

Synthesis of Anemoclemoside B, the First Natural Product with an Open-Chain Cyclic Acetal Glycosidic Linkage

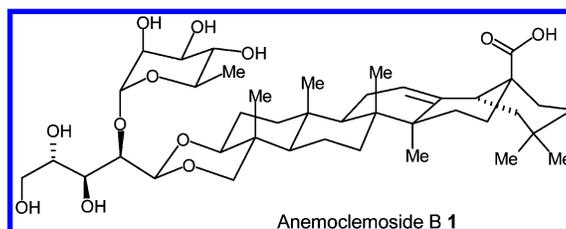
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ABSTRACT



Anemoclemoside B (1), the first natural product containing a brand-new glycosidic linkage, the open-chain cyclic acetal linkage, was synthesized.

In 1999, Vinogradov and Bock discovered a new type of sugar–sugar linkage in the core region of the lipopolysaccharides (LPS) from the outer membrane of two *Proteus* bacteria.¹ The new linkage consisted of an open-chain *N*-acetylgalactosamine linked as a cyclic acetal to positions 4 and 6 of a normal galactosamine α -pyranoside unit (Figure 1), which has since been found in several other strains of Gram-negative bacteria.² The new glycosidic linkage probably arises from a new, but as yet unknown, biosynthetic

pathway.³ Prior to the 1999 report, an open-chain cyclic acetal glycosidic linkage had only been found in two compounds isolated from plant extracts. Thus, Li et al., in

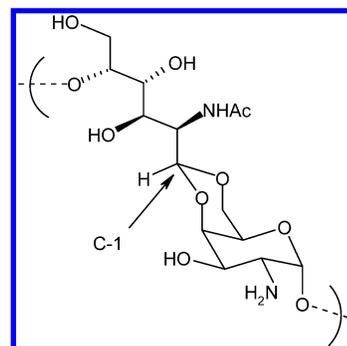


Figure 1. Open-chain linkage in the LPS of bacteria.

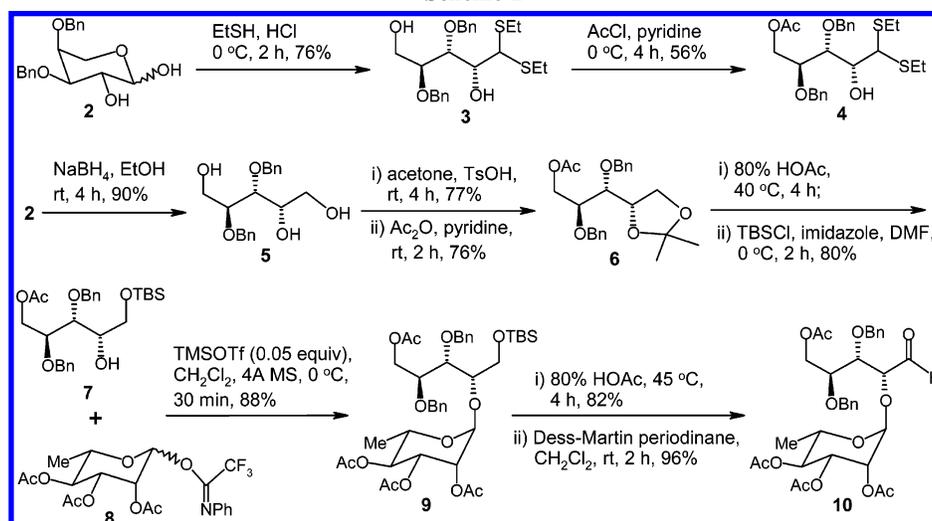
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Scheme 1



1995, disclosed the structure of the two triterpenoid glycosides, anemoclemosides A and B (Figure 2; congener A lacks the terminal α -rhamnopyranosyl residue in B), which they had obtained from extracts of the roots of *Anemoclema glaucifolium*, a folk medicinal plant distributed at an altitude of 1600–3000 m in the Yangtse River valley region of China.⁴ The unique structures of anemoclemosides A and B make them chemotaxonomic markers of the native plant. Herein, we report an effective approach to the synthesis of open-chain cyclic acetal glycosidic linkages in the context of a synthesis of anemoclemoside B **1**.

