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Cyclic Sulfites and Cyclic Sulfates in Organic Synthesis

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Contents

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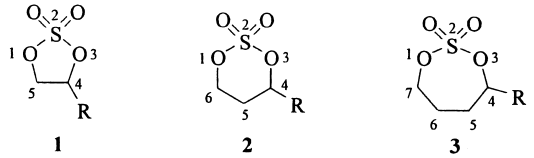
1. Introduction

Although cyclic sulfate esters have been known since 1932,[1] the lack of an efficient method for preparing cyclic sulfates limited their applications. The oxidation of cyclic sulfites with sodium periodate catalyzed by ruthenium tetroxide[2] represents an important development that has broadened the use of cyclic sulfate intermediates in synthesis. The advent of the catalytic asymmetric dihydroxylation reaction provides a route to chiral 1,2-diols from a wide spectrum of olefins,[3] which can be further elaborated to cyclic sulfates.[4] The significant role of cyclic sulfates in organic synthesis originates from several properties. First, they have high reactivity toward various nucleophiles and are more reactive than epoxides. Second, they can activate nucleophilic attack at one position while serving as a protecting group at a second position; under more vigorous conditions they can serve as an activator for two sequential reactions. Third, the reactions of five-membered cyclic sulfates with nucleophiles provide two contiguous stereocenters; moreover, a remote stereocenter can be controlled by cyclic sulfates of 1,3- and 1,4-diols. Finally, since the intermediate of nucleophilic substitution is generally the salt form of a monosulfate ester, separation of the product from the nonsalt byproduct is typically a facile process.

2. Nomenclature

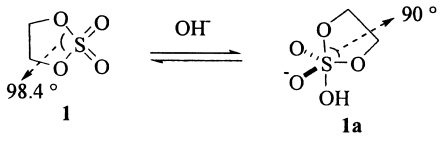
The IUPAC nomenclature system for heterocyclic systems[5] is used in the naming of cyclic sulfites and cyclic sulfates. The appropriate stem is selected according to the size of the ring and the degree of unsaturation. Since the ring contains two oxygen atoms and one sulfur atom, the prefix *dioxathi* is used; the suffixes 2-oxide and 2,2-dioxide are used to distinguish between cyclic sulfites and cyclic sulfates, respectively. The numbering of the ring begins with one oxygen atom and proceeds around the ring to give the lowest numbers possible to the other heteroatoms and substituents. For example, the IUPAC names of ethylene sulfate (**1**), trimethylene sulfate (**2**), and tetramethylene sulfate (**3**) are 1,3,2-dioxathiolane 2,2-dioxide, 1,3,2-dioxathiane 2,2-dioxide, and 1,3,2-dioxathiepane 2,2-dioxide, respectively. The IUPAC and trivial names were used together in the first Eighth Collective Volume of *Chem. Abstr.*, but the IUPAC name was used in *Chem. Abstr.* afterward. However, most authors tend to use the common names originating from the sulfate esters of alcohols.



1 **2** **3**

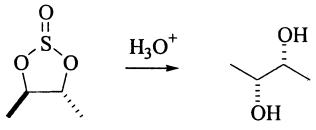
3. Reactivity

The carbon atoms in the cyclic sulfate moiety are highly reactive toward nucleophilic reagents. The enhanced reactivity relative to an acyclic sulfate may originate from two sources: (i) ring strain and (ii) partial double bond character between the ring oxygen atoms and the sulfur atom.[6a] Ring strain may arise from the difference in the internal O–S–O bond angle in the cyclic sulfate vs. that in the pentacoordinate intermediate. The internal O–S–O bond angle, as determined by X-ray crystallography,[7] is 98.4° in ethylene sulfate (**1**) and 97.1° in catechol cyclic sulfate. However, during alkaline hydrolysis of a cyclic sulfate, a pentacoordinate intermediate with an approximately trigonal-bipyramidal geometry such as **1a** may be formed. The ring angle at sulfur is ~90° when the five-membered ring spans one apical and one equatorial position (Eq. (1)[6c]). Relief of the ring-strain in the pentacoordinate state is supported by MO calculations.[8] The partial double bond character arises from either pπ–dπ dative π bonding interactions or 1,3-nonbonding interactions between the ring oxygen and the exocyclic oxygen. These interactions in cyclic sulfates may be essential for the kinetic acceleration observed in the hydrolysis of cyclic sulfates. The relative rates of hydrolysis in basic media decreased on going from catechol cyclic sulfate to ethylene sulfate to dimethyl sulfate.[6]

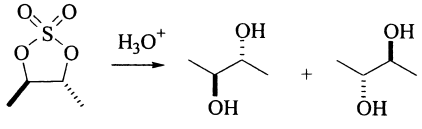


1 **1a** (1)

With cyclic sulfites, the presence of an unshared pair of electrons on sulfur partially represses the double-bond character of the sulfur atom and the ring oxygen atoms. Thus, cyclic sulfites and cyclic sulfates are expected to display different reactivities. In the nucleophilic substitution of cyclic sulfites, attack at the sulfur atom competes with substitution at carbon; however, in cyclic sulfates this competing reaction is only observed when the carbon-centered S_N2 chemistry is severely hindered. For example, hydrolysis of the cyclic sulfite of D-(−)-2,3-butanediol (Eq. (2a)) takes place with retention of chirality, since water attacks the sulfur atom. In contrast, inversion takes place in the cyclic sulfate of the same butanediol, indicating that attack occurs mainly at the carbon atoms (Eq. (2b)).[9]



(2a)



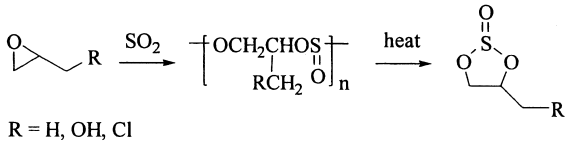
meso (2b)

4. Preparation

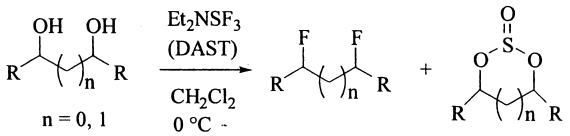
4.1. Preparation of cyclic sulfites

4.1.1. Via non-chiral induction at the sulfur atom. Cyclic sulfites have been prepared by the reaction of epoxides with sulfur dioxide and by the reaction of 1,2- or 1,3-diols with Et_2NSF_3 (DAST) (Eq. (3)).[10] The most efficient synthesis of cyclic sulfites is the reaction of thionyl chloride with a diol[11] or transesterification of a dialkyl sulfite with a diol (Eq.

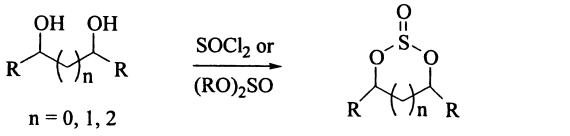
(4)).[12] The neat reaction of ethylene glycol with thionyl chloride furnished ethylene sulfite in moderate yields; however, the yield was improved by the addition of methylene chloride.[9] It is necessary to expel hydrogen chloride formed during the reaction by heating the reaction mixture or by using a stream of nitrogen. Two preparations of 3-*O*-benzylglycerol 1,2-cyclic sulfite have been reported: (i) by reaction of 3-*O*-benzylglycerol with thionyl chloride at −78°C, giving the desired cyclic sulfite in quantitative yield,[13] (ii) by slow addition of thionyl chloride to a solution of 3-*O*-benzyl-*sn*-glycerol in carbon tetrachloride at reflux, furnishing the cyclic sulfite in high yield.[14] In the reaction of thionyl chloride with substrates that contain an acid-labile functionality (such as the bisacetonide shown in Eq. (5)), a base such as triethylamine, imidazole, or pyridine is required to scavenge the hydrogen chloride liberated during the reaction.[15]



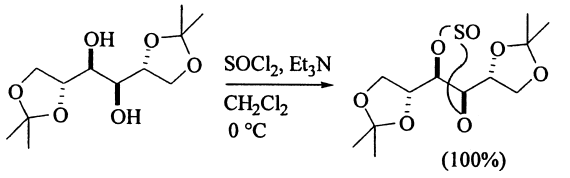
(3a)



(3b)

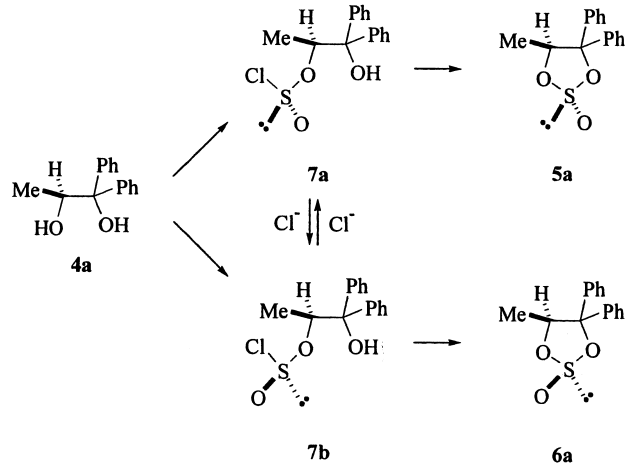


(4)

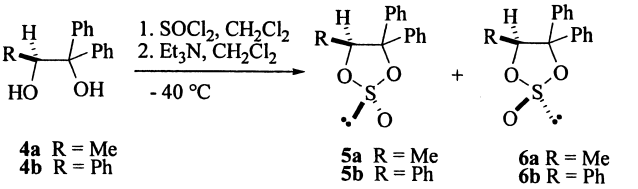


(5)

4.1.2. Via chiral induction at the sulfur atom. Since the sulfur atom in dialkyl sulfites has tetrahedral geometry, some sulfites are stereoisomeric.[16] Slow addition of triethylamine to a solution of thionyl chloride and (*S*)-1,1-diphenylpropane-1,2-diol (**4a**) in CH_2Cl_2 at −40°C gave a 90:10 diastereomeric mixture of (2*R*,5*S*)-*trans*-4,4-diphenyl-5-methyl-1,3,2-dioxathiolane 2-oxide (**5a**) and its epimer **6a** (Eq. (6)).[17] However, a change in the order of addition (adding $SOCl_2$ to diol **4a** and Et_3N at −40°C) provided a 1:1 mixture of the two diastereomers. Since cyclic sulfites are formed via a chlorosulfite intermediate,[16] it was postulated that the chlorosulfite was formed preferentially at the secondary hydroxy site. To explain the favored formation of *trans*-sulfite **5a**, two mechanisms have been proposed (Scheme 1). First, a slow and stereoselective reaction of diol **4a** with thionyl chloride provides chlorosulfite **7a**, which cyclizes with inversion of stereochemistry at the sulfur atom. Second, a slow cyclization of **7a** combined with an epimerization equilibrium between **7a** and **7b** furnishes **5a**. Rebiere et al.[17] favor the latter hypothesis, since the addition of triethylamine in the presence of *n*-Bu_4NCl improved the *trans*/*cis* ratio slightly (**5a**:**6a**=92:8). Similarly, the reaction of (*S*)-triphenylglycol (**4b**) with thionyl chloride gave chiral cyclic sulfites **5b** and **6b** in a *trans*/*cis* ratio of 90/10 (Eq. (6)).[18]



Scheme 1. Suggested possible mechanisms for the diastereoselective formation of *trans*-sulfite **5**.

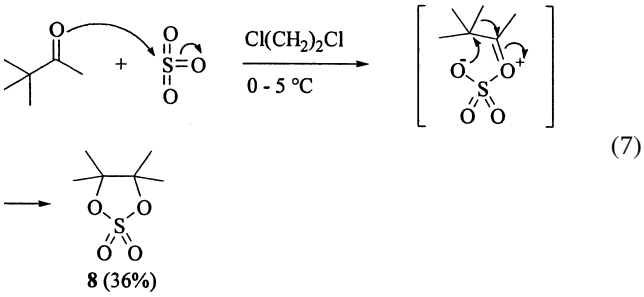


(6)

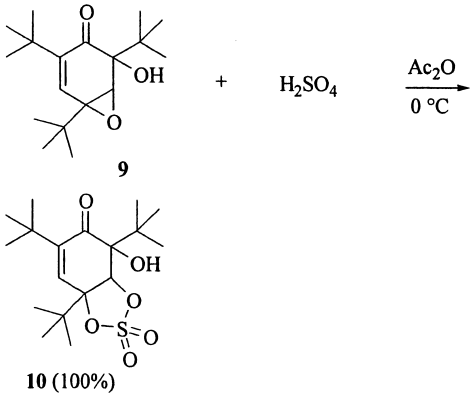
A typical procedure for the preparation of a diastereomeric cyclic sulfite such as **5a** is as follows.[17] To a solution of diol **4a** (46 g, 0.20 mol) in 300 mL of CH_2Cl_2 was added a solution of $SOCl_2$ (0.30 mol) in 100 mL of CH_2Cl_2, followed by a solution of Et_3N (67 mL, 0.50 mol) in 600 mL of CH_2Cl_2 at −40°C. After the reaction was quenched by the addition of 250 mL of H_2O, the product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated, and the residue was recrystallized from cyclohexane–hexane to give 38 g (67%) of **5a**.

4.2. Preparation of cyclic sulfates

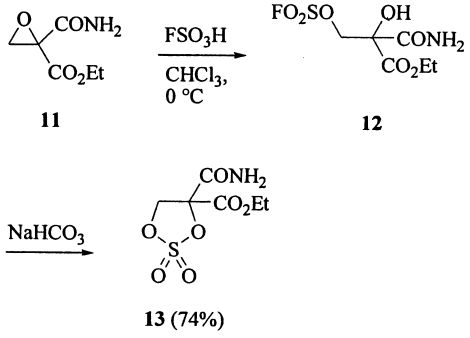
4.2.1. Via reaction with sulfate derivatives. Since the first reported synthesis of ethylene sulfate by the reaction of 1,2-dibromoethane and silver sulfate,[1] cyclic sulfates have been prepared by various methods. A retro pinacol-type rearrangement of pinacolone with sulfur trioxide at 0–5°C afforded 4,4,5,5-tetramethyl-1,3,2-dioxathiolane 2,2-dioxide (**8**) in 36% yield (Eq. (7)).[19] The reaction of 2,4,6-tri-*tert*-butyl-4,5-epoxy-6-hydroxy-2-cyclohexenone (**9**) with an equimolar amount of sulfuric acid gave cyclic sulfate **10** in 100% yield (Eq. (8)).[20] Opening of epoxide **11** with fluorosulfonic acid, a very poor nucleophile, provided fluorosulfate **12**, which upon treatment with base gave cyclic sulfate **13** in 74% yield (Eq. (9)).[21]



(7)

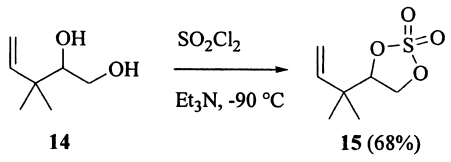


(8)

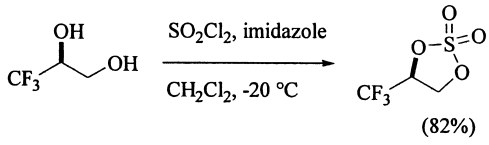


(9)

Cyclic sulfates have also been prepared by treatment of acyclic diols with sulfuryl chloride (SO_2Cl_2) at extremely low temperature, but only moderate yields were obtained because of the chlorinating nature of SO_2Cl_2.[22] For example, the reaction of SO_2Cl_2 with 3,3-dimethyl-4-pentene-1,2-diol (**14**) in the presence of triethylamine at −90°C provided cyclic sulfate **15** in 68% yield (Eq. (10a)).[23] Treatment of a diol containing an electron-withdrawing group at the carbon adjacent to the alcohol with SO_2Cl_2 provided a cyclic sulfate in good yield (Eq. (10b)).[24] Reaction of rigid diols such as methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, methyl 4,6-benzylidene-D-glucopyranoside, and 16-epi-estriol derivatives with sulfuryl chloride or diimidazolyl sulfate provided cyclic sulfates **16**–**19** in moderate yields.[25] The reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**20**) with 2 equiv. of phenyl chlorosulfate at room temperature afforded cyclic sulfate **18** (77% yield), whereas at −25°C the major product was 2-phenylsulfate **21** (79% yield). Addition of sodium hydride was needed for the formation of the cyclic sulfate **18** (Eq. (11)).[26]



(10a)



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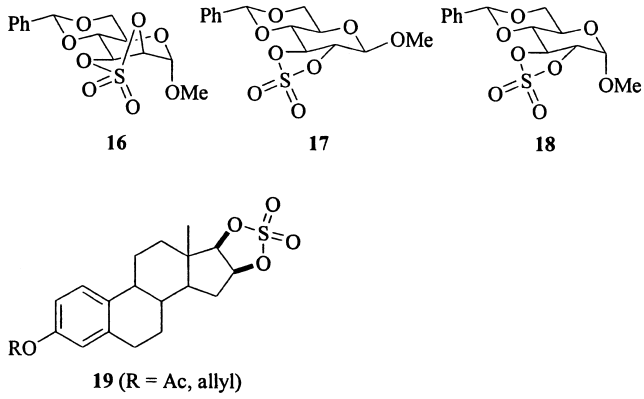
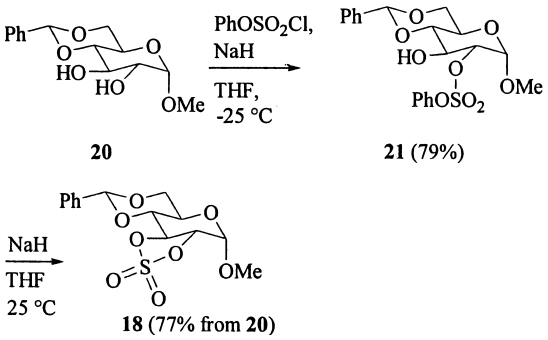
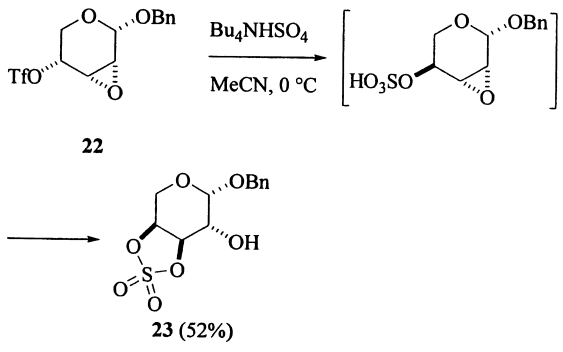




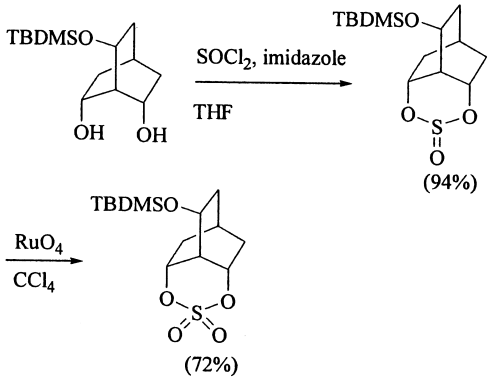
(11)

In the aforementioned methods of cyclic sulfate preparation, the configuration of the stereogenic centers in the parent diol substrate is conserved in the cyclic sulfate. However, treatment of epoxytriflate **22** with tetrabutylammonium hydrogen sulfate provided cyclic sulfate **23** with inversion of configuration (Eq. (12)).[27]



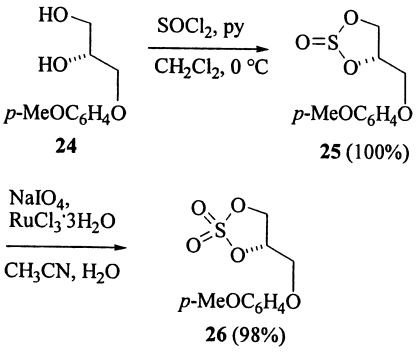
(12)

