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NITRONE CYCLOADDITIONS WITH VINYL SILANES: THE TOTAL SYNTHESIS OF DEOXYSUGARS.

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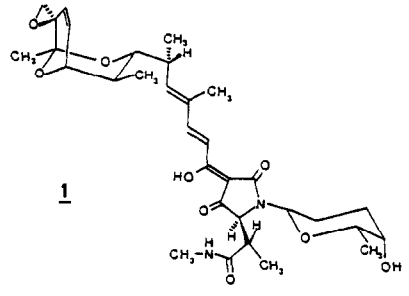
Abstract The total synthesis of (±)-rhodinose (2) and benzoxocin 4, a model system for the glycosidic moiety of nogalomycin, are reported. The key transformation in each reaction sequence involves the cycloaddition of a nitrone with vinyltrimethylsilane to produce 5-TMS-isoxazolidines followed by fluoride-induced fragmentation of the isoxazolidines to give α,β-unsaturated aldehydes.

The total synthesis of sugars from non-carbohydrate precursors remains one of the challenging problems in organic synthesis.[1] The key role played by deoxysugars in the biological action of many medicinally active compounds (i.e., daunomycin, adriamycin, gentamycin) has encouraged synthetic chemists to develop diverse strategies for their preparation. We are presently engaged in two projects which require the synthesis of deoxysugars. The first is the total synthesis of streptolydigin (1) in which the trideoxyhexose rhodinose (2)[2] is attached to the tetramic acid moiety. The second project concerns studies directed toward the preparation of tricyclic acetal 4, a model system of the glycosidic portion (rings D, E, and F) of the antitumor antibiotic nogalomycin (3).[3]



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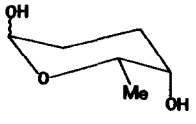

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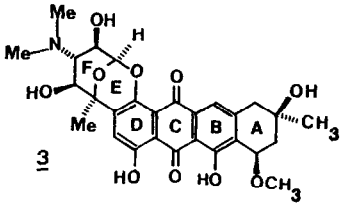

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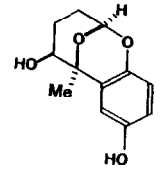

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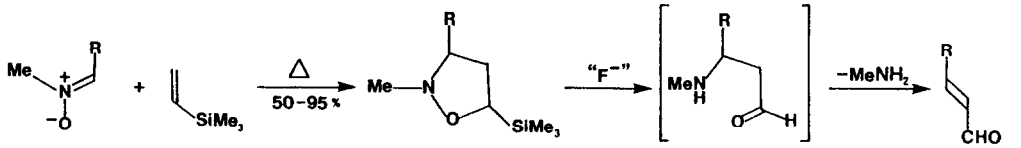
Previously we had demonstrated that nitrones react in a completely regioselective fashion with vinyltrimethylsilane to produce 5-TMS-isoxazolidines 5 as shown in Scheme I.[4] Treatment of 5 with dilute HF triggers a cascade of bond cleavage reactions ultimately resulting in the formation of an α,β-unsaturated aldehyde 6. The application of this homologation reaction to the synthesis of rhodinose (2) and acetal 4 are shown in Schemes II and III, respectively.

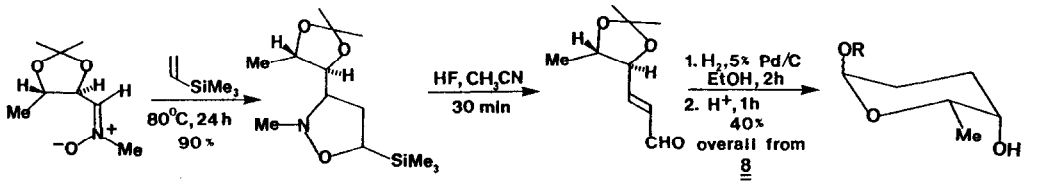
Scheme I



5 6

The rhodinose synthesis originated with nitrone 7[5]. Cycloaddition of nitrone 7 with vinyltrimethylsilane proceeded smoothly to give a 90% yield of two stereoisomeric 5-TMS-isoxazolidines 8. The stereochemical consequences of this reaction were not determined since the subsequent fragmentation of the isoxazolidine ring removes any asymmetry produced in the cycloaddition. Treatment of 8 with either 50% aqueous HF in acetonitrile or tetrabutylammonium fluoride in THF gave the unstable aldehyde 9. Nucleophilic attack of fluoride at silicon results in the formation of a transient β-amino aldehyde as indicated in Scheme I. Catalytic reduction of enal 9 followed by removal of the acetonide group with 2% HCl in methanol yielded racemic methyl rhodinoside[5a] as a mixture of anomers in 37% overall yield from nitrone 7.

Scheme II. Synthesis of (±)-Rhodinose.

