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Stereoselective Synthesis of Methyl 7-Dihydro-trioxacarcinoside B

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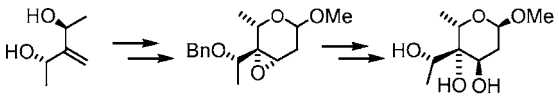
ABSTRACT



methyl 7-dihydro-trioxacarcinoside B

A stereoselective synthesis of 7-dihydro-triocacarcinose B, a branched octose from the quinocyclines, has been achieved. The biocatalytic resolution of a Baylis–Hillman adduct and a subsequent ring-closing metathesis were used to assemble the molecular framework. Subsequent key steps were a highly stereoselective epoxidation and a regio- and stereoselective opening of the epoxide by allyl alcohol and $HClO_4$ to introduce the C(3)-OH group in protected form. The 7-dihydro-triocacarcinose B could be converted into the corresponding 1,7-anhydrosugar.

Trioxacarcinose B (**1**) and 7-dihydro-trioxacarcinose B (**2**) are structurally related γ-branched octoses found in the quinocyclines (Figure 1).[1] Quinocycline B and isoquinocycline B contain trioxacarcinose B (**1**), while quinocycline A and isoquinocycline A are glycoconjugates of 7-dihydro-trioxacarcinose B (**2**) and the anthracycline-type aglycone.[2] Quinocycline B was found to be identical with the recently isolated kosinostatin.[3] Trioxacarcinose B (**1**) is also part of trioxacarcin A[4] and gutingimycin.[5]

The antibiotic and cytotoxic activities of natural products containing the octoses **1** or **2** make these rare sugars interesting to synthetic chemists. So far, a synthetic path to 7-dihydro-trioxacarcinose B (**2**) has been reported by Paulsen,[6] and Suami[7] has published a route to trioxacarcinose B (**1**). Both made use of a chiral-pool approach starting from sugar building blocks.

As part of a synthetic project toward the quinocyclines, glycoconjugates of **1** and **2** have to be prepared. Glycoconjugates of **1** shall be accessible from glycoconjugates of **2** in a post-glycosylation step by selective oxidation of the C7 hydroxy group. These considerations led us first to develop an efficient stereoselective synthesis of 7-dihydro-trioxacarcinose B (**2**).

A retrosynthetic analysis reveals the regio- and stereoselective ring opening of an epoxide as a possible key step (Figure 1). The properly protected target molecule **3** in its low-energy chair conformation **4** has the 3,4-oxygen substituents in *trans* diaxial positions. This substructure should be accessible by a regio- and stereoselective attack of a HOR^2-nucleophile at C3 of the epoxide **6**,[8] which leads to the α-epoxide[9] **5** as a key intermediate.

The starting point of the synthesis was a Baylis−Hillman reaction of methylvinylketone and acetaldehyde followed by a biocatalytic resolution[10] to obtain the α-methylene-β-

