), 3.93 (1H, dd, J = 8.4, 6.2 Hz), 3.84–3.70 (2H, m), 3.42 (1H, AB, J = 14, 3 Hz), 3.02 (1H, AB, J = 14, 8.8 Hz), 2.84 (1H, d, J = 2.2 Hz), 2.37 (1H, d, J = 2.8 Hz), 1.41 (3H, s), 1.36 (3H, s); IR 3293 (b), 2985 (s), 2935 (m), 2888 (m), 1570 (m), 1480 (s) cm^{-1}; MS 284 (M^+), 123 ($PhSCH_2^+$). Anal. Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09; O, 22.50. Found: C, 59.0; H, 7.1; O, 22.8.

(1*R*,2*R*)-1-Phenyl-3-(phenylthio)propane-1,2-diol (13). (1*R*,2*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylpropane-1,2-diol was converted to the corresponding cyclic sulfate as described above in quantitative yield. The cyclic sulfate was then treated with TBAF·3H_2O followed by PhSNa as described above for the synthesis of **9**. The concd H_2SO_4 hydrolysis took 8 h. The title product was isolated in 82% yield after a column chromatography (hexane–EtOAc 3:2): mp 87–89 °C; $[\alpha]_D$ −79.1° (*c* 0.585, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.38–7.33 (5H, m), 7.26–7.20 (5H, m), 4.93 (1H, d, J = 4.4 Hz), 3.93–3.84 (1H, m), 3.05 (1H, AB, J = 14, 3.4 Hz), 2.91 (1H, AB, J = 14, 9.2 Hz), 2.75 (1H, d, J = 2.8 Hz), 2.55 (1H, br); IR 3554 (s), 3250 (b), 2878 (m), 1450 (m), 1440 (m) cm^{-1}; MS 260 (M^+), 123 ($PhSCH_2^+$). Anal. Calcd for $C_{15}H_{16}O_2S$: C, 69.19; H, 6.19; O, 12.29. Found: C, 68.9; H, 6.1; O, 12.2.

(2*R*,3*R*)-1-(Phenylthio)-2,3-decanediol (15). (2*R*,3*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]decane-2,3-diol was converted to the corresponding cyclic sulfate as described above in 93% yield. The cyclic sulfate was then treated with TBAF·3H_2O followed

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by PhSNa as described above for the synthesis of **9**. The concd H_2SO_4 hydrolysis took 2.5 h. The title product was isolated in 86% yield after column chromatography (hexane–EtOAc 2:1): mp 95–100 °C; $[\alpha]_D$ −36.1° (*c* 0.635, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.43–7.22 (5H, m), 3.80–3.71 (1H, m), 3.63–3.53 (1H, m), 3.59 (1H, dt, *J* = 9.8, 3.6 Hz), 3.24 (1H, AB, *J* = 13.9, 2.8 Hz), 2.96 (1H, AB, *J* = 13.9, 9.8 Hz), 2.77 (1H, br), 2.04 (1H, br), 1.50–1.39 (2H, m), 1.32–1.20 (10H, m), 0.88 (3H, t, *J* = 6.7 Hz); IR 3280 (b), 3178 (b), 2956 (m), 2916 (s), 2851 (s), 1481 (s), 1469 (m), 1437 (m) cm^{-1}; MS 283 (MH^+), 123 ($PhSCH_2^+$). Anal. Calcd for $C_{16}H_{26}O_2S$: C, 68.04; H, 9.28; O, 11.33. Found: C, 68.3; H, 9.3; O, 11.2.

