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ACYCLIC STEREOSELECTION. 19. TOTAL SYNTHESIS OF (±)-RISTOSAMINE AND (±)-MEGALOSAMINE.[1]

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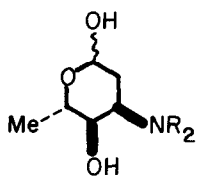
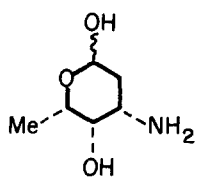
Abstract: (±)-Ristosamine (**1**) has been synthesized in seven straightforward operations from ketone **5** and O-benzyllactaldehyde. The key step is a stereoselective aldol addition reaction in which diastereomeric aldols **7** and **8** are produced in a ratio of 78:22. A simple modification of the synthesis provides (±)-megalosamine (**4**).

Ristosamine (**1**) is a rare amino sugar that was first isolated as the glycone of the antibiotic ristomycin.[2,3] It is a diastereomer of daunosamine (**2**) and acosamine (**3**), which are important as the glycones of anthracycline antitumor agents.[4] Megalosamine (**4**) is the N,N-dimethyl derivative of ristos-



1: R = H
4: R = Me



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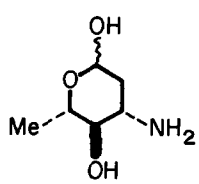

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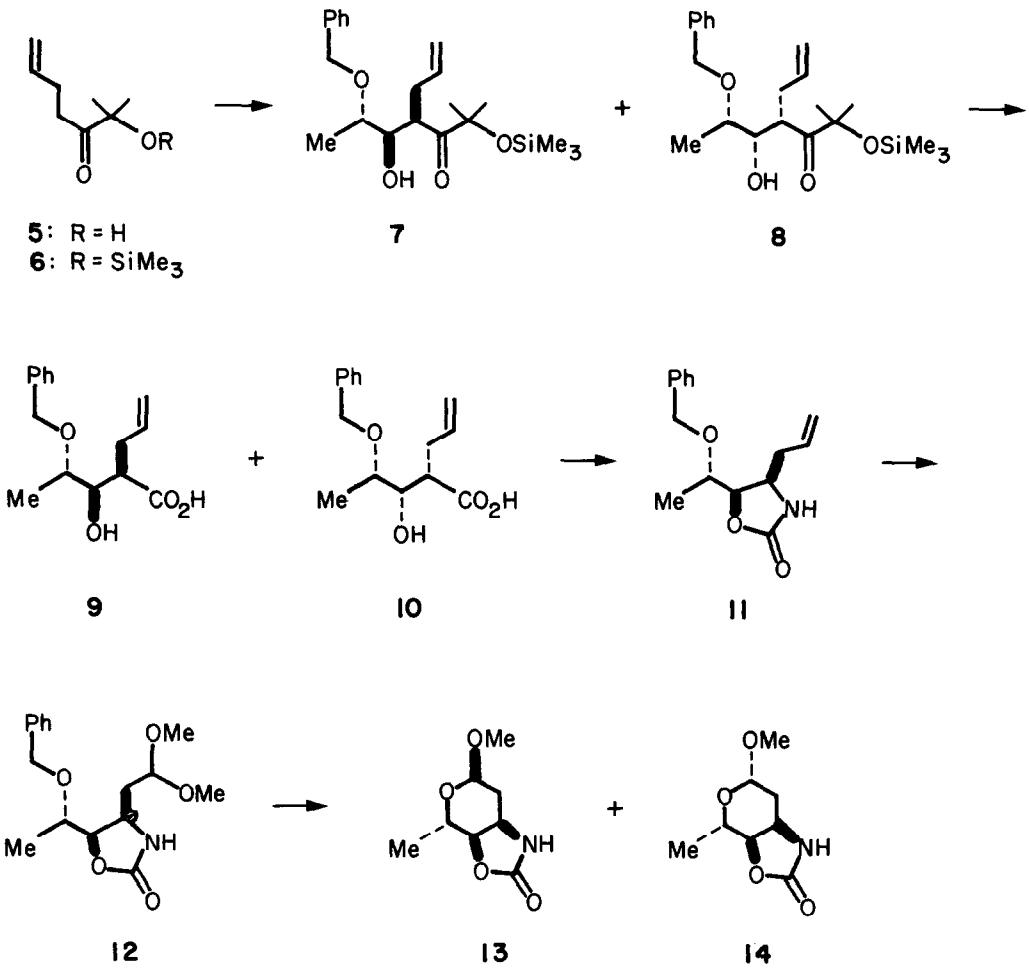
amine.[5] As part of a long-range program to develop the aldol addition reaction as a reliable method for the diastereoselective synthesis of natural products, we have carried out total syntheses of (±)-ristosamine and (±)-megalosamine.[6,7]