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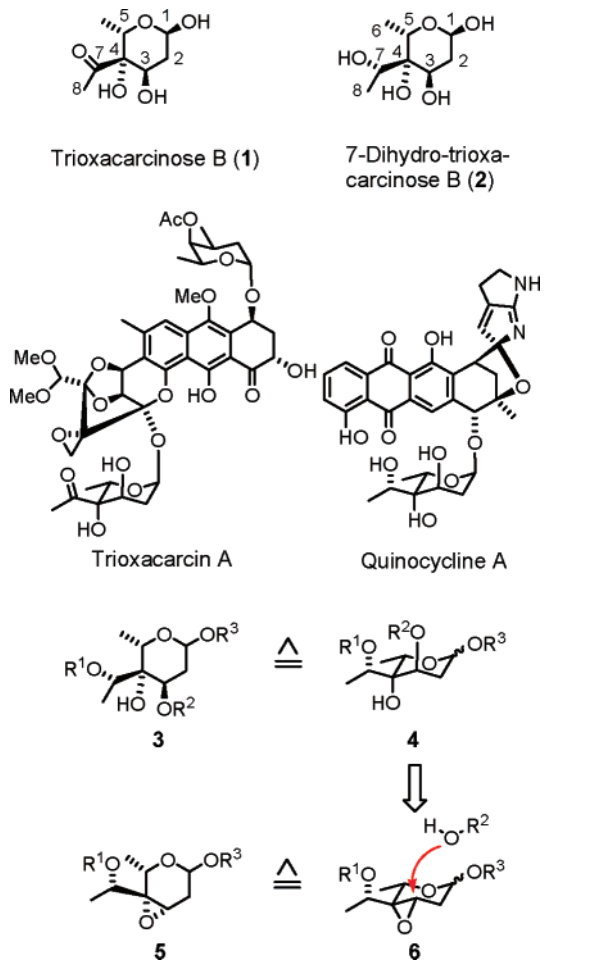
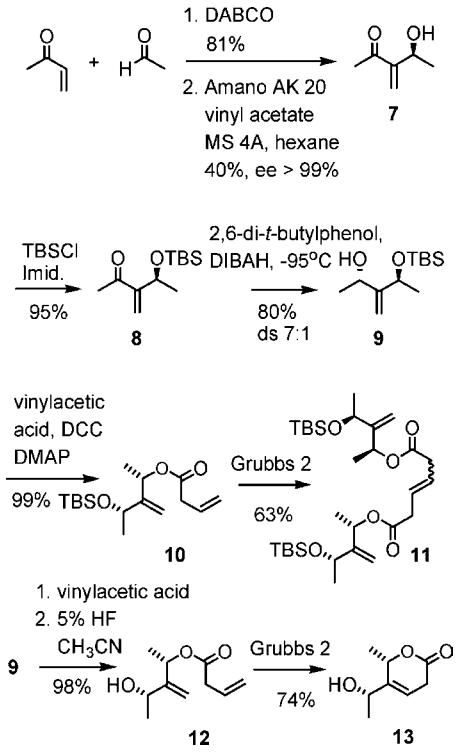


Figure 1. Structures of octoses **1**, **2**, and their glycoconjugates. Epoxide opening as a synthetic key step.

hydroxy ketone **7** (Scheme 1). The use of *Pseudomonas AK 20* (Amano) led to an ee >99%. Next in the synthetic plan was an *anti* selective reduction of the α-methylene-*β*-hydroxyketone. $Me_4NBH(OAc)_3$ gives excellent *anti*-selectivities for *β*-hydroxyketones[11] but failed for this α-methylene-*β*-hydroxyketone. After TBS-protection to **8** the reduction with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide[12] led to the formation of the *anti* alcohol **9** with a 7:1 diastereoselectivity. The assignment of the relative configuration of the reduction product was done via NMR analysis of the corresponding benzylidene acetals (Supporting Information [SI]). Esterfication of **9** with vinylacetic acid gave the diene **10**. All attempts to convert **10** into a dihydropyran by ring-closure olefin methathesis resulted in the intermolecular reaction with the formation of the triene **11**. The bulky substituents at the disubstituted double bond in **10** prevented the desired intramolecular reaction. Therefore, the bulky TBS−ether was converted into a smaller hydroxy group via desilylation. The obtained dienol **12** underwent a

Scheme 1. Synthesis of the Dihydropyrane **13**



successful ring-closing olefin methathesis[13] to produce the dihydropyran **13**.

The further synthesis is summarized in Scheme 2. A DIBAH reduction converted the lactone **13** into the corresponding lactol which was transformed into the methyl glycoside **14** (mixture of α- and *β*-anomers). As pointed out above, the synthetic plan required the stereoselective formation of an α-epoxide **5**. By avoidance of *syn*-pentane interactions[14] compound **14** is expected to adopt a conformation **15** with an α-oriented[15] C7-OH group. This OH group should allow a substrate-directed stereocontrolled epoxidation.[16] Indeed, treatment of **14** with $VO(acac)_2$ and *tert*-butyl hydroperoxide[17] yielded the α-epoxide **16** as the only observed stereoisomer.

In the following acid-catalyzed epoxide opening the possibility for the formation of an anhydrosugar exists if the 7-OH remains unprotected (vide infra). To circumvent this problem, the epoxyalcohol **16** was protected in form of the benzylic ether **17**. Initial attempts to open the epoxide in **17** directly to the corresponding *trans*-diol failed. For example, the use of $HClO_4$ in THF/H_2O led mainly to starting-material decomposition.

