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Medium-ring aminocyclitols: a concise synthesis of nine-membered aminocarbasugar analogs and the solid-state supramolecular architectures of two key precursors

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ABSTRACT

A stereocontrolled synthesis of nine-membered aminocarbasugar analogs (amino-cyclononanoses) from a rigid bicyclo[4.3.1]deca-2,4-dien-10-one platform, harboring a latent functionalized cyclononane ring, is described.

1. Introduction

Cyclitols or carbocyclic polyols have emerged as an important, rapidly expanding and diversified family of bioactive entities that include inositols, conduritols and carbasugars among other variants.[1] These molecules are involved in the function and regulation of a number of biological processes, critical for the sustenance of life, such as cellular recognition, signal transduction and selective inhibition of carbohydrate processing enzymes (glycosidases).[2] These attributes make cyclitols and carbasugars desirable substrates for targeting many key pathways that have been implicated in disorders ranging from diabetes to viral infections and cancer.[2b–d] Hence, it is hardly surprising that there has been a sustained interest over the past few decades in synthetic endeavors directed toward creating diversity within the basic framework of these polyhydroxylated entities. Amino substituted siblings of cyclitols and carbasugars, such as **1** and **2**, have invoked particular attention in this regard as their scaffolds have proved to be quite promising in drug discovery and development.[3] Indeed, voglibose **3** (Basen®),[4a] being currently employed as a therapeutic for type 2 diabetes, and *N*-octylvalienamine **4** (being developed for Gaucher's disease)[4b] vouch for the continued quest for newer analogs.

Among the many tactics that can be deployed for diversity creation and analoging around cyclitols and carbasugars, an interesting concept is ring size variation with the intent of realizing the cyclitol motif in medium-sized rings so as to fine tune the hydrophilic–hydrophobic balance and also impart the cyclitol with a conformational flexibility not available in the five- and six-membered rings. We and others have previously reported synthetic studies directed toward imprinting a cyclitol motif on seven-,[5] eight-,[6] and nine-membered[7] rings. An extension of these efforts has led to the quest for and realization of various seven- and eight-membered aminocyclitols, and aminocarbasugar analogs.[8] As a further advance in this area, we report herein the first synthesis of nine-membered aminocarbasugar (amino-carbanonanose) motif **5**. The interesting patterns of hydrogen bonding and self-assembly, encountered en route, in two of the crystalline advanced intermediates will also be discussed in some detail.

2. Synthesis of the amino-carbanonanoses

While contemplating an approach to the amino-carbanonanose system **5**, we were cognizant of the often encountered deviant behavior of medium rings in undergoing undesirable transannular reactions so as to render manipulation of functionalities on the

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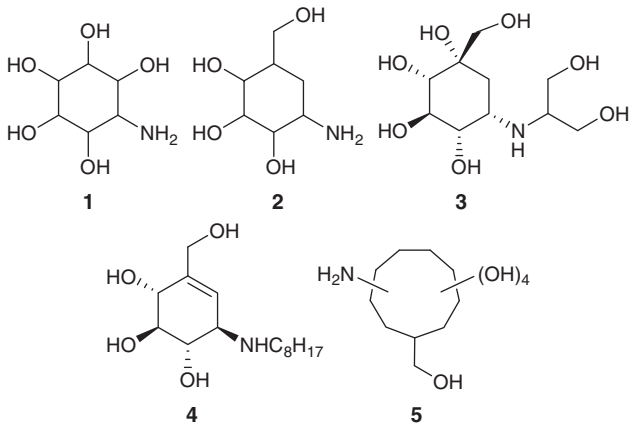
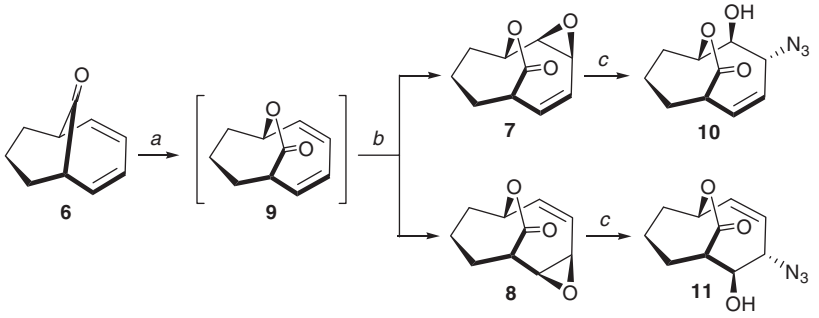


