Cyclic Sulfates: Useful Substrates for Selective Nucleophilic Substitution

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Received July 31, 1989

The reactions of cyclic sulfates were studied with fluoride ion, phenoxide ion, and high specific activity [^{18}F]fluoride. Cyclic sulfates of low molecular weight acyclic diols were produced by synthesis and permanganate oxidation of the corresponding sulfites. The sulfites were not good substrates for substitution. Cyclic sulfates containing five-, six-, and seven-membered rings were included. Reactions of cyclic sulfates of 3-*O*-acetylepiestriol, methyl 4,6-*O*-benzylideneglucopyranosides, and methyl 4,6-*O*-benzylidene-β-mannopyranoside, each produced by reaction of a diol with sulfuryl chloride, were included. The reaction of cyclic sulfates with nucleophiles was complete in minutes in refluxing acetonitrile. The nucleophilic reactions on cyclic sulfates are sensitive to steric and electronic direction. Steric direction of phenoxide was nearly completely regiospecific, and incorporation of fluoride showed pronounced regioselectivity. Sulfates of cyclic diols showed the greatest degree of steric control. The cyclic sulfate group appears to be a generally useful means of simultaneously facilitating nucleophilic reactions and protecting nearby hydroxyl functions.

Introduction

Reactions for incorporation of fluorine-18 into organic molecules must proceed rapidly in good yield and be amenable to a rapid workup procedure. This requirement is due to the short half-life (1.8 h) of the radionuclide. In earlier work, we have demonstrated the utility of cyclic sulfites and sulfates (1,2 thionyl and sulfuryl groups) as substrates for incorporation of fluorine-18 into organic molecules by nucleophilic substitution. Fluoroethanol was prepared from glycol sulfite,[1] and 2-deoxy-2-fluoroglucose and 16-fluoroestradiol were prepared from appropriately protected mannose 2,3-cyclic sulfates and epiestriol 16,17-cyclic sulfates.[2-4] The use of a cyclic sulfate in these cases served the dual purpose of activating a hydroxylic position to nucleophilic substitution and simultaneously protecting a second, nearby, hydroxyl group.

As a result of these preliminary successes with compounds of practical importance, a series of model compounds have been examined to probe the characteristics of cyclic sulfates as substrates for nucleophilic substitution. Sterically simple cyclic sulfites and sulfates were prepared from 1,3-propanediol and 1,2-, 1,3-, and 1,4-butanediols, extending the reaction to six- and seven-membered rings. Protected glucose 2,3-cyclic sulfates and epiestriol 16β,17β-cyclic sulfates were also prepared. These cyclic sulfates were then tested as substrates for nucleophilic substitution using fluoride ion and phenoxide ion as nucleophiles.

In this paper we report the results of these reactions and their implications for the use of cyclic sulfates as general substrates for nucleophilic substitution reactions.

Results

Sulfate Synthesis. Surprisingly,[5-9] the direct reaction of cyclic diols with sulfuryl chloride or diimidazolyl sulfate to produce bicyclic sulfates (**9**, **10**, **14**, **15**) proceeded well. However, as one would expect,[5-9] the corresponding reactions with acyclic diols were not successful. Therefore, the sulfates of acyclic (propyl, butyl) diols were produced by permanganate oxidation of the corresponding sulfites (Scheme I). The necessary cyclic sulfites were easily produced by the reaction of diols with thionyl chloride (see Charts I–III).

Scheme I

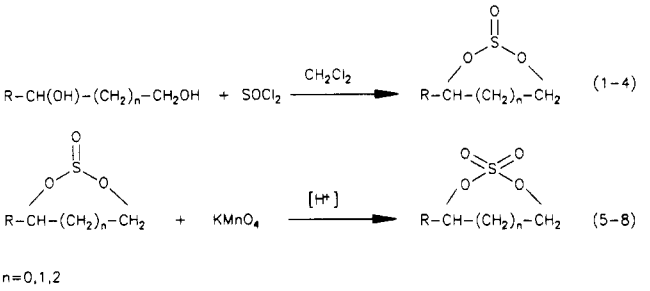
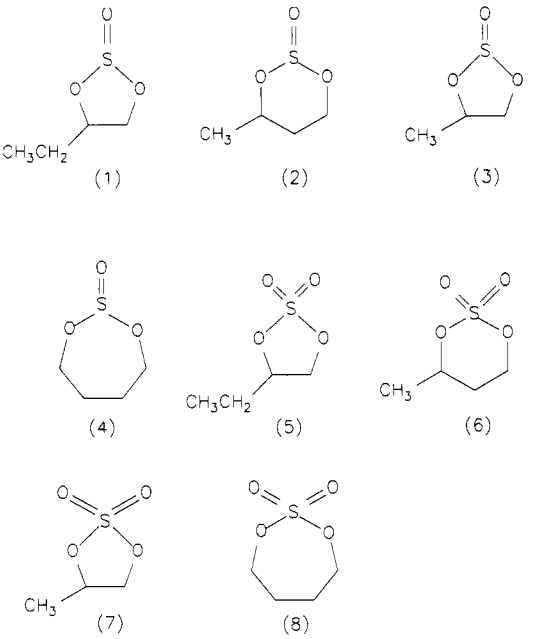


Chart I



Oxidation of the sulfites to sulfates was performed in a two-phase system to avoid further reaction and decom-

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(1) Tewson, T. J.; Welch, M. J. *J. Nucl. Med.* **1983**, *21*, 559.
(2) Tewson, T. J. *J. Org. Chem.* **1983**, *48*, 3507.
(3) Tewson, T. J. *J. Nucl. Med.* **1983**, *24*, P52.
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(5) Garner, H. K.; Lucas, H. J. *J. Am. Chem. Soc.* **1950**, *72*, 5497.
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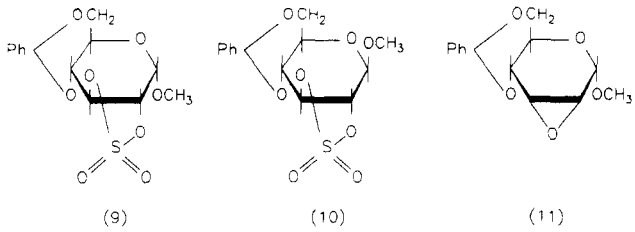
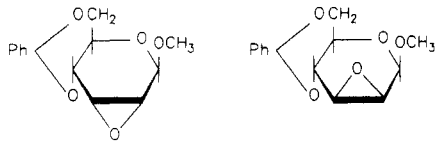
Chart II

