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Structure Assignment, Total Synthesis, and Antiviral Evaluation of Cycloviracin B_1

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Abstract: The first total synthesis of the antivirally active glycolipid cycloviracin B_1 (**1**) is described. The approach is based on a two-directional synthesis strategy which constructs the C_2-symmetrical macrodiolide core of the target by an efficient template-directed macrodilactonization reaction promoted by 2-chloro-1,3-dimethylimidazolinium chloride **14** as the activating agent. Attachment of the lateral fatty acid chains to the lactide core thus formed features not only one of the most advanced ligand-controlled addition reactions of a functionalized dialkyl zinc reagent to a polyfunctional aldehyde, but also a highly demanding Julia−Kocienski olefination of a tetrazolyl sulfone bearing electrophilic and base-labile β-hydroxy ester motifs. By virtue of the flexibility of this synthesis plan, it was possible to prepare a series of macrodiolide cores differing only in the absolute stereochemistry at the branching points as well as a host of model compounds for the fatty acid appendices of cycloviracin. