ORGANIC LETTERS

2009
Vol. 11, No. 13
2948−2950

Synthesis of the Deoxyaminosugar (+)-D-Forosamine via a Novel Domino−Knoevenagel−Hetero-Diels−Alder Reaction

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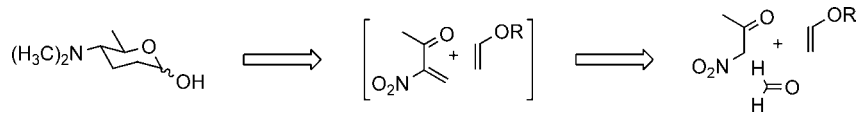
Received April 24, 2009

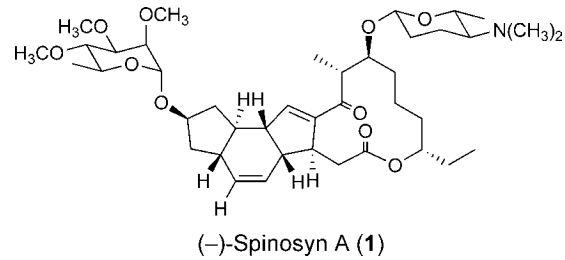
ABSTRACT



A synthesis of (+)-D-forosamine was developed. The sugar-scaffold was constructed by a new domino−Knoevenagel−hetero-Diels−Alder reaction from easily available starting materials.

Deoxyaminosugars play an important role as glycosidic units in many natural products such as aminoglycosides, macrolides, anthracyclines, or spinosyns[1] such as **1** (Figure 1), in which the electron-rich amino group of the glycosyl moiety is often attributed to the biological activity of these compounds.

Hetero-Diels−Alder reactions offer an elegant and efficient route to the tetrahydropyran skeleton of carbohydrates.[2] Therefore, cycloaddition of a 1-oxa-1,3-butadiene and an enol ether yields a substituted dihydropyran, which is then transformed into the corresponding tetrahydropyran by hydrogenation. Thus, several deoxy-3-aminosugars such as acosamine and 4-deoxydaunosamine[2b,j] have been prepared using this procedure with good yields and high regioselectivity.



(−)-Spinosyn A (**1**)

Figure 1. Naturally occurring spinosyn A.

The 2,3,6-trideoxy-4-dimethylaminosugar forosamine (**2**) is an integral part of the *Streptomyces* metabolites spiramycins I−III[3a] and of the spinosyns such as **1**,[4] which show high antibiotic and insecticidal acitivity, respectively.

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10.1021/ol900899a CCC: $40.75
Published on Web 06/11/2009

Within our attempts to prepare novel analogues of the spinosynes using multiple Pd-catalyzed transformations,[5] efficient access to forosamine was required. Several syntheses of the 4-aminosugar forosamine (**2**) by transformation of glucose derivatives or by epoxidation of sorbic acid and successive reaction with dimethylamine have been published so far.[4a,6]

Herein, we describe a very short approach to **2** using a three-component domino−Knoevenagel−hetero-Diels−Alder reaction in which a 2-alkoxy-6-methyl-5-nitro-3,4-dihydro-2*H*-pyran (**3**) is formed in one process from simple and easily accessible starting materials.

The retrosynthetic analysis of **2** leads to the dihydropyran **3**, which can be constructed by a hetero-Diels−Alder reaction with inverse electron demand of nitrobutenone (**5**) and an alkyl vinyl ether **4**. Compound **5** is accessible in situ by a Knoevenagel condensation of nitroacetone (**7**) and formaldehyde (**6**) (Figure 2). Thus, reaction of nitroacetone, which