(2*R*,3*S*)-4-Azido-1-(benzyloxy)-2,3-butanediol (16). The cyclic sulfate **5** (0.23 g, 0.55 mmol) was treated with TBAF·3H_2O (0.21 g, 0.66 mmol) in THF (10 mL) as described above. Sodium azide (0.18 g, 2.7 mmol) and water (1 mL) were added, and the mixture was heated at 60 °C for 2 h. Concentrated sulfuric acid (0.11 mL, 2 mmol) was added and the mixture was stirred overnight. Extractive workup (EtOAc–$NaHCO_3$) was followed by chromatographic purification (hexane–EtOAc 1:1) to yield **16** as a waxy solid (105 mg, 81%): $[\alpha]_D$ −0.05° (*c* 0.25, $CHCl_3$), −8.8° (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.35–7.26 (5H, m), 4.57 (2H, s), 3.67 (2H, m), 3.66–3.64 (2H, m), 3.52–3.50 (2H, m), 2.52 (1H, br), 2.45 (1H, br); IR 3360 (b), 3000, 2925, 2875, 2101, 1500, 1453 cm^{-1}; MS 238 (MH^+). Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 55.69; H, 6.37. Found: C, 55.7; H, 6.3.

A small amount of the product was peracetylated as described above to afford (2*R*,3*S*)-4-azido-1-(benzyloxy)-2,3-butanediol diacetate as an oil: ^{1}H NMR ($CDCl_3$) δ 7.37–7.28 (5H, m), 5.33–5.20 (2H, m), 4.58, 4.47 (2H, AB, *J* = 12.1 Hz), 3.62–3.47 (4H, m), 2.10 (3H, s), 2.05 (3H, s).

(2*R*,3*S*)-1-(Benzyloxy)-2,3,4-butanetriol Triacetate. The cyclic sulfate **5** (0.26 g, 0.62 mmol) was treated with TBAF·3H_2O (0.29 g, 0.93 mmol) in THF (10 mL) as described above. Ammonium acetate (0.24 g, 3 mmol) and glacial acetic acid (0.36 mL, 6.2 mmol) were added, and the reaction mixture was heated at 60 °C for 24 h. Concentrated sulfuric acid (0.12 mL, 2.2 mmol) was added and the mixture was stirred at rt overnight. Aqueous sodium bicarbonate solution (50 mL) was added and it was extracted with EtOAc (2 × 50 mL) and then with dichloromethane (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield the crude (2*R*,3*S*)-4-acetoxy-1-(benzyloxy)-2,3-butanetriol (**17**).[23] It was directly peracetylated as described above. Column chromatography (hexane–EtOAc, gradient mixture) afforded the title product as an oil (0.13 g, 64%): $[\alpha]_D$ −1.15° (*c* 0.39, EtOH), 3.24° (*c* 1.295, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36–7.28 (5H, m), 5.38–5.20 (2H, m), 4.58, 4.47 (2H, AB, *J* = 12.1 Hz), 4.35, 4.22 (2H, ABX, *J* = 12.2, 5.9, 2.9 Hz), 3.68–3.52 (2H, m), 2.08 (3H, s), 2.04 (3H, s), 2.02 (3H, s); IR 3031, 2870, 1761, 1497, 1454 cm^{-1}; MS 229 (MH^+).

A small amount of the product was converted to erythritol tetraacetate (i. H_2, Pd/C. ii. Ac_2O/pyridine), and the structure was confirmed by NMR spectroscopy.[23b]

(3*S*,4*R*)-5-(Benzyloxy)-3,4-dihydroxy-1-pentanenitrile (18). The cyclic sulfate **5** (0.26 g, 0.62 mmol) was treated with TBAF·3H_2O (0.29 g, 0.93 mmol) in THF (10 mL) as described above. Potassium cyanide (0.20 g, 3.1 mmol) was added and the mixture was heated to reflux for 24 h. Concentrated sulfuric acid (0.12 mL, 2.1 mmol) was added (Warning: HCN gas. The reaction should be performed in a fume hood) and the mixture was stirred at rt for 3 h. Extractive workup (EtOAc–$NaHCO_3$) was followed by chromatographic purification (hexane–EtOAc 1:1) to yield the title compound as an oil (100 mg, 70%): $[\alpha]_D$ −1.15° (*c* 0.39, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.38–7.26 (5H, m), 4.57 (2H, s), 4.02–3.94 (1H, m), 3.81–3.70 (1H, m), 3.68–3.65 (2H, m), 2.75, 2.62 (2H, ABX, *J* = 15.8, 6, 5 Hz), 1.68 (2H, br); IR 3441, 2920, 2870, 2254, 1497, 1454 cm^{-1}; MS 222 (MH^+).