4.2.2. Via oxidation of cyclic sulfites. The reaction of acyclic diols with SO_2Cl_2 often provides low yields of cyclic sulfates. Therefore, these cyclic sulfates are prepared by other methods, such as oxidation of cyclic sulfites. The oxidation of the sulfite with potassium permanganate was performed in a biphasic system (e.g. H_2O and CH_2Cl_2) to avoid further reaction and decomposition of the sulfate product.[25] Alternatively, the oxidation of cyclic sulfites with a stoichiometric amount of ruthenium tetroxide furnishes cyclic sulfates in satisfactory yield (Eq. (13));[28] however, this procedure is expensive and is therefore limited to small-scale preparations. The discovery that a catalytic amount of RuO_4 is generated in situ by the reaction of ruthenium trichloride or ruthenium dioxide with sodium periodate made available an expedited route for the oxidation of cyclic sulfites.[2]



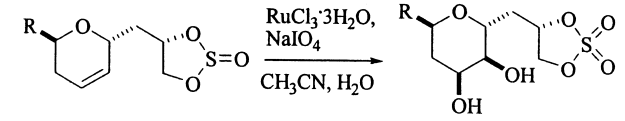
(13)

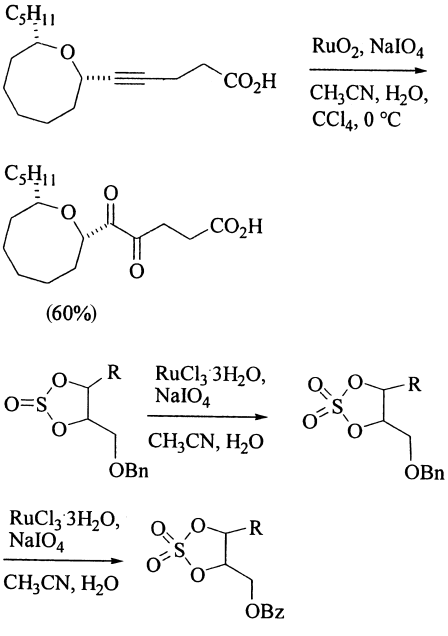
A typical procedure for the preparation of (*R*)-1-(4′-methoxyphenyl)glycerol 2,3-cyclic sulfate (**26**) is as follows (Eq. (14)).[29] To an ice-cooled solution of 6.9 g (35 mmol) of (*R*)-1-(4′-methoxyphenyl)glycerol (**24**) and 7.7 g (97 mmol) of pyridine in 100 mL of CH_2Cl_2 was added 3.5 mL (48 mmol) of $SOCl_2$. The reaction mixture was stirred at 0°C for 30 min and then filtered through a pad of silica gel, which was washed with hexane–EtOAc (2:1). The filtrate was concentrated in a rotary evaporator, and the residue was dried using a vacuum pump (1 h, 0.5 Torr). Cyclic sulfite **25** (8.5 g, 100% yield) was obtained as a mixture of two diastereoisomers (colorless oil, R_f 0.70, 0.64; hexane/EtOAc 2:1). To a solution of the cyclic sulfite in 100 mL of CH_3CN were added 10.4 g (48.7 mmol) of crystalline $NaIO_4$ and 80 mg (0.35 mmol) of $RuCl_3 \cdot 3H_2O$ in 20 mL of H_2O. After the purple suspension was stirred at room temperature for 20 min, 80 mL of H_2O and 100 mL of Et_2O were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2×100 mL). The combined ether layer was dried over Na_2SO_4, the solvents were evaporated (2-PrOH was used to remove the residual H_2O), and the residue was further dried under vacuum to give 8.9 g (98%) of pure (*R*)-1-(4′-methoxyphenyl)glycerol 2,3-cyclic sulfate (**26**) as a white solid: mp 90.0–91.0°C; R_f 0.46 (hexane/EtOAc 2:1).



(14)

4.2.3. Limitations of the catalytic oxidation approach. Since RuO_4 is a powerful oxidizing agent, it is important to consider what functionalities can survive the catalytic oxidation of cyclic sulfites. Ruthenium tetroxide cleaves C=C bonds, precluding application of the catalytic method to alkenes and alkynes. Simultaneous oxidation of the alkene and cyclic sulfite in **27** provided the desired dihydroxy cyclic sulfate **28** in a single step.[30] Non-terminal alkynes are oxidized without cleavage of the C≡C bond, yielding vicinal diketones (Eq. (15)).[31] Thus, a cyclic sulfate containing a triple bond cannot be prepared by this method.[32] Ruthenium tetroxide can also oxidize methylene groups bearing an oxygen and nitrogen atom. However, the benzyl ether moiety was stable during the short reaction time (20 min).[33] Upon longer exposure to the oxidation conditions, benzyl ethers undergo oxidation to benzoate esters (Eq. (16)).[33] The methoxymethyl (MOM)[32] (e.g. in **29**) and 2-methoxyethoxymethyl (MEM)[34] protecting groups also survived the oxidation conditions.

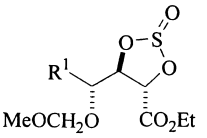




(15)

(16)

Catalytic oxidation of a cyclic sulfite to the corresponding sulfate could not be achieved in the presence of an amine or pyridine[15] or a hydroxamate functionality such as in **30**.[35] However, the azide group in **31**,[36] amide in **32**,[2] and carbamate in **33**[37] did not affect the oxidation.



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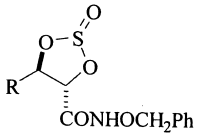

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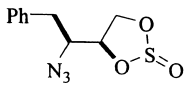

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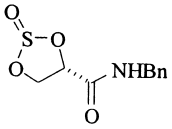

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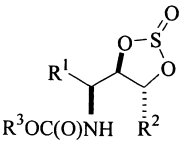

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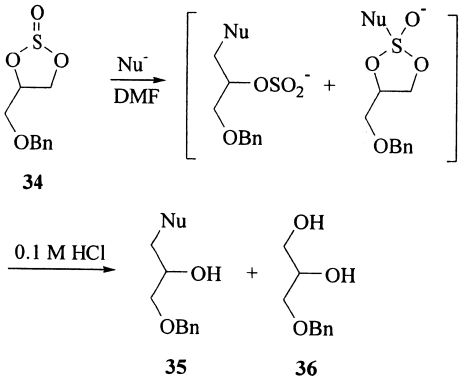
5. Reactions

5.1. Regioselectivity of nucleophilic substitution

We consider here the regioselective nucleophilic ring opening of 3-*O*-benzyl 1,2-cyclic sulfite (**34**) and 1-(4′-methoxyphenyl)-glycerol 2,3-cyclic sulfate (**37**). These substrates have been chosen because one of the carbon atoms of the cyclic ester groups is a primary and the other is a secondary carbon. In addition to nucleophilic substitutions by external nucleophiles, intramolecular opening and Payne rearrangement of cyclic sulfates are also emphasized in view of their different regioselectivities.

5.1.1. Intermolecular opening of cyclic sulfites. Nucleophiles attack the sulfite **34** exclusively at C-1 or the sulfur positions, even though **34** possesses three different reacting sites (i.e., C-1, C-2, and the sulfur atom) (Eq. (17)).[13] If the nucleophile attacks the sulfur atom of the sulfite, 3-*O*-benzylglycerol (**36**) is recovered after hydrolysis. The regioselectivity depends on the nature of the nucleophile. For example, in the reactions of sodium phenoxide, sodium thiophenoxide, sodium azide, sodium cyanide, benzylamine, and isopropylamine, attack takes place exclusively at the C-1 atom. However, in the reactions of the sodium salts of benzylamine, aniline, benzyl alcohol, and benzylmercaptan, attack occurs at both the sulfur and the C-1 atoms, giving 3-*O*-benzylglycerol (**36**) and the C-1 product **35** in a ratio of **36**:**35**=9:1, 3:1, 1:6, and 1:18, respectively. The differences in the regioselectivity of the nucleophiles may be explained in terms of the hard and soft acid and base principle (HSAB principle).[13] Since polarizability is considered intrinsically associated with chemical softness, the observed regioselectivities may arise from changes in softness because of reduced polarizability. The harder, less polarizable ions (such as $BnNH^-$, $PhNH^-$, BnO^-, BnS^-) display an increased reactivity toward the harder sulfite sulfur-atom site relative to the soft C-1 site.[13]



34

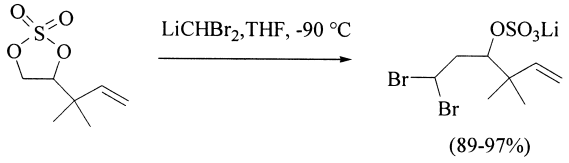
35 **36**

(17)

Nu = PhO^-, PhS^-, N_3^-, NC^-, $BnNH_2$, *i*-$PrNH_2$

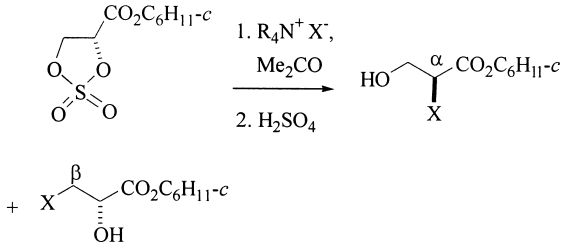
Nu = $BnNH^-$, $PhNH^-$, BnO^-, BnS^-

5.1.2. Intermolecular opening of cyclic sulfates. The regioselectivity in the ring opening of both cyclic sulfates and epoxides is controlled simultaneously by the steric interaction between the substrates and nucleophiles and by the electronic distribution of the substrates. For instance, Eq. (18) shows a typical example in which the regioselectivity of the reaction was controlled by the steric hindrance of the substrate. On the other hand, Eq. (19) exemplifies a reaction in which the electronic distribution of the substrate or the transition state instead of steric hindrance was the predominating factor controlling the regioselectivity of the reaction.



(89-97%)

(18)



1. Et_4NF: α/β = 6/1
2. Bu_4NCl: α/β = 5/1

(63-95% overall yield)

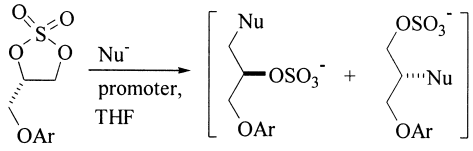
(19)

To demonstrate the advantageous properties of a cyclic sulfate, ring-opening reactions of cyclic sulfate **37** and epoxide **40** with various nucleophiles as shown in Eqs. (20) and (21)[29,38] are compared. The results are summarized in Table 1.[29,38] The reactions of **37** and **40** with sodium azide provided azido alcohols **38** and **39**. The ratio of **38**:**39** was 19:1 in the reaction of **37** with azide ion, and 53:1 in the glycidol opening reaction.[29] Ring openings of both **37** and **40** with *n*-$C_{16}H_{33}SH$ gave excellent yields of **38**.[29] However, when 1-hexadecylamine was refluxed with the glycidol in ethanol, a complex mixture was obtained.[29] This was

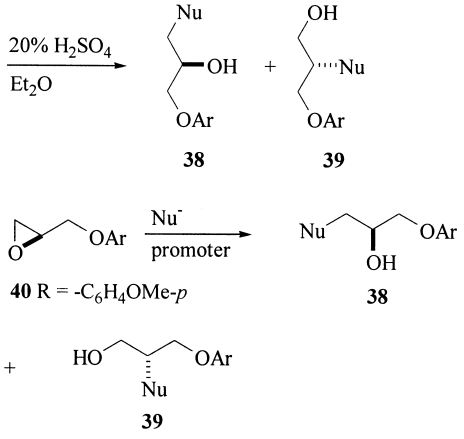
Table 1. Opening of cyclic sulfate **37** and glycidol **40** with nucleophiles

Cyclic sulfate **37**		Epoxide **40**		
Nucleophile	Yield of **38** (%)	Nucleophile	Promoter	Yield of **38** (%)
N_3^-	95	N_3^-	NH_4Cl	96
$C_{16}H_{33}SLi$	94	$C_{16}H_{33}SH$	$NaBH_4$	93
$C_{16}H_{33}OLi$	90	$C_{16}H_{33}OH$	$BF_3{\cdot}OEt_2$	50
$C_{16}H_{33}NH_2$	95	$C_{16}H_{33}NH_2$	$Ti(OPr\text{-}i)_4$	–
$C_{13}H_{27}{-}{\equiv}{-}Li$	90	$C_{13}H_{27}{-}{\equiv}{-}H$	$BF_3{\cdot}OEt_2$	65

presumably due to polyalkylation of the amine. Reaction of glycidol **40** with cetyl alcohol in the presence of $BF_3{\cdot}Et_2O$ was incomplete (50% yield). In contrast, reaction of cyclic sulfate **37** with cetyl alcohol mediated by *n*-BuLi provided product **38** in excellent yield (90%). Similar results were observed in the reactions of **37** and **40** with lithium pentadecyne (Table 1).



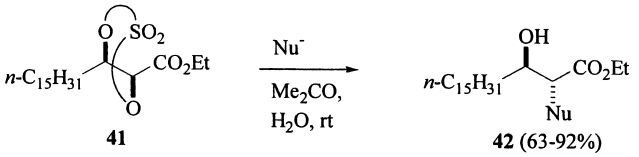
37 Ar = -C_6H_4OMe-*p* (20)



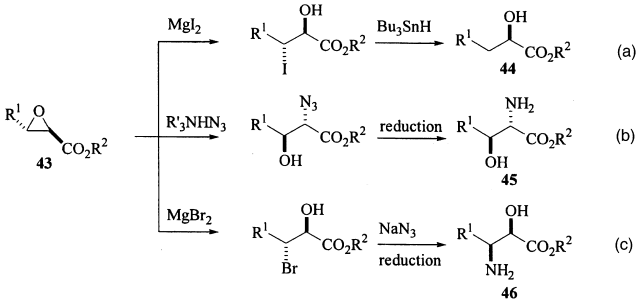
(21)

The substituent electronic effect of the substrate is more obvious in the opening reactions of epoxides. The reaction of cetyl alcohol with glycidol tosylate catalyzed by $BF_3{\cdot}OEt_2$ produced exclusively 1-*O*-hexadecyl-*sn*-glycerol tosylate; the same reaction with *tert*-butyldiphenylsilyl glycidol gave 1-*O*-hexadecyl-3-*tert*-butyldiphenyl-*sn*-glycerol and its regioisomer (even at 0°C) in a ratio of 9:1.[39] The substituent electronic effect can be explained by the fact that the ring opening of epoxides proceeds by a borderline S_N2 mechanism in which the S_N2 transition state possesses substantial S_N1 character.[40] Thus, the electronic effect contributed to the regioselectivity in the nucleophilic substitution of epoxides.

α,β-Dihydroxy ester cyclic sulfate **41** undergoes nucleophilic attack at the α-position almost exclusively (Eq. (22)), whereas with α,β-epoxyester **43** (R_1=a long-chain hydrocarbon) attack occurs at either the α- or β-position, depending on the reaction conditions used.[41–43] For example, epoxyester **43** was opened regioselectively: (1) at the β-position with MgI_2, giving an intermediate which upon reduction with Bu_3SnH provided α-hydroxyester **44** (Eq. (23a));[41] (2) at the α-position with R_3NHN_3, giving an intermediate that was converted to 2-amino-3-hydroxyester **45** after reduction of the azido functional group (Eq. (23b));[42] (3) at the β-position with $MgBr_2$, giving an intermediate that underwent azide substitution and reduction to afford 3-amino-2-hydroxyester **46** (Eq. (23c)).[43]



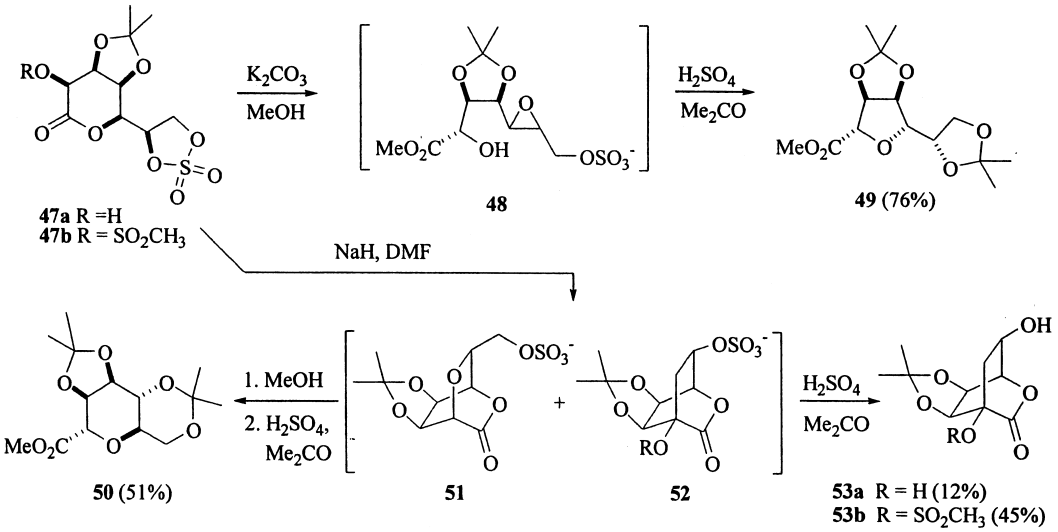
$Nu^- = H^-, N_3^-, PhCO_2^-, SCN^-, F^-$ (22)



(23)

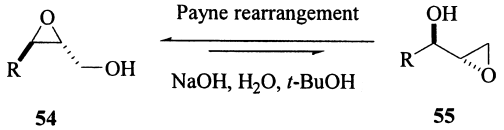
5.1.3. Intramolecular opening of cyclic sulfates. Treatment of cyclic sulfate **47** with base resulted in the formation of a complex mixture of tetrahydrofuran **50**, tetrahydropyran **49**, and cyclohexane **53** derivatives (Scheme 2).[44] Intramolecular nucleophilic attack can take place at either the primary or secondary carbon atoms of the cyclic sulfate. The synthesis of **49** from **47a** involves overall inversion of configuration at C-5 and C-6 of lactone **47a**. In order to prepare tetrahydropyran **50** from **47a**, nucleophilic opening of the lactone ring by base should be avoided, except for removal of the proton from the C-2 hydroxy group. Treatment of **47a** with sodium hydride in DMF, followed by acidic workup, gave tetrahydropyran diacetonide **50** in 51% yield, together with the carbocyclic lactone **53a** in 12% yield.[44] The yield of carbocycle **53** was improved (e.g. **53b** in 45% yield) when pyran formation was blocked by masking the C-2 hydroxy group (e.g. by use of a methanesulfonyl group) before sodium hydride treatment.

5.1.4. Payne rearrangement of cyclic sulfates. In the Payne rearrangement,[45] a 2,3-epoxy-1-ol **54** equilibrates with the isomeric 1,2-epoxy-3-ol **55** in a protic solvent in



Scheme 2. Intramolecular nucleophilic substitution of cyclic sulfate **47**.

the presence of aqueous sodium hydroxide. The terminal 1,2-epoxy-3-ol **55** can be captured selectively and irreversibly by a nucleophile such as a mercaptan (Eq. (24)).[46] Treatment of 1-*O*-*tert*-butyldimethylsilyltriol 2,3-cyclic sulfate **57** with *n*-Bu_4NF (TBAF) furnished a 1,2-epoxy-3-sulfate **58**, which can react with various nucleophiles (Eq. (25)).[47] This process is analogous to the Payne rearrangement of 2,3-epoxy-1-ol **54**. The difference between the two rearrangements is that the sulfate method is an irreversible process because the 3-hydroxy group in **58** is protected in situ as a sulfate ester. Reaction of 1,2-epoxy-3-sulfate **58** with nucleophiles took place exclusively at C-1. Even substrates containing an aryl or alkyl substituent at the C-3 position such as **57a**,**b** produced *erythro*-2,3-diols **56a**,**b** exclusively (Eq. (25)). In contrast to the rearrangement of **57**, nucleophilic attack of epoxy alcohol **54**, **55** is regioselective only when the competitive C-3 opening is suppressed.



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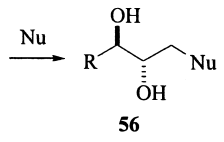

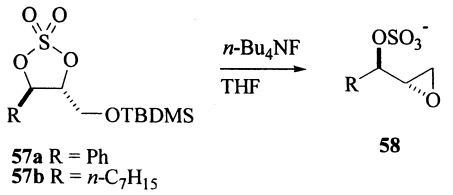

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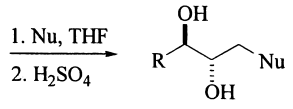
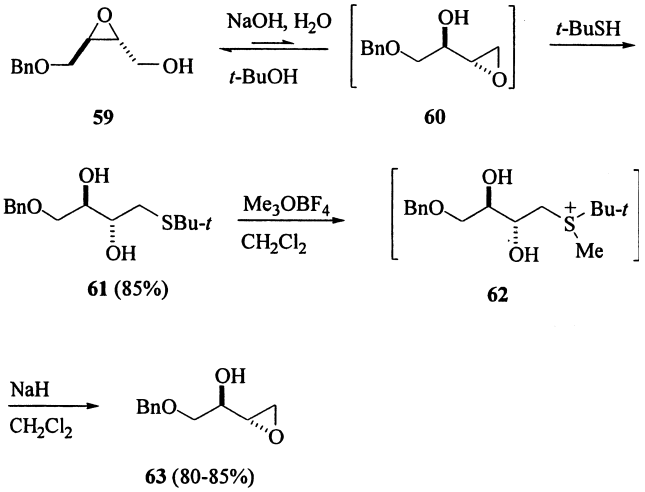


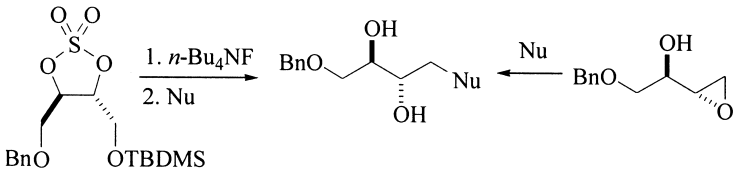
56a R = Ph (Nu = PhSH, 82%)
56b R = *n*-C_7H_{15} (Nu = PhSH, 86%)



Scheme 3. Synthesis of 1,2-epoxy-3-ol **63** from 2,3-epoxy-1-ol **59**.

In the rearrangement of 2,3-epoxy-1-ol **54**, the rate of addition of mercaptan is important to control the regioselectivity. A faster rate of mercaptan addition depleted 1,2-epoxy-3-ol **55**, resulting in increased formation of C-2 and/or C-3 opened products, whereas a slower rate gave lower yields attributable to the formation of triol via opening of epoxide **55** by hydroxide ion.[46] Since the cyclic sulfate rearrangement processes are usually performed in THF, a variety of nucleophiles can be used. Because the epoxy alcohol rearrangement processes are often performed in aqueous alkaline solution at high temperature, nucleophiles such as cuprates, organolithiums, metal hydrides, etc., are not applicable. In order to avoid formation of undesired C-3 opening products in the opening of a 2,3-epoxy alcohol, 1,2-epoxy-3-ol **63** must be prepared by the following sequence of reactions (Scheme 3): treatment of

Table 2. Payne rearrangement of cyclic sulfate **64** and 1,2-epoxy-3-ol **63**



Nucleophile	Yield of **65** from **64** (%)	Yield of **65** from **63** (%)
N_3^-	81	83
CN^-	70	89
R_2CuLi	73 (R=Bu)	75 (R=Me)
$LiAlH_4$	84	75
R—≡—Li	84 (R=Ph)	55 (R=CH_2OTHP)

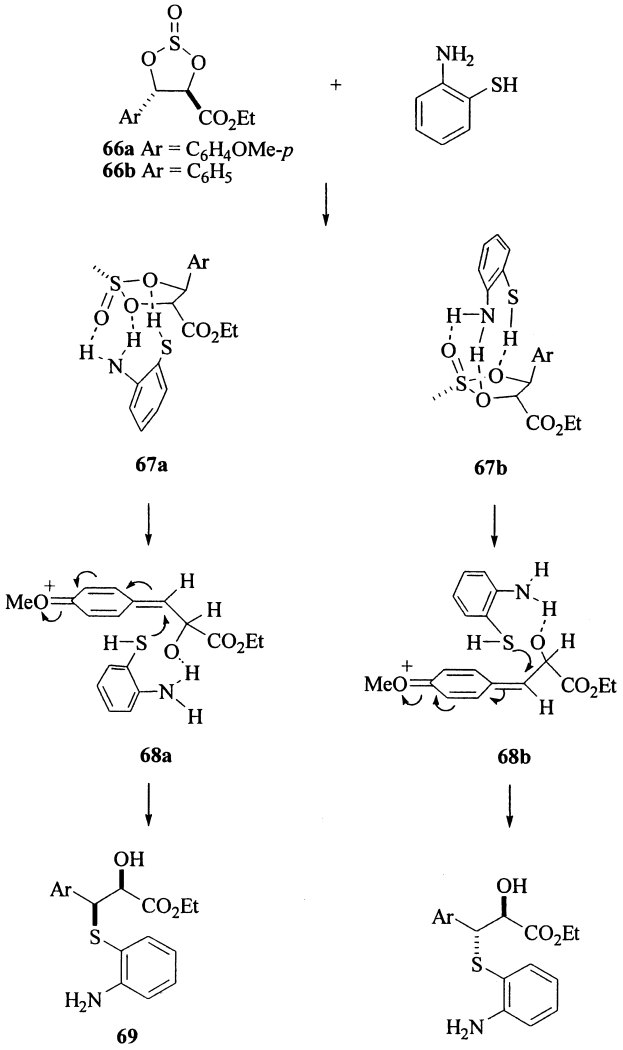
the 2,3-epoxy alcohol **59** with bulky *tert*-butyl thiol under the rearrangement conditions gave 2,3-diol **61**; reaction of the latter with Meerwein's reagent (Me_3OBF_4) afforded methyl sulfonium salt **62**, which provided **63** on treatment with a base.[46]

Table 2 shows the yields obtained for nucleophilic attack on the 1,2-epoxy-3-*O*-sulfate generated by Payne rearrangement of **64**. Also shown are the yields for reaction with **63**. The isolated 1,2-epoxy-3-ol was reacted with various nucleophiles, and the results are compared with cyclic sulfate rearrangement (Table 2). Cyclic sulfate rearrangement requires additional steps, but gave a higher overall yield than that of the corresponding 2,3-epoxy alcohol rearrangement.

5.2. Stereoselectivity of sulfite and sulfate opening

Since most ring-opening reactions of cyclic sulfites and cyclic sulfates with nucleophiles proceed by the S_N2 pathway with inversion at the reacting stereogenic center, it is noteworthy to discuss the stereoselectivity of an abnormal case. Reaction of chiral cyclic sulfite **66a** and *o*-aminothiophenol in toluene afforded ethyl (2*S*,3*S*)-2-hydroxy-3-(*o*-aminophenyl)thio-3-(*p*-methoxyphenyl)propionate (**69**) as the major product (Scheme 4).[48] In this reaction, the nucleophile approaches from the same face as the leaving group of the cyclic sulfite, and net retention of configuration was observed. However, the reaction of cyclic sulfite **66a** with thiophenol provided ethyl 2-hydroxy-3-(phenylthio)-3-(*p*-methoxyphenyl)propionate (10%) and ethyl (*p*-methoxybenzyl)acetate (15%). In contrast, when cyclic sulfite **66b** was treated with either thiophenol or 2-aminothiophenol under identical experimental conditions, only decomposition of **66b** was observed. These results imply that the methoxy group in cyclic sulfite **66a** and the amino group in the nucleophile played an important role in the reaction.

In order to explain the result the following sequence of reaction was assumed. Addition of thionyl chloride to a mixture of ethyl (2*R*,3*S*)-3-(4′-methoxyphenyl)-2,3-dihydroxypropionate and pyridine provided a diastereomeric mixture of **66a** in a ratio of 60:40. The diastereomeric mixture was treated with 0.9 equiv. of aminothiophenol. Weak hydrogen bonding between the sulfite group in the substrate and the amino group in the nucleophile was proposed to provide transition state species **67a**,**b**. Hydrogen bonding was confirmed by ^1H NMR. Extrusion of SO_2 at elevated temperatures and anchimeric assistance of the

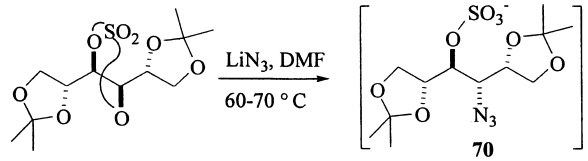


Scheme 4. Mechanism of the reaction of cyclic sulfite **66a,b** and 2-aminothiophenol.

p-methoxyphenyl group furnished intermediate **68a**,**b**. The intermediate **68a**,**b** underwent nucleophilic S_N^i type attack by the thiol lone pair of the aminothiophenol from the same face or from the opposite face, resulting in overall retention or inversion of configuration at the reacting stereogenic center.

5.3. Chemoselective hydrolysis of sulfates

The sulfate ester intermediate formed in the reaction of cyclic sulfates with nucleophiles is usually hydrolyzed with an equal volume of 20% aqueous sulfuric acid and Et_2O.[2] A chemoselective hydrolysis of sulfate esters in the presence of acid-labile groups was achieved by treating sulfate intermediate **70** in THF with a catalytic amount of concentrated sulfuric acid and 0.5–1.0 equiv. of water (Eq. (26)).[15] The use of a minimum amount of water is crucial to achieve the desired chemoselectivity. If the nucleophilic opening of cyclic sulfates in THF is fast enough, especially in the case of terminal diols or diols with an α-carbonyl group, both the opening and hydrolysis reactions can be accomplished in one pot, furnishing the desired alcohols in high yields (Eq. (27)).



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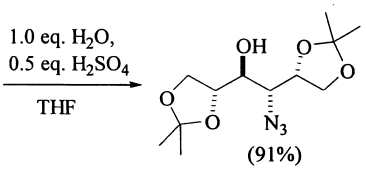
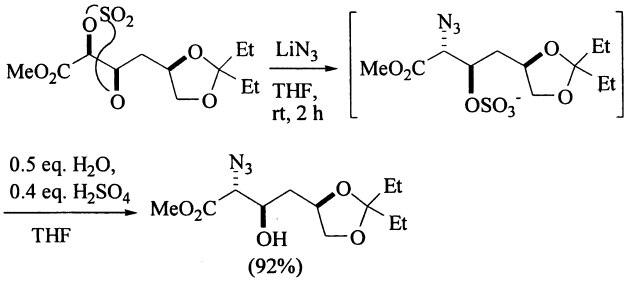
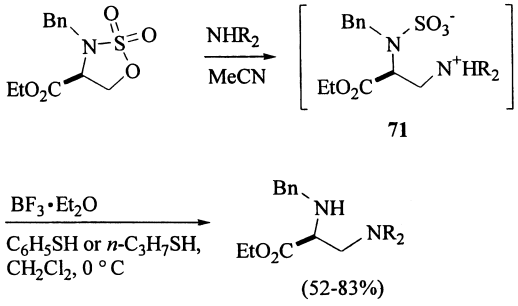




(27)

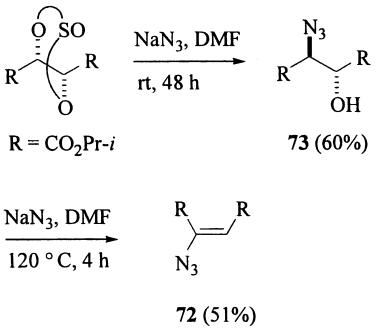
Hydrolysis of simple sulfamidates has been carried out by using aqueous hydrochloric acid or sulfuric acid.[49] After reaction of *N*-benzyl serine ethyl ester cyclic sulfamidate with amine nucleophiles (Eq. (28)), the hydrolysis of β-aminosulfamic acid **71** in aqueous mineral acids produced several products, presumably because of instability of the ester functionality under the reaction conditions.[50] Since the hydrolysis of sulfamic acids in aqueous acids is generally believed to proceed through an A2 mechanism,[51] the S–N bond cleavage must occur via nucleophilic attack of water at the sulfur atom. Since aliphatic and aromatic benzyl ethers are readily cleaved to alcohols upon treatment with $BF_3{\cdot}Et_2O$ and thiol,[52] this deprotection method was applied to the hydrolysis of sulfamidate. Indeed, treatment of the β-aminosulfamic acid **71** with $BF_3{\cdot}Et_2O$ and thiophenol followed by neutralization with ammonium hydroxide furnished the desired product in 65% yield (Eq. (28)).[50] In this reaction, the Lewis acid could activate the sulfamic acid through coordination from the nitrogen atom, and the thiol would serve as an excellent nucleophile for the sulfur atom, thus facilitating the cleavage of the S–N bond. Thiophenol was replaced by the more volatile 1-propanethiol, which provided almost the same result.



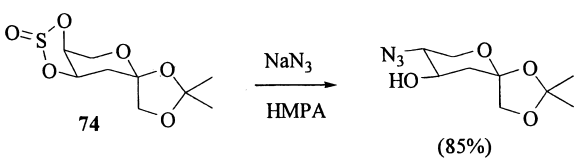
(28)

5.4. Reactions with nucleophiles

5.4.1. Nitrogen nucleophiles. Various cyclic sulfites react with sodium azide or lithium azide at elevated temperature, giving azido alcohols in high yield. The substitution reaction of a cyclic sulfite containing an ester group with sodium azide at 120°C afforded the elimination product **72** in 51% yield, whereas the same reaction at 20°C provided azido alcohol **73** in 60% yield (Eq. (29)).[53] Opening of cyclic sulfites obtained from partially protected sugars furnished azido sugars. Because the cyclic sulfite group is fused to the pyranose ring, nucleophiles replaced the axial sulfite group of 3,4- or 2,3-bicyclic sulfite **74** (Eq. (30)).[54] On the other hand, with 1,2-cyclic sulfite **75**, nucleophilic substitution took place at the anomeric sulfite group (Eq. (31)).[55]



(29)



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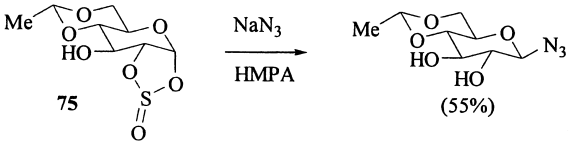


(31)

Table 3. Reactions of cyclic sulfites with nitrogen nucleophiles[35,54,55,112–116]

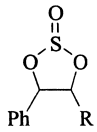
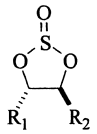
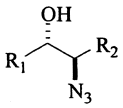
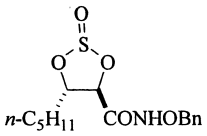
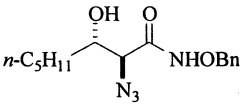
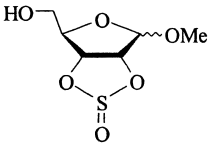
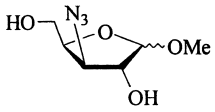
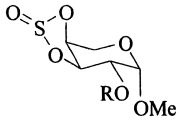
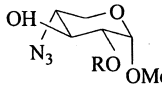
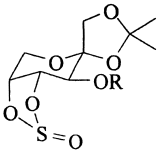
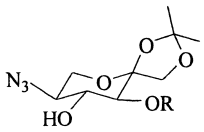
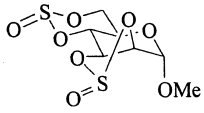
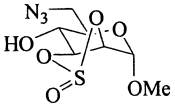
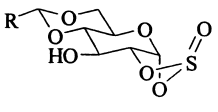
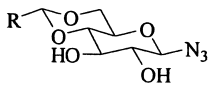
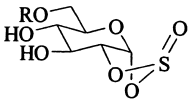
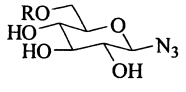
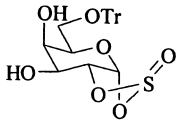
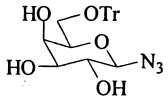
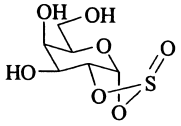
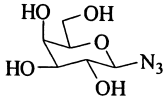
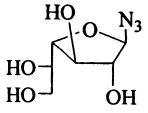
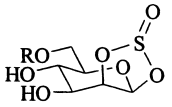
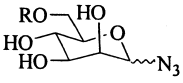
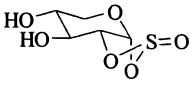
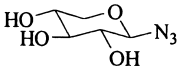
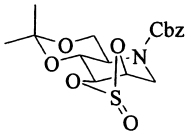
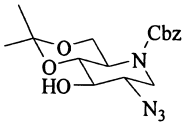
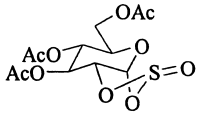
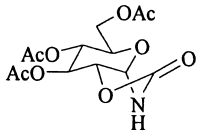
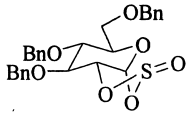
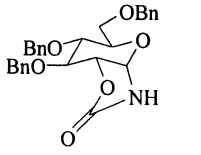
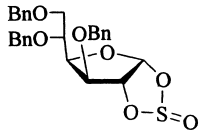
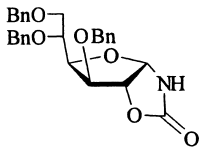
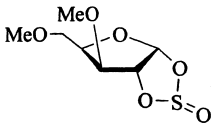
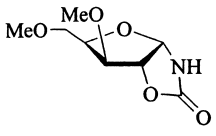
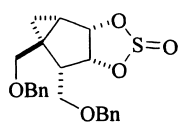
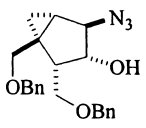
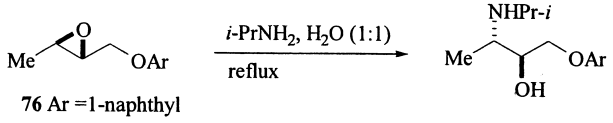
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	NaN_3	DMF/CH_3CN, -70 °C, 24 h	$PhCH(N_3)CH(OH)R$ R = H (93) R = CH_3 (98) R = Ph (99)	112
	LiN_3	DMF, 120 °C	 R_1 = Ph, R_2 = Ph (81) R_1 = H, R_2 = Ph (81) R_1 = c-C_6H_{11}, R_2 = H (79) R_1 = CO_2Et, R_2 = CO_2Et (85)	113
	LiN_3	DMF, 100 °C, 12 h	 (76)	35
	NaN_3	HMPA	 α (65) β (62)	54
	NaN_3	HMPA	 R = H (80) R = Bz (92)	54
	NaN_3	HMPA	 R = Me (80) R = Bz (85)	54
	NaN_3	DMF, 105 °C, 4 h	 (72)	54
	LiN_3	DMF, rt, >24 h	 R = CH_3 (64) R = Ph (55)	55
	LiN_3	DMF, rt, >24 h	 R = Tr (72) R = H (70)	55

Table 3 (*continued*)

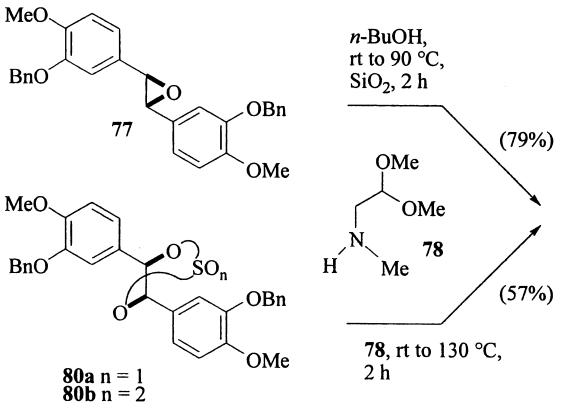
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs
	LiN_3	DMF, rt, >24 h	 (58)	55
	LiN_3	DMF, rt, >24 h	 (32) +  (27)	55
	LiN_3	DMF, rt, >24 h	 R = Tr (53) (α/β = 5); R = H (16) (α only)	55
	LiN_3	DMF, rt, >24 h	 (72)	55
	LiN_3	DMF, 90 °C, 8 h	 (52)	114
	NaSCN	DMF, 90 °C	 (60)	115
	NaSCN	DMF, 90 °C	 (90)	115
	NaSCN	DMF, 90 °C	 (80)	115
	NaSCN	DMF, 90 °C	 (70)	115
	NaN_3	DMF, 105 °C, 6 h	 (80)	116

Cyclic sulfates react with amine nucleophiles to give amino alcohols. In contrast, although epoxy crotyl ether **76** is selectively opened at C-3 by isopropylamine (Eq. (32)),[56] cleavage of epoxides with amines seems to be problematic, especially when long-chain amine nucleophiles are used.[57] However, epoxides that contain a carbonium ion stabilizing group at an adjacent carbon behave differently because of resonance. Opening of epoxide **77** by amine **78** in the presence of SiO_2 proceeded smoothly to give the *erythro*-amino alcohol **79** in 79% yield and high stereospecificity (Eq. (33)). However, aminolysis of cyclic sulfite **80a** or cyclic sulfate **80b** with **78** in *n*-butanol in the presence of SiO_2 provided amino alcohol **79** together with a minor amount (10–20%) of the threo isomer. The formation of the threo byproduct indicated that the reaction involved a mixed S_N1/S_N2 reaction mechanism.[58] In the absence of SiO_2 catalyst, aminolysis of **80** in a polar solvent such as **78** itself afforded the desired *erythro*-amino alcohol **79** exclusively (Eq. (33)).[58]



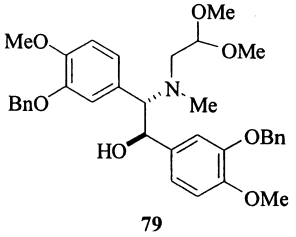
76 Ar =1-naphthyl

(32)



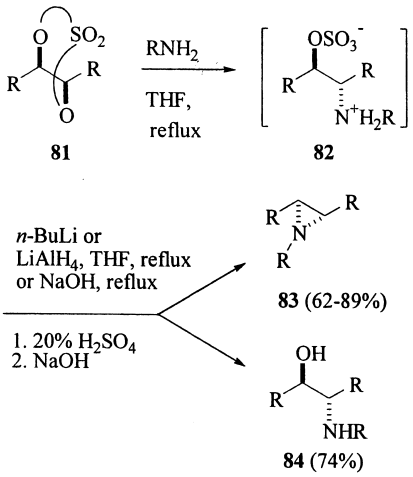
80a n = 1
80b n = 2

(33)



79

Vicinal diamines have played important roles in medicinal chemistry, coordination chemistry, and asymmetric catalysis.[59] The reported preparation methods of vicinal diamines involve a multistep reaction sequence.[60] Treatment of cyclic sulfate **81** with an excess of a primary amine in THF at reflux afforded aminosulfate intermediate **82**, which provided aziridine **83** in good yield on deprotonation (*n*-BuLi or $LiAlH_4$) (Eq. (34)).[61] Hydrolysis of aminosulfate **82** with 20% aqueous H_2SO_4 followed by adjustment of the pH to 10 with 20% NaOH furnished amino alcohol **84** in good yield.



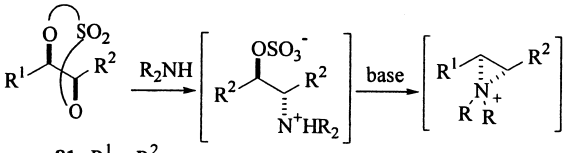
81 **82**

83 (62-89%)

84 (74%)

(34)

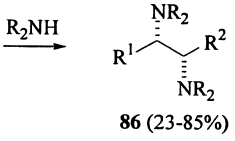
Opening of the cyclic sulfate **81a** with an excess of a secondary amine gave *erythro*-diamine **86** after basic work-up (Eq. (35)).[62] Surprisingly, the reaction with terminal cyclic sulfate **81b** afforded poor yields of the diamine regardless of the secondary amine used. When the initial opening was performed with a secondary amine, intramolecular displacement furnished a quaternary aziridinium ion **85**, which can be opened by a second nucleophile in a sequential triple displacement. This reaction was carried out stepwise: first cyclic sulfate **81a** or **81b** underwent reaction with an excess of amine at room temperature in methylene chloride; methylene chloride was replaced by toluene, powdered sodium hydroxide was added, and the resulting mixture was heated at reflux. Since these substitutions proceed via the aziridinium intermediate, the opening of **85** with different nucleophiles can provide a variety of unsymmetrically substituted amino derivatives. This procedure complements the ring opening of terminal epoxides with amines, which leads to 1-amino-2-alkanols.



81 $R^1 = R^2$
81a R^2 = H

85

(35)



86 (23-85%)

The double replacement of cyclic sulfate **81c** of enantiomerically pure (*R,R*)-stilbene diol by benzamidine (**87**) in toluene gave imidazoline **88** in 74% yield, which can be converted to diamine **89** by hydrolysis of the imidazoline ring of **88** (Eq. (36)).[63]

Table 4. Reactions of cyclic sulfates with nitrogen nucleophiles[2,15,29,36,47,58,61–63,111,116–127]

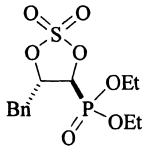
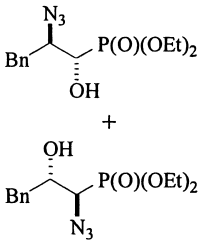
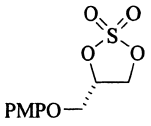
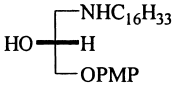
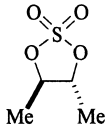
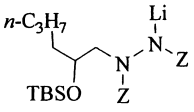
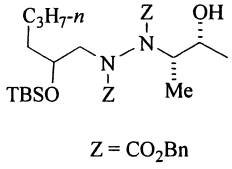
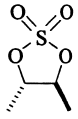
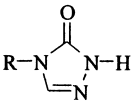
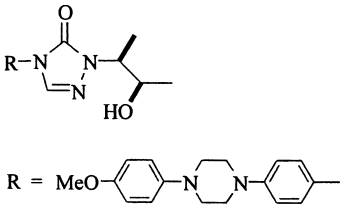
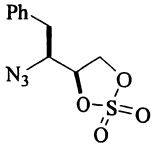
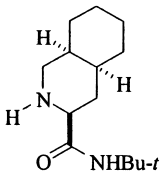
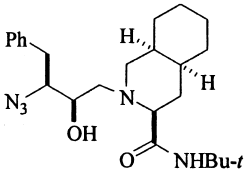
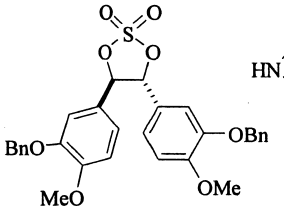
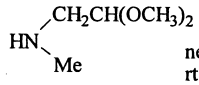
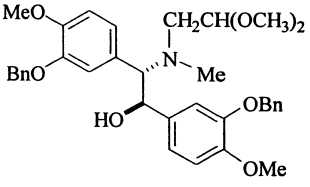
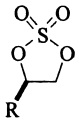
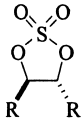
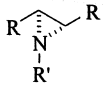
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)		Refs.
	LiN_3	DMF, rt, 2 h		(13) (25)	117
	$C_{16}H_{33}NH_2$	1. THF, rt, 4 h 2. 20% aq. H_2SO_4, Et_2O, rt, then NaOH		(95)	29
		1. THF, HMPA, rt, 2 d 2. 5 mol % H_2SO_4, dioxane, rt, 20 min	 Z = CO_2Bn	(93)	118
		1. KH, 18-Crown-6, DMF, 0 °C, 1 h 2. 48% HBr, 50 °C, 20 min	 R = MeO–	(68)	119
		1. THF, rt 2. H_2SO_4, MeOH, reflux		(67)	36
		neat, rt to 130 °C, 2 h		(>67)	58

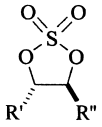
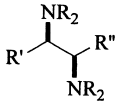
Table 4 (*continued*)

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	$R'NH_2$	$LiAlH_4$ or *n*-BuLi or NaOH, THF		61

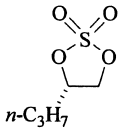
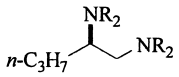
R	R'	Yield (%)
R' = *c*-C_6H_{11}	$PhCH_2$–	(78)
R' = *c*-C_6H_{11}	$Ph(CH_2)_3$–	(81)
R' = *c*-C_6H_{11}	(*S*)-Et(Me)CH–	(79)
R' = *c*-C_6H_{11}	(*S*)-Ph(Me)CH–	(79)
R' = Bn	$PhCH_2$–	(81)
R' = Ph	(*S*)-Et(Me)CH–	(89)

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	$R'NH_2$	1. THF, reflux 2. *n*-BuLi, rt		61

R	R'	Yield (%)
n-Bu	$PhCH_2$–	(62)
Ph	$PhCH_2$–	(73)
Ph	(*S*)-Et(Me)CH–	(82)

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	R_2NH	reflux in neat amine		62

R_2NH	R'	R"	Yield (%)
Et_2NH	C_3H_7	C_3H_7	(8)
pyrrolidine	C_3H_7	C_3H_7	(70)
piperidine	C_3H_7	C_3H_7	(61)
morpholine	C_3H_7	C_3H_7	(77)
pyrrolidine	C_5H_{11}	C_3H_7	(51)
piperidine	C_5H_{11}	C_3H_7	(43)
morpholine	C_5H_{11}	C_3H_7	(62)
$(PhCH_2)_2NH$	C_8H_{17}	H	(43)
piperidine	C_8H_{17}	H	(46)
morpholine	C_8H_{17}	H	(41)
$(i\text{-}Pr)_2NH$	C_8H_{17}	H	(24)

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	R_2NH	toluene, NaOH, reflux,		62

R_2NH	Yield (%)
Et_2NH	(23)
pyrrolidine	(78)
piperidine	(62)
morpholine	(64)
Et_2NH	(81)
$(PhCH_2)_2NH$	(82)

R_2NH — 1. CH_2Cl_2, rt; 2. toluene, NaOH, reflux

Table 4 (*continued*)

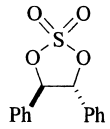
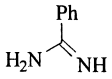
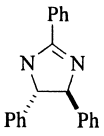
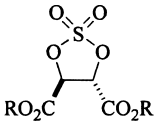
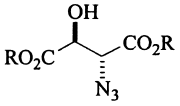
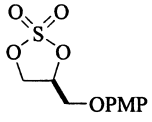
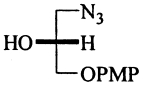
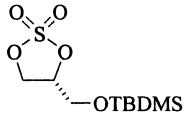
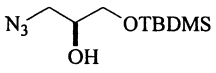
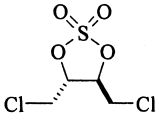
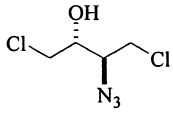
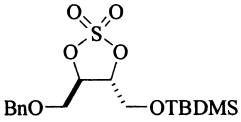
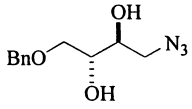
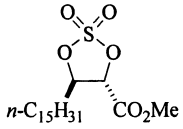
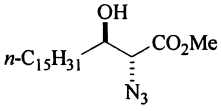
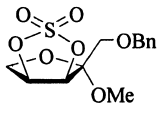
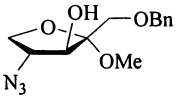
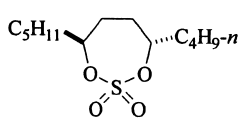
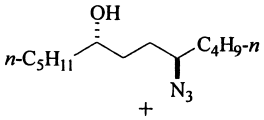
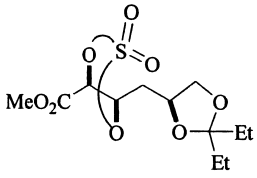
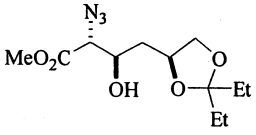
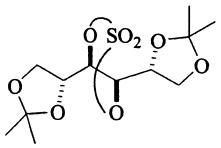
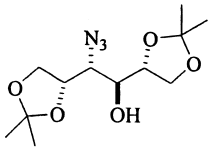
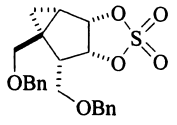
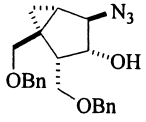
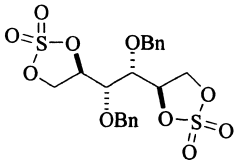
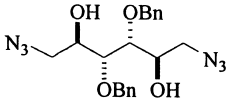
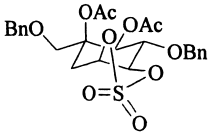
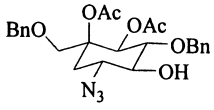
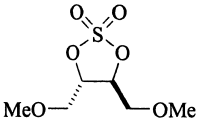
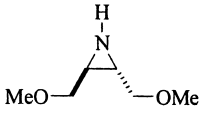
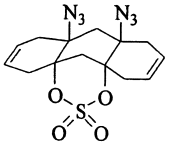
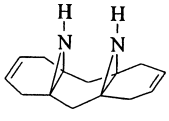
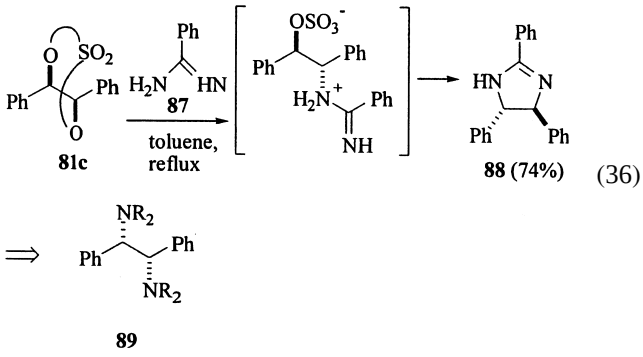
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)		Refs.
		DME, reflux, 12 h		(81)	63
	NaN_3	Me_2CO, H_2O, rt	 R: Et (82); *i*-Pr (81); $CH_2C_6H_5$ (82)		2, 111, 120
	NaN_3	1. MeCN-H_2O 1:1, rt 2. 20% aq. H_2SO_4, Et_2O, rt, 4 h		(95)	29
	LiN_3	DMF, rt		(88)	15
	LiN_3	1. THF, rt 2. cat. conc. H_2SO_4, 1 eq H_2O		(95)	121
	NaN_3	1. TBAF·$3H_2O$, THF, rt 2. NaN_3, H_2O, 60 °C 3. conc. H_2SO_4		(81)	47
	NaN_3	1. Me_2CO, H_2O, rt 2. 20% aq. H_2SO_4, Et_2O, rt, 4 h		(92)	2
	NaN_3	1. DMF, 80 °C, 3 h, 2. THF, H_2O, H_2SO_4, rt		(93)	122

Table 4 (*continued*)

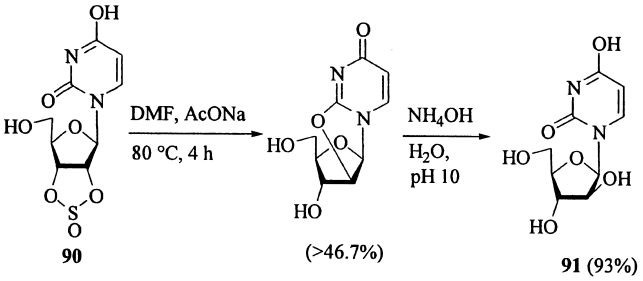
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)		Refs.
	LiN_3	1. DMF, rt 2. cat. H_2SO_4, THF		(46) (46)	123
	LiN_3	1. DMF, rt, 2 h 2. 0.5 eq H_2SO_4, 1.0 eq H_2O, 20 min		(92)	15
	LiN_3	1. DMF, 60-70 °C, 5 h 2. 0.5 eq H_2SO_4, 1.0 eq H_2O, 20 min		(91)	15
	NaN_3	1. DMF, 0 °C, 30 min 2. H_2SO_4, THF, rt overnight		(47)	116
	LiN_3	1. DMF, 25 °C, 2 h 2. conc. H_2SO_4, H_2O, THF		(80)	124
	LiN_3	1. DMF 2. 20% aq. H_2SO_4, THF, rt		(50)	125
	LiN_3	THF, reflux, 6 h; then $LiAlH_4$, reflux		(61)	126
	intramolecular nucleophile	$LiAlH_4$, THF		(75)	127



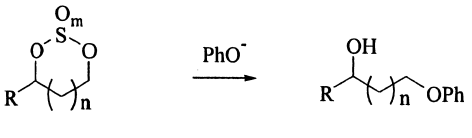
(36)

Azido alcohols are often prepared by opening of cyclic sulfates with azide ion (see Tables 3–5). Introduction of the azide group has the following advantages: (1) since azide ion is a good nucleophile, mild reaction conditions can be used; (2) the azido group is readily converted to an amine via a broad variety of reducing agents; (3) an amide or carbamate group can be introduced in situ.[38]

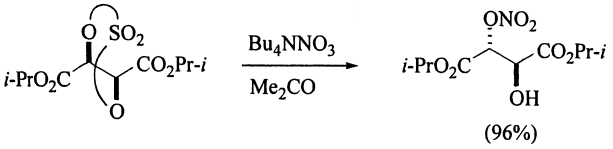
5.4.2. Oxygen nucleophiles. Phenol derivatives are generally used to react with cyclic sulfites because other oxygen nucleophiles can attack the sulfur atom of the cyclic sulfite.[13] Anhydronucleoside **91** can be prepared by intramolecular substitution of cyclic sulfite **90** with an internal oxygen nucleophile (Eq. (37)).[64] In the reactions of the cyclic sulfates of 1,2-, 1,3-, 1,4-butanediols and 1,3-propanediol with phenoxide ions, attack takes place at the primary position (Eq. (38)).[25] Even very weak nucleophiles such as RCO_2^-, amine-*N*-oxide, and NO_3^- open the cyclic sulfate as shown in Eq. 39.[2]



(37)



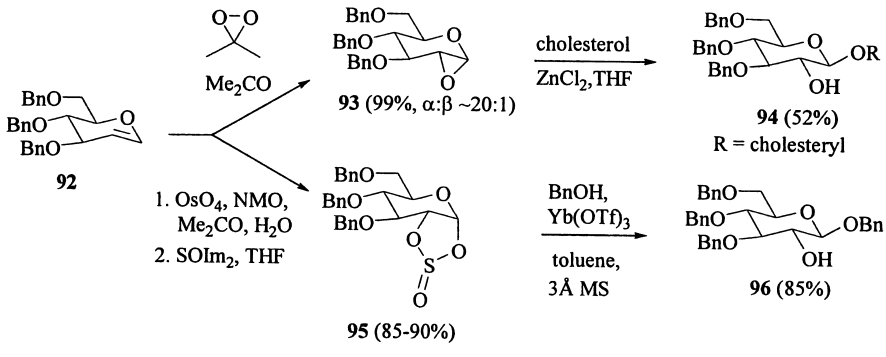
(38)



(39)

Cyclic sulfites have been used for selective β-glycosylation.[65] Although 1,2-anhydro sugars **93** serve as stereoselective glycosyl donors, the anhydrosugar must be generated by the direct epoxidation of glycals with dimethyl dioxirane (Eq. (40)).[66] Since the anhydrosugars are not stable and the oxidation with dimethyl dioxirane is operationally difficult on a large scale, glucosyl 1,2-cyclic sulfites **95** have been used for β-glycosylation.[65] The glucosyl 1,2-cyclic sulfites were prepared by osmylation of glycals, followed by reaction with thionyl diimidazole (Eq. (41)). Dihydroxylation of protected glycals with osmium tetroxide furnished diols with greater than 19:1 facial selectivity. Cyclic sulfite **95** was formed stereoselectively for the 1,2-*cis* fused product, with a mixture of *endo* and *exo* diastereomers at sulfur. The diastereomers can be separated by column chromatography on florisil (3:1 hexane–EtOAc). Glycosylation of tri-*O*-benzyl cyclic sulfite **95** with primary and secondary alcohols catalyzed by ytterbium(III) triflate provided β-glycoside **96** exclusively (Eq. (41)). The stereochemistry at sulfur did not affect the β-selectivity of the reaction; the isolated *exo*-tri-*O*-benzoyl cyclic sulfite (P=Bz), endo isomer, and mixture of diastereomers gave similar ratios of anomers (β/α=11:1, see Table 6).

Polyepoxide cascade cyclizations[67] are an appealing strategy for the synthesis of oligo(tetrahydrofurans) common to many polyether ionophore natural products. Diastereomerically pure polyepoxide precusors for the cyclizations cannot be prepared by direct enantioselective epoxidation of a linear polyene; therefore, optically pure polyepoxides were synthesized by either the step by step introduction of



(40)

(41)

epoxides by Sharpless asymmetric epoxidation[68] or by face-selective epoxidation of macrocyclic polyenes.[69] Enantio-selective dihydroxylation of a polyene such as squalene is possible,[70] but no cascade cyclization has been reported using these chiral polyols. As a model study, solvolysis of the cyclic sulfates **97** was carried out (Eq. (42)).[71] The free alcohol **99** rather than the expected sulfate ester **98** was formed through a 5-*exo-tet* cyclization process. The most interesting feature of these reactions is that sulfate ester **98** was hydrolyzed by acid produced during the reaction in an autocatalytic process. To prove the cascade cyclization, tris(sulfate) **100** was subjected to solvolysis, and tris(tetra-hydrofuran) **101** was obtained in 93% yield (Eq. (43)) (Table 7).

Table 5. Reactions of cyclic sulfamidites with nitrogen nucleophiles[50,128–130]

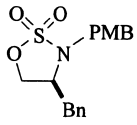
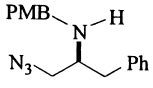
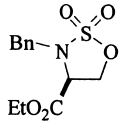
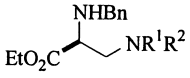
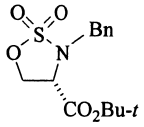
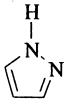
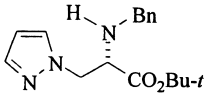
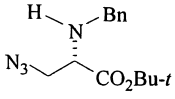
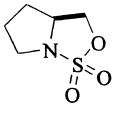
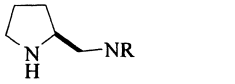
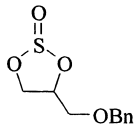
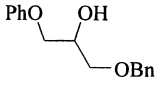
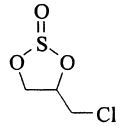
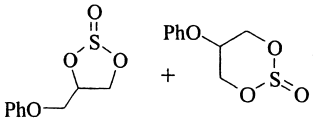
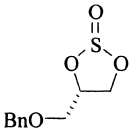
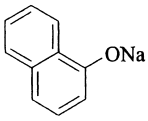
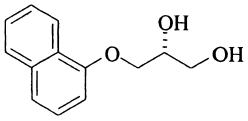
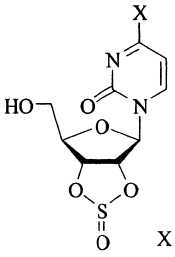
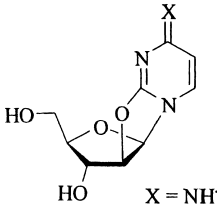
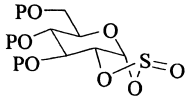
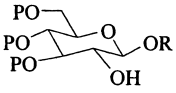
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	NaN_3	1. DMF, rt, 4 h 2. 20% aq. H_2SO_4, Et_2O, rt, 5 h	 (79)	128
		$BF_3{\cdot}Et_2O$, *n*-PrSH, CH_2Cl_2, 0 °C		50
			R^1NHR^2 — Yield (%) piperidine — (68) imidazole — (80) pyrazole — (83) morpholine — (65) Et_2NH — (57) $PhCH_2CH_2NH_2$ — (52)	
		DMF, 60 °C, 11 h	 (55)	129
	NaN_3	Me_2CO-H_2O 1:1, 20 °C, 12 h	 (93)	129
	R_2NH	1. TFA (1 drop), $CHCl_3$, reflux, 24 h 2. 2 M aq. NaOH, 90 °C, 1 h		130
			R_2NH — Yield (%) Et_2NH — (45) pyrazole — (45) piperidine — (62) morpholine — (47)	

Table 6. Reactions of cyclic sulfites with oxygen nucleophiles[13,64,65,131–133]

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	PhONa	1. DMF, rt 2. HCl-H_2O	 (81)	13
	NaOPh	EtOH, 1 h, reflux	 (8) (66)	131
		DMF, rt, 5 h	 (74)	132
 X = NH_2 X = OH	intramolecular nucleophile	NaOAc, DMF, 80 °C, 4 h	 X = NH·HCl (80) X = O (78)	64
	ROH	$PhCH_3$, $Yb(OTf)_3$ or $Ho(OTf)_3$, 3Å MS, 80-100 °C		65, 133

P	ROH	Yield	(β/α)
P = Bz	allyl alcohol	(86)	10:1
	benzyl alcohol	(92)	11:1
	cyclohexanol	(83)	8:1
P = Ac	allyl alcohol	(82)	9:1
	benzyl alcohol	(81)	5:1
	cyclohexanol	(74)	10:1
P = Bn	allyl alcohol	(71)	100:0
	benzyl alcohol	(85)	100:0
	cyclohexanol	(75)	100:0

Table 7. Reactions of cyclic sulfates with oxygen nucleophiles[2,15,29,30,33,44,47,71,122,134,135]

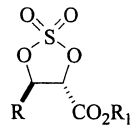
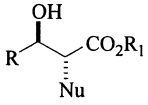
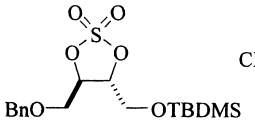
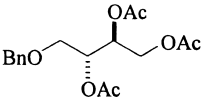
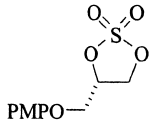
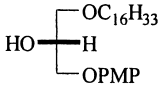
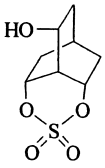
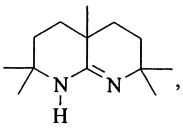
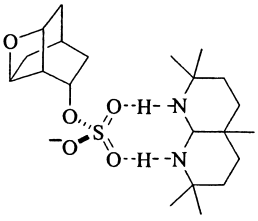
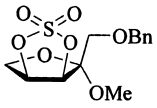
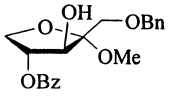
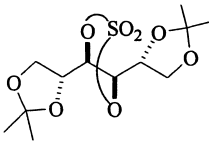
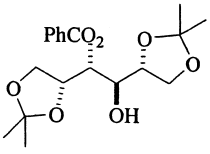
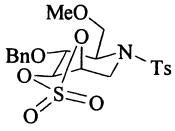
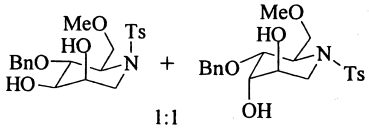
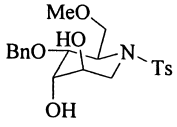
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	$PhCO_2^-$ or NO_2^-	Me_2CO, H_2O, rt	 R = CO_2Pr-*i*, R_1 = Pr-*i*, Nu = $PhCO_2$, yield = (95) R = CO_2Pr-*i*, R_1 = Pr-*i*, Nu = NO_2, yield = (96) R = $C_{15}H_{31}$, R_1 = Me, Nu = $PhCO_2$, yield = (83)	2
	$CH_3CO_2NH_4$	1. TBAF, THF; then CH_3CO_2H, 60 °C, 24 h 2. conc. H_2SO_4, rt, overnight	 (64)	47
	$C_{16}H_{33}OLi$	THF, 0 °C to rt	 (90)	29
	intramolecular nucleophile	 DMF, rt, 9 d	 (46)	134
	$PhCO_2NH_4$	DMF, 80 °C	 (70)	122
	$PhCO_2NH_4$	DMF	 (85)	15
	hydrolysis	20% H_2SO_4, THF	 1:1	135
	H_2O	50% H_2SO_4, THF	 (77)	135

Table 7 (*continued*)

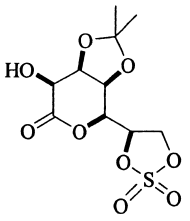
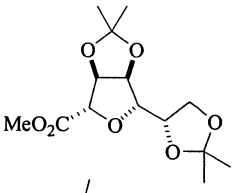
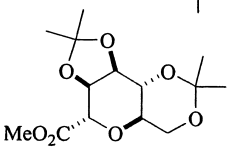
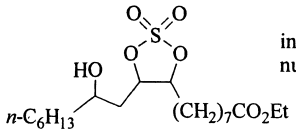
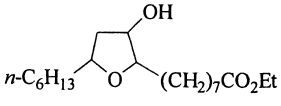
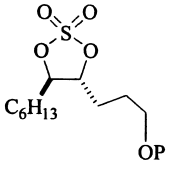
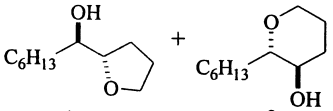
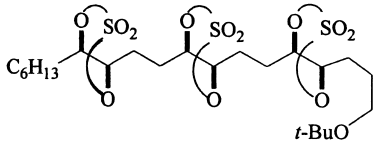
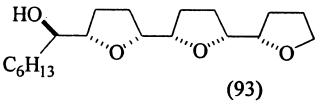
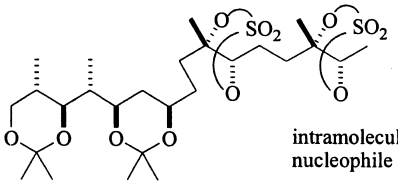
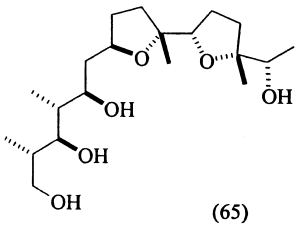
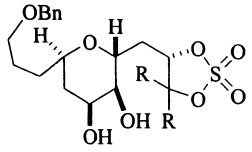
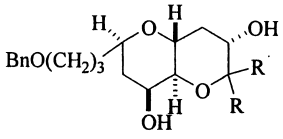
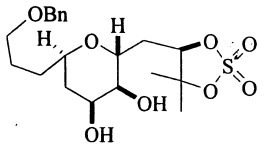
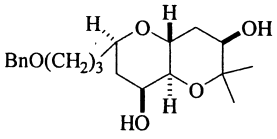
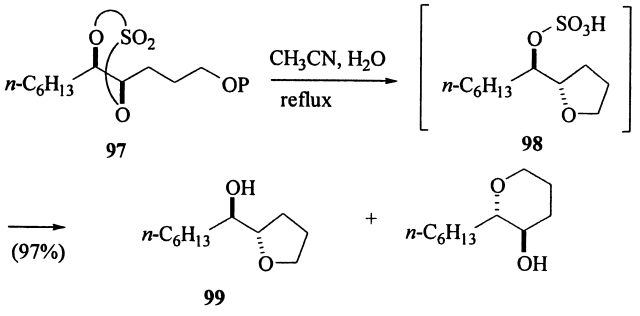
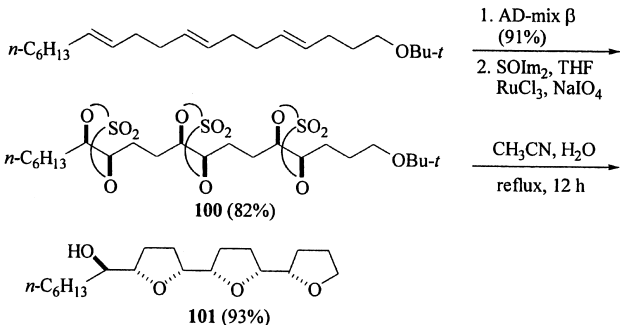
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	intramolecular nucleophile	1. K_2CO_3, MeOH, rt 2. $(CH_3)_2CO$, conc. H_2SO_4	 (76)	44
	intramolecular nucleophile	1. NaH, DME 2. MeOH; then Me_2CO, conc. H_2SO_4	 (51)	44
	intramolecular nucleophile	1. NaH, DME 2. MeOH; then Me_2CO, conc. H_2SO_4	 (82)	33
	intramolecular nucleophile	CH_3CN, H_2O, reflux	 **1** **2** **P** **1/2** **Yield (1+2)** Bn >50 (97) MOM 32 (90) TBS 10 (98) *t*-Bu 32 (91) Me 3 (18)	71
	intramolecular nucleophile	CH_3CN, H_2O, reflux, 12 h	 (93)	71
	intramolecular nucleophile	50 eq H_2O, heat, 0.01 M in CH_3CN	 (65)	71
	intramolecular nucleophile	cat. *p*-TsOH, 1% H_2O in CH_3CN, reflux, 6 h	 R = Me (15-21) R = H (15-21)	30

Table 7 (*continued*)

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	intramolecular nucleophile	cat. *p*-TsOH, 1% H_2O in CH_3CN, reflux, 6 h		(15-21)

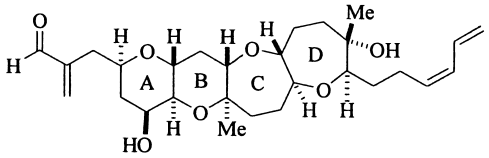


(42)



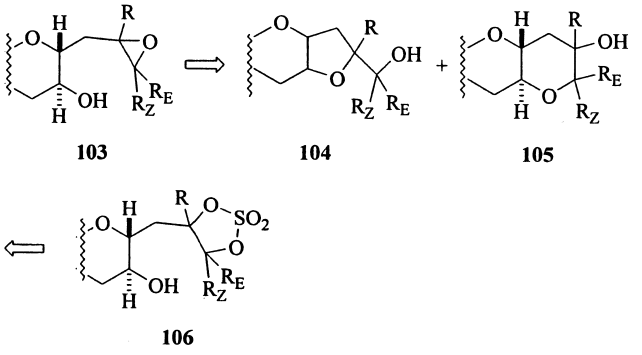
(43)

The enantioselective synthesis of the *trans–syn–trans* fused AB bis-pyran ring system of brevetoxin (**102**) was achieved by acid-catalyzed *endo*-cyclization of hydroxy-cyclic sulfate **107**.

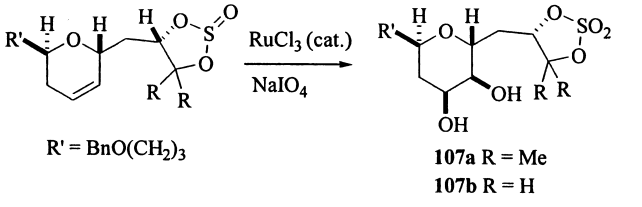


hemibrevetoxin B (**102**)

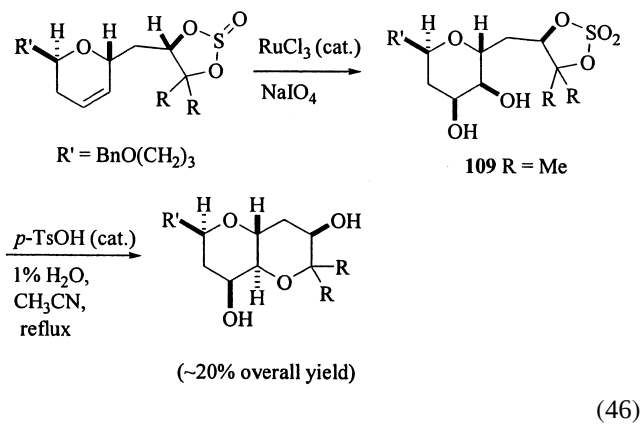
Acid-catalyzed cycloisomerization of epoxide **103** proceeds via exocyclic pathways to give **104** unless carbocation-stabilizing groups are present at the epoxy-bearing carbon (R_E and/or R_Z, Eq. (44)).[72] Although hydroxyepoxide *endo*-cyclizations are generally disfavored by the early transition state associated with opening of the strained oxirane ring, the relatively unstrained cyclic sulfate electrophile **106** may permit *endo*-cyclization to afford exclusively or predominantly regioisomer **105**. Heating a solution of crude cyclic sulfate **107a** in acetonitrile in the presence of 1% water and a catalytic amount of *p*-toluenesulfonic acid gave bicyclic product **108a** (Eq. (45)). *Endo*-regioselectivity is not restricted to diastereomer **109** (Eq. (46)). Cyclic sulfate **107b** provided predominantly the endocyclic product **108b** (*endo*/*exo*=4:1), indicating the generality of this *endo*-cyclization strategy for C–O bond formation even at primary carbon centers.[30]



(44)

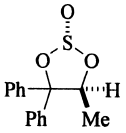
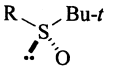
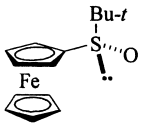
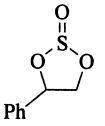
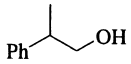
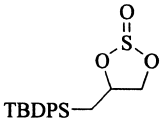
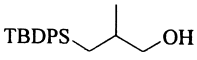
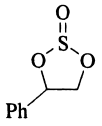
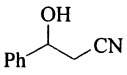
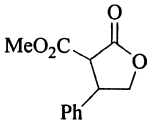
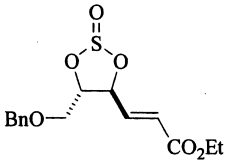
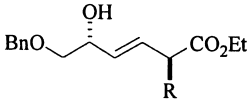
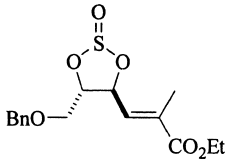
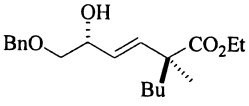
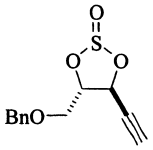
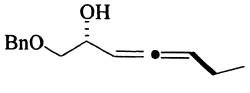
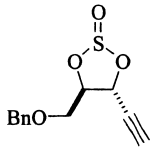
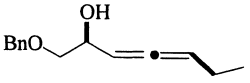


(45)

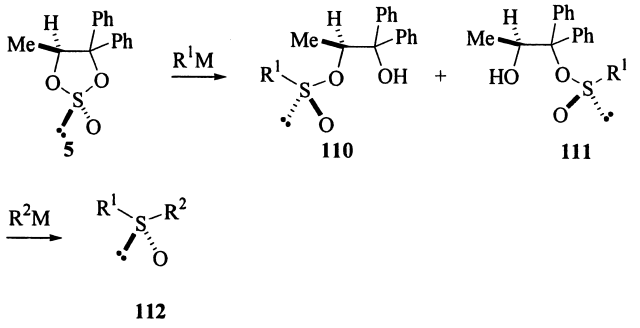


(46)

Table 8. Reactions of cyclic sulfites with carbon nucleophiles[136–142]

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)		Refs.
	PhMgBr	THF	PhSOPh	(42-60)	136
	*t*-BuMgBr; then PhLi *t*-BuMgBr; then *n*-BuLi *t*-BuMgBr; then vinylMgCl	1. THF, -78 °C 2. THF, rt		R = Ph (60%) R = Bu (60%) R = vinyl (60%)	137
	t-BuMgBr; then ferrocenyllithium			(60)	138
	$(CH_3)_3Al$ 1-6 eq	$PhCH_3$ or CH_2Cl_2, 0 °C, 1 h		(7-94)	139
	$(CH_3)_3Al$ 1-6 eq	$PhCH_3$ or CH_2Cl_2, 0 °C, 1 h		(11-62)	139
	Et_4NCN	DMF, 70 °C, 24 h		(65)	140
	$(CH_3O_2C)_2CH^-Na^+$	MeCN, 70 °C 24 h		(23)	140
	$Me_2Cu(CN)Li_2$ n-$Bu_2Cu(CN)Li_2$ n-BuCu(CN)Li	$BF_3{\cdot}Et_2O$ $BF_3{\cdot}Et_2O$ $BF_3{\cdot}Et_2O$		R = Me (84) R = *n*-Bu (90) R = *n*-Bu (79)	141
	n-$Bu_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$		(72)	141
	EtMgBr	CuI (10 mol %) $BF_3{\cdot}Et_2O$		(31)	142
	EtMgBr	CuI (10 mol %) $BF_3{\cdot}Et_2O$		(32)	142

5.4.3. Carbon nucleophiles. Enantiomerically pure cyclic sulfites are used as precursors of chiral sulfoxides, which are useful auxiliaries in asymmetric synthesis.[73] Chiral cyclic sulfite **5a** was converted to chiral sulfoxides R^1–SO–R^2 by two consecutive substitution reactions at sulfur with R^1 and R^2 (Eq. (47)).[17] This nucleophilic substitution at sulfur occurs with full inversion of configuration.[74] The following difficulties may be encountered during transfer of the chirality from a cyclic sulfite to a sulfoxide: preventing overreaction of intermediate sulfinates **110** or **111** with the first organometallic reagent, overcoming regioselective cleavage of two potential leaving sites, and achieving substitution at sulfur with the highest possible stereospecificity. The reaction of cyclic sulfite **5** with *tert*-butylmagnesium chloride gave a mixture of sulfinates **110** and **111** in a ratio of 90:10 (Eq. (47)).[17] The pure sulfinate **110** was obtained in 70% yield after recrystallization. In contrast, when ethylmagnesium bromide was used as the organometallic reagent, sulfinate **111** was the major product (80% yield, **111**:**110**=93:9). The pure sulfinate **110** or **111** reacted with another organometallic reagent (R^2M), giving chiral sulfoxide in 100% ee (Tables 8–10).

