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

Jiansong Sun,[†] Xiuwen Han,[†] and Biao Yu*[,‡]

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China, and State Key Laboratory of Catalyst, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

byu@mail.sioc.ac.cn

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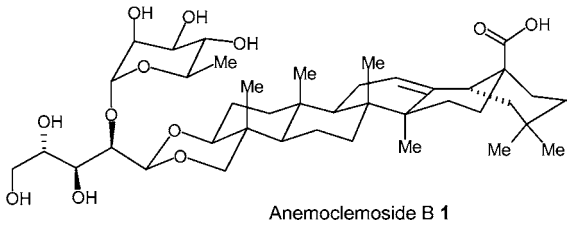
ABSTRACT



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

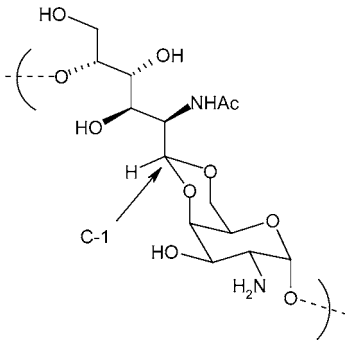


Figure 1. Open-chain linkage in the LPS of bacteria.

[†] Dalian Institute of Chemical Physics.
[‡] Shanghai Institute of Organic Chemistry.

(1) (a) Vinogradov, E.; Bock, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 671. (b) Vinogradov, E.; Bock, K. *Carbohydr. Res.* **1999**, *319*, 92. (c) Vinogradov, E.; Bock, K. *Carbohydr. Res.* **1999**, *320*, 239.

(2) (a) Vinogradov, E.; Sidorczyk, Z. *Carbohydr. Res.* **2001**, *330*, 537. (b) Vinogradov, E.; Korenevsky, A.; Beveridge, T. J. *Carbohydr. Res.* **2003**, *338*, 1991. (c) Moule, A. L.; Galbraith, L.; Cox, A. D.; Wilkinson, S. G. *Carbohydr. Res.* **2004**, *339*, 1185. (d) Michael, F. S.; Brisson, J. R.; Larocque, S.; Monteiro, M.; Li, J. J.; Jacques, M.; Perry, M. B.; Cox, A. D. *Carbohydr. Res.* **2004**, *339*, 1973.

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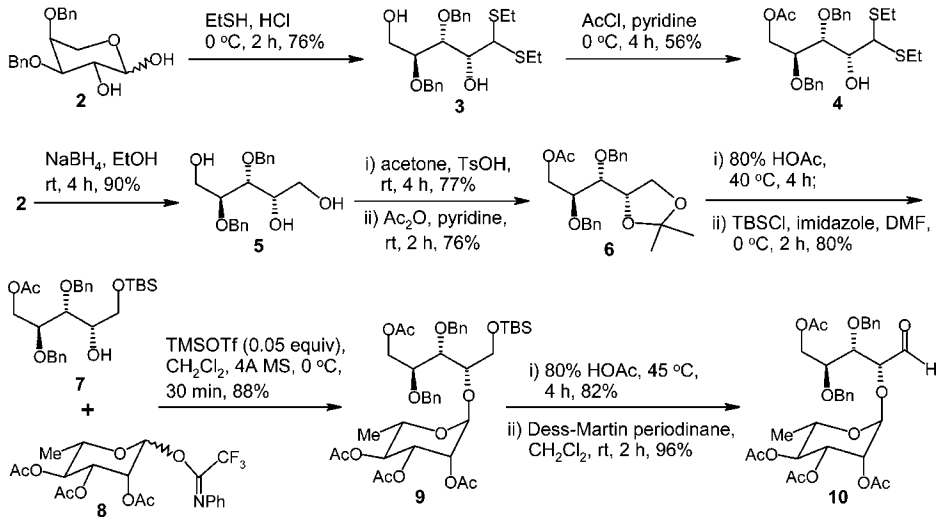
Scheme 1



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**.

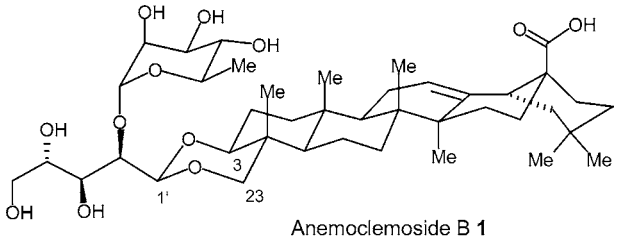


Figure 2.

