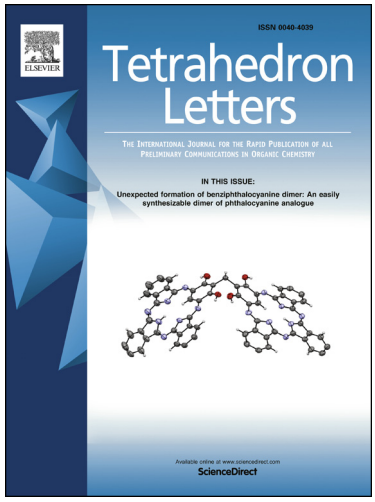


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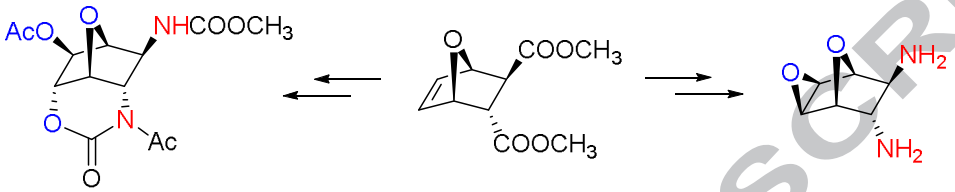

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# A New Synthon for the Synthesis of Aminoinositol Derivatives

Nalan Korkmaz Cokol,[a] Serdal Kaya,[a,b] Metin Balci*,[a]

[a]*Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey*
[b]*Department of Chemistry, Giresun University, 28200 Giresun, Turkey*

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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.



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.

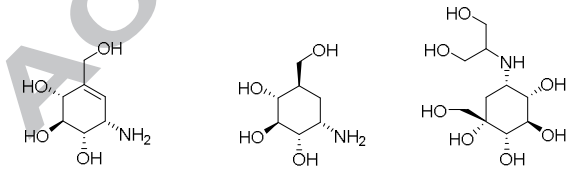



**Figure 1**. Selected biologically active aminocyclitols

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.l]heptene (**4**), 7-oxabicyclo[2.2.l]-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.

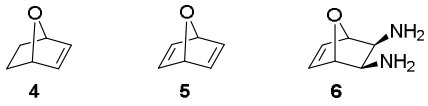
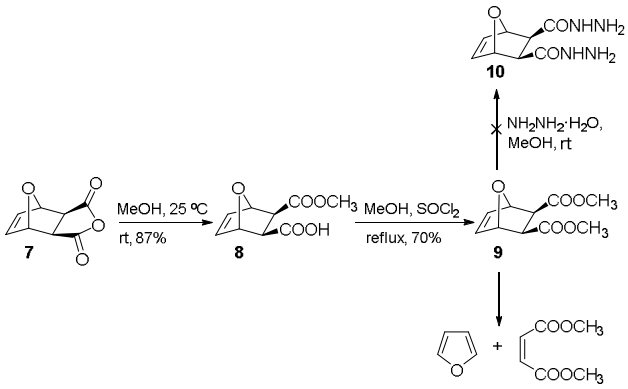



**Figure 2**. 7-Oxanorbornane derivatives **4-6**.

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] Our primary goal was the synthesis of 7-oxabicyclo[2.2.l]hept-5-ene-2,3-diamine (**6**) and its derivatives starting from the adduct **7**.