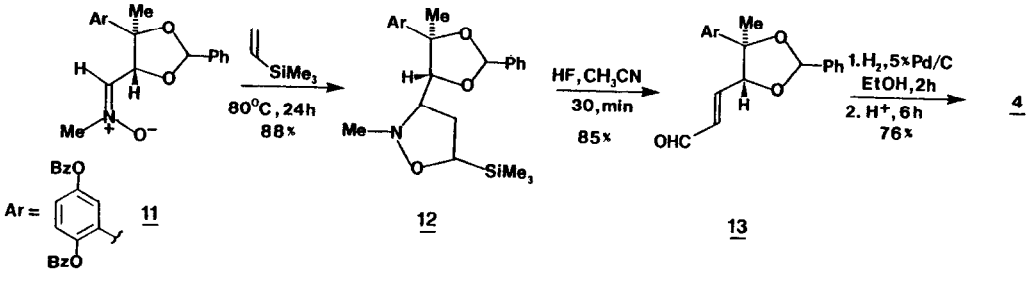


7 8 9 10: R = Me
2: R = H

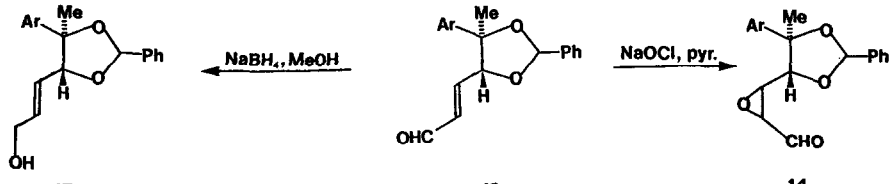
Rhodinose could be obtained from either the intermediate saturated aldehyde or from methyl glycoside 10 by treatment with 2% HCl in aqueous acetone at room temperature.

Having shown that simple deoxysugars could be prepared using the nitrone methodology, we turned our attention to the preparation of the more complex benzoxocin moiety found in the DEF-ring system of nogalomycin. The approach follows the pattern established in the earlier synthesis and is outlined in Scheme III. Nitrone 11[6] underwent dipolar cycloaddition with vinyltrimethylsilane to produce a 1:1 mixture of isomeric 5-substituted isoxazolidines 12 in 88% yield. In analogy to the rhodinose synthesis, fluoride treatment triggered isoxazolidine ring fragmentation and elimination of methyl amine to produce the unsaturated aldehyde 13[5b] (85%). Saturation of the double bond by catalytic reduction (91%) also resulted in the cleavage of the benzyl ethers on the protected hydroquinone. Mild acid hydrolysis of the benzylidene protecting group gave benzoxocin 4[5c] in 76% yield. Therefore, in four steps from nitrone 11, tricyclic acetal 4 had been realized in an overall yield of 52%.

Scheme III. Synthesis of Benzoxocin 4.



Unsaturated aldehyde 13 would appear to be a valuable intermediate in the preparation of more functionalized deoxysugars related to nogalomycin. In this regard, we have demonstrated that 13 can be epoxidized with NaOCl in pyridine to give epoxyaldehyde 14 in 49% yield. In addition, reduction of aldehyde 13 with $NaBH_4/CeCl_3$ produced the allylic alcohol 15 in 93%. The incorporation of nitrogen functionality into 14 and 15 is currently under investigation.



15 13 14

The ability of silicon to activate the N,O-bond of isoxazolidines towards heterolytic cleavage offers considerable synthetic potential. Studies are underway to explore the limitations of this reaction.

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5.a) Small quantities of the methyl furanoside were also formed which is consistent with the findings of Dyong, I.; Knollmann, R.; Jersch, N. **Chem. Ber. 1977, 110,** 2729. ^{1}H NMR data are in agreement with those provided in this reference. b) ^{1}H NMR δ 8.86 (d,J=7.5,CHO), 6.33-6.49 (m,CH=CH); IR 1698 cm^{-1}. c) ^{1}H NMR (acetone d_6) δ 1.52(s,3H,-CH_3), 1.7-2.1(m,4H), 3.64(dd,J=4.2,11.5, 1H,H_4), 5.41(dd,J=2.3,1.9.1H,H_1), 6.5-6.7(m,3H); IR(CCl_4) 3620(m), 2960(s), 1480(s), 1080(vs) cm^{-1}; mass spectrum (m/z,%) 222(M^+,64), 204(11), 178(36), 137(100); Anal. Calcd for $C_{12}H_{14}$: C, 64.85; H, 6.35. Found: C, 64.44; H, 6.53; mp 151-154°C.
6. Nitrone 11 was prepared by 1) olefination of 2',5'-dibenzyloxyacetophenone with triethylphosphonoacetate, 2) cis hydroxylation using OsO_4/N-methyl morpholine N-oxide, 3) protection of the diol as the benzylidine, 4) reduction to the aldehyde with DIBAL, and 5) condensation with N-methyl hydroxylamine to form nitrone 11.

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