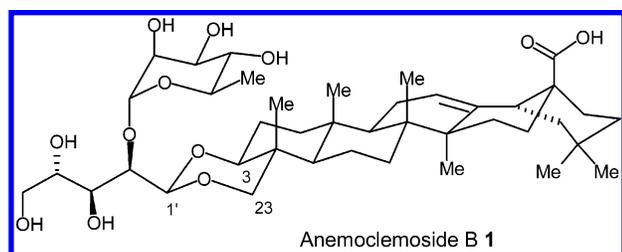


Figure 2.

A major challenge in the synthesis of anemoclemoside B **1** is construction of the unique open-chain cyclic acetal linkage between the 2-*O*- α -L-rhamnopyranosyl-(1 \rightarrow 2)-L-arabinose component and the 3,23-diol of hederagenin. A suitably protected disaccharide derivative **10** having the L-arabinose C1-aldehyde component in open-chain form was synthesized as shown in Scheme 1. Initially, we converted

the known L-arabinose derivative **2**⁵ into open-chain thioketal **3** and O-acetylated the primary OH of **3** selectively to obtain **4**. Unfortunately, however, the subsequent glycosylation of **4** with 2,3,4-tri-*O*-acetyl-L-rhamnopyranosyl (*N*-phenyl)-trifluoroacetimidate (**8**) using TMSOTf or BF₃·OEt₂ as promoters failed to afford the desired coupling product.⁶ Instead, intermolecular ethylthio transfer prevailed, and ethyl 2,3,4-tri-*O*-acetyl-1-thio- α -L-rhamnopyranoside was obtained as the major reaction product.⁷

In light of this, we began investigating a new strategy that did not involve us glycosylating with a thioketal present. Accordingly, we converted the pyranose hemiacetal **2** into linear alcohol **5** by reduction with NaBH₄.⁸ Protection of the vicinal 1,2-OHs as an *O*-isopropylidene acetal followed by protection of the remaining 5-OH as an *O*-acetate provided **6**. The 1,2-*O*-isopropylidene on **6** was then removed with 80% aq HOAc, and the resulting C1–OH was selectively protected with a TBS group, giving **7** with its C2-hydroxyl free. Coupling of **7** with the rhamnopyranosyl trifluoroacetimidate **8**⁶ using 0.05 equiv of TMSOTf in CH₂-Cl₂ in the presence of 4 Å MS at 0 °C afforded the desired disaccharide **9** in a satisfactory 88% yield. The C1–OH on **9** was then desilylated with 80% aq HOAc at 45 °C,⁹ and the resulting alcohol was oxidized with Dess–Martin periodinane to give the desired disaccharide **10** in excellent yield.

To construct the targeted open-chain cyclic acetal linkage, model reactions between 2,3,4,5-tetra-*O*-benzyl-L-arabinose

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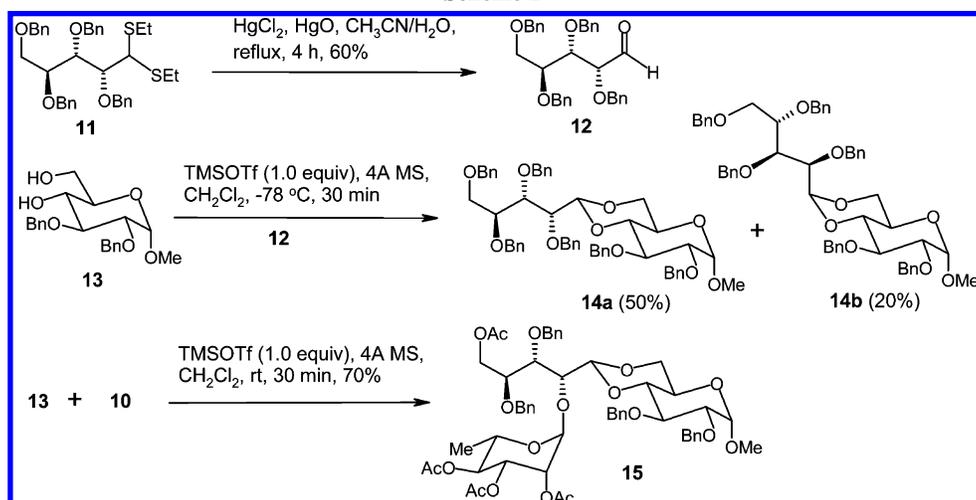
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Scheme 2