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→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 $BF_3{\cdot}OEt_2$ 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 $NaBH_4$.[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 CH_2Cl_2 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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(4) Li, X.-C.; Yang, C.-R.; Liu, Y.-Q.; Kasai, R.; Ohtani, K.; Yamasaki, K.; Miyahara, K.; Shingu, K. *Phytochemistry* **1995**, *39*, 1175.
(5) Yang, G.; Kong, F. *J. Carbohydr. Chem.* **1994**, *13*, 909.
(6) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405. (b) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099.
(7) (a) Du, Y.; Lin, J.; Linhardt, R. J. *J. Carbohydr. Chem.* **1997**, *16*, 1327. (b) Yu, H.; Yu, B.; Wu, X.; Hui, Y.; Han, X. *J. Chem. Soc., Perkin Tran. 1* **2000**, 1445. (c) Leigh, D. A.; Smart, J. P.; Truscello, A. M. *Carbohydr. Res.* **1995**, *276*, 417. (d) Belot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **1996**, *290*, 79. (e) Zhu, T.; Boons, G. J. *Carbohydr. Res.* **2000**, *329*, 709.
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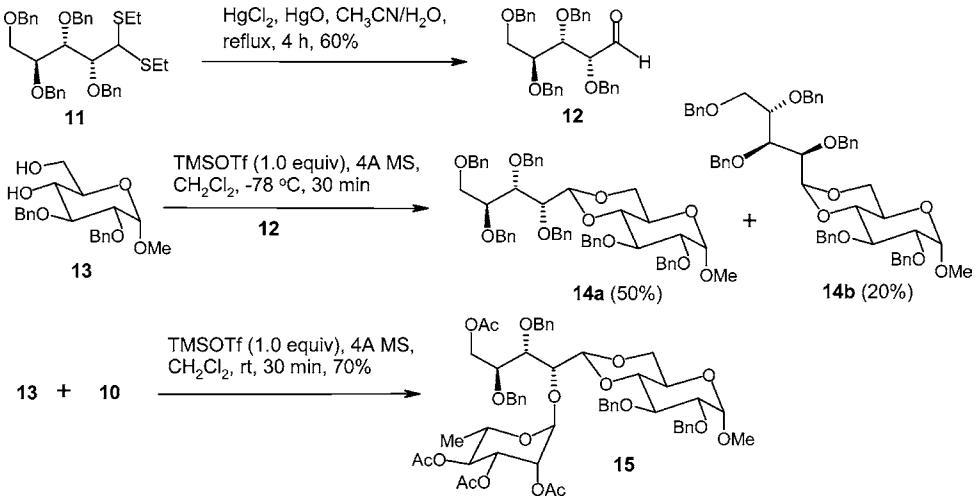
(9) Kawai, A.; Hara, O.; Hamada, Y.; Shiari, T. *Tetrahedron Lett.* **1998**, *29*, 6331.

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 alkoxysilane 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), CH_2Cl_2)[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 $PhCH(OTMS)CH_3$ 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 (Tf_2O, 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, CH_2Cl_2) 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

(10) Formation of methyl 4,6-D-glucosylidene-α-D-glucopyranoside derivatives has been reported; see: Micheel, F.; Velker, E.; Witte, E. A. *Tetrahedron Lett.* **1971**, *12*, 451.

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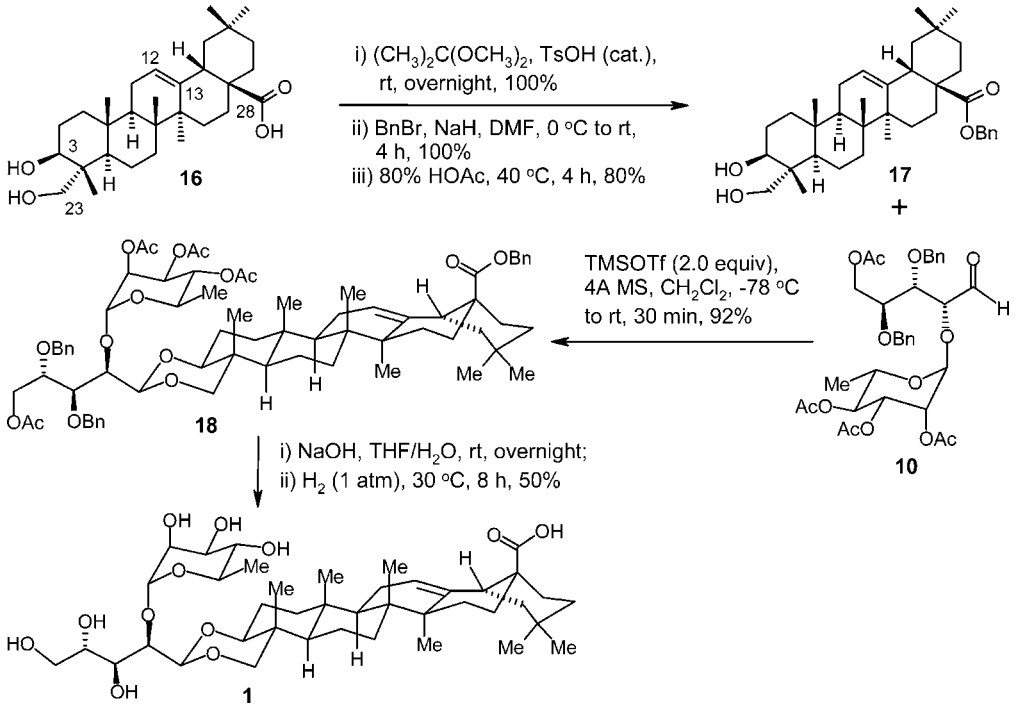
(13) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.

(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 ^{1}H 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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