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Total Synthesis of the Antiviral Glycolipid Cycloviracin B_1

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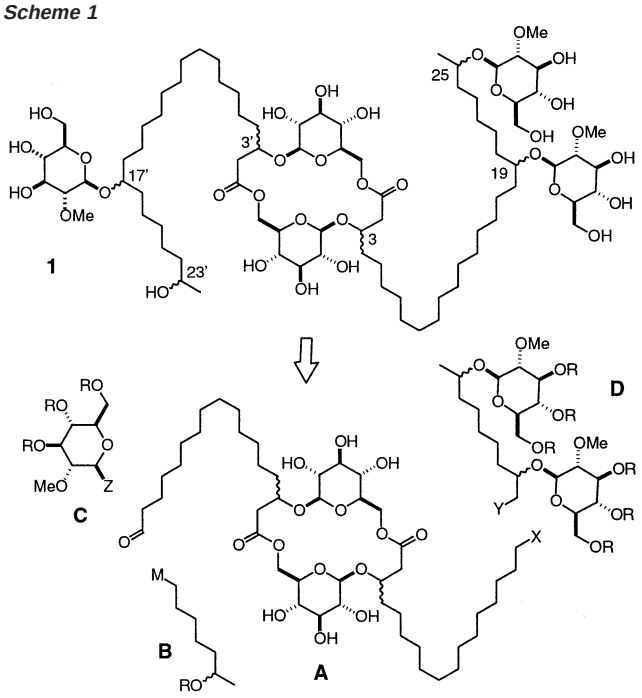
The actinomycete strain *Kibdelosporangium albatum* so. nov. (R761-7) isolated from a soil sample collected on Mindanao Island, the Philippines, was found to produce the complex glycolipid cycloviracin B_1 (**1**) which exhibits pronounced antiviral activity.[1] Extensive spectroscopic investigations established the constitution of this metabolite, while the absolute stereochemistry of the six chiral centers along its alkyl chains remained elusive.

As part of a long-term project on bioactive glycolipids,[2] we embarked upon the structure determination and total synthesis of this remarkable target. Its complexity together with the stereochemical ambiguities mentioned above calls for a highly convergent and flexible synthesis route. Assuming that the lactide core of **1** is C_2-symmetrical, a two-directional synthesis strategy[3] seemed to be most promising. Given the different length of the lateral chains, however, this plan bears a considerable risk for the final assembly stages (Scheme 1). While established methodology should allow control of the configuration of the −OH group at C-17′ generated by coupling of fragments **A** and **B**, the formation of the C−C-bond at the symmetry-related C-17/C-18 position joining segments **A** and **D** is highly problematic. Any attempt to convert fragment **D** into a carbon nucleophile (Y = metal) must result in reductive elimination with loss of the adjacent glycoside; the inverse manoeuvre implying the conversion of the entire lactide **A** into a suitable nucleophile (X = metal) is similarly endangered by the presence of electrophilic and C−H acidic sites in this molecule. More specifically, deprotonation α to the lactones will necessarily entail the opening of the macrocycle by expulsion of the adjacent sugar and formation of an α,β-unsaturated ester. Only a highly stabilized nucleophile X, if any, might kinetically resist these self-destructive pathways.

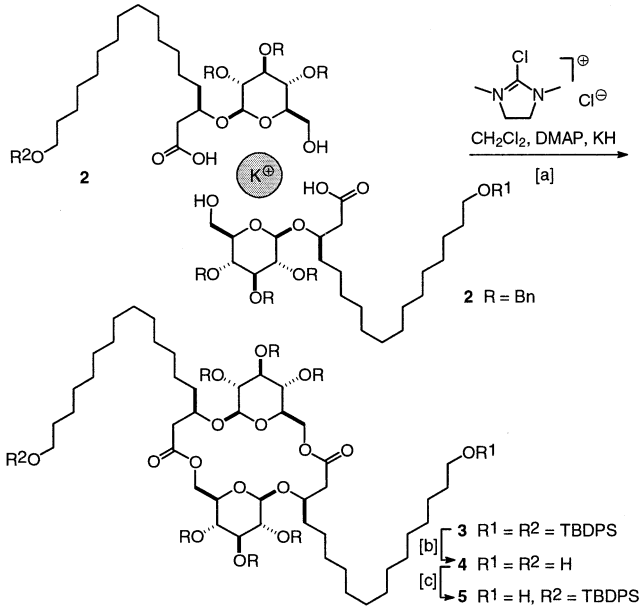
Contemplating that the specific array of O-atoms in the core region of **1** might endow the molecule with some degree of ionophoric character, a template directed cyclodimerization of the hydroxyacid **2** was envisaged for the rapid assembly of the macrodiolide motif. In fact, this key step turned out to be highly productive if carried out in the presence of admixed potassium cations.[4] Under optimized conditions, the desired lactide **3** is obtained in 71% isolated yield (Scheme 2). As an additional bonus, the inherent flexibility of this approach made it possible to prepare all conceivable stereoisomers without undue preparative efforts. Comparison of their quite characteristic NMR data with those of **1** allowed us to deduce the absolute stereochemistry at the branching points as 3*R*,3′*R*.[4] Routine protecting-group manipulations then led to the required desymmetrization of the termini (**3** → **4** → **5**).