(**12**) and methyl 2,3-di-*O*-benzyl- α -D-glucopyranoside (**13**) were first examined (Scheme 2).¹⁰ Acetalization with diols in the presence of an excess amount of an alkoxy silane and a catalytic amount of TMSOTf^{11a} has previously been successfully applied for the effective condensation of sugar lactones with pyranoside-4,6-diols.^{11b} However, our application of similar conditions as described in the literature (TMSOMe (5–10 equiv), TMSOTf (catalyst), CH₂Cl₂)^{11b} provided the acetalization product **14** in less than 46% yield. The bulk of aldehyde **12** had been transformed mainly into the corresponding dimethylacetal derivative, and diol **13** into the 4,6-di-*O*-TMS product. Treatment of the 4,6-di-*O*-TMS compound with aldehyde **12** under the catalysis of TMSOTf led to **14** in only trace amounts.^{11b,c} Replacing MeOTMS with PhCH(OTMS)CH₃ prevented formation of the alkylacetal byproduct, but did not improve the yield of **14**. We also tried the condensation of dithioacetal **11**¹² and diol **13** under glycosylation conditions for thioglycosides (Tf₂O, 1-benzensulfinylpiperidine (BSP))¹³ but failed to obtain the desired adduct **14**. Fortunately, acetalization between **12** and **13** could be achieved nicely under the action of 1.0–2.0 equiv of TMSOTf at low temperature (–78 °C) in the presence of 4 Å MS; this afforded a pair of the diastereoisomers **14a** and **14b** in 50 and 20% yields, respectively.

Cyclic acetals **14a** and **14b**, with the open sugar chain in equatorial (1'*R*) and axial (1'*S*) orientations, respectively,¹⁴ should be in a thermodynamic equilibrium favoring the formation of the thermodynamically more stable **14a**. Evidently, treatment of **14b** with TMSOTf at room temperature produced an equilibrium in favor of **14a**.

Treatment of diol **13** with disaccharide aldehyde **10** under similar conditions (1.0 equiv of TMSOTf, 4 Å MS, CH₂Cl₂)

at –78 °C produced the desired **15** in only trace amount. Nevertheless, upon raising the temperature to ~15 °C, **15** was generated as a single isomer in 70% yield.¹⁴ Apparently, the hindered 2-*O*- α -L-rhamnopyranosyl substituent discouraged formation of the corresponding axially (1'*S*) oriented isomer.

With an effective protocol for the construction of the open-chain cyclic acetal glycosidic linkage now available, we set about our final assembly of the target natural product, anemoclemoside B **1** (Scheme 3). Hederagenin **16** was converted into its 28-benzyl ester **17** in three convenient steps, involving protection of the 3,23-di-OHs with an *O*-isopropylidene acetal, C28-benzyl ester formation, and cleavage of the 3,23-*O*-isopropylidene unit. Condensation of hederagenin 3,23-diol **17** with disaccharide aldehyde **10** under conditions similar to those described above (2 equiv of TMSOTf, –78 °C to rt) furnished **18** as a single isomer in an excellent 92% yield. Removal of the acetyl group was best achieved with NaOH at room temperature. This left the 28-benzyl ester group intact. Finally, all the benzyl groups were removed by hydrogenolysis in the presence of Pd/C; notably, the 12,13-double bond in the triterpenoid skeleton was not affected.¹⁵ The sample of thus obtained synthetic **1** matched the natural product in every respect.^{4,16}