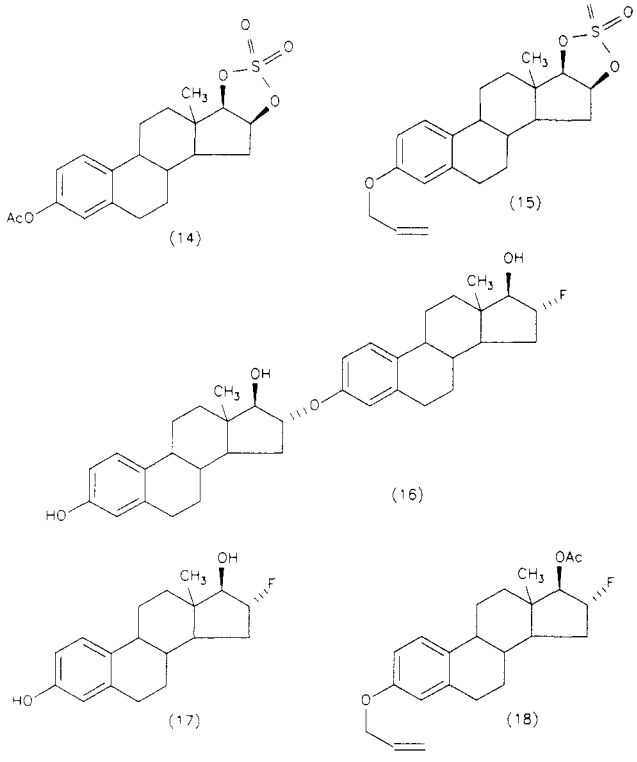


(9) (10) (11)



(12) (13)

Chart III



(14) (15) (16) (17) (18)

position of the sulfate product. Sulfites in dichloromethane solution reacted rapidly with aqueous permanganate. The product was not recoverable from the crude mixture by filtration, but reduction and dissolution of the precipitate with bisulfite allowed recovery of a fair yield of sulfate.

The intermediate sulfites were also tested as substrates for nucleophilic substitution. Under standard conditions (acetonitrile at reflux), no reaction products were detected with either phenoxide or fluoride as the nucleophile. Under forcing conditions (potassium phenoxide in neat sulfite at reflux), decomposition occurred but no products of substitution were detected. We conclude that these compounds are not substrates for substitution, and our previous success using a commercial cyclic sulfate as a substrate[1] represents an anomalous case.

Table I. Results of Phenoxide Attack on Cyclic Sulfates[a]

cyclic sulfate	phenyl ether yield, %	% primary
butane 1,2 (**5**)	80	100
butane 1,3 (**6**)	80	100
propane 1,2 (**7**)	85	75
butane 1,4 (**8**)	83	na[b]
glucose 2,3 (**9**, **10**)	0[c]	na[b]

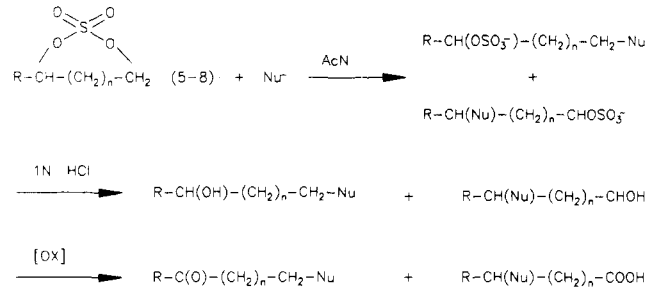
[a] Recovered yield of combined phenyl ether products based on cyclic sulfate, and percent of recovered phenyl ether products representing substitution at the primary carbon. [b] Not applicable. [c] No phenoxide substitution observed; attack at sulfur gave phenyl sulfate (>90%) and 88% recovery of 2,3-epoxides.

Table II. Fluoride Attack on Cyclic Sulfates[a]

cyclic sulfate	alkyl fluoride yield, %	% primary	^{18}F inc., %	recovered prod., %
butane 1,2 (**5**)	63	75	95	88
butane 1,3 (**6**)	77	64	94	90
propane 1,2 (**7**)	70	72	86	80
butane 1,4 (**8**)	80	na	80	75
acetylepiestriol **14**	>90	*b*	80	<20[c]
propenylepiestriol **15**	95	*b*	88	88
glucose 2,3 (**9**, **10**)	0[d]	na	0	0

[a] Recovered yield of combined fluorinated products based on cyclic sulfate, and percent of fluorinated products representing substitution at the primary carbon, as determined by ^{19}F NMR. The last two columns represent the chemical yield of ^{18}F-fluorinated sulfate based on [^{18}F]fluoride, and the recovered chemical yield of labeled fluoro alcohol after hydrolysis, based on starting [^{18}F]fluoride. [b] A 100% regioselectivity for the 16-position was observed. [c] Labeled material was a mixture of oligomers; see text. [d] Starting material was recovered in good yield.

Scheme II



Reactions of Simple Sulfates. The results of nucleophilic attack by phenoxide on sulfates of acyclic diols are shown in Table I. In all cases, the reaction with phenoxide required less than 5 min. The recovered phenoxyalkyl sulfate yield was quantitative. In no case was phenyl sulfate, the expected product of phenoxide attack at sulfur, observed. The spectral data obtained from the ring-opened phenoxy sulfates and from the phenoxy alcohols obtained by hydrolysis did not allow determination of the position of substitution. The alcohols were therefore oxidized, and the resulting ketone and acid (Scheme II) were separated to determine the regiospecificity of the phenoxide reaction. The product distribution, initially determined chromatographically, was confirmed by isolation and identification of products. The combined isolated product yield was greater than 90%, and all products gave spectral and physical data in agreement with literature values. Substitution of the nucleophile at the 1-position (primary) is reported as 100% when no product of secondary substitution (position 2 or 3) could be detected

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chromatographically or spectroscopically.

The yields of the fluoride substitutions on cyclic sulfates were determined by isolation of the tetramethylammonium fluoroalkyl sulfates and are given in Table II. These compounds produced infrared and NMR spectra indicative of their identity and purity which were, in some cases, sufficient for a reasonable determination of the isomeric composition. However, this determination was at best approximate and in some cases was not possible. Therefore, integrated fluorine-19 NMR spectra were obtained and used to determine the regioselectivity. Fluorine at primary and secondary carbon was readily distinguishable in the fluorine-19 spectra. Nucleophile attack at the primary position was predominant in all cases, but by comparison to phenoxide substitution, a relatively low regioselectivity (64–75%) was observed.

All of the simple cyclic sulfates (5–8) reacted rapidly and in high yield with fluorine-18 fluoride to give the expected fluoro sulfates. The labeling efficiency was measured by quantitatively separating ionic fluoride from fluoroorganics on alumina and by thin-layer chromatography. The incorporation yields based on ^{18}F are shown in Table II. The fluoro sulfate was hydrolyzed to yield the corresponding labeled alcohol. The hydrolyzed products were characterized by HPLC and thin-layer chromatography. The recovered yields of the labeled fluoro alcohols are shown in Table II.

