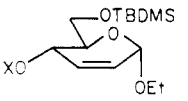
An Efficient Synthesis of Ristosamine Utilizing the Allylic Hydroxyl of an Hex-2-enopyranoside

Summary: A program is outlined for the use of allylic alcohols in cis oxyamination. The requirement is to prepare a nitrogen-containing derivative of the alcohols in which the nitrogen is the nucleophilic center. Several derivatives have been examined, but the trichloromethyl imidate ester was the only successful candidate. The methodology is illustrated by means of a synthesis of methyl ristosaminide. The trichloromethyl imidate ester from a hex-2-enopyranoside was cyclized with iodonium dicollidine perchlorate. When the resulting oxazoline was reduced with 4.4 equiv of Bu_3SnH and then subjected to acid hydrolysis, methyl *N*-acetylristosaminide was obtained directly.

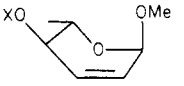
Sir: A vicinal cis hydroxy amino grouping occurs frequently in amino sugars,[1] particularly those of antibiotic origin, and recent studies in our laboratory exemplified by synthesis of garosamine,[2] holacosamine,[3] and sibirosamine[4] have shown how this traditionally troublesome structural feature can be introduced simply and efficiently. The procedure, summarized in Scheme I, eq a, is seen to begin with an allylic amine, **1**, in which the nitrogen controls the oxygenation at the adjacent site. However, this protocol does not provide a suitable approach to a number of important amino sugars such as ristosamine[5] **12c**. For the latter, the requisite allylamine precursor would be a hex-4-enopyranoside (a vinyl ether), and the product of iodocyclization (equivalent to **2**) would be a 5-iodopyranoside. Such a compound would be a tertiary iodode as well as an α-iodoether and hence would be labile and readily solvolyzable. As a result, the configuration at C5 would be insecure.

The foregoing problem could be overcome by the processes depicted in Scheme I, eq b or c, in which the allylic oxygen of **3** acts as the fulcrum to guide the entry of the nitrogen function by way of intermediates **4a** or **4b**, respectively. One obvious advantage of the latter approach is that unsaturated sugars with allylic hydroxyl groups are readily prepared;[6,7] indeed, as indicated in Scheme I, they were precursors of the allylamines in the aforementioned syntheses.[2-4] Furthermore, for a given precursor, eq a and b or c, Scheme I, would lead to regioisomeric hydroxy amines and may therefore be considered as complementary. In this report we describe some of our efforts that have culminated in the realization of the sequence in eq c, Scheme I.

For the route in eq b or c to be successful, the nitrogen in the substrate must be the most nucleophilic center. The readily available alcohols **5a**[6] or **6a**[7] were used to evaluate



5a, X = H
b, X = CSNHPh
c, X = CONHPh
d, X = C(*p*-NO_2Ph)=NH



6a, X = H
b, X = $CONH_2$
c, X = C(*p*-NO_2Ph)=NH

$I[collidine]_2ClO_4$

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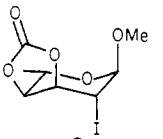

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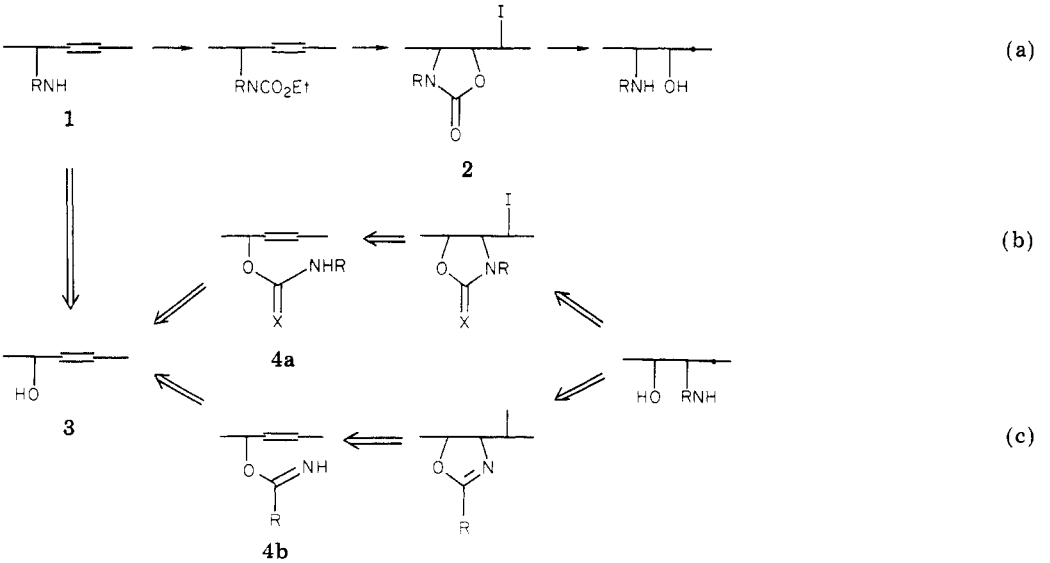
the reaction of several derivatives. The thiourethane **5b** (PhNCS/NaH/THF) was an early choice since the nitrogen in such systems is sometimes the better nucleophile.[8] However, in our hands, treatment of **5b** with complex **7**[9] led to a mixture of products. It has been reported[10] that under the influence of mercury electrophiles, allylurethanes cyclize to give the corresponding oxazolidinones. However,