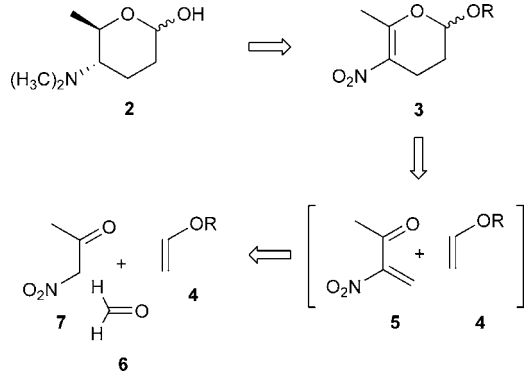
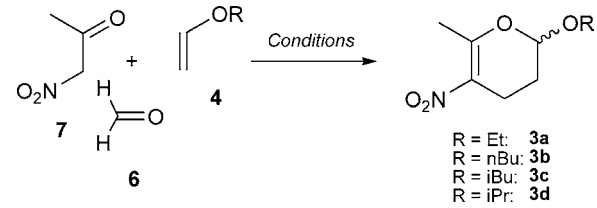


Figure 2. Retrosynthetic analysis.

is prepared by acetylation of nitromethane[7] with 2.0 equiv of aqueous formaline and 20 equiv of ethyl vinyl ether, gave the corresponding racemic dihydropyran **3** in 37% yield. The addition of ethylenediammonium diacetate (EDDA) as a proton source did not increase the yield, and using a Lewis acid led to decomposition of the substrates and the products. Dichloromethane proved to be the best solvent for the reaction, in contrast to diethyl ether and toluene. When other alkyl vinyl ethers were applied, a dependence of the yield on the steric bulk of the alkyl moiety could be observed. While the isobutyl vinyl ether gave almost the same yield as **4a**, the corresponding cyclohexyl or *tert*-butyl ether did not react at all (Table 1).

Table 1. Synthesis of Dihydropyrans **3a**−**d**[a]



R	yield (%)
ethyl	37
n-butyl	27
isobutyl	33
isopropyl	23
cyclohexyl	
tert-butyl	

[a] Conditions: 1.0 equiv of **7**, 2.0 equiv of formaldehyde, 20 equiv of vinyl ether, CH_2Cl_2, 3 h, 80 °C.

The moderate yield of **3** might be attributed to the formation of an unstable nitroacetal[8] (**9**) as a side reaction. Due to the strong electrophilicity of the nitrobutenone (**5**), a

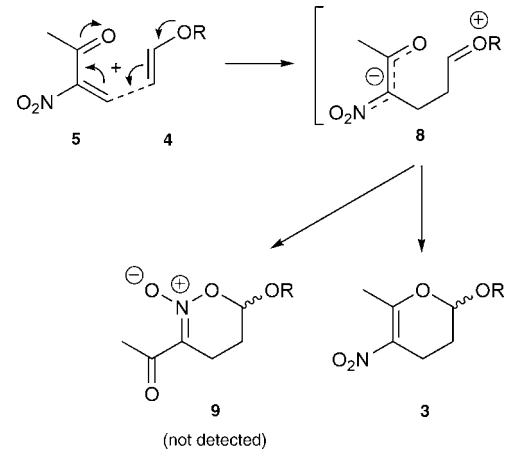


Figure 3. Proposed reaction mechanism.

two-step mechanism can be proposed in which the enol ether first attacks at the 4-position of **5**, forming a zwitterionic species **8**. In the following step, the ring closure can either occur via the oxygen of the keto group to form **3** or via the oxygen of the nitro group to give the nitroacetal **9**. However,

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all attempts to identify **9** or intercept it have not been successful so far (Figure 3).

For the synthesis of **2**, an *anti*-selective hydrogenation of the C−C double bond in **3a** was required to establish the configuration of forosamine (**2**) at C-4 and C-5.

A conjugate hydride attack at C-6 of **3a** was possible with sodium trimethoxyborohydride according to a procedure of Shechter et al.[9] to give the two diastereomeric nitro sugars **10** and **11** in an overall yield of 75% as a 2:1 mixture in favor of the thermodynamically more stable **10** with an equatorially orientated nitro group. The two diastereomers can easily be separated by column chromatography on silica gel. However, the isomer **11** could be isomerized in a base-catalyzed step to yield the desired isomer **10** (Figure 4).