A small amount of the product was peracetylated to afford (3*S*,4*R*)-5-(benzyloxy)-3,4-diacetoxy-1-pentanenitrile: ^{1}H NMR ($CDCl_3$) δ 7.40–7.26 (5H, m), 5.34–5.20 (2H, m), 4.58, 4.48 (2H, AB, *J* = 10 Hz), 3.62 (2H, d, *J* = 4.3 Hz), 2.88, 2.79 (2H, ABX, *J* = 15, 6, 5 Hz), 2.13 (3H, s), 2.07 (3H, s).

(2*R*,3*R*)-1-(Benzyloxy)-4-iodo-2,3-butanediol (19). The cyclic sulfate **5** (0.27 g, 0.63 mmol) was treated with TBAF·3H_2O (0.23 g, 0.73 mmol) in THF (10 mL) as described above. Sodium iodide (0.48 g, 3.2 mmol) and glacial acetic acid (0.18 mL, 3.2 mmol) were added and the mixture was stirred at rt for 2 h. Concentrated sulfuric acid (0.035 mL, 0.63 mmol) was added and the mixture was stirred at rt for 1 h. Brine (60 mL) and EtOAc (60 mL) were added and the phases were separated. The aqueous phase was further extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with 10% sodium thiosulfate and dried ($MgSO_4$). Column chromatography of the crude product (hexane–EtOAc 2:1) afforded the product **19** as a white solid (180 mg, 85%): $[\alpha]_D$ 5.93° (*c* 0.27, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.35–7.34 (5H, m), 4.57 (2H, s), 3.78 (2H, m), 3.67 (2H, m), 3.52 (2H, m), 2.47 (2H, br); IR 3367, 3226, 2870, 1454 cm^{-1}; MS 323 (MH^+).

(2*R*,3*S*)-1-(Benzyloxy)-2,3-dihydroxy-6-phenylhex-5-yne (20). Conditions A. The cyclic sulfate **5** (0.51 g, 1.22 mmol) was treated with TBAF·3H_2O (0.58 g, 1.83 mmol) in THF (10 mL) as described above. The mixture was cooled to −70 °C and lithium phenylacetylide (1 M solution in THF, 12.2 mL, 12.2 mmol) was added followed by BF_3·OEt_2 (0.75 mL, 6.1 mmol). The mixture was stirred at −70 °C for 1 h and then slowly warmed to −30 °C, where it was stirred for 2.5 h. Concentrated sulfuric acid (0.68 mL, 12.2 mmol) was added and the mixture was warmed to rt where it was stirred for 1 h. Extractive workup (EtOAc–$NaHCO_3$) was followed by column chromatography (hexane–EtOAc 1:1) to yield the product **20** as a solid (0.30 g, 84%): mp 69–71 °C; $[\alpha]_D$ 8.14° (*c* 0.86, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.54–7.26 (10H, m), 4.58 (2H, s), 3.93–3.80 (2H, m), 3.80–3.68 (2H, m), 2.76 (2H, d, *J* = 5.4 Hz), 2.55 (2H, br); IR 3231, 3061, 1491, 1453 cm^{-1}; MS 297 (MH^+).

Conditions B. The cyclic sulfate **5** (0.67 g, 1.59 mmol) was treated with TBAF·3H_2O (0.52 g, 1.65 mmol) in THF (10 mL) as described above. The solvent was evaporated on a rotary evaporator, and the mixture was further concentrated with the aid of dichloromethane (2 × 20 mL). Finally the mixture was dried under high vacuum for 2 h. The flask was then equipped with a septum and the residue was redissolved in dry THF (10 mL). The solution was cooled to −70 °C, and lithium phenylacetylide (1 M, 3.0 mL, 3 mmol) was added followed by BF_3·OEt_2 (0.36 mL, 3 mmol). The mixture was stirred at −70 to −30 °C as described above. Acidic workup and chromatographic purification as described above afforded the product **20** (0.34 g, 72%).