Model studies had provided strong evidence that the distal stereocenters in **1** at C-23′ and C-25 are also likely *R*-configured.[5] Although no stringent conclusions concerning C-19 and C-17′ could be gleaned, it seemed reasonable to assume the symmetry-related *S*-configuration[6] at these sites for biosynthetic reasons. Therefore,

Scheme 1



Scheme 2 [a]



[a] Conditions: [a] 71%, see ref 4; [b] TBAF, THF, 92%; [c] tBuPh$_2$SiCl, Et$_3$N, CH_2Cl_2, 85%.

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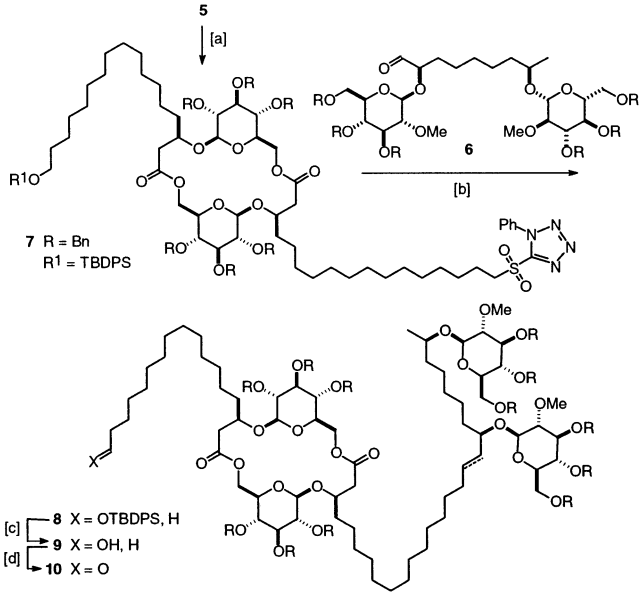
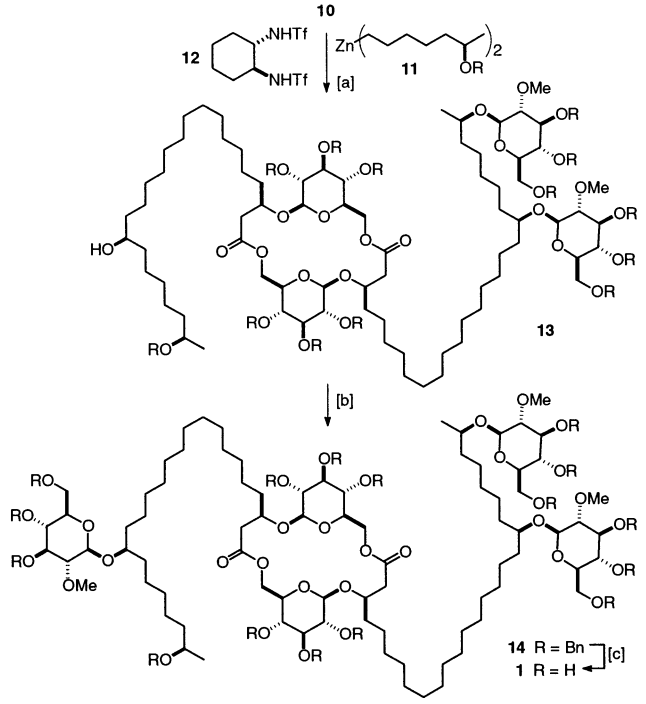
Scheme 3 [a]



[a] Conditions: [a] (i) 1-phenyl-5-mercapto-tetrazole, DIAD, PPh_3, THF, 91%; (ii) $(NH_4)_6Mo_7O_{24}(H_2O)_7$, EtOH/$CH_2Cl_2$, 67%; [b] (i) LiHMDS, DME, −78 °C, then **6**, 61%; (ii) H_2 (1 atm), Pd/C, EtOAc, 72%; [c] TBAF, THF, 95%; [d] PCC, CH_2Cl_2, 83%.