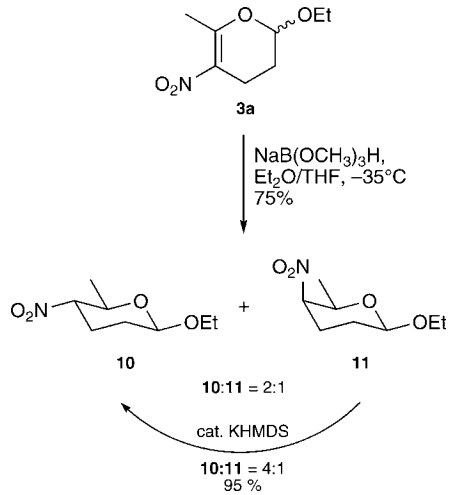

Figure 4. Reduction of the double bond in **3a** and isomerization.

In the next step, the nitro group in **10** was reduced by hydrogenation using Raney-nickel under a hydrogen atmosphere to give the corresponding desoxyaminoglycoside in 81% yield. Successive dimethylation under Eschweiler−Clarke conditions[10] then led to the forosaminylglycoside in 73% yield. Deprotection at the anomeric position could be successfully achieved by treatment of the ethyl glycoside with 1 M sulfuric acid to give the racemic deoxysugar **2** in 81% yield (Figure 5).

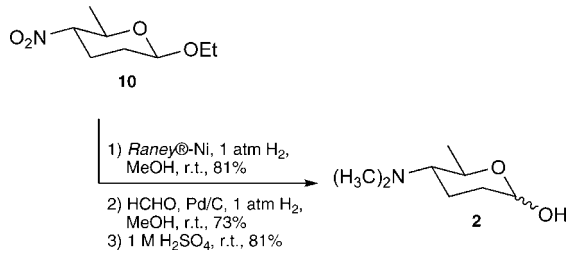

Figure 5. Synthesis of racemic forosamine (**2**).

For the preparation of the enantiopure compound **2**, several organo catalysts were used in the domino−Knoevenagel−hetero-Diels−Alder reaction, which, however, was not successful. On the other hand, the racemic benzylcarbamate **13**, easily accessible by reaction of **12** with CBzCl, could be resolved using HPLC on chiral support. The enantiomers (+)-**13** and (−)-**13** were obtained in ee = 99% and 95% (Figure 6). Removal of the Cbz group in (−)-**13** with

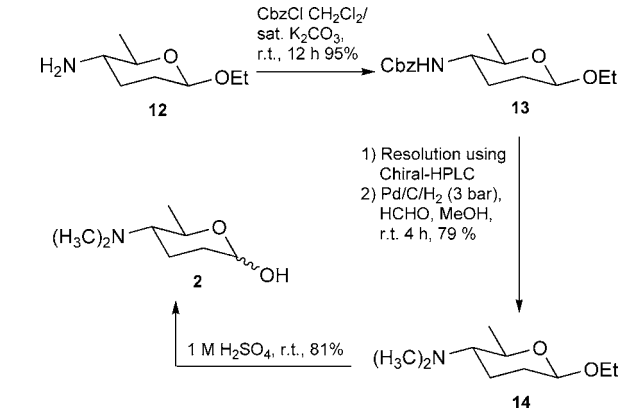

Figure 6. Synthesis of D-(+)-forosamin (**2**).

simultaneous dimethylation with formaline and Pd/C using hydrogen (3 bar) led to the enantiopure ethyl glycoside (−)-**14** in 79% yield, which can be transformed into (+)-**2** as already described.

In conclusion, we reported on a simple access to deoxysugars such as (+)-forosamin (**2**) via a novel domino−Knoevenagel−hetero-Diels−Alder reaction. The sugar scaffold **3** was obtained in a three-component reaction by using simple and easily accessible precursors. Selective reduction of the double bond in **3a** led to the corresponding nitrosugars **10** and **11**, which was followed by isomerization, reduction of the nitro group, and successive Cbz-protection. Chromatographic resolution, deprotection of the amino group with simultaneous dimethylation, and removal of the anomeric protecting group led to (+)-D-forosamine (**2**) in an enantiomeric excess of up to 95% in just six steps.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der chemischen Industrie.

Supporting Information Available: General and experimental procedures and analytical data for all componds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900899A

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