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Communications

Synthesis of Carbohydrate Sulfonates and Sulfonate Esters

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Summary: The reaction of α-lithio sulfonate esters with primary carbohydrate iodides provides a facile route to sulfonate analogues of important carbohydrate phosphates such as glucose 6-phosphate, ribose 5-phosphate, and uridine 5-phosphate. This method also facilitates the synthesis of complex sulfonate esters.

Isosteric replacements for the phosphate group have played an increasingly important role in the synthesis and development of enzyme inhibitors,[1] analogues of phosphorylated metabolites,[2] stable analogues of DNA,[3] phospholipids,[4] and a number of other compounds that display a wide variety of biological activities.[5] The most frequently employed analogues of phosphates are those where the peripheral substituents about the phosphate moiety have been substituted or altered; phosphonates,[6] thiophosphates,[7] phosphoramidates and phosphonamidates,[8] and phosphate triesters[9] all typify such phosphate surrogates. To a lesser extent, the replacement of phosphate monoesters by sulfate esters has also been studied.[10] In contrast to the use of sulfate monoesters, sulfonates have received almost no attention as possible phosphate monoester isosteres.

Sulfonate analogues of naturally occurring phosphate monoesters and diesters (such as RNA, DNA, and phospholipids) are potentially useful for several reasons. First, the sulfonate group is relatively stable. This is not true of sulfate monoesters, which are degraded chemically, under acidic or basic conditions,[11] and biochemically by the action of a variety of sulfatases. Although phosphonates are stable, phosphonate monoesters and diesters are appreciably less so, and are prone to undergo cyclization or rearrangement when the molecule contains a vicinal hydroxyl group (such as the 2'-OH of RNA).[12] Furthermore, in contrast to phosphonate analogues of nucleic acids, sulfonate analogues will be uncharged, and, unlike methyl phosphonate analogues of DNA, sulfonate analogues will be stereoregular. RNA containing a sulfonate backbone should also be more stable than any of the phosphorus-containing oligoribonucleotides. Stability and neutrality are factors that are generally considered to be of importance in the design of artificial antisense oligo-

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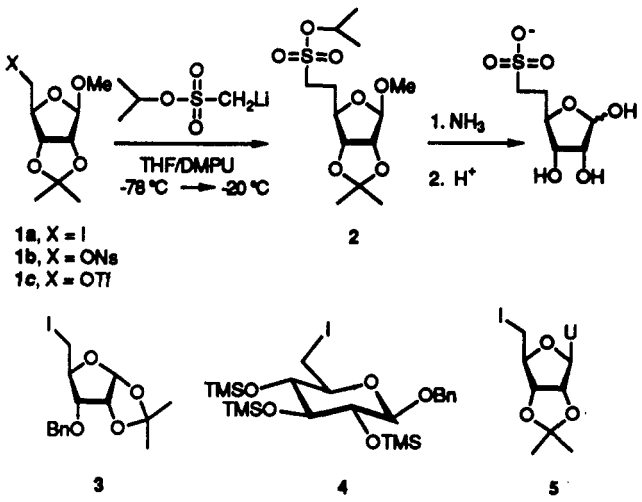
Scheme I

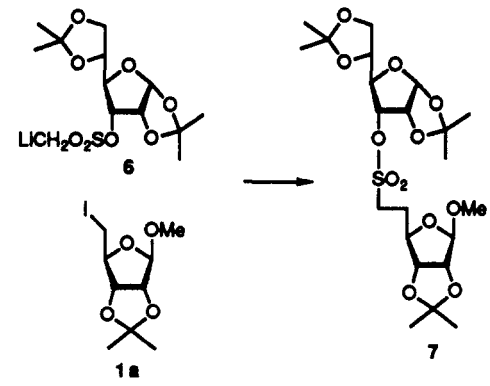


nucleotides capable of inhibiting gene expression.[13] Carbohydrate sulfonates are also likely to be good inhibitors of a variety of important sulfatases.[14] This paper details a facile method for the synthesis of carbohydrate and nucleoside containing sulfonates.

The synthesis of simple sulfonates is generally accomplished by one of several well-known reactions: (1) insertion or addition of SO_3 to hydrocarbons; (2) free-radical addition of bisulfite to terminal olefins; (3) displacement of a halide by sulfite ion (the Strecker reaction); or (4) oxidation of the corresponding mercaptan, or preferably thioester.[15] These methods have a number of significant disadvantages when applied to the synthesis of complex systems. First, these methods yield sulfonic acids, thereby requiring that the sulfonate group be protected before further elaboration of the molecule may be accomplished. Such protecting group methodology is quite limited.[15a] In addition, the conditions of the sulfonation reactions described above are often not compatible with the complex functionalities associated with carbohydrates or nucleosides.