Reactions of Bicyclic Sulfates. The substitution reactions on the sulfates of glucose (methyl 2,3-*O*-sulfuryl-4,6-*O*-benzylidene-α- and β-glucopyranoside, **9** and **10**) gave none of the expected products. This contrasted sharply with the reactions of other cyclic sulfates. The corresponding sulfate of mannose (methyl 2,3-*O*-sulfuryl-4,6-*O*-benzylidene-β-mannopyranoside) in particular gave excellent substitution yields, to produce the 2-fluoro sugar.[2,4] Similarly, no phenyl incorporation into the glucose ring was observed from reaction of glucose sulfates with phenoxide. However, potassium phenyl sulfate ($PhOSO_3K$) was recovered from this reaction in good yield, along with protected glucose 2,3-epoxides **11–13**. The α anomer gave exclusively the α-epoxide, and the β anomer gave both the α- and β-epoxides. Reaction of these sulfates with fluoride ion as the nucleophile similarly resulted in no fluorinated sugars. Although the reactions seemed to proceed normally as indicated by thin-layer chromatography and by dissolution of the insoluble tetramethylammonium fluoride, unchanged starting material was recovered in good yield.

The estrogen sulfates **14** and **15** reacted with stoichiometric tetramethylammonium fluoride, to give a major and a minor product when acetate was used to protect the 3-position (**14**) and a single product when an *O*-propenyl group was used (**15**). The minor product from **14** was identified from mass spectral data as the dimer **16**, formed by intermolecular nucleophilic attack at position 16 by the anion created from hydrolysis of the 3-acetate. However, the reaction of **14** with high specific activity [^{18}F]fluoride (~5400 Ci/mmol; 50 mCi, ~10 nmol) followed a different course from the reaction with stoichiometric [^{19}F]fluoride. The minor product from the stoichiometric reaction became the major product at high specific activity, and a further five or six radioactive products were formed in decreasing amounts with increasing retention times on reverse-phase HPLC. Close inspection of the chromatography traces from the stoichiometric reaction suggested that these products were in fact present in very small amounts in that reaction as well. The reaction of **15** with [^{18}F]fluoride gave a single product, with a retention time on HPLC identical with that of the single product formed in the stoichiometric reaction.

The observed acid-catalyzed hydrolysis rate of ring-opened sulfate was primarily dependent on the position of the sulfate, as would be expected. Sulfate on primary carbon hydrolyzed in 1 N HCl at 80 °C with a pseudo-first-order rate constant of 0.025 min^{-1}, or a half-life of 28 min. The rate constant for secondary sulfate was 0.018 min^{-1}, with a half-life of 39 min. The corresponding phenoxy sulfates hydrolyzed at a slightly faster rate. Hydrolysis of the secondary sulfates derived from cyclic diols[2–4] was about 1 order of magnitude faster, allowing completion of the reaction in 10 min at reflux.

Discussion

Sulfuryl chloride and diimidazolyl sulfate each react easily with cyclic diols (sugars, estradiol) to produce good yields of cyclic sulfates.[2–4] Sulfuryl chloride was preferred for simplicity. However, use of diimidazolyl sulfate was required in the presence of the *O*-propenyl protecting group because this group was chlorinated by sulfuryl chloride. In spite of the ease with which the reaction with sulfuryl chloride proceeded on cyclic diols[2–4] to give the cyclic sulfates, the direct reaction of acyclic diols with sulfuryl chloride did not give any detectable quantities of the desired product. A variety of gentle conditions on acyclic diols resulted in predominantly polymeric material. Since the synthesis of the corresponding sulfites using thionyl chloride was straightforward, their oxidation to sulfates was attempted. Methods reported previously[6–8,10] were less than attractive, and of the several alternatives we investigated, a biphasic oxidation using potassium permanganate in methylene chloride and water was moderately successful. The yields obtained (30–80%) were at least equal to those obtained by other methods, and the procedure was convenient to perform. Communications that have appeared since the completion of this work[9,11] demonstrate similar difficulties with direct synthesis of sulfates from acyclic diols. They have provided a preferable method for the one-pot synthesis and catalytic oxidation of sulfites to produce cyclic sulfates in excellent yield and have provided additional examples of the synthetic utility of these intermediates.

The substitution reactions on cyclic sulfates fulfilled our expectations for rapid reaction and high yield. These reactions are stereospecific and remarkably regiospecific. The observation of a reasonable degree of regioselectivity even on very simple substrates indicates the potential usefulness of the procedure for applications in synthetic work. Although it has been reported that the second sulfate functionality in a cyclic sulfate is also susceptible to substitution,[9] under our conditions, the second substitution appears to be much slower than the first, which is complete in a few minutes. Hydrolysis of the ring-opened sulfates in this work required considerably more vigorous conditions than the initial substitutions, and in no case was double substitution observed. Thus, the cyclic sulfate can serve as an activator at one position and as a protecting group at the second or, with more vigorous conditions, can be a selective activator for two sequential reactions.

The regioselectivity of these reactions is sensitive to steric factors. Phenoxide is much more strongly directed to the primary position than is fluoride. The only substrate to exhibit any phenoxide substitution at a secondary

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(11) Brandes, S. J.; Katzenellenbogen, J. A. *Mol. Pharmacol.* **1987**, *32*, 391–403.

position was the propane 1,2-cyclic sulfate. This compound has both more steric hindrance at the 1-position and less at the 2-position than the butane 1,3-cyclic sulfate. This is due to the difference in structure and bond angles imposed by the six-membered ring of butane 1,3-cyclic sulfate. Therefore, propane 1,2-cyclic sulfate would be expected to allow the greatest percentage of secondary substitution. Butane 1,2-cyclic sulfate is much more hindered at the secondary position due to the rotating C_2 fragment and would therefore be expected to show pronounced selectivity. Fluoride, on the other hand, does not show significant variation in selectivity among the small acyclic compounds. Due to its small size, it is only weakly directed to the primary position. The more severe constraints imposed by the bicyclic structure of the larger substrates (**9**, **10**, **14**, **15**; refs 2 and 4) do result in complete control of fluoride substitution.