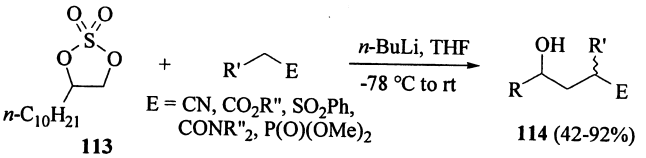


R^1M = *t*-BuMgCl **110**:**111** 90:10 (70% isolated yield of **110**)
R^1M = EtMgBr **110**:**111** 9:92 (80% isolated yield of **111**)

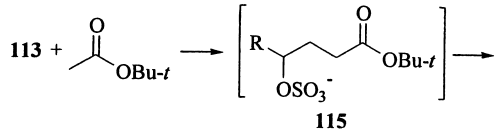
R^1, R^2 = Me, Et, Ph, Bu, $PhCH_2$, n-C_8H_{17}, etc

(47)

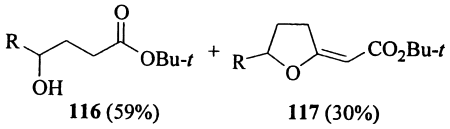
Reactions of cyclic sulfates **113** with enolates of esters and amides as well as α-cyano-, α-phosphonyl-, and α-sulfonyl-substituted anions gave hydroxylated products (Eq. (48)).[75] The reaction of *tert*-butyl acetate provided γ-hydroxyester **116** in 59% yield together with cyclic product **117** in 30% yield (Eq. (48a)). The latter arises from the Claisen condensation of γ-sulfate ester **115** with *tert*-butyl acetate. Opening of **113** with the enolate of ethyl 2-cyclohexane carboxylate formed γ-lactone **118** exclusively when the hydrolysis of the sulfate ester was carried out for a longer period (Eq. (48b)). A minor amount of cyclopropropyl product **119** was formed by double displacement in the reaction with lithiated dimethyl methylphosphonate (Eq. (48c)). However, opening of **113** with ketone enolates provided the starting ketone and 1,2-dodecanediol (Eq. (48d)). In this reaction, the enolate reacted with **113**, affording *O*-alkylated product **120**, which was converted to the starting ketone and 1,2-dodecanediol after acid hydrolysis.

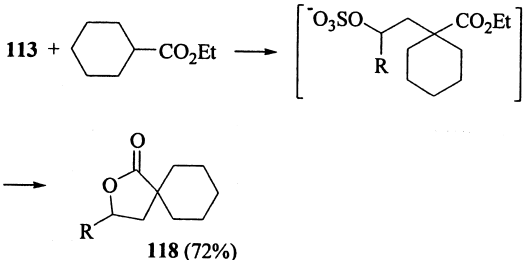


(48)

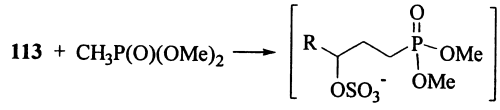


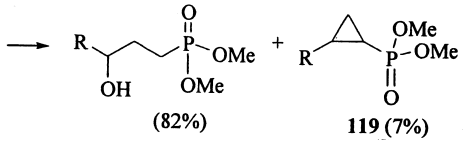
(48a)



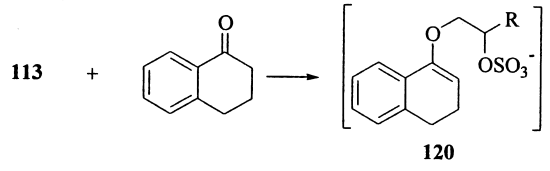


(48b)

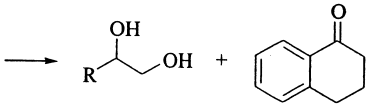




(48c)



(48d)



Opening of cyclic sulfates with thioacetal anions gave hydroxy thioketal derivatives. The reaction of 1,4-cyclic sulfate **121** with the anion of thioacetal **122** provided ring-opened product **123**, which was converted to manno-2-octulosonic acid **124** (Eq. (49)).[76] Alkylation of phenylthio hex-2-eno-pyranoside **125** with 1,2-cyclic sulfate **126** gave rise to a very polar product, presumably **127**, which was subjected to the chemoselective hydrolysis conditions described above (Eq. (50)).[77] When the hydrolysis was performed at pH>3.5, the enol ether **128** was formed as the major product, along with a small amount of diene **129**. When the hydrolysis was carried out at pH<3.0, diene **129** was the major product. The formation of **128**

Table 9. Reactions of cyclic sulfates with carbon nucleophiles[2,23,38,44,47,75–77,79–81,84,143–150]

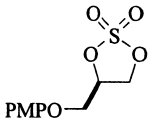
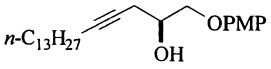
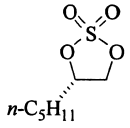
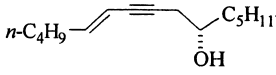
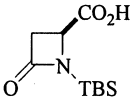
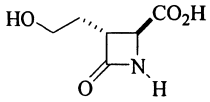
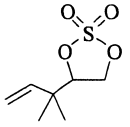
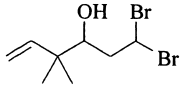
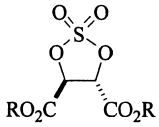
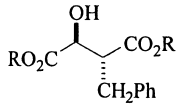
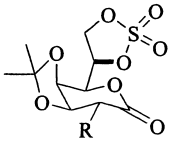
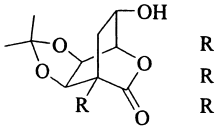
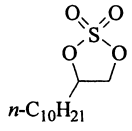
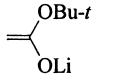
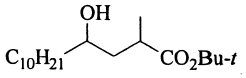
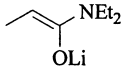
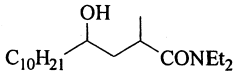
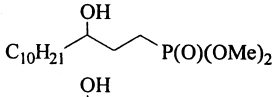
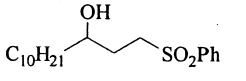
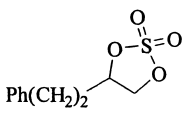
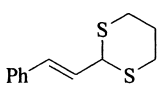
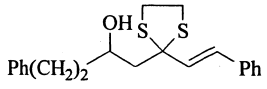
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	PhLi Ph—≡—Na	1. THF, rt 2. H_2SO_4	$PhCH_2CH_2OH$ (95) Ph—≡—CH_2CH_2OH (95)	143
	n-$C_{13}H_{27}$—≡—Li	1. THF 2. 20% H_2SO_4, Et_2O, rt	 (90)	38
	n-C_4H_9—≡—Li	1. THF 2. 20% H_2SO_4, Et_2O, rt	 (63)	144
		LDA, THF	 (75)	145
	$LiCHBr_2$	THF, -90 °C	 (89-97)	23
	$PhCH_2MgCl$	Li_2CuCl (cat.)	 R = *i*-Pr (73) R = Et (50) R = Me (33)	2
	intramolecular nucleophile	1. NaH, DME 2. conc. H_2SO_4	 R = OSO_2Me (69) R = $OSiMe_2Bu$-*t* (45) R = N_3 (59)	44
	$LiCH_2CN$	1. CH_3CN, THF, -78 °C to 0 °C 2. H_2O-conc. H_2SO_4 3/1, rt	n-$C_{10}H_{21}CHOHCH_2CH_2CN$ (73)	75
			 (59)	75
		1. CH_3CN, THF, -78 °C to 0 °C 2. H_2O-conc. H_2SO_4 3/1, rt	 (72)	75
	$LiCH_2P(O)(OMe)_2$	1. CH_3CN, THF, -78 °C to 0 °C 2. H_2O-conc. H_2SO_4 3/1, rt	 (82)	75
	$LiCH_2SO_2Ph$		 (42)	75
		n-BuLi, THF	 (-)	146

Table 9 (*continued*)

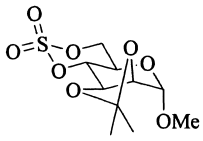
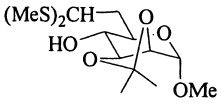
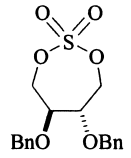
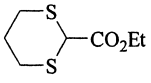
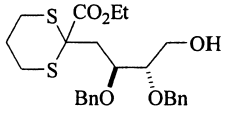
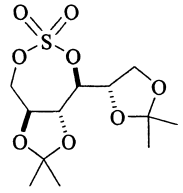
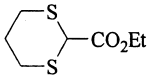
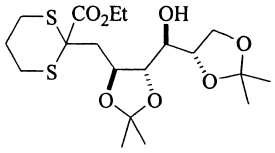
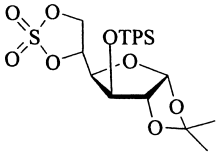
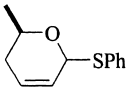
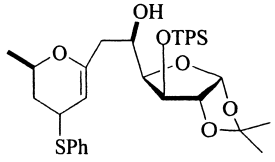
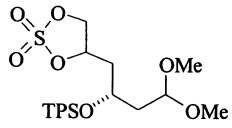
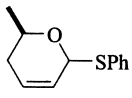
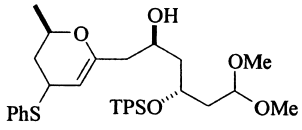
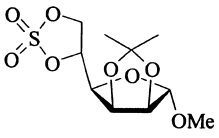
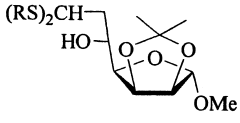
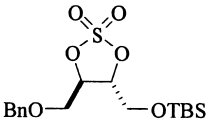
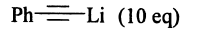
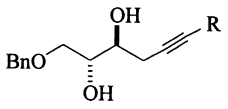
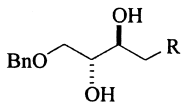
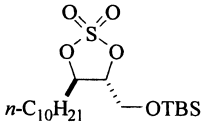
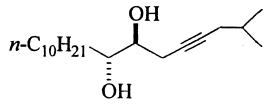
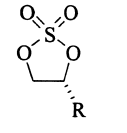
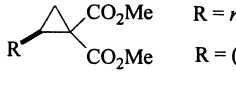
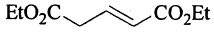
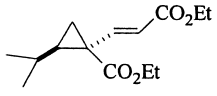
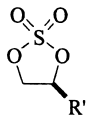
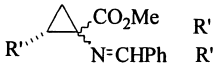
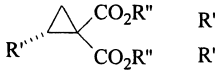
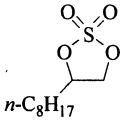
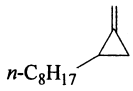
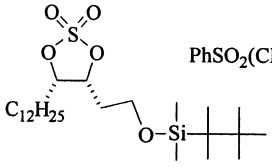
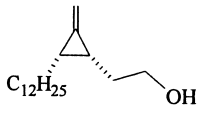
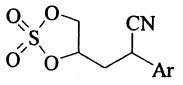
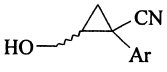
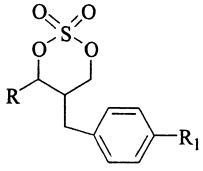
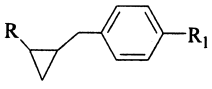
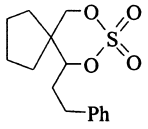
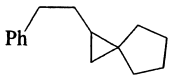
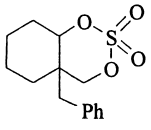
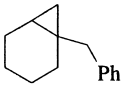
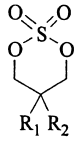
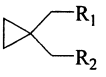
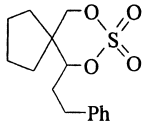
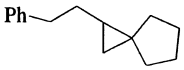
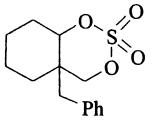
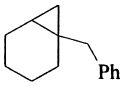
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)		Refs.
	$CH_2(SCH_3)_2$	*n*-BuLi, THF, HMPA		(81)	147
		*n*-BuLi, THF		(70)	148
		*n*-BuLi, THF		(82)	76
		pH >3.5		(–)	77
		pH <3.5		(–)	77
	$CH_2(SCH_3)_2$ 	*n*-BuLi, THF, HMPA		(81)	147
		1. TBAF 2. $BF_3{\cdot}Et_2O$, THF		R = Ph (84) R = Ph (72)	47
	Bu_2CuLi (10 eq) Bu_2CuLi (2 eq) KCN (5 eq)	1. TBAF 2. $BF_3{\cdot}Et_2O$, THF		R = *n*-Bu (70) R = *n*-Bu (73) R = CN (70)	
		1. TBAF 2. $BF_3{\cdot}Et_2O$, THF		(66)	149
	$CH_2(CO_2Me)_2$	NaH, DME 85 °C		R = *n*-C_8H_{17} (72) R = $(CH_3)_2CH$ (95)	2 79
		NaH, DME 85 °C		(61)	79

Table 9 (*continued*)

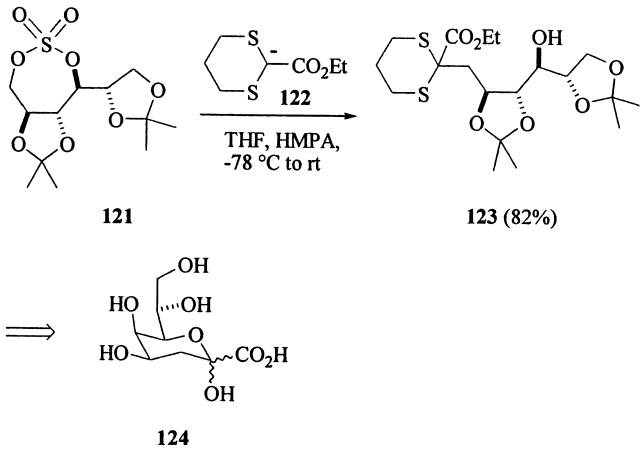
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	$PhCH{=}NCH_2CO_2Me$	NaH (2 eq), DME, rt, 4 h	 R' = $Cl(CH_2)_3$ (99) R' = CH_3 (100)	80
	$CH_2(CO_2Bn)_2$ $CH_2(CO_2Bu\text{-}t)_2$	NaH, DME, reflux, 22 h	 R' = $BnOCH_2$ (76) R" = *t*-Bu	79
	$PhSO_2CH_2CH_2SiMe_3$	1. *n*-BuLi, THF, rt, 18 h 2. *n*-BuLi, TABF, THF, rt, 18 h	 (74)	81
	$PhSO_2(CH_2)_2SiMe_3$	1. BuLi, THF, rt, 18 h 2. BuLi, TABF, THF, rt, 18 h	 (36)	81
	intramolecular nucleophile	1. *t*-BuOK 2. 20% aq. H_2SO_4		150
	intramolecular nucleophile	1. Li, DTBB (cat.), 5 mol %, THF, 0 °C 2. H_2O	 R = H R_1 = Bu-*t* (85) R = CH_3 R_1 = H (84)	84
	intramolecular nucleophile	1. Li, DTBB (cat.), 5 mol %, THF, 0 °C 2. H_2O	 (96)	84
	intramolecular nucleophile	1. Li, DTBB (cat.), 5 mol %, THF, 0 °C 2. H_2O	 (91)	84
	intramolecular nucleophile	1. Li, DTBB (cat.), 5 mol %, THF, 0 °C 2. H_2O		84

R_1	R_2	Yield (%)
$CH_2C_6H_4Bu\text{-}t$	$CH_2C_6H_4Bu\text{-}t$	(78)
$CH_2C_6H_5$	$CH_2C_6H_5$	(83)
Me	$CH_2C_6H_5$	(60)
Et	$CH_2C_6H_5$	(81)

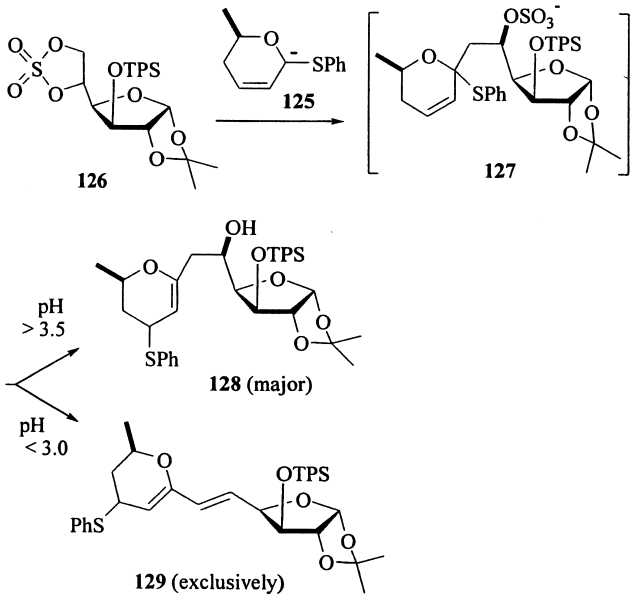
Table 9 (*continued*)

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	intramolecular nucleophile	1. Li, DTBB (cat.), 5 mol %, THF, 0 °C 2. H_2O	 (96)	84
	intramolecular nucleophile	1. Li, DTBB (cat.), 5 mol %, THF, 0 °C 2. H_2O	 (91)	84

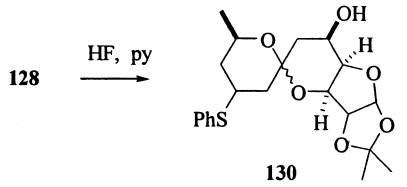
and **129** indicated that a 1,3-allylic rearrangement of the thiophenol group had occurred to give the more substituted double bond. Desilylation of **128** with HF-pyridine or $(n\text{-Bu})_4$NF furnished spiroketal **130**.[77]



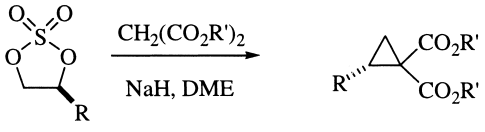
(49)



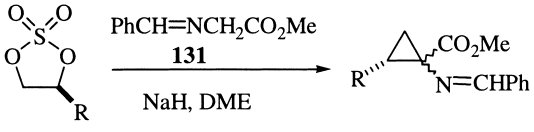
(50)