Treatment of ketone **6**[8] with lithium diisopropylamide in THF, followed by (±)-O-benzyllactaldehyde gives a mixture of diastereomeric aldols **7** and **8**. If two molar equivalents of ketone **6** are employed, the ratio of **7**:**8** is 78:22 and the combined yield (based on aldehyde) is 97%. The observed stereoselectivity in this reaction is in accord with previous observations with regard to stereoselection in the aldol addition reaction.[9] Treatment of the mixture with periodic acid in tetrahydrofuran[10] provides β-hydroxy acids **9** and **10** in 83% yield. In this mixture, the **9**:**10** ratio is enhanced, indicating that isomer **7** undergoes cleavage more rapidly than **8**. Control experiments with mixtures of **7** and **8** of

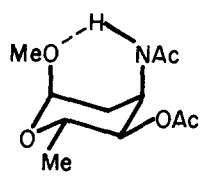
various composition showed that, under the conditions that convert 7 to **9** in 96% yield, isomer **8** is converted to **10** in only 38% yield. Acids **9** and **10** are readily separable by chromatography on silica. Modified Curtius degradation of **9**[11] provides an oxazolidone (**11**) in 69% yield. Lemieux-Johnson oxidation[12] of this substance provides an aldehyde which is treated with acidic methanol to obtain acetal **12** in 87% yield. Catalytic hydrogenolysis of **12** gives a 68:32 mixture of anomeric methyl glycosides **13** and **14** in 87% yield. That this mixture corresponds to the thermodynamic ratio was established by treatment of the isolated minor isomer (**14**) with acidic methanol for varying periods of time, whereupon the same 68:32 ratio of **13** and **14** was restored. It has been reported



5: R = H
6: R = $SiMe_3$

7 **8** **9** **10** **11** **12** **13** **14**

that the ristosamine derivative **15** exists overwhelmingly as the α-anomer,[3] presumably because of hydrogen bonding between the amide N-H and the axial methoxy group. Dreiding stereomodels of bicyclic oxazolidone **13** show that it is not possible for the N-H to hydrogen bond to the methoxy, if one assumes that the H-N-C=O array is planar. Hydrolysis of the anomeric mixture of **13** and **14**



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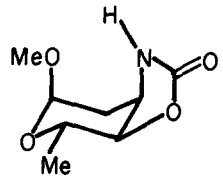

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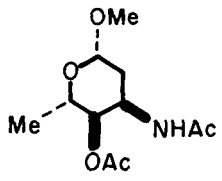
with aqueous barium hydroxide, followed by aqueous acid provides (±)-ristosamine (**1**) in 87% yield as the reported[3] anomeric mixture. The synthetic (±)-ristosamine was identified by conversion into an anomeric mixture of N,O-diacetyl methyl glycosides **16** and **17**, the ^{1}H NMR spectra of which have been reported.[3,6k]



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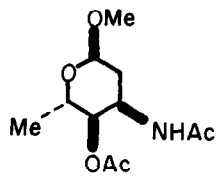

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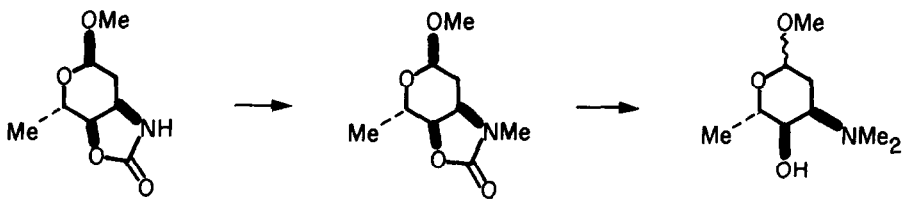
For the synthesis of (±)-megalosamine, oxazolidone **13** is methylated with sodium hydride and methyl iodide (85%). The resulting N-methyl derivative (**18**) is reduced with lithium aluminum hydride to give a 70:30 mixture of the anomeric methyl glycosides of (±)-megalosamine (**19a** and **19b**). Compounds **19a** and **19b** were identified by comparison of their ^{13}C NMR spectra with those reported for the methyl glycosides of megalosamine.[5]



13 **18**

19a: α-anomer
19b: β-anomer

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References and Notes

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