Analysis of the results obtained with sugar cyclic sulfates (methyl 4,6-*O*-benzylidene-2,3-*O*-sulfuryl-α- and -β-D-glucopyranosides and -mannopyranosides) underscores the importance of steric factors in the reactions of these compounds. In both (gluco and manno) sugar derivatives, the 3-position is equatorial, and substitution at this position is not observed with any nucleophile. In the mannose configuration (methyl and propenyl 4,6-*O*-benzylidene-2,3-*O*-sulfuryl-β-mannopyranosides[2,4]), the axial 2-position is easily attacked to form the protected 2-fluoro-2-deoxyglucose in excellent yield. However, in the glucose configuration (**9**, **10**) both the 2- and 3-positions are equatorial and substitution at carbon is not observed. Reaction of phenoxide with the α-glucopyranoside gave the 2,3-α-epoxide and potassium phenyl sulfate as the only isolated products. Therefore, the ring had opened by phenoxide attack at sulfur in one direction to give exclusively the 3-(phenyl sulfate), which was then displaced by the α oxygen anion which remained at the 2-position. The β-methyl gluco compound gave potassium phenyl sulfate and both epoxides (2,3-α and -β), indicating that the ring opened in both directions, giving the α-2 and β-3 oxygen anions. This formation of epoxides by reaction of the glucopyranoside cyclic sulfates is reminiscent of previous work using the sulfates formed from cyclohexane-1,2-diol.[6] In that work, hydrolyses were performed in ^{18}O-enriched water and epoxides were postulated to be intermediate products resulting from half-hydrolysis and displacement of the cyclic sulfate, much as we have observed. It should be noted, however, that the only isolated products from the hydrolyses were ^{18}O-enriched *cis*- and *trans*-cyclohexane-1,2-diol and that an epoxide intermediate is not strictly required to explain the ^{18}O enrichment or the products observed. These isotope enrichment experiments established that the sequential attacks of hydroxide on each side of the cyclic sulfate took place at sulfur. This is consistent with our observation of phenoxide attack at sulfur.

Both of the glucose sulfates which exhibited phenoxide attack at sulfur also appeared to react with fluoride. In their reaction with tetramethylammonium fluoride, a new spot was observed on thin-layer chromatography, and the otherwise insoluble fluoride salt rapidly and completely dissolved. This suggests that a fluoride substitution product was formed. On workup, however, a good yield of starting material was recovered. Although we have no direct evidence of a fluorinated intermediate, we therefore postulate that attack on sulfur occurred with fluoride, as was noted above for phenoxide and hydroxide, to give a sulfonyl fluoride. The ring-opened sulfonyl fluoride would then undergo intramolecular ring closure on workup to re-form the cyclic sulfate in good yield. In any event, it is clear that the steric limitations of the equatorial configuration are sufficient to prevent substitution at carbon.

In the estriol cyclic sulfates (**14**, **15**), the 16- and 17-positions present the same geometry of nucleophile approach. However, a nucleophile attacking at the 17-position will experience two 1,3 diaxial interactions (with positions 12 and 13) while at the 16-position it will experience only one (with position 13). This, apparently, is a sufficient steric difference to produce reaction at the 16-position exclusively. Another reported steroid cyclic sulfate[11] (a five-membered ring formed by sulfonation between the 17-position hydroxyl and a 17-hydroxymethyl) showed similar results. A 70% recovered yield of the product of primary substitution (17-fluoromethyl) by fluoride was obtained, and no ring-substituted (17-fluoro) product was mentioned.

The reactions of 3-*O*-acetyl-16β,17β-*O*-sulfurylepiestriol (**14**) present an interesting example of the difference between normal fluoride displacement reactions and those involving no-carrier-added fluorine-18. In the fluorine-19 reactions, the expected 16α-fluoro 17β-sulfate was the major product, comprising over 90% of the product by HPLC, with a second minor product detectable. This minor product was difficult to produce and isolate on a large scale. However, its mass spectrum initially suggested that it was an isomer of the 16α-fluoro compound as its spectrum appeared identical with the spectrum of that material with the exception of one additional peak at M − 20 for the loss of HF. When high specific activity (~10 nmol) [^{18}F]fluoride was used, this minor product became the major product and was accompanied by several other radioactive products decreasing in quantity as their retention times on reverse-phase HPLC increased. Closer examination of the mass spectrum of the minor product from the ^{19}F reaction revealed a molecular ion of 560, indicating a dimeric product (**16**). Presumably, the necessary excess of base over fluoride under high specific activity conditions allowed hydrolysis of the 3-acetate. The resulting phenoxide could then react with cyclic sulfate intermolecularly to form a dimer, which could be fluorinated in its turn. We presume the additional peaks to be trimers, tetramers, etc., from the continued process, made possible by the 100-fold excess of cyclic sulfate over fluoride. Estriol cyclic sulfate protected at the 3-position by an *O*-propenyl group stable to basic conditions (**15**) was then synthesized. Chlorination of the *O*-propenyl group by sulfuryl chloride required that diimidazolyl sulfate be used in place of sulfuryl chloride to form the cyclic sulfate. When the fluorination reaction was performed on this substrate, a single product was observed, which was identical in both the ^{18}F and ^{19}F reactions.

Conclusion

Cyclic sulfates containing five-, six-, and seven-membered rings were easily prepared and isolated. The compounds, which are sufficiently stable to pose no handling problems, serve as excellent substrates for nucleophilic substitution. All substitution reactions were rapid, giving good yields within a few minutes. Hydrolysis of the ring-opened sulfate was achieved by using reasonably mild conditions. The sensitivity of the substitution reaction to steric control provides the necessary regioselectivity for use in practical synthetic applications. The resulting ability to simultaneously activate and protect two different (1,2-, 1,3- or 1,4-) hydroxyl groups of a substrate provides a useful synthetic tool for selective incorporation of nucleophiles. The rapidity of the reaction makes it especially suitable for use in isotopic labeling with short-lived ra-

dionuclides such as fluorine-18.

Experimental Section

Proton NMR spectra were recorded at 300 MHz on a General Electric QE-300 spectrometer. Carbon-13 NMR spectra were recorded on the same instrument. Fluorine-19 NMR spectra were recorded at 270 MHz on a JEOL 270 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 299B spectrometer using thin films or Nujol mulls. Melting points were taken on an Electrothermal capillary melting point apparatus and are uncorrected. Gas chromatography was performed on a Hewlett-Packard 5890 instrument using a 530-μm (nonpolar capillary), 10-m column and FID detection. Liquid chromatography (HPLC) was performed by using a Gilson System 41 package, a reverse-phase column (Alltech C-8), and a gradient of 2 mL/min acetonitrile in water, 0–100%, over 10 min after 2 min at 0% (all ring-opened sulfates, 1.8 min; fluoro alcohols: propane 1,2-cyclic sulfate, 2.5 min; butane 1,2-cyclic sulfate 3.6 min; butane 1,3-cyclic sulfate, 3.3 min; butane 1,4-cyclic sulfate, 3.0 min). Thin-layer chromatography was performed on silica gel eluted with 3% MeOH/CH_2Cl_2 (fluoride, R_f = 0; fluoro alcohols, R_f = 0.8).

