Tetrahedron Letters 58 (2017) 2732–2735

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new synthon for the synthesis of aminoinositol derivatives

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ARTICLE INFO

Article history:
Received 28 March 2017
Revised 25 May 2017
Accepted 31 May 2017
Available online 1 June 2017

Keywords:
Oxabicycloheptene
Aminoinositol
Diacylazide
Curtius rearrangement
Neighbouring group participation

ABSTRACT

The regio- and stereoselective synthesis of a new synthon, *trans*-3,8-dioxatricyclo[3.2.1.0^{2,4}]octane-6,7-diamine, from 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate is reported. Transformation of the acid functionalities to acyl azides followed by Curtius rearrangement gave the corresponding *trans*-diisocyanate, which was reacted with HCl to produce a *trans*-diamino compound that is a potentially important synthon for the versatile synthesis of aminocyclitols.

Introduction

Aminocyclitols,[1] also known as amino-carbasugars, are an important class of compounds that have received wide attention in recent years due to their varied medicinal applications. Carbasugars,[2] formed by replacing the ring-oxygen atom in monosaccharides with a methylene moiety, are thought to be more potent drug candidates than natural sugars because of their enhanced hydrolytic stability. The aminocyclitol moiety has also been used by medicinal chemists as a versatile scaffold in drug design. Natural aminocyclitols such as valienamine (**1**) and validamine (**2**) are secondary metabolites which were first isolated as fragments of the pseudooligosaccharide validamycin.[3] Valienamine (**1**), validamine (**2**) and their analogues were reported to show inhibitory activity against certain glycosidases.[1] An aminocyclitol, voglibose (**3**), is primarily used in the treatment of diabetes mellitus type 2 for establishing greater glycemic control by preventing the digestion of carbohydrates (Fig. 1).

Various aminocyclitol derivatives have been synthesized from either natural products or commercially available starting materials.[4] The development of regio- and stereoselective synthetic methodologies leading to aminocyclitol and analogues is desirable. Recently, we developed different methodologies for the synthesis of various aminocyclitols.[5]

7-Oxabicyclo[2.2.1]heptene (**4**), 7-oxabicyclo[2.2.1]-heptadiene (**5**) and their derivatives are valuable intermediates in the total synthesis of natural products and analogues.[6] These 7-oxanorbornane derivatives can be easily synthesized *via* the Diels–Alder addition of furans to alkenes and alkynes (Fig. 2).

The ring-opening chemistry of oxabicyclic compounds has undergone significant growth in recent decades with the oxabicyclic template becoming an increasingly common starting material for the preparation of both cyclic and acyclic compounds. Cleavage of the carbon-oxygen bond in these systems produces functionalized cyclohexenes or cyclohexenols. The ring-opening reactions can be triggered by acid catalysts,[7] bases,[8] and metals.[9]

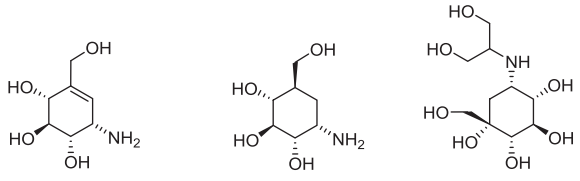

Fig. 1. Selected biologically active aminocyclitols.

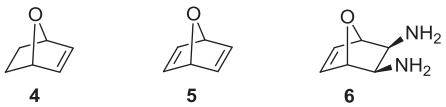

Fig. 2. 7-Oxanorbornane derivatives **4**–**6**.

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http://dx.doi.org/10.1016/j.tetlet.2017.05.099
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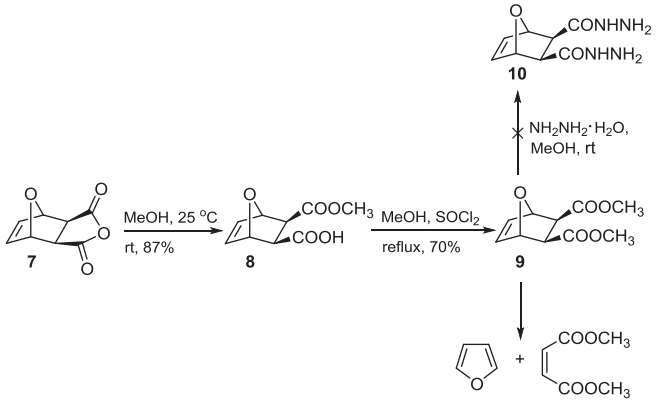
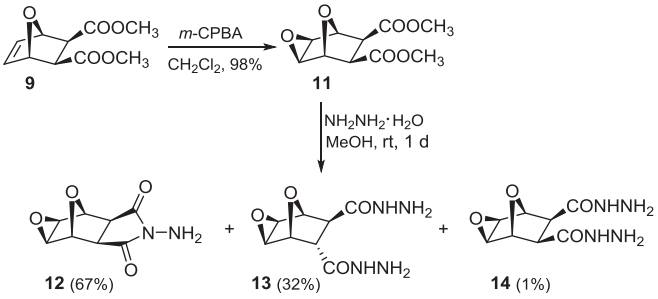
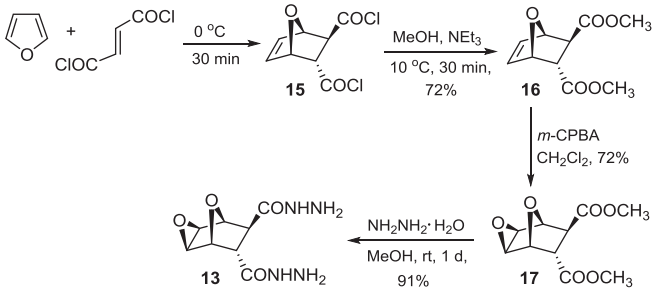