Other ROH nucleophiles, which result in a protected form of the C3-OH group such as benzylic alcohol or allyl alcohol,

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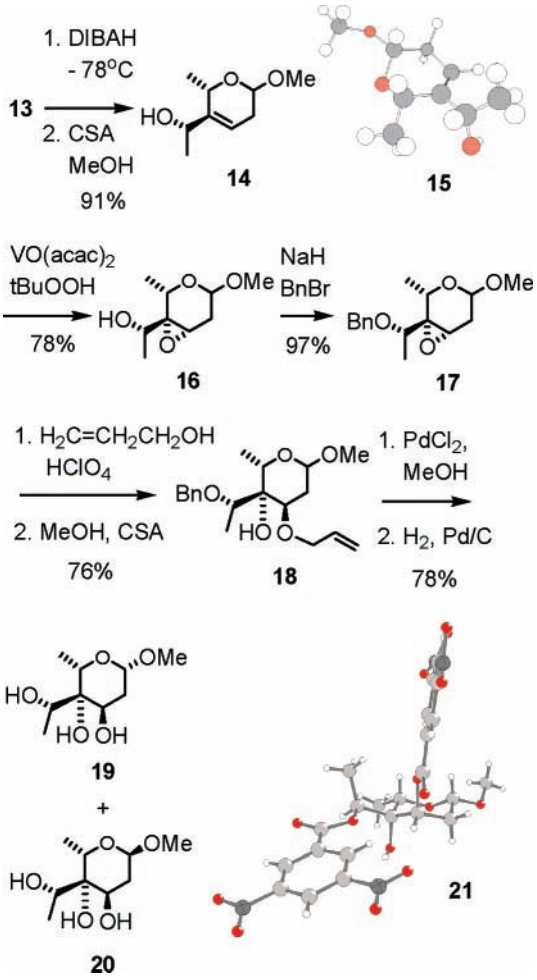
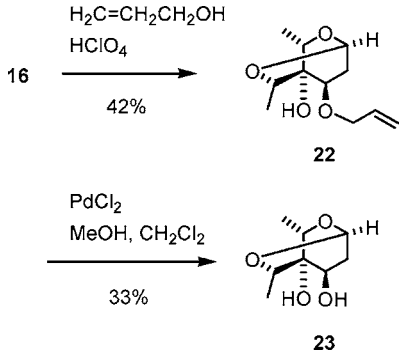
Scheme 2. Synthesis of Methyl 7-Dihydro-trioxacarcinoside B



were evaluated. It was found that use of the alcohol as the solvent and 2−5 equiv of $HClO_4$ as acid was optimal. Due to its lower boiling point allyl alcohol was the reagent of choice. The reaction temperature should not exceed 20 °C to avoid decomposition of the starting material. The epoxide opening was accompanied by a transacetalization at the anomeric center leading to the allyl glycoside. A subsequent treatment with CSA in MeOH gave the 3-allyloxy methyl glycoside **18** (mixture of α- and *β*-anomers).

The deprotection of the C3-allyl and C-7-benzyl ether could be done in a stepwise manner. First, the cleavage of the allyl ether with $PdCl_2$ in MeOH was possible.[18] Second, hydrogenolysis of the benzyl ether gave the target compound **2** as methyl glycosides **19** (*β*-anomer) and **20** (α-anomer) (22% from **7**). Both anomers were separated by chromotography. The spectral data and specific rotation for **19** and **20** were identical in all respects with those of the natural products reported previously.[2] An independent structural proof was possible by an X-ray crystal structure of the 3,7-bis-(3,5-dinitrobenzoate) of **19**. Structure **21** in Scheme 3 is a structural representation of this X-ray structure.

Scheme 3. Synthesis of the Anhydrosugar **23**



As pointed out already, the acid treatment of compounds such as **16** with an unprotected 7-OH group led to the formation of a 1,7-anhydrosugar (Scheme 3). The reaction of **16** with allyl alcohol resulted in a combined epoxide opening and anhydrosugar formation leading to the allyl ether **22**. After a Pd-mediated cleavage of the allyl ether the deprotected anhydrosugar **23** was obtained. The spectral data and specific rotation for synthetic **23** were identical in all respects with those of the natural product reported by Webb et al.[19]

In conclusion, an efficient, stereoselective route to methyl 7-dihydro-trioxacarcinoside B as well as its 1,7-anhydrosugar was developed. Key steps are a Baylis−Hillman/biocatalytic resolution sequence, a ring-closing metathesis reaction, a substrate-controlled epoxidation, and stereo- and regiocontrolled expoxide opening by allyl alcohol. The application of this branched octose for the synthesis of quinocyclines is currently under investigation.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds and synthetic methyl glycosides **19**, **20**; single-X-ray crystallographic data for **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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