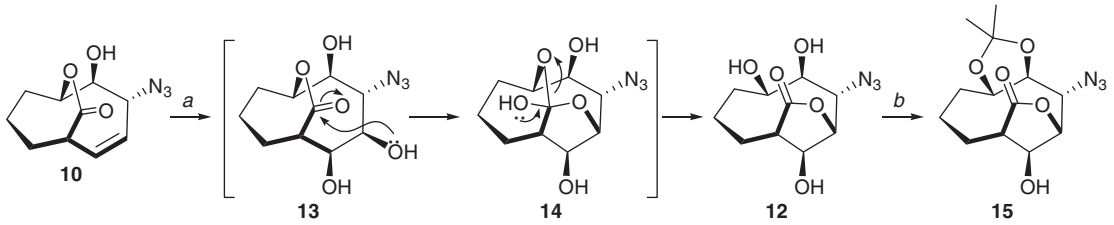
carbocyclic scaffold difficult. Thus, we opted for a strategy which will keep the key functionalities internally locked, enable functional group alterations on the rigid framework and permit extrication of the nine-membered ring at the very end. Keeping in mind the salient features of this strategy, the readily available bicyclo[4.3.1]deca-2,4-dien-10-one **6** was once again selected as the starting point.

Oxidation of **6** in the presence of *m*-chloroperbenzoic acid furnished two epoxides **7** and **8** (1:1) through the intermediacy of the Baeyer–Villiger oxidation lactone **9**,[7] Scheme 1. While the formation of **7** and **8** exhibited little regioselectivity, epoxidation leading to them was stereoselective with a preferential approach of the peracid from the β-face and could be attributed to either inherent topological bias of the substrate or to possible hydrogen bonding interactions of the peracid with the lactone oxygens. Azide mediated epoxide ring opening in **7** was both regio- and stereo-selective, and furnished a single azidoalcohol **10**, Scheme 1. In a similar manner, epoxylactone **8** delivered upon treatment with sodium azide the regioisomeric azidoalcohol **11**, Scheme 1.

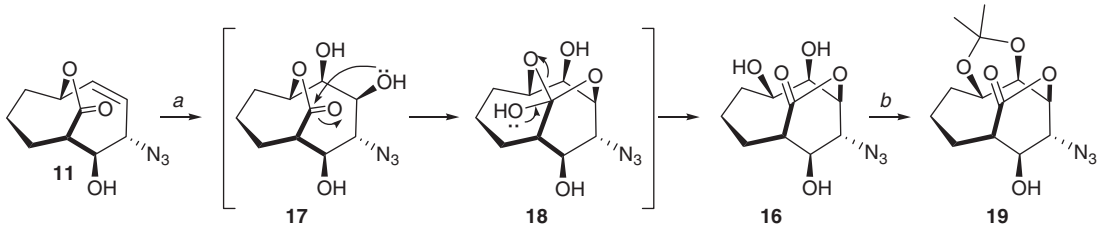
Catalytic OsO_4 mediated dihydroxylation of the hydroxyazide **10** smoothly delivered a rearranged trihydroxy γ-lactone **12**[9] through the intermediacy of the initially formed triol **13** and tetrahedral intermediate **14** as shown in Scheme 2. The *cis*-diol moiety in **12** was readily protected as a crystalline acetonide **15** and single crystal X-ray structure determination secured its stereostructure as well as those of its precursors (vide infra).[10] In a complementary sequence, the regioisomeric hydroxyazide **11** on OsO_4 mediated dihydroxylation furnished the rearranged δ-lactone **16**[9] via the intermediates **17** and **18**, Scheme 3. The *cis*-diol moiety in **16** was smoothly protected to deliver a crystalline acetonide **19** whose formulation was unambiguously established through single crystal X-ray diffraction studies (vide infra).[11] It is to be noted that the intramolecular lactone rearrangements in both **13** and **17** are



Scheme 1. Reagents and conditions: (a) Ref. 7; (b) *m*-CPBA (1 equiv), aq $NaHCO_3$, DCM, 0 °C, 30 min, 90–95% (**7**:**8** = 1:1); (c) NaN_3, NH_4Cl, $EtOH/H_2O$, reflux, 4 h, 56% for **10** and 84% for **11**.



Scheme 2. Reagents and conditions: (a) OsO_4, NMMO, acetone/water (4:1), rt, 12 h, 79%; (b) 2,2-dimethoxypropane, PTSA, DCM, rt, 3 h, 83%.



Scheme 3. Reagents and conditions: (a) OsO_4, NMMO, acetone/water (4:1), rt, 15 h, 74%; (b) 2,2-dimethoxypropane, PTSA, DCM, rt, 3 h, 88%.