(2*R*,3*S*)-1-(Benzyloxy)-2,3-octanediol (22). Conditions A. A round-bottomed three-necked flask was charged with CuI (1.14 g, 6.0 mmol). THF (15 mL) was added and the mixture was cooled to −40 °C. Butyllithium (1.6 M in hexane, 7.5 mL, 12 mmol) was added slowly and the mixture was stirred at −40 °C for 30 min.

Meanwhile, the cyclic sulfate **5** (0.25 g, 0.6 mmol) was treated with TBAF·3H_2O (0.21 g, 0.66 mmol) in THF (10 mL) as described above. The mixture was cooled to −40 °C and then added via syringe to the Bu_2CuLi solution prepared above. The mixture was stirred at −40 °C for 6 h. Sulfuric acid (20%, 6.7 mL) was slowly added and the mixture was warmed to rt where it was stirred overnight. Saturated ammonium chloride solution (10 mL) was added and the mixture was further stirred for 1 h. Extractive workup with EtOAc and $Na_2S_2O_3$ as described above for the synthesis of **19**, followed by column chromatography (hexane–EtOAc 1:1) yielded the product **22** as a waxy solid (105 mg, 70%): $[\alpha]_D$ −8.77° (*c* 0.57, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.37–7.32 (5H, m), 4.56 (2H, s), 3.80–3.63 (4H, m), 2.72 (1H, br), 2.28 (1H, br), 1.58–1.24 (8H, m), 0.89 (3H, t, *J* = 6.5 Hz); IR 3342, 3034, 2967, 2917, 1453 cm^{-1}; MS 253 (MH^+).

Conditions B. The cyclic sulfate **5** (0.21 g, 0.5 mmol) was treated with TBAF·3H_2O (0.165 g, 0.52 mmol) in THF (10 mL) and then the solvent was removed as described above. The residue

(23) (a) Due to the possibilities of ester hydrolysis and/or migration (transesterification) during the acidic workup, the crude product at this stage may contain the triol and secondary acetates. To simplify the product isolation, the crude product was therefore peracetylated. As a consequence, the exact course of the reaction, i.e., the position of the nucleophilic attack, was not fully established in this case. (b) The comparison with known erythritol tetraacetate confirms the *relative* but not the absolute stereochemistry of product **17** and its triacetate, since erythritol tetraacetate is achiral. Judging from the intermediacy of **7**, however, the configurations are most likely to be 2*R*,3*S*.

was redissolved in THF (15 mL) and the solution was treated with Bu_2CuLi (1 mmol, as prepared above) at −40 °C. Workup and purification was performed as above to afford the product **22** (92 mg, 73%).

(2*R*,3*S*)-1-(Benzyloxy)-2,3-butanediol (23). The cyclic sulfate **5** (0.78 g, 1.85 mmol) was treated with TBAF·$3H_2O$ (0.87 g, 2.77 mmol) in THF (10 mL) as described above. The mixture was cooled to −50 °C and LAH (1 M in THF, 7 mL, 7 mmol) was added dropwise followed by BF_3·OEt_2 (0.43 mL, 3.5 mmol). The mixture was stirred at −50 °C for 4 h. Concentrated sulfuric acid (1 mL, 18 mmol) was added and the mixture was slowly warmed to rt, where it was stirred overnight. Extractive workup (EtOAc–$NaHCO_3$) was followed by chromatographic purification (hexane–EtOAc 1:2) to yield the product **23** as an oil (0.30 g, 84%): $[\alpha]_D$ −7.2° (*c* 1.02, EtOH, lit.[3a] $[\alpha]_D$ −7.2°); ^1H NMR ($CDCl_3$) δ 7.38–7.26 (5H, m), 4.55 (2H, s), 3.92–3.80 (4H, m), 3.74–3.60 (3H, m), 2.45 (2H, br), 1.18 (3H, d, J = 6.5 Hz); IR 3409, 3031, 2974, 2912, 2870, 1497, 1454 cm^{-1}; MS 197 (MH^+).