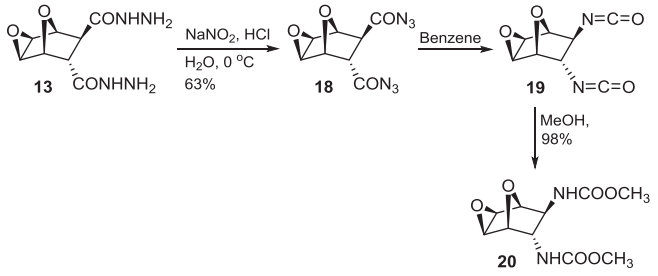
Scheme 1. Synthesis of diester **9** and its reaction with hydrazine.



Scheme 2. Synthesis of diester **11** and its reaction with hydrazine.



Scheme 3. Synthesis of *trans*-dihydrazide **13**.



Scheme 4. Synthesis of diurethane **20**.

Our primary goal was the synthesis of 7-oxabicyclo[2.2.1]hept-5-ene-2,3-diamine (**6**) and its derivatives starting from the adduct **7**.

The starting material **7** with an *exo*-configuration, was synthesized in almost quantitative yield by the addition of maleic anhydride to furan at room temperature according to the literature procedure.[10,11] It is well established that the Diels–Alder reaction between furan and maleic anhydride is reversible and the more thermodynamically stable *exo*-adduct **7** is formed as the final product. The reaction of diacyl chlorides with NaN_3 has been reported as an efficient method for the synthesis of acyl azides. Reaction of the diacid derived from **7** with thionyl chloride produced the corresponding anhydride. Therefore, we decided to first synthesize diester **9**. Thus, adduct **7** was dissolved in MeOH and the half-ester **8** was isolated in 87% yield. Reaction of half-ester **8** with $SOCl_2$ in MeOH[11] provided the desired diester **9** (Scheme 1).[10a,12]

Acyl azides can also be prepared by the diazotization of acyl hydrazines.[13] The reaction of diester **9** with hydrazine in MeOH did not provide the desired dihydrazide **10**, instead a retro Diels–Alder reaction occurred to give furan and dimethyl maleate (Scheme 1). To prevent the retro Diels-Alder reaction and to introduce additional oxygen functionalities into the molecule, diester **9** was reacted with *m*-chloroperbenzoic acid in CH_2Cl_2 to give the *exo*-epoxide **11** in 98% yield.[14] Exclusive formation of the *exo*-isomer can be explained by double bond pyramidalization[15] as well as the directing effect of the bridge oxygen atom (Scheme 2).

Epoxide **11** was treated with hydrazine monohydrate in MeOH at room temperature. However, NMR spectroscopy indicated the presence of three products, with the desired product **14** formed in only 1% yield. The major product was a cyclic imide **12**, formed *via* formation of the corresponding monohydrazide and subsequent intramolecular cyclization. Diacyl hydrazide **13** was also formed in 32% yield, however, the configuration of the acyl hydrazide functionalities was changed from *cis* to *trans*. It is expected that carbonyl groups having an α-proton can easily undergo configurational isomerization in the presence of a base. At this stage we decided to replace the starting material, *cis*-diester **11**, with

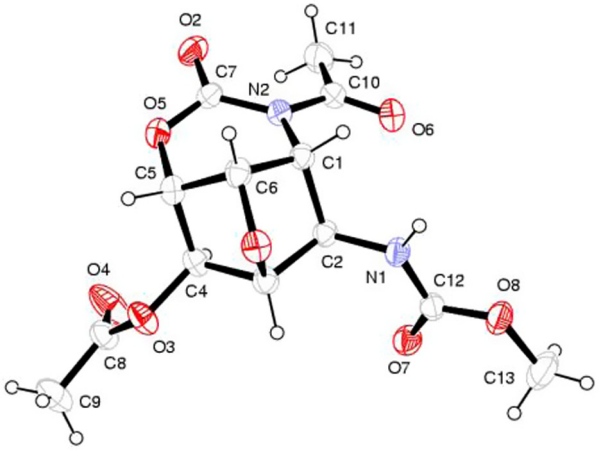
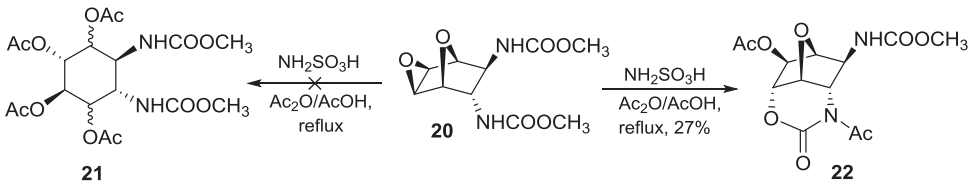


Fig. 3. Crystal structure of **22**.



Scheme 5. Sulfamic acid catalyzed ring-opening reaction of **20**.