Cyclopropanes have been prepared by the reaction of 1,2-cyclic sulfate with dimethyl malonate (Eq. (51)).[2] The potential value of cyclopropane amino acids was recognized some time ago.[78] All four stereoisomers of 2,3-methanomethionine and cyclopropane amino derivatives were prepared by opening of glycidol triflate with di-*tert*-butyl malonate anion, followed by introduction of an amino group at the cyclopropane ring.[79] However, the starting glycidol is not optically pure, and it is difficult to carry out the reaction on a large scale.[14] Thus, *O*-benzyl 2,3-cyclic sulfate **132** was used to prepare cyclopropane amino acids (Schemes 5 and 6). Alkylation of methyl benzylidene glycinate (**131**) also provided the cyclopropane derivative shown in Eq. (52).[80]



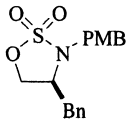
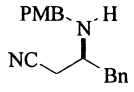
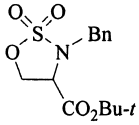
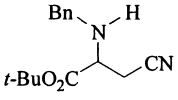
(51)

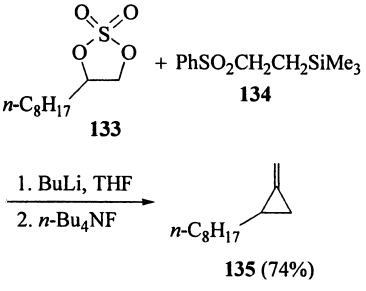


(52)

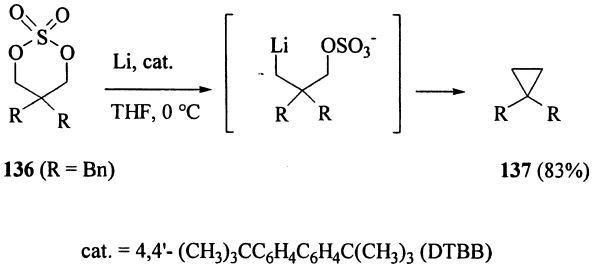
Double displacements of the 1,2-cyclic sulfate (**133**) with β-(trimethylsilyl)ethyl phenyl sulfone (**134**)[81] followed by the elimination of the silyl and sulfone groups represent an efficient synthesis of methylenecyclopropane **135** (Eq. (53)). The application of **134** in the synthesis of the methylenecyclopropane **134** from epoxides has been reported.[82,83] Dissolving metal reductions of 1,3-cyclic sulfates **136** also lead to cyclopropanes **137** (Eq. (54)).[84]

Table 10. Reactions of cyclic sulfamidates with carbon nucleophiles[128,129]

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)		Refs.
	NaCN	1. DMF, rt, 4 h 2. Et_2O, 20% aq. H_2SO_4		(86)	128
	NaCN	DMF, 20 °C, 12 h		(82)	129

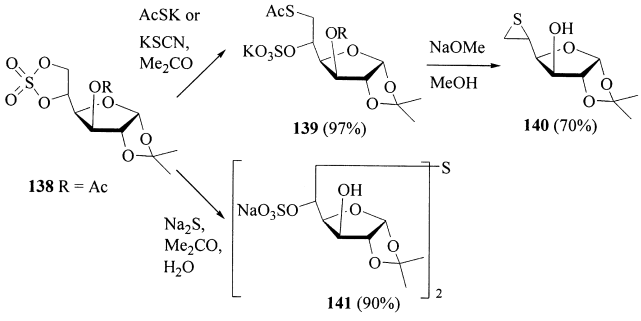


(53)

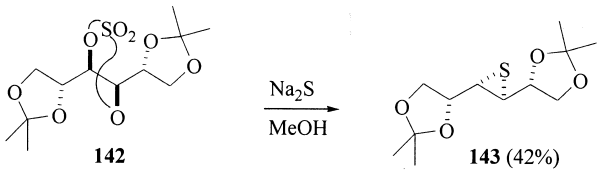


(54)

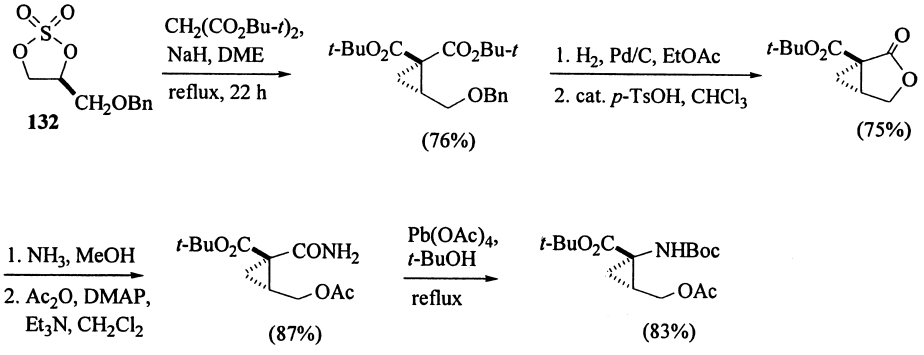
5.4.4. Sulfur nucleophiles. The reaction of terminal cyclic sulfate **138** with potassium thioacetate or potassium thiocyanate gave β-acetylthio or β-thiocyanate sulfate salts **139** by regiospecific attack at the less hindered primary position.[85] Treatment of the potassium salt with NaOMe–MeOH generated the sodium thiolate, which was converted to the episulfide **140** via intramolecular displacement of the β-sulfate groups (Eq. (55)). Opening of the nonterminal cyclic sulfate **142** with potassium thioacetate did not take place even when the experimental conditions (temperature and solvent) were varied. However, the reaction with sodium sulfide in boiling methanol furnished the desired episulfide **143** in 42% yield (Eq. (56)). An attempt to prepare episulfides from terminal cyclic sulfate **138** using sodium sulfide gave dimeric sulfide **141** (Eq. (55)).[85] The different behavior of terminal and nonterminal cyclic sulfates **138** and **142**, respectively, implied that intramolecular attack is favored when the cyclic sulfate is sterically hindered as in **142**. With the less hindered terminal cyclic sulfate **138**, intermolecular displacement was favored, giving dimeric sulfide **141** exclusively (Table 11).



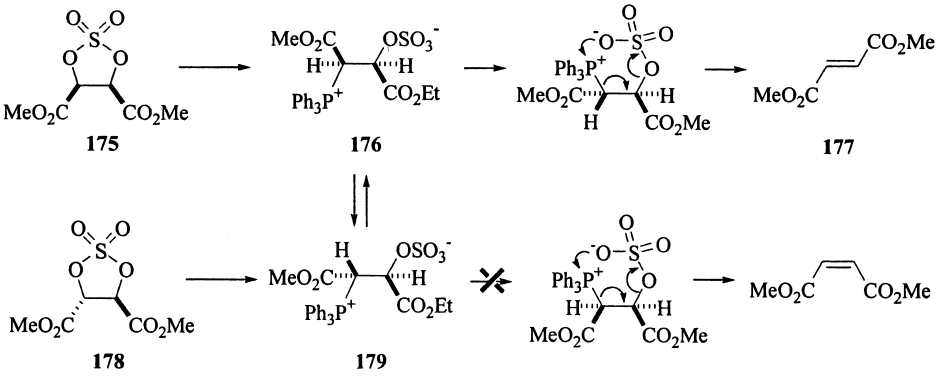
(55)



(56)

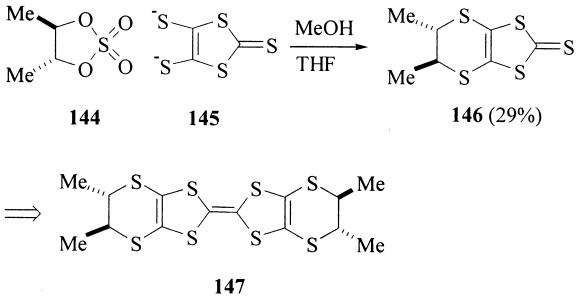


Scheme 5. Synthesis of cyclopropane amino acids.

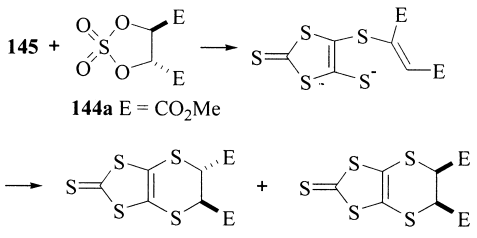


Scheme 6. Conversion of cyclic sulfates **175** and **178** to olefin **177**.

Many radical cation salts have been prepared from bis(ethylenedithio)tetrathiofulvalene **147** that possess electrical properties.[86] Fulvalene **146** and its derivatives have been prepared by double displacements of cyclic sulfates with dithiolate **145**, followed by treatment of the substitution adduct with mercury(II) acetate and then with $(EtO)_3P$.[86] The double displacement reaction of cyclic sulfate **144** took place stereoselectively (Eq. (57a)). However, the reaction with dimethyl L-tartrate cyclic sulfate **144a** produced both meso and dl isomers in a 1:3 ratio. The lack of stereospecificity probably arises by the sequential reaction sequence shown in Eq. (57b).[87]

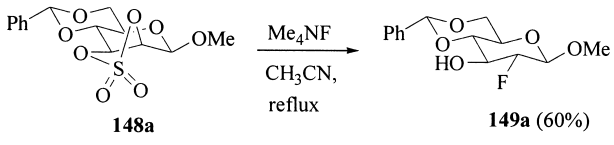


(57a)

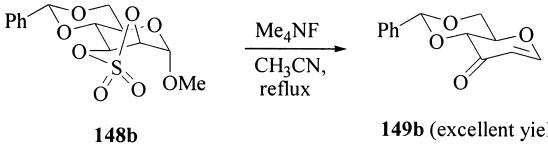


(57b)

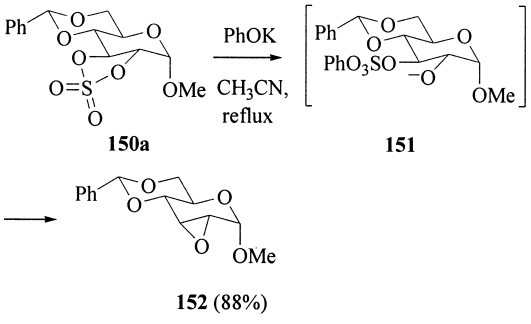
5.4.5. Halogen nucleophiles. Replacement of hydrogen atoms by fluorine at appropriate positions often results in pronounced biological[88] and ferroelectric effects.[89] Moreover, interest in fluorine chemistry has been stimulated by the use of ^{18}F-labeled radiotracers for the study of biochemical processes in animals and humans by positron emission tomography.[88] The cyclic sulfate of methyl 4,6-*O*-benzylidene-β-D-mannopyranoside (**148a**) underwent substitution by Me_4NF to give 2-fluoro derivative **149a** in good yield (Eq. (58)).[25] In contrast, the α-anomer **148b** underwent an elimination reaction to give **149b** in high yield, presumably because of the steric hindrance of the α-OMe group (Eq. (59)). Reaction of the cyclic sulfates of methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranoside (**150a**,**b**) with fluoride ion resulted in no fluorinated sugar; instead, starting sugar was formed in high yield. In β-mannopyranoside **148**, the axial 2-position was attacked readily, forming 2-fluoro-2-deoxyglucose. However, in the glucosyl derivatives **150a**,**b** the 2- and 3-positions are equatorial, and substitution at either carbon was not observed. The dependence of substitution on the configuration of the sulfate-bearing carbon atom can be confirmed by the following reaction. Reaction of phenoxide ion with the α-glucopyranoside **150a** gave 2,3-α-epoxide **152** and potassium phenyl sulfate as the only isolated products (Eq. (60)). Presumably, opening of cyclic sulfate **150a** by phenoxide attack at the sulfur site gave the 3-phenyl sulfate **151**, which was then displaced by the α-oxygen anion, providing epoxide **152**. β-Glucopyranoside **150b** gave potassium phenyl sulfate and 2,3-β-epoxides **153** together with α-epoxide **154**, indicating that the ring was opened in both directions, giving the α-2 and β-3 oxygen anion (Eq. (61)).



(58)



(59)



(60)

Table 11. Reactions of cyclic sulfites and cyclic sulfates with sulfur nucleophiles[2,29,47,48,85,97,143,151]

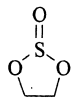
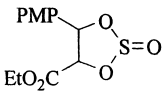
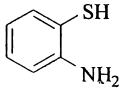
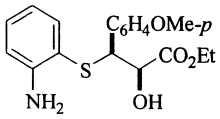
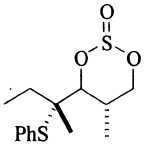
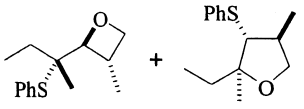
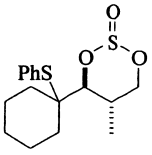
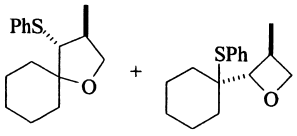
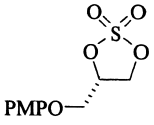
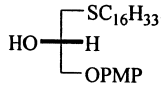
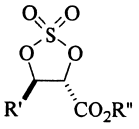
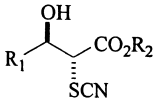
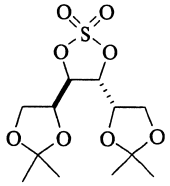
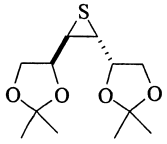
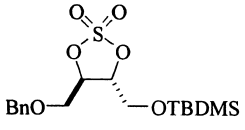
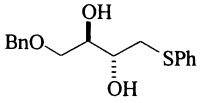
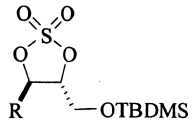
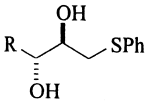
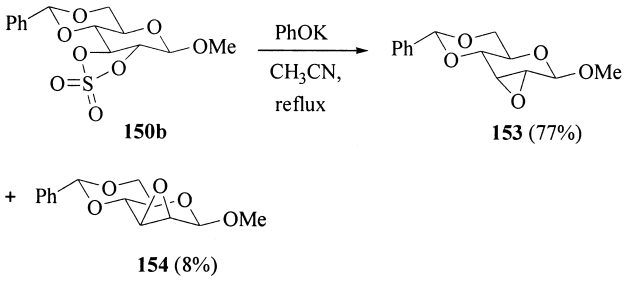
Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)		Refs.
	PhSNa	THF	$PhSCH_2CH_2OH$	(75)	143
		toluene, 110 °C, 12 h		(60)	48
	intramolecular nucleophile	$CDCl_3$, rt	 14:46		97
	intramolecular nucleophile	$CDCl_3$, rt	 97 : 3		97
	PhSNa Me_2S	1. CH_2Cl_2, reflux, 17 h 2. 2 N H_2SO_4	$PhSCH_2CH_2OH$ $Me_2S^+CH_2CH_2OH$	(70-80)	151
	$C_{16}H_{33}SH$	1. *n*-BuLi, THF, rt 2. 20% aq. H_2SO_4, Et_2O, rt, 10 h		(94)	29
	NH_4SCN	Me_2CO, 25 °C, 5 h	 R' = CO_2Pr-*i*, R" = Pr-*i* R' = *n*-$C_{15}H_{31}$, R"= Me	(87) (90)	2
	Na_2S	MeOH, reflux		(42)	85
	PhSNa	1. TBAF, THF, rt 2. conc. H_2SO_4, rt		(82)	85

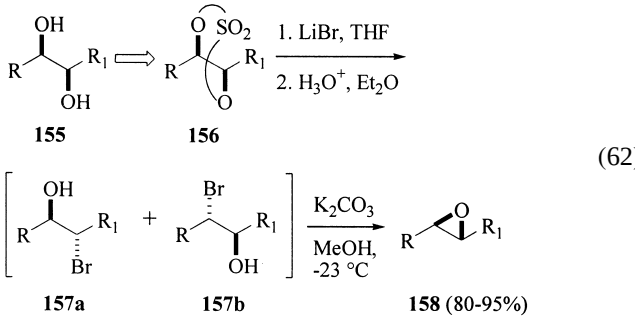
Table 11 (*continued*)

Substrate	Nucleophile	Conditions	Product(s) and (Yield, %)	Refs.
	PhSH	1. TBAF, THF 2. NaH, THF 3. conc. H_2SO_4	 R = $BnOCH_2$ (89) R = Ph (82) R = $CH_3(CH_2)_6$ (86) R =  (52)	47



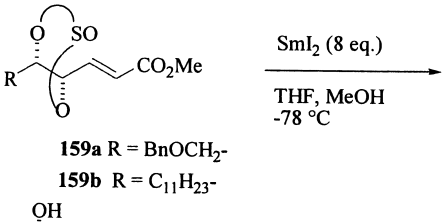
(61)

Ring opening of cyclic sulfates **156** with bromide ion has also been utilized in the stereospecific conversion of a diol **155** to the corresponding epoxide **158** (Eq. (62)).[29,90] Chiral α,β-epoxyester **158** (R_1=CO_2Me), a versatile chiral building block for the synthesis of natural and nonnatural products, was synthesized in high yields (80–95%). Even though there are two regiochemical possibilities for opening of the cyclic sulfate **156** with bromide ion, both regioisomers **157a**,**b** lead to the same chiral product, since bromide serves as a leaving group in the base-induced epoxidation step, and a double inversion of the reaction center is involved.