One little explored method for the synthesis of sulfonates exploits the ability of α-lithio sulfonates to undergo reactions with alkylating agents such as methyl iodide, or, less satisfactorily, simple alkyl bromides.[16] In principle, addition of these lithiated sulfonates to the primary iodide derivatives of protected carbohydrates should be a facile method for the rapid synthesis of carbohydrate sulfonate esters, providing that two problems can be overcome: first, the low reactivity of carbohydrate iodides (especially those in the ribose series); the second, the high electrophilicity of the product sulfonate esters. In our hands we found that primary carbohydrate iodides such as the one derived from ribose (**1a**) do not undergo reaction with α-lithio sulfonates under conditions previously reported for the successful alkylation of methyl iodide. Since the expected products of these reactions (sulfonate esters) are themselves electrophiles, adjusting the reactivity of the lithiated mesylate so that it would react with the starting electrophile and not the electrophilic product was deemed crucial to the success of the alkylation. We found that adding dimethylpropyleneurea (DMPU) to the reaction mixture enhances the reactivity of the nucleophile sufficiently to lead to good yields of the protected sulfonate products provided that the starting mesylate is protected as an isopropyl group. Thus, the iodide **1a**[17] underwent smooth reaction with lithiated isopropyl mesylate to give the protected sulfonate **2** in 68% yield (Scheme I).[18] The use of more reactive alkylating agents such as the nosylate **1b** gave none of the desired products. Use of the triflate **1c** as the electrophile led to low yields and complicated mixtures, possibly because of participation by the anomeric methoxy group.[19] When the sulfonate anion is masked with less hindered protecting groups (such as ethyl), low yields of the desired products resulted, presumably because the product (an ethyl sulfonate) is a more reactive alkylating agent than the starting iodide. Further enhancing the reactivity of the nucleophile by using the potassium derivative in the presence of DMPU gave lower yields of the carbohydrate sulfonates. Another ribose derivative (**3**) also underwent substitution readily. The protected iodoglucose (**4**) suffered an even more facile reaction to yield the corresponding isopropyl sulfonate ester in 57% yield (79% based on recovered iodide), although the related tosylate proved relatively unreactive. Even the uridine iodide (**5**) could be alkylated smoothly and in reasonable yield (52%), providing an extra equivalent of the nucleophile is added to deprotonate the ureido nitrogen of the base. (Attempted alkylation of the analogous 5′-*O*-tosylate led to formation of the cyclonucleoside.)

Scheme II



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(18) **General Procedure for the Alkylation of Iodides with Lithium–Isopropyl Methanesulfonate.** To a solution of isopropyl methanesulfonate (2.764 g, 20.0 mmol) in THF (40 mL) and DMPU (12 mL) was added dropwise at −78 °C the solution of butyllithium in hexanes (2.3 N, 9.12 mL, 21.0 mmol). After 15 min, the solution of the iodide **1a** (3.141 g, 10.0 mmol) in THF (4 mL), precooled at −78 °C, was added dropwise. The stirring was continued at the same temperature for 1 h and then at −20 °C for 1 h. The reaction was quenched with acetic acid (1 mL) followed by saturated $NaHCO_3$ solution, and the product was isolated by repeated extraction with ether. The organic phase was washed with water and was then dried over $MgSO_4$. After solvent evaporation, the residue was purified by column chromatography (silica gel, hexanes–EtOAc, 6:1, 4:1) to afford the isopropyl sulfonate **2** (2.205 g, 68%) as a viscous oil. **General Procedure for the Deprotection of Isopropyl Sulfonates.** The isopropyl sulfonate **2** (285 mg, 0.879 mmol) in methanol (25 mL) was boiled under reflux while gaseous ammonia was bubbled through the solution for 9 h. TLC (hexanes–EtOAc, 2:1) indicated disappearance of the starting material. The solvent was then evaporated, and the residue was triturated with ether–THF. The white solid that formed upon trituration was filtered, dissolved in water, and applied to an ion-exchange column (AG 50W-X8 Na^+ form). Elution with water and evaporation of the product containing fractions afforded the sodium salt of the sulfonate (224 mg, 84%) as a white solid.