Butane 1,2-Cyclic Sulfite (4-Ethyl-2-oxo-1,3,2-dioxathiolane) (1). Butane-1,2-diol (50 g, 0.55 mol) was dissolved in 150 mL of methylene chloride under argon, stirred at 0 °C. Thionyl chloride (90 g, 0.74 mol) in 100 mL of methylene chloride was added dropwise over 40 min, and then the reaction mixture was refluxed for 1 h. The methylene chloride solution was then cooled, washed three times with water, once with saturated bicarbonate solution, and once with water, dried over magnesium sulfate, and distilled under vacuum (bp 31 °C, 1 mmHg), to yield 63 g (85%) of pure cyclic sulfite.

Elemental anal. Calcd: C, 35.28; H, 5.92; S, 23.5. Found: C, 35.26; H, 6.01; S, 23.88. Proton NMR was indicative of the two stereoisomers present. ^{1}H NMR ($CDCl_3$): δ 4.79 (1 H, m, 2-H), 4.55 (1 H, dd, J = 6.4, 8.9, 1-H), 3.85 (1 H, dd, J = 8.3, 6.4, 1-H), 1.68, 1.59 (0.6 H, 1.4 H, pair of M's, 3-H's two isomers), 0.9 (3 H, m, 4-H's).

Butane 1,3-Cyclic Sulfite (4-Methyl-2-oxo-1,3,2-dioxathiane) (2). The same procedure was used for this synthesis from butane-1,3-diol as for the synthesis of the butane 1,2-sulfite above. The yield after distillation (bp 38 °C, 1 mmHg) was 80% (59 g).

Elemental anal. Calcd: C, 35.28; H, 5.92; S, 23.5. Found: C, 35.58; H, 5.99; S, 23.77. ^{1}H NMR ($CDCl_3$) (mixture of stereoisomers): δ 6.2 (1 H, m, 3-H), 6.1 (1 H, tm, J = 12.8, 1-H), 5.0 (1 H, ddt, J = 11.5, 4.7, 1.4, 1-H), 3.3 (1 H, m, 2-H), 2.8 (1 H, dm, J = 14.3, 2-H), 2.4 (3 H, dd, J = 1.2, 6.3, 4-H's).

Propane 1,2-Cyclic Sulfite (4-Methyl-2-oxo-1,3,2-dioxathiolane) (3). The procedure was followed as above; however, the amount of thionyl chloride was increased to 100 g (0.82 mol) to react with 50 g (0.66 mmol) of propane-1,2-diol. The reaction afforded 90% (72 g) propane 1,2-cyclic sulfite, bp 40 °C, 5 mmHg.

Elemental anal. Calcd: C, 29.0; H, 4.95; S, 26.25. Found: C, 29.26; H, 4.96; S, 26.18. ^{1}H NMR ($CDCl_3$) (mixture of stereoisomers): δ 5.0 (1 H, m, 2-H), 4.6 (1 H, dd, J = 5.5, 7.9, 1-H), 3.8 (1 H, dd, J = 6.8, 7.5, 1-H), 1.5, 1.3 (3 H together, both d, J = 6.5, 3-H's). IR: 2900 (m), 1460 (w), 1205 (s), 1050 (m), 960 (s), 820 (s) cm^{-1}.

Butane 1,4-Cyclic Sulfite (2-Oxo-1,3,2-dioxathiepane) (4). The following modifications were made to the above procedures to avoid excessive polymerization: Methylene chloride (150 mL) solutions of diol and thionyl chloride, as for 1 above, were simultaneously added dropwise over 40 min to a chilled, stirred 100-mL portion of methylene chloride. The yield of cyclic sulfite (bp 35 °C, 1 mmHg) was 25% (19 g).

Elemental anal. Calcd: C, 35.28; H, 5.92; S, 23.5. Found: C, 35.38; H, 5.86; S, 23.01. ^{1}H NMR ($CDCl_3$): δ 4.3 (2 H, m, 1-H, 4-H), 3.8 (2 H, m, 1-H, 4-H), 0.9 (4 H, m, 2-H's, 3-H's). IR: 2980 (m), 1460 (w), 1200 (s), 1070 (w), 1020 (w), 950 (s), 910 (m), 855 (m) cm^{-1}.

Oxidation of Cyclic Sulfites to Cyclic Sulfates. To the sulfite (86 mmol) in 50 mL of methylene chloride in an ice bath was added a cold solution of H_2SO_4 (25 g) in 200 mL of water. $KMnO_4$ (15 g) was then added in small portions with vigorous stirring. Additional methylene chloride was added as necessary to replace that lost to evaporation. Stirring was continued until no further permanganate color was detectable from a drop of solution on filter paper. Sodium bisulfite was then added in a fume hood slowly and in small portions to entirely dissolve the brown precipitate. The methylene chloride layer was separated, washed with sodium bicarbonate, dried over magnesium sulfate, and evaporated on a rotary evaporator at 35 °C. The crude sulfate was then either distilled under reduced pressure or recrystallized from a suitable solvent.

Butane 1,2-cyclic sulfate (4-ethyl-2,2-dioxo-1,3,2-dioxathiolane) (5): yield 50% (6.5 g); bp 62 °C, 1 mmHg; ^{1}H NMR ($CDCl_3$) δ 4.74 (1 H, m, 2-H), 4.61 (1 H, m, 1-H), 4.39 (1 H, m, 1-H), 2.89 (2 H, m, 3-H's), 2.39 (3 H, m, 4-H's); IR 2980 (m), 1375 (s), 1205 (s), 980 (s), 850 (s) cm^{-1}.

Butane 1,3-cyclic sulfate (4-Methyl-2,2-dioxo-1,3,2-dioxathiane) (6): yield 35% (4.5 g); bp 70 °C, 0.1 mmHg; ^{1}H NMR ($CDCl_3$) δ 4.9 (1 H, m, 3-H), 4.7 (1 H, m, 1-H), 4.5 (1 H, m, 1-H), 2.05 (1 H, m, 2-H), 1.85 (1 H, m, 2-H), 1.41 (3 H, d, J = 6.5, 4-H's); IR 2990 (m), 1385 (s), 1195 (s), 1045 (m), 1010 (m), 950 (m), 890 (m), 860 (m), 810 (m) cm^{-1}.