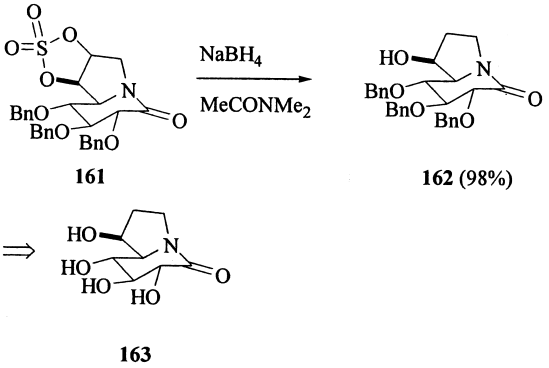


(62)

5.4.6. Hydrogen nucleophiles. In diols, one hydroxy group can be removed by the reaction of corresponding cyclic sulfite and cyclic sulfate with hydride ion. Similar to the reduction of γ,δ-epoxy α,β-unsaturated esters, the reduction of the cyclic sulfite of γ,δ-dihydroxy α,β-unsaturated esters **159a**,**b** with samarium diiodide (8 equiv.) furnished δ-hydroxy-β,γ-unsaturated esters **160a**,**b** in 60 and 73% yield, respectively (Eq. (63)).[91] Cyclic sulfate **161** was treated with sodium borohydride in dimethyl acetamide to yield a monosulfate ester intermediate, which gave lactam **162** upon hydroysis (Eq. (64)). In the reduction, hydride ion attacked the sterically less hindered side exclusively. Finally, lactam **162** was transformed to (+)-castanosperimine **163**, which is a member of a large family of polyhydroxylated alkaloids[92] and is a potent inhibitor of several α- and β-glycosidases.[93]



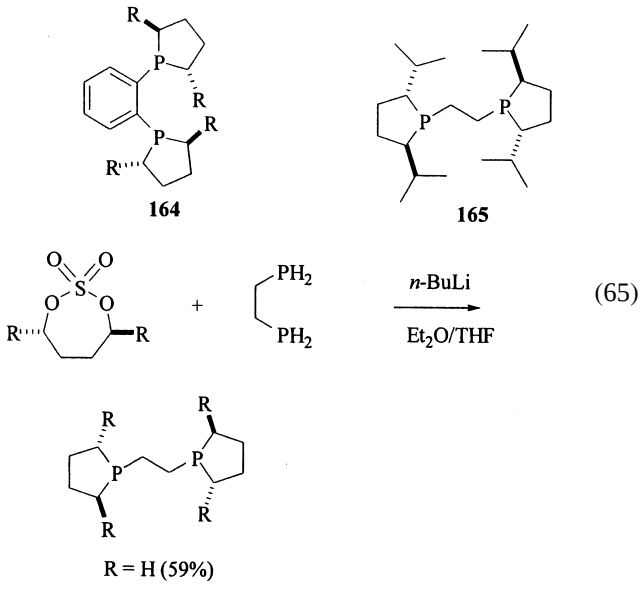
(63)



(64)

5.4.7. Phosphorus nucleophiles. Chiral phosphines based on the *trans*-2,5-disubstituted phospholane moiety are valuable ligands for transition metal catalyzed asymmetric synthesis.[94] High enantiomeric excesses have been achieved by asymmetric hydrogenations of various unsaturated substrates catalyzed by using rhodium and ruthenium complexes of 1,2-bis(phospholano)benzene derivatives **164**.[94] Enantioselective hydrogenation of ketones have been reported by use of a ruthenium(II) complex with

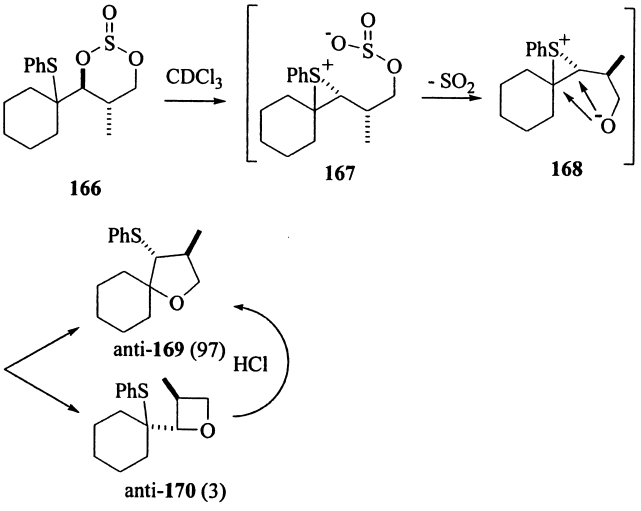
1,2-bis(*trans*-2,5-disopropylphospholano)ethane (**165**).[95] To explore the potential application of analogues of such phosphorus heterocycles having different ring sizes, various phosphine ligands were prepared by alkylations of phosphine with cyclic sulfates (Eq. (65)).[96]



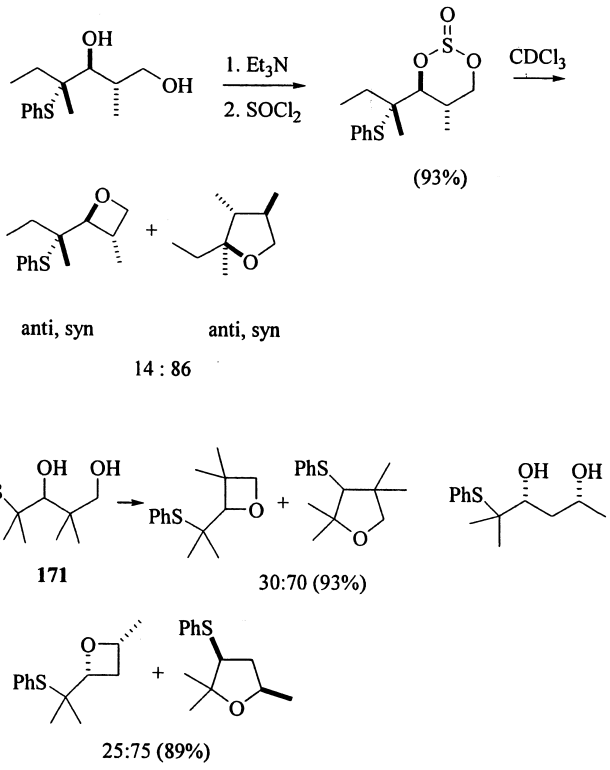
(65)

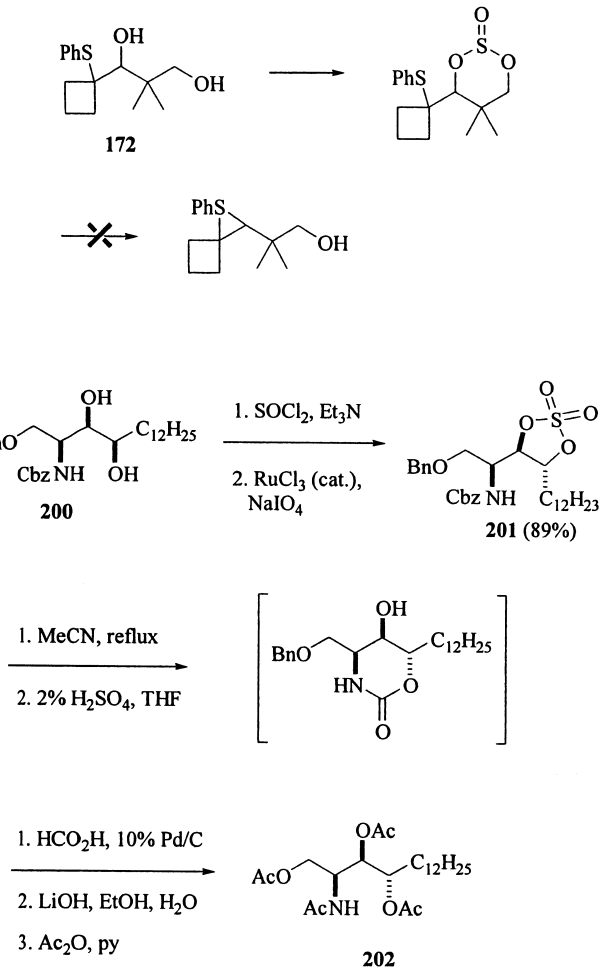
5.5. Rearrangement reactions

Cyclic sulfite *anti*-**166** underwent rearrangement to furan *anti*-**169** and oxetane *anti*-**170** in a ratio of a 97:3 (Eq. (66)). In the rearrangement sulfide attacks C-3 sulfite to form episulfonium ion **167**.[97] The primary alkoxide in **168** attacks the more substituted end of the episulfonium ion. Similarly, other 1,3-diol cyclic sulfites also underwent rearrangement to furans and oxetenes. The cyclic sulfite derived from 1,3-diol **171** could not be isolated, and the cyclization products were formed directly in 93% yield. Treatment of the mixtures with a trace of HCl furnished pure furans (see Eq. (66) for an example). However, the cyclic sulfite prepared from diol **172** did not undergo the rearrangement at all. Some other cyclic sulfites also undergo rearrangement (Eqs. (67) and (68)).[98,99]

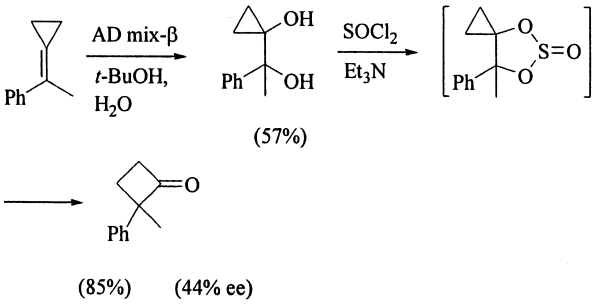


(66)

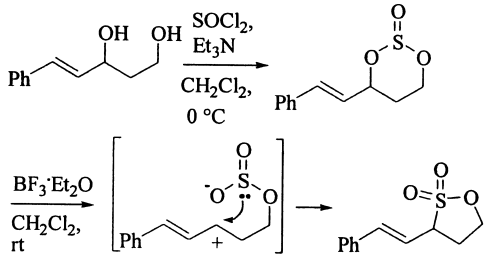




Scheme 7. Synthesis of phytosphingosine **202** from **200**.

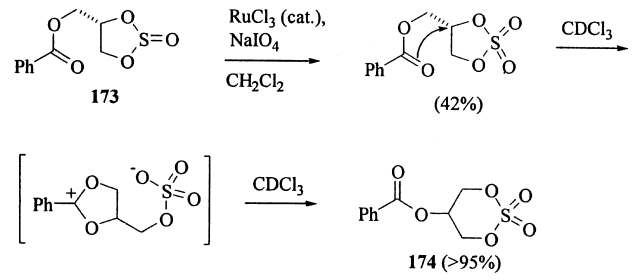


(67)



(68)

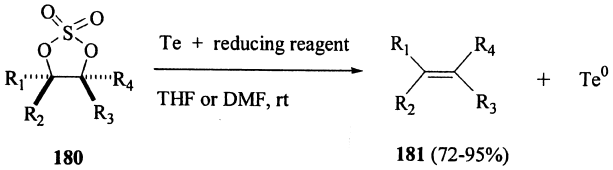
(2*R*)-3-Benzoylglycerol 1,2-cyclic sulfate **173** underwent a rearrangement in $CHCl_3$ at room temperature to give the six-membered isomeric cyclic sulfate **174** (Eq. (69)). The 1,2-cyclic sulfate **173** is characterized by signals in the ^{13}C NMR spectrum at δ 62.3, 69.5, and 79.9 ppm for the sp^3-carbon atoms, whereas the 1,3-cyclic sulfate **174** shows only two signals (at δ 63.3 and 75.6 ppm). Observation of the ^{13}C NMR spectrum in $CDCl_3$ over a period of two days showed the disappearance of the first set of peaks and the appearance of the latter set.[34]



(69)

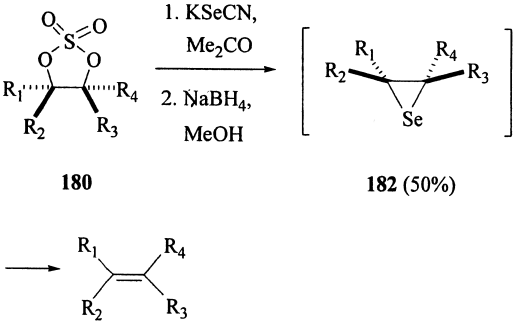
5.6. Elimination reactions

Several methods have been developed for the regio- and stereospecific deoxygenation of vicinal diols[100] since the discovery of the Corey–Winter reaction.[101] Treatment of dimethyl *meso*-tartrate cyclic sulfate **175** with Ph_3P at 110°C in xylene afforded *trans*-olefin **177** in 45% yield (Scheme 5).[102] The reaction of dimethyl L-tartrate 2,3-cyclic sulfate **178** with Ph_3P in xylene, acetonitrile, or methylene chloride also provided *trans*-olefin **177**. The unexpected *trans* double bond was probably formed via *threo* salt **176**, which may be produced by epimerization of the initially formed *erythro* salt **179**. Stereospecific conversion of cyclic sulfate **180** to olefin **181** was achieved by using telluride ion (Te^{2+}) generated in situ (Eq. (70)).[103] Since Te(0) was regenerated during the reaction, the conversion can be achieved by using a catalytic amount (e.g. 10 mol%) of tellurium metal.[103] Alternatively, cyclic sulfate **180** can also be converted to the corresponding olefin in one pot and in moderate to excellent yields via selirane intermediate **182**, which is formed by ring opening of **180** with potassium selenocyanate and subsequent reduction with $NaBH_4$ and pyrolysis (Eq. (71)).[85]



reducing agent = $LiEt_3BH$ or NaH

(70)

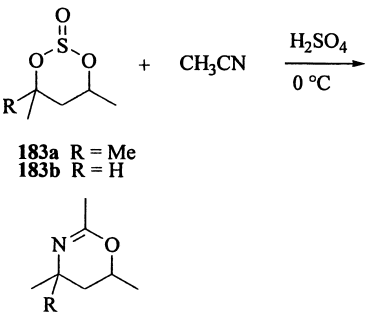


(71)

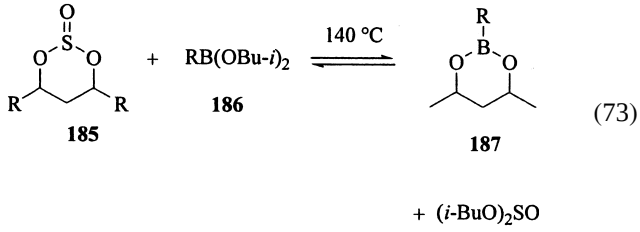
5.7. Other reactions

Cyclic sulfites undergo a Ritter-type reaction (Eq. (72)). Reaction of 2-methyl-2,4-pentanediol cyclic sulfite (**183a**) with acetonitrile catalyzed by sulfuric acid in pentane at 0°C furnished 2,4,4,6-tetramethyl dihydrooxazine (**184**) in 85% yield. However, the analogous reaction with 1,4-pentanediol cyclic sulfite (**183b**) gave only a trace of dihydrooxazine **184b**.[104]

Heating a mixture of 1,3-cyclic sulfites **185** and alkyl borate diisobutyl esters (**186**) led to the corresponding cyclic alkyl borate esters **187** (Eq. (73)). The transesterification reaction is reversible, although the equilibrium favors the cyclic alkylborates.[105]



(72)

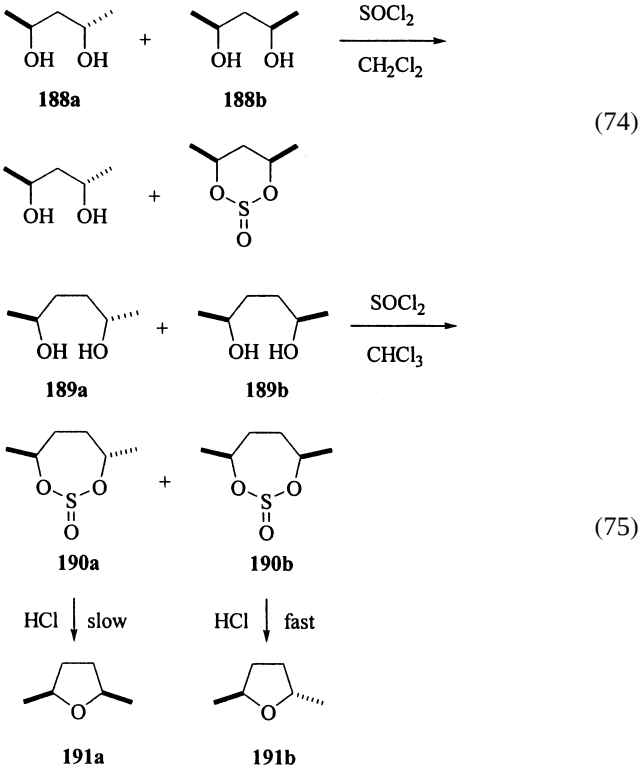


(73)

6. Applications

6.1. Resolution of chiral diols

Enantiomerically pure diols, especially with C_2 symmetry, are used as chiral auxiliaries or as precursors of diethers, bis(phospholanes), and diamines.[106,107] Lipases has been used for efficient separation of racemic diols. However, lipases cannot efficiently resolve racemic diols if the corresponding meso diols are also present, which is often the case in commercially available diols.[108] Cyclic sulfite chemistry has been used to remove meso diols from racemic diols, since the reaction of a *meso* diol (e.g. *meso*-2,4-pentanediol **188b**) with thionyl chloride is faster than that of the racemic mixture (e.g. the mixture of **188a** and its enantiomer) in the absence of base or catalyst (Eq. (74)). Although both meso and racemic 2,5-hexanediols **189a**,**b** react with thionyl chloride rapidly to give the corresponding cyclic sulfites **190a**,**b**, the cyclic sulfites derived from *meso* diol **189b** rearranged to *trans*-2,5-dimethyltetrahydrofuran **191** much faster than those from **189a** (Eq. (75)). Therefore, *meso* diol **189b** can still be removed as a THF derivative **191b** via distillation, and racemic diol **189a** can be recovered via hydrolysis of cyclic sulfite **190a**.

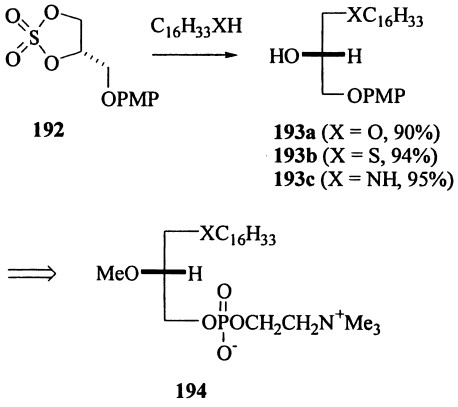


(74)

(75)

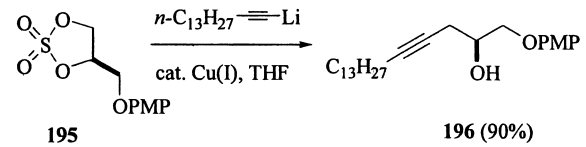
6.2. Use of cyclic sulfates in the synthesis of glycerolipids and sphingolipids

Ring-opening reactions of protected glycerol 2,3-cyclic sulfate **192** with a long-chain alcohol, thiol, and amine provided intermediates **193a**–**c** in high yields after acidic hydrolysis (Eq. (76)).[29] These intermediates can be converted to the corresponding ether glycerolipids and the corresponding thio and aza analogs via known procedures.[109] Several ether glycerolipids, such as ET-18-OCH_3 (**194a**: X=O) and the corresponding thio and aza analogs, have found potential applications as anticancer drugs in clinical trials.[110]

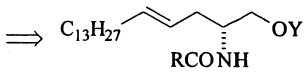


(76)

Nucleophilic ring opening of **195** with lithium pentadecyne gave protected yne-diol **196**, which was readily converted to deoxyceramide **197a** and deoxysphingomyelin **197b** in high overall yields (Eq. (77)).[38] Other applications of cyclic sulfate chemistry in the preparation of sphingolipids included the synthesis of ceramide **199** from dimethyl tartrate as shown in Eq. (78),[111] and the conversion of one phytosphingosine stereoisomer (2*S*,3*S*,4*R*)-**200** to the other (2*S*,3*S*,4*S*)-**202** via intramolecular nucleophilic ring opening of a cyclic sulfate intermediate **201** (Scheme 7).[37] Eq. (79) demonstrates our most recent application of cyclic sulfate chemistry in the very efficient total synthesis of D-*ribo*-phytosphingosine **205a** (nine steps, 45% overall yield) and D-*erythro*-4,5-dihydrosphingosine **205b** (five steps, 73% overall yield).[32] The uniquely high reactivity (discussed in Section 3) and regioselectivity (discussed in Section 5.1.2) of cyclic sulfates (such as **203a**,**b**, Eq. (79)) derived from α,β-dihydroxyesters were utilized for a highly regioselective azidation at the C-2 position in the syntheses of both D-*ribo*-phytosphingosine **205a** and D-*erythro*-4,5-dihydrosphingosine **205b**. As shown in Eq. (79), 2-azido-3-hydroxyester **204a**,**b** was obtained in 95% high yield from the corresponding cyclic sulfates **203a**,**b**. The azido and ester groups in **204a**,**b** were simultaneously reduced by $LiAlH_4$ to give the corresponding sphingosines in high yields.



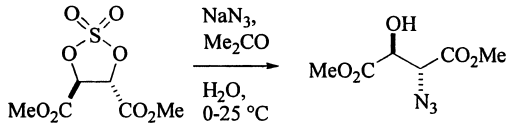
195 196 (90%)



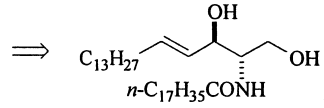
(77)

197a (Y = H)

197b [Y = P(=O)(O⁻)–OCH2CH2N+(CH3)3]

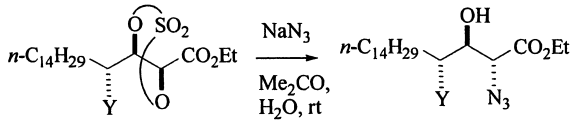


198 (74%)



(78)

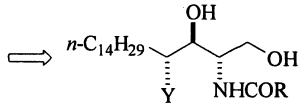
199



203a (Y = OMOM)
203b (Y = H)

204a (95%, Y = OMOM)
204b (95%, Y = H)

(79)



205a (Y = OH)
205b (Y = H)

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