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The isopropyl ester is a surprisingly stable and versatile protecting group for sulfonic acids. It is stable to a wide variety of acidic and basic conditions that are commonly used to modify carbohydrate protecting groups, yet may be easily cleaved by treatment with boiling methanolic ammonia.[18] (The crude sulfonate resulting from this reaction is a mixture of ammonium and isopropylammonium salts, indicating that, in accord with the stability of this sulfonate toward base (see below), deprotection most likely occurs through an S_N2 displacement and not elimination.) The isopropyl sulfonate survived conditions required for the removal of carbohydrate isopropylidene and anomeric methoxy protecting groups, as well as basic conditions such as boiling Et_3N. A bulkier sulfonate ester, neopentyl mesylate,[16] was readily alkylated, but could not be deprotected with ammonia.

By taking advantage of the alkylation of isopropyl mesylate anions and the subsequent deprotections described above we have been able to synthesize the sulfonate analogues of ribose 5-phosphate, (three steps from the iodide **1a**, 51% overall yield); glucose 6-phosphate, (four steps from the iodide **4**, 51% overall yield); and uridine 5-phosphate (three steps from the iodide **5**, 43% overall yield). The biological activity of these phosphate analogues is currently being studied.

We have also found that complex alcohols can be used in place of the isopropyl protecting group. The anion of the relatively hindered 3-*O*-mesylate of 1,2:5,6-diacetone allose **6** could be alkylated using the iodide **1a** (49%) (Scheme II). Thus, we were able to synthesize a disaccharide **7** linked by a sulfonate group, simply by alkylating the α-lithio anion of a carbohydrate mesylate. The alkylation of mesylates should therefore provide easy access to disaccharides or oligosaccharides linked by a sulfonate backbone in analogy to the oligonucleotide backbone of ribonucleic acids. We are also currently using this methodology to synthesize and design analogues of phosphatidic acid, as well as a variety of isosteric and uncharged phospholipid analogues, to be used as potential phospholipase inhibitors and to probe the processing and recognition of phospholipids in vivo. The results of these efforts will be communicated shortly.

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Supplementary Material Available: Experimental data and NMR spectra for the compounds in this paper (14 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis of 4,4-Disubstituted 1-Naphthalenones. Diastereoselectivity as a Function of Metal Alkoxides

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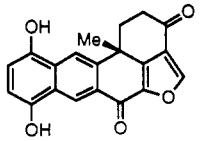
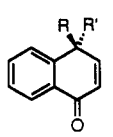
Summary: Chiral tricyclic lactam (**5**) was sequentionally metalated (LDA or LDA/zirconocene halides) and alkylated to give quaternary alkylation products (**8**) in 6–54:1 diastereomeric ratio. Reduction and hydrolysis furnish the title compound in three steps with >99% enantiomeric purity.

During the course of reaching biologically significant molecules via asymmetric synthetic routes, we were interested in the recently isolated antimicrobial,[2] halenoquinol **1**, which possesses the elements of a 4,4-disubstituted naphthalenone, **2**.[3] Since there are no known routes



(+)-1



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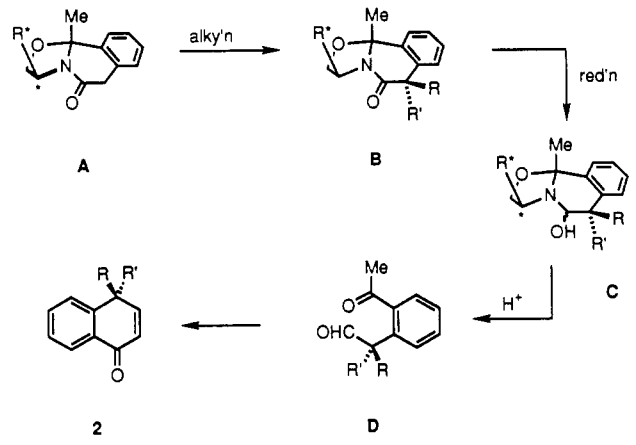
to reach these systems with absolute stereochemistry at the quaternary center,[4] we embarked on a study to initially obtain a general route to **2** and ultimately employ these as pivotal intermediates to pursue the asymmetric total synthesis of **1**. We now can report in preliminary form that our initial goal has been reached. Based on our previous reports utilizing chiral bicyclic lactams to reach a number of enantiomerically pure cyclopentenones and cyclohexenones and their application to asymmetric total syntheses,[5] we envisioned a route to chiral naphthalenones.

Scheme I



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