Scheme I



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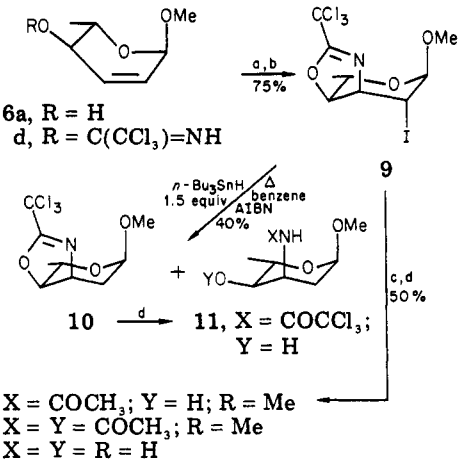
Scheme II[a]



[a] (a) Cl_3CCN (1 equiv)/CH_2Cl_2/NaH/0 °C/2h, (b) **7** (1.4 equiv)/CH_3CN/room temperature/24 h, (c) n-Bu_3SnH (4.4 equiv)/benzene/AIBN/reflux/4 h, (d) pyridine/TsOH/H_2O/1.5 h/80 °C.[14]

when either **5c** (PhNCO/NaH/THF) or **6b**[11] was treated with mercuric ion followed by sodium borohydride, the starting material was recovered unchanged in each case. On the other hand, for **6b**, use of **7** as the electrophile led to the undesired cyclic carbonate **8**.

We next turned our attention to imidate esters; however, derivatives **5d** and **6c** could not be prepared by reaction of the corresponding alcohols with sodium hydride and *p*-nitrobenzonitrile in tetrahydrofuran. Prompted by the work of Overman,[12] it was decided to examine trichloromethyl imidates, and our successful use of this species is demonstrated with a synthesis of methyl *N*-acetylristosaminide[13] (**12a**) as outlined in Scheme II.

Methyl α-L-*erythro*-2,3,6,-trideoxyhex-2-enopyranoside[7] (**6a**) was converted[12] into the imidate **6d**, and treatment of the latter with complex **7** afforded the oxazoline **9** in good yield. Subsequent reactions of **9** proved to be very interesting. Reaction with 1.5 equiv of tri-*n*-butyltin hydride gave a mixture of the deiodinated compound **10** in addition to the *N*-trichoroacetyl derivative **11**. The latter material could be obtained by hydrolysis of the former (**10**) with *p*-toluenesulfonic acid in excess aqueous pyridine.[14]

On the other hand, reaction of the oxazoline **9** with 4.4 equiv of tri-*n*-butyltin hydride followed by hydrolysis led directly to the *N*-acetyl derivative **12a**, which upon O-acetylation gave the diacetylristosaminide **12b**. The identity of **12b** was confirmed by comparison with an authentic sample.[15]

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Registry No. **5b**, 83803-01-4; **6a**, 40246-38-6; **6b**, 83803-02-5; **6d**, 83803-03-6; **7**, 69417-67-0; **8**, 83803-04-7; **9**, 83803-05-8; **10**, 83803-06-9; **11**, 83803-07-0; **12a**, 53626-04-3; **12b**, 51869-35-3.

Supplementary Material Available: Experimental details are given for the preparation of **6d**, **9**, and **12b** (3 pages). Ordering information is given on any current masthead page.

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(15) We are grateful to Drs. E. A. Acton and W. W. Lee of Stanford Research Institute for the authentic sample.[13]
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Henry W. Pauls[16]
Guelph-Waterloo Centre for Graduate Work in Chemistry
University of Waterloo
Waterloo, Ontario, Canada N2L 3G1

Bert Fraser-Reid*
Chemistry Department
University of Maryland
College Park, Maryland 20742

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