In summary, an effective approach to the synthesis of the open-chain cyclic acetal linkage, a new glycosidic linkage in Nature, was developed. Acetalization of linear sugar aldehyde with 1,3-diols proceeds smoothly under the action

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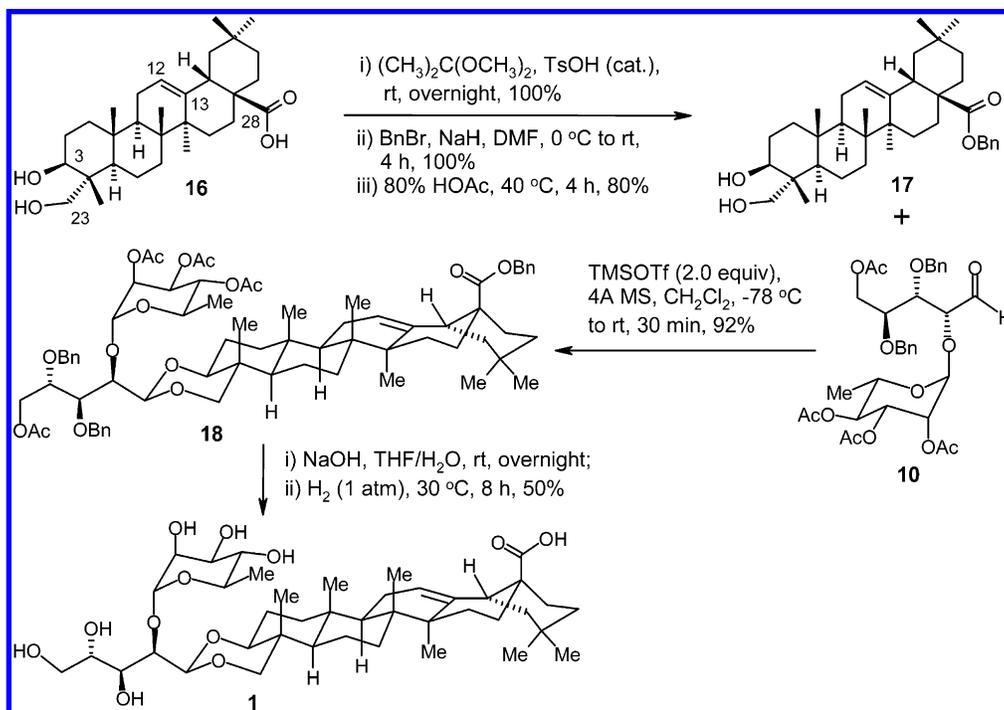
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(14) Acetal **14a** was transformed into the corresponding 2,3,2',3',4',5'-hexa-*O*-acetyl derivative **19** via hydrogenolysis and acetylation (see Supporting Information), which provided diagnostic NOE correlations between the 1'-H and the 4-H and 6-H, thus confirming the 1'*R* configuration in **14a**. Similarly, compound **15** was converted into the corresponding 2,2'',3,3',3'',4',4'',5'-octa-*O*-acetyl derivative **20** (see Supporting Information). Compound **20** provided diagnostic NOE correlations between the 1'-H and the 4-H and 6-H.

(15) Hydrogenolysis of the diphenylmethyl oleanolate derivatives has been performed; see: Seebacher, W.; Weis, R.; Jurenitsch, J.; Rauchensteiner, K.; Haslinger, E. *Monatsh. Chem.* **2000**, *131*, 985.

(16) For the preparation and characterization of all compounds mentioned in the context, see Supporting Information.

Scheme 3



of 1–2 equiv of TMSOTf in the presence of 4 Å MS, leading to the successful synthesis of anemoclemoside B **1**, the first natural product discovered to possess such a glycosidic linkage.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds and reproduction of ^1H NMR spectra for compounds **1**, **4–7**, **9**, **10**, **14a/b**, **15**, and **17–20** and ^{13}C NMR spectra for compounds **10**, **14a/b**, **15**, and **17–20**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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