Propane 1,2-cyclic sulfate (4-methyl-2,2-dioxo-1,3,2-dioxathiolane) (7): yield 61% (7.3 g); bp 50 °C, 1 mmHg; ^{1}H NMR ($CDCl_3$) δ 5.0 (1 H, m, 2-H), 4.62 (1 H, m, 1-H), 4.18 (1 H, m, 1-H), 1.41 (3 H, m, 3-H's); IR 3000 (m), 1380 (s), 1205 (s), 1055 (m), 975 (s), 815 (s) cm^{-1}.

Butane 1,4-cyclic sulfate (2,2-dioxo-1,3,2-dioxathiepane) (8): yield 53% (7 g); crystallized from EtOH/H_2O or CCl_4/hexane, needles, mp 41–42 °C; ^{1}H NMR ($CDCl_3$) δ 4.40 (4 H, m, 1-H's, 4-H's), 2.06 (4 H, m, 2-H's, 3-H's); IR 2950 (m), 1360 (m), 1190 (s), 1120 (m), 960 (s), 895 (s), 790 (m) cm^{-1}.

Preparation of Potassium Phenoxide. Phenol (20 g, 210 mmol, dried by azeotropic distillation with toluene and crystallized from petroleum ether) was dissolved in 300 mL of toluene and reacted with potassium hydroxide (9.25 g, 170 mmol). Product water and excess toluene were removed by distillation, and the product was crystallized from dry ethanol/toluene.

Reaction of Cyclic Sulfates with Phenoxide Ion. Potassium phenoxide (0.2 g, 1.52 mmol) was added to 10 mL of dry acetonitrile. The salt was only partially soluble. A solution of 0.2 g of propane 1,2-cyclic sulfate (1.4 mmol) in 3 mL of acetonitrile was added and and the mixture shaken. The remaining phenoxide dissolved completely, followed by precipitation of a finely divided solid. The solution was refluxed for 5 min and rotary evaporated.

Preparation of Tetramethylammonium Fluoride. Hydrofluoric acid (15.0 mL of a 1.0 N solution in water) was added to tetramethylammonium hydroxide (15.5 mL of a 1.0 N solution). Dry acetonitrile (50 mL) was then added and evaporated on a rotary evaporator at 80 °C. The acetonitrile evaporation was repeated three times or until solid was noted on the vessel walls. The salt was then used immediately as a solution in dry acetonitrile. These quantities were varied as required, and the product was not handled or subdivided further after preparation.

Reaction of Cyclic Sulfates with Tetramethylammonium Fluoride. Cyclic sulfate (2.5 mmol) in dry acetonitrile was added to tetramethylammonium fluoride (4 mmol in 15 mL) prepared as above, and the mixture was refluxed for 10 min. The acetonitrile was evaporated, and the product crystallized from ethanol/water. For NMR, tetramethylammonium was exchanged for sodium by passage of an aqueous solution (50 mL) of the salt (2 g) over a 20-mL bed volume of Dowex AG501-X8 in the sodium form. The sodium fluoroalkyl sulfate, obtained in nearly quantitative yield, was dried at 80 °C under vacuum and taken up in D_2O for proton NMR analysis or in distilled water with 10% D_2O for fluorine-19 NMR analysis.

Propane 1,2-fluoro sulfate: mixture of isomers; ^{1}H NMR (D_2O) δ 4.05–5.2 (3 H, m, 1-H's, 2-H's), 1.38, 1.41 (3 H together, pair of dd's, J = 6.6, 1.8 and J = 24.6, 6.6, 1-H's). The downfield group contained a clear double multiplet at δ 5.05 with J = 49 Hz integrating to 0.3 H. Additionally, the ratio of the integrations of the upfield pair of double doublets (2.3:1) supports the interpretation of a 70:30 ratio of fluoride substitution at the 1- and 2-positions. ^{19}F NMR (D_2O) (ppm from CF_3COONa): (primary) −105.6 (0.72 F, td, J = 47.4, 21.5, 1-fluoro 2-sulfate), (secondary) −57.6 (0.28 F, m, 2-fluoro 1-sulfate).

Butane 1,2-fluoro sulfate: mixture of isomers; ^{1}H NMR (D_2O) δ 4.0–4.95 (3 H, m, 1-H's, 2-H), 1.91 (2 H, m, 3-H's), 1.00 (3 H, t, J = 7.5, 4-H's); IR 2985 (m), 1190 (s), 1060 (m), 1020 (m),

885 (s), 815 (m) cm^{-1}; ^{19}F NMR (D_2O) (ppm from CF_3COONa) −108.4 (0.75 F, td, J = 47.5, 23.75, 1-fluoro 2-sulfate), −64.3 (0.25 F, m, 2-fluoro 1-sulfate).

Butane 1,3-fluoro sulfate: mixture of isomers; ^1H NMR (D_2O) δ 4.0–6.0 (3 H, m, 1-H's, 3-H), 2.05 (1 H, m, 2-H), 1.73 (1 H, m, 2-H), 1.42, 1.41 (3 H together, d, J = 6.4, dd, J = 27, 6.4, 4-H's from 1-fluoro 3-sulfate and 3-fluoro 1-sulfate, respectively). Integration of the subgroup at 1.42, 1.41 was supportive of an interpretation of 64% primary fluoride substitution. IR: 2950 (m), 1185 (s), 1050 (m), 1000 (m), 805 (s), 815 (m) cm^{-1}. ^{19}F NMR (D_2O) (ppm from CF_3COONa) (1-fluoro 3-sulfate): −107.5 (0.64 F, m, 1-fluoro 3-sulfate), −61.7 (0.36 F, m, 3-fluoro-2-sulfate).

Butane 1,4-fluoro sulfate: ^1H NMR (D_2O) δ 4.62 (2 H, dt with additional fine splitting, J = 47, 6.0, CH_2F), 4.15 (2 H, t with additional fine splitting, J = 4.5, $CH_2OSO_3^-$), 1.86 (4 H, m, 2-H's, 3-H's); IR 2980 (m), 1050 (m), 1010 (m), 885 (s) cm^{-1}; ^{19}F NMR (D_2O) (ppm from CF_3COONa) −95 (1 F, m, CH_2F).

Hydrolysis of Ring-Opened Sulfates. The dried ring-opened crude sulfate from nucleophilic displacement was hydrolyzed in HCl (3 mL, 1 N). The solution was refluxed for up to 3 h, based on hydrolysis rate. Acyclic products were isolated by extraction with methylene chloride, and sugar products were isolated by passage over ion retardation resin, to remove the acid, and evaporation. Due to their low boiling points, acyclic fluorinated products were analyzed in solution by HPLC.