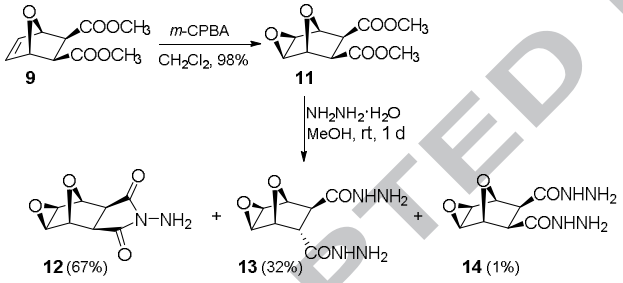
The starting material **7** with an *exo*-configuration, was synthesized in almost quantitative yield by the addition of maleic anhydride to furan at room temperature according to the literature procedure.[10,11] It is well established that the Diels–Alder reaction between furan and maleic anhydride 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]




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

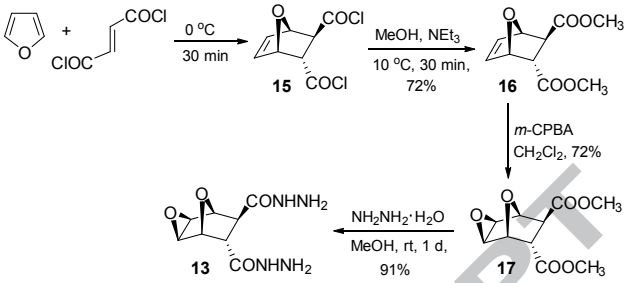
Acyl azides can also be prepared by the diazotization of acyl hydrazines.[13] The reaction of diester **9** with hydrazine in MeOH did not provide the desired dihydrazide **10**, instead a retro Diels–Alder reaction occurred to give furan and dimethyl maleate (Scheme 1). To prevent the retro Diels-Alder 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).




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

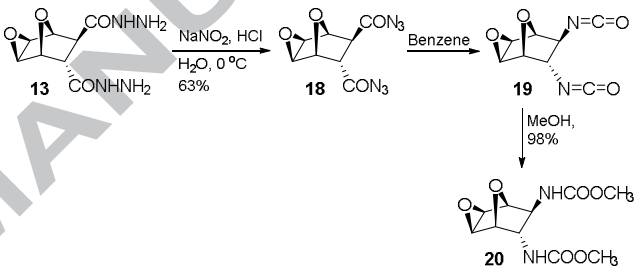
Epoxide **11** was treated with hydrazine monohydrate in MeOH at room temperature. However, NMR spectroscopy indicated the presence of three products, with the desired product **14** formed in only 1% yield. The major product was a cyclic imide **12**, formed *via* formation of the corresponding monohydrazide 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 the corresponding *trans*-diester **16** in which intramolecular cyclization cannot occur.

*trans*-Diester **16** was prepared *via* the cycloaddition of fumaroyl dichloride with furan to give **15**,[16] followed by reaction with MeOH in the presence of $NEt_3$ (Scheme 3). To avoid a retro-Diels–Alder reaction, the double bond in **16** was epoxidized with *m*-chloroperbenzoic acid as described above. Epoxide **17** was successfully converted into the desired dihydrazide **13** upon treatment with hydrazine hydrate in MeOH (Scheme 3).




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

The resulting compound **13** was treated with $NaNO_2$ and HCl at 0 °C to give the corresponding diacylazide **18**. Heating **18** at reflux in benzene gave diisocyanate **19**, which was carried onto the next step without purification. Heating a solution of **19** in MeOH at reflux temperature afforded diurethane **20** in 98% yield (Scheme 4).

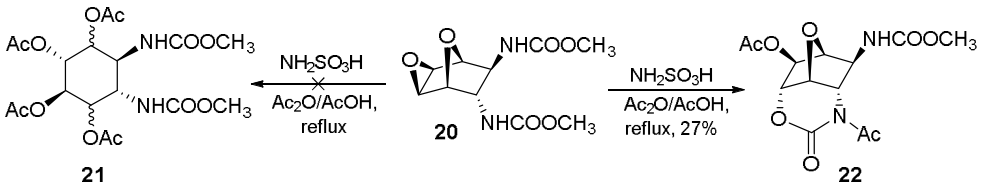



**Scheme 4.** Synthesis of diurethane **20**.

The $^1$H- and $^{13}$C-NMR spectra of **20** are in agreement with the proposed structure. The epoxide protons give rise to an AB-system with a coupling constant of $J = 3.2$ Hz which is within the expected range for epoxide protons. Bridgehead protons appear at 4.25 and 4.73 ppm as singlet and broad singlet peaks, respectively. The presence of two different NH-proton resonances at 5.25 and 5.15 ppm supports the *trans*-configuration of the urethane groups. Furthermore, the 10 resonance $^{13}$C-NMR is also in agreement with the structure as well as with the *trans*-configuration.