Scheme 4 [a]



[a] Conditions: [a] $Ti(OiPr)_4$, ligand **12** (cat.), reagent **11** (5 equiv), 81%; [b] 3,4,6-tri-*O*-benzyl-2-*O*-methyl-α-D-glucopyranosyl trichloroacetimidate,[8] TMSOTf cat., CH_2Cl_2/MeCN, 87%; [c] H_2 (1 atm), Pd/C, EtOH/EtOAc (2:1), 88%.

aldehyde **6** was prepared in high overall yield as surrogate of first choice for the lateral fragment **D**.[8]

With this building block in hand, the delicate fragment coupling **A** + **D** was investigated by taking recourse to a Julia−Kocienski olefination strategy.[7] The somewhat higher kinetic acidity together with the better accessibility of the terminal sulfone in **7** might allow for selective deprotonation at that site without damaging the more encumbered lactone moieties; the resulting anion should be sufficiently stabilized to withstand attack on the ester groups. After some experimentation it was found that the use of LiHMDS in DME at −78 °C in fact meets these stringent criteria. Specifically, reaction of the lithio sulfone derived from **7** with aldehyde **6** delivers the corresponding alkene in 61% yield (*E:Z* ≈ 1:1) (Scheme 3) which was hydrogenated over Pd/C in EtOAc to facilitate the analysis of the NMR spectra. We are unaware of any precedence for Julia-type olefination reactions involving sulfones bearing such a base-labile β-hydroxy ester motif.

Standard deprotection of the residual silyl ether in **8** followed by oxidation of the resulting alcohol **9** with PCC affords the rather labile aldehyde **10** which readily reacts with the diorganozinc reagent **11**[8] in the presence of a catalyst formed in situ from $Ti(OiPr)_4$ and the (*S*,*S*)-configured bistriflate **12** as the controller ligand to give alcohol **13** in 81% yield.[9] Subsequent β-selective glucosidation via the trichloroacetimidate method was ensured by using TMSOTf in CH_2Cl_2/MeCN as the promotor system.[10] Exhaustive debenzylation of product **14** thus formed by hydrogenolysis over Pd/C cleanly provided cycloviracin B_1 (**1**) (Scheme 4). Not only are all analytical and spectroscopic data in excellent agreement with those reported in the literature, but the pattern signature in the ^1H NMR spectrum is superimposable to that depicted in ref 1. This completes the first total synthesis of this antiviral agent and provisionally establishes the absolute stereochemistry of the chiral centers residing on the fatty acid residues as (3*R*,19*S*,25*R*,3′*R*,17′*S*,23′*R*).[6] Studies aiming at the elucidation of the pharmacophore of this compound as well as at the synthesis of related glycolipids will be reported soon.

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Supporting Information Available: Full experimental details, spectroscopic data, and copies of pertinent NMR spectra of compounds **1** and **14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Tsunakawa, M.; Komiyama, N.; Tenmyo, O.; Tomita, K.; Kawano, K.; Kotake, C.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1467. (b) Tsunakawa, M.; Kotake, C.; Yamasaki, T.; Moriyama, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1472.
(2) (a) Fürstner, A.; Müller T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (b) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758. (c) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072. (d) Fürstner, A.; Jeanjean, F.; Razon, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2097. (e) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.
(3) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.
(4) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M. *J. Am. Chem. Soc.* **2002**, *124*, 1168.
(5) Details will be reported in a forthcoming full paper.
(6) If the fatty acids are drawn in a zigzag conformation, all hydroxyl groups are located on the same side; the fact that the centers at C-17′ and C-19 are *S*-configured while the other ones are *R*-configured simply reflects the formalism of the Cahn−Ingold−Prelog nomenclature.
(7) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
(8) For details see the Supporting Information.
(9) (a) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691. (b) Knochel, P. *Synlett* **1995**, 393.
(10) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

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