Hydrolysis rates of fluorinated sulfates were determined by ^{19}F NMR. Following acquisition of sulfate spectra, each sample was brought to 1 N with HCl and incubated at 80 °C. The growth of fluoro alcohol signals was observed as a function of time to yield pseudo-first-order hydrolysis rate constants. Splitting patterns were identical with those of the respective fluoro sulfates; chemical shifts for each group are noted below. The products were not isolated due to their high volatility; however, the ^{19}F NMR spectra indicated that the hydrolysis went to completion.

Observed fluoro alcohol ^{19}F chemical shifts (D_2O) (ppm from CF_3COOH): 1-fluoro-2-hydroxypropane, −77.6; 2-fluoro-1-hydroxypropane, −32.2; 1-fluoro-2-hydroxybutane, −77.2; 2-fluoro-1-hydroxybutane, −36.6; 1-fluoro-3-hydroxybutane, −78.0; 3-fluoro-1-hydroxybutane, −32.7; 1-fluoro-4-hydroxybutane, −65.4. Note that shifts in parts per million from CF_3COOH are 29 higher than from CF_3COONa.

Oxidation of Hydrolysis Products. In a typical experiment, 1.0 g of crude alcohol from the above procedure was dissolved in 5 mL of acetone, Jones' reagent added slowly to a persistent orange color, and the solution filtered and evaporated. The product mixture of an acid and a ketone was analyzed by HPLC and gas chromatography. The solution was then made basic (sodium carbonate) and extracted with methylene chloride. The organic layer was treated with charcoal, passed through a short (3 cm × 5 mm) alumina column to remove chromium salts, dried over magnesium sulfate, and evaporated to isolate the phenoxy ketone. The aqueous layer was acidified (sulfuric acid) and extracted with methylene chloride, which was then dried over magnesium sulfate and treated with charcoal. The solvent was evaporated, and the phenoxy acid product crystallized from hexane/methylene chloride. Products were weighed and identified by comparison of infrared and NMR spectra and melting/boiling point data to published results.

Preparation of Methyl 4,6-*O*-Benzylidene-2,3-*O*-sulfuryl-α-glucopyranoside (9). Methyl 4,6-*O*-benzylidene-α-glucopyranoside[12] (2.82 g, 10 mmol) was dissolved in 150 mL of dry ethyl acetate and 8.0 g (80 mmol) of triethylamine added. Sulfuryl chloride (4.60 g, 30 mmol) in dry ethyl acetate (150 mL) was added and the mixture stirred for 2 h at room temperature. The solution was filtered and evaporated and the residual oil dissolved in methylene chloride and chromatographed on Florisil (3 × 20-cm column). Crystallization from methylene chloride/petroleum ether gave **9**: 1.6 g (46%); mp 107–110 °C dec; ^1H NMR ($CDCl_3$) δ 7.45 (5 H, m, aromatic H's), 5.6 (1 H, s, benzylic H), 5.26 (1 H, t, J = 10.6, 3-H), 5.17 (1 H, d, J = 3.1, 1-H), 4.65 (1 H, dd, J = 3.1, 10.4, 2-H), 4.34 (1 H, dd, J = 10.6, 3.2, 4-H), 4.15 (1 H, m, 6α-H), 3.92 (2 H, m, 5-H, 6β-H), 3.55 (3 H, S, OCH_3); IR 1400, 1240 cm^{-1}; mass spectrum m/e 344 (M^+), 343 ($M - 1^+$).

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Preparation of Methyl 4,6-*O*-Benzylidene-2,3-*O*-sulfuryl-β-glucopyranoside (10). Methyl 4,6-*O*-benzylidene-β-glucopyranoside[12] (2.82 g) was treated as above and gave **10**: 2.0 g (58%); mp 101–105 °C; mass spectrum 344 (M^+), 343 ($M - 1$); NMR ($CDCl_3$) δ 4.88 (1 H, t, J = 9.6, 3-H), 4.86 (1 H, d, J = 8.75, 1-H), 4.47 (1 H, dd, J = 8.75, 9.6, 2-H), 4.42 (1 H, dd, J = 5.1, 10.2, 6α-H), 4.12 (1 H, dd, J = 9.6, 10.2, 4-H), 3.94 (1 H, dd, J = 10.2, 11.4, 6-H), 3.62 (1 H, ddd, J = 11.4, 10.2, 5.1, 5-H); IR 1400, 1240 cm^{-1}.

Reaction of Methyl 4,6-*O*-Benzylidene-2,3-*O*-sulfuryl-α-glucopyranoside (9) with Potassium Phenoxide. To **9** (0.8 g, 2.3 mmol) dissolved in acetonitrile (60 mL) was added potassium phenoxide (0.3 g), and the mixture was refluxed for 1 h. Potassium phenyl sulfate was filtered off, and the residue from evaporation recrystallized from methylene chloride/petroleum ether, to give methyl 4,6-*O*-benzylidene-2,3-anhydro-α-allopyranoside (**11**) (0.55 g, 88%), mp 199–200 °C.[13]

Reaction of Methyl 4,6-*O*-Benzylidene-2,3-*O*-sulfuryl-β-glucopyranoside (10) with Potassium Phenoxide. **10** (0.8 g) was heated with potassium phenoxide as above. Chromatography of the product on silica and elution with methylene chloride gave methyl 4,6-*O*-benzylidene-2,3-anhydro-β-allopyranoside (**12**) (0.47 g, 77%), mp 175–178 °C, and methyl 4,6-*O*-benzylidene-2,3-anhydro-β-mannopyranoside (**13**) (0.05 g, 8%), mp 137 °C.[13]

Preparation of 3-*O*-Acetyl-16β,17β-*O*-sulfurylepiestriol (14). (16β,17β)-3-*O*-Acetylepiestriol (estra-1,3,5(10)-triene-3,16β,17β-triol 3-acetate) (960 mg, 3 mmol) was dissolved in ethyl acetate (25 mL) containing triethylamine (1 g). Sulfuryl chloride (405 mg, 3 mmol) in ethyl acetate (10 mL) was added slowly with stirring. The solution was stirred for 2 h, filtered, and evaporated to dryness. Crystallization from methylene chloride/heptane gave **14** (830 mg, 72%): mp 212–214 °C; NMR ($CDCl_3$) δ 7.2 (1 H, d, J = 8, 4-H), 6.7 (1 H, dd, J = 8.2, 2-H), 6.65 (1 H, d, J = 2, H-1), 5.0 (1 H, m, 16α-H), 4.45 (1 H, d, J = 7, 17α-H), 2.15 (3 H, s, 3-acetate), 0.87 (3 H, s, 18-CH_3); IR 1750, 1380, 1190 cm^{-1}.

Preparation of 3-*O*-(2-Propenyl)-16β,17β-*O*-sulfurylepiestriol (15). Epiestriol (864 mg, 3 mmol) was dissolved in 100 mL of acetone containing 3 mL of 1 N sodium hydroxide solution. Allyl bromide (0.5 g) was added and the mixture stirred for 24 h. The acetone was evaporated and the residue dissolved in methylene chloride, washed with bicarbonate and water, and evaporated. Crystallization in ethanol gave 800 mg, 2.4 mmol (80%), of 3-*O*-(2-propenyl)epiestriol, mp 155–156 °C.

This was dissolved in THF (50 mL), sodium hydride (10 mmol, 240 mg) added, and the mixture stirred for 10 min. Diimidazolyl sulfate,[14] 475 mg, 2.4 mmol in 10 mL of THF, was added, and the solution was stirred for 30 min. The solution was filtered and evaporated and the residue recrystallized from heptane, to give **15**: mp 201–205 °C; NMR ($CDCl_3$) δ 7.18 (1 H, d, J = 8, aromatic H), 6.66 (1 H, dd, J = 8, 2, aromatic H's), 6.0 (1 H, m, propenyl CH=), 5.5, 5.7 (2 H, AB q, propenyl $=CH_2$), 5.25 (1 H, q, m, 16α-H), 4.55 (1 H, d, J = 7, 17α-H), 4.49 (2 H, m, propenyl OCH_2), 0.97 (3 H, s, 18-CH_3); IR 1630, 1405, 1196 cm^{-1}.

Reaction of Epiestriol Cyclic Sulfates with Tetramethylammonium Fluoride. 3-*O*-Acetyl-16β,17β-*O*-sulfurylepiestriol (**14**) (392 mg, 1 mmol) was refluxed for 10 min with tetramethylammonium fluoride (1.1 mmol) in acetonitrile (25 mL). HPLC examination of the reaction mixture showed one major and one minor peak. The major peak corresponded to >90% of the product. Acid hydrolysis, 20-min reflux in 2 N HCl, followed by extraction with methylene chloride and evaporation gave[15] 16α-fluoroestradiol (**17**), 210 mg (72%) on crystallization from ethanol. The second HPLC peak, hydrolyzed as before, gave mass spectrum peaks at 560 and 290 (M − 270), 272 (M − 288), 270 (M − 290).

3-*O*-(2-Propenyl)-16β,17β-*O*-sulfurylepiestriol (**15**) (391 mg, 1 mmol) was reacted with tetramethylammonium fluoride as above. HPLC of the product showed only one product, and acid hydrolysis as above and acetylation with acetic anhydride and

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pyridine gave 3-*O*-(2-propenyl)-16α-fluoroestradiol 17β-acetate (18): 355 mg (95%); mp 105–108 °C; mass spectrum 372 (M^+); NMR ($CDCl_3$) δ 7.15 (1 H, d, J = 8.5, aromatic 1-H), 6.7 (1 H, dd, J = 8.5, 2.2, aromatic 4-H), 6.62 (1 H, d, J = 2.2, aromatic 4-H), 6.0 (1 H, m, propenyl CH=), 5.25 (2 H, dd, J = 10.5, 1.4, propenyl $=CH_2$), 4.5 (2 H, d, J = 5, propenyl OCH_2), 5.03 (1 H, complex d, J = 50, 16β-H), 4.95 (1 H, s, 17α-H), 2.1 (3 H, s, acetate), 0.87 (3 H, s, 18-CH_3).

Preparation of Fluorine-18 and Reaction with Cyclic Sulfates. [^{18}F]Fluoride was produced by the $^{18}O(p,n)^{18}F$ reaction[16] on [^{18}O]water using 17-MeV protons.[17] After bombardment, the water, containing approximately 10 nmol of ^{18}F-labeled fluoride, was removed from the silver target and added to 10 μmol of tetramethylammonium hydroxide. The water was then evaporated under vacuum (25 cmHg at 120 °C). Three 3-mL portions of dry acetonitrile were then added and evaporated. The sulfate in 3 mL of acetonitrile was then added and refluxed for 10 min. The labeled products were analyzed by HPLC and TLC and then hydrolyzed, except as noted elsewhere, with 3 mL of 1 N HCl at reflux for 10 min–3 h as necessary.

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Hydroboration. 85. Synthesis and Hydroboration of (−)-2-Phenylapopinene. Comparison of Mono(2-phenylapoisopinocampheyl)borane with Its 2-Methyl and 2-Ethyl Analogues for the Chiral Hydroboration of Representative Alkenes

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Received August 2, 1989

The dehydration of (+)-2-phenylnopinol with $POCl_3$ provides a new chiral ligand, (−)-2-phenylapopinene (87% ee), with higher steric requirements than those of α-pinene or its 2-ethyl analogue. Hydroboration of (−)-2-phenylapopinene with BH_3·SMe_2 (BMS) (1.2:1 ratio, respectively) provides an equilibrium mixture of the mono(2-phenylapoisopinocampheyl)borane ($PapBH_2$) and the corresponding dialkylborane. Treatment of this mixture with tetramethylethylenediamine (TMEDA) precipitates crystalline $(PapBH_2)_2$·TMEDA. Liberation of the $PapBH_2$ using BF_3·OEt_2 provides the monoalkylborane in ≥99% ee, thus providing the required reagent in significantly higher optical purity than the starting olefin. Hydroboration of a series of representative olefins using $PapBH_2$ at −25 °C, followed by oxidative workup, provides the corresponding chiral alcohols in unexpectedly lower enantiomeric purities than those obtained from the 2-methyl and 2-ethyl analogues under identical conditions. Liberation of the starting auxiliary from the borane reagent provides (−)-2-phenylapopinene of ≥99% ee. The hydroboration of (−)-2-phenylapopinene with 9-borabicyclo[3.3.1]nonane (9-BBN) at 28 °C in THF proceeds at an extremely retarded rate compared to its 2-methyl and 2-ethyl analogues. Fortunately, this lack of reactivity is easily circumvented by reacting $PapBH_2$ with 1,5-cyclooctadiene at room temperature for 1 h, followed by thermal isomerization to provide the desired trialkylborane.

The current surge of activity in asymmetric synthesis has prompted searches for improved, easily accessible chiral auxiliaries and reagents. Our efforts in the area have centered on chiral, pinene-based borane reagents to perform such asymmetric transformations as the hydroboration of prochiral olefins,[2] reduction of prochiral ketones,[3] asymmetric allyl- and crotylboration,[4] and epoxide ring opening.[5]

The hydroboration of α-pinene can provide either the chiral monoalkylborane ($IpcBH_2$, **1a**) or the dialkylborane (Ipc_2BH, **2**), depending on the reaction conditions. The former reagent has been shown to hydroborate hindered prochiral trans and trisubstituted alkenes with optical

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