Next, the ring opening reaction of **20** was studied. Sulfamic acid[17] was used as an efficient catalyst to promote opening of the epoxide ring as well as the tetrahydrofuran ring. Diurethane **20** was reacted with sulfamic acid in a mixture of acetic anhydride and acetic acid, however, instead of the expected tetraacetate **21**, the rearranged compound **22** was formed as the isolable product (Scheme 5).

The $^1$H NMR spectroscopic studies on **22** clearly indicated the removal of one of the two methoxy groups and the incorporation of two acetyl groups into the molecule. Furthermore, with the help of 2D–NMR, we were able to determine that the oxygen bridge was intact and did not undergo a ring-opening reaction. The structure of **22** was confirmed by single crystal X-ray analysis (Fig. 3). During the conversion of **20** to **22**,




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

two successive reactions occurred; opening of the epoxide ring by nucleophilic attack of the carbonyl group of the *endo*-urethane moiety, followed by acetylation. Therefore, we decided to first convert diisocyanate **19** to diamine **24**. Diisocyanate **19** was reacted with 8 M HCl at room temperature to give salt **23** in 95% yield. The reaction of **23** with a solution of 0.5 M NaOH at 0 °C gave the desired compound diamine **24** in 23% yield.

Within **24** the epoxide protons resonated as doublets at 3.62 and 3.34 ppm with a coupling constant of $J$ = 3.4 Hz. The bridge proton resonances appear at 4.07 and 4.70 ppm as a singlet and doublet ($J$ = 4.7 Hz), respectively. The 6 resonance $^{13}$C-NMR spectrum was also in agreement with the proposed structure.

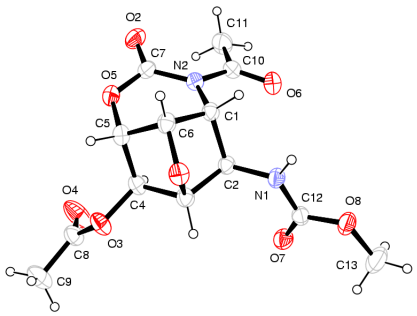
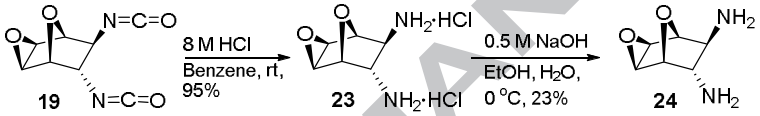



**Figure 3.** Crystal structure of **22**.




**Scheme 6.** Synthesis of diamine **24**.

The synthesis of synthons **22** and **24** was achieved from *trans*-7-oxabicyclo[2.2.1]-ept-5-ene-2,3-dicarboxylate. The amine functionalities were introduced by Curtius rearrangement of the corresponding acyl azide while the oxygen functionality was introduced to the molecule by epoxidation of the double bond in **16**. This methodology opens up a way to synthesize versatile isomeric aminoinositol derivatives and further reactions with compounds **22** and **24** are currently in progress.

## Acknowledgments

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**Supplementary Material**

Supplementary data (1D and 2D NMR spectra and the X-ray crystal structure of can be found in the online version, at http://dx.doi.org/.....

Highlights

A new synthon for accessing more complex azacarbasugars was synthesized.

Concise route to unusual, highly oxygenated small molecules was developed.

A double Curtius rearrangement was applied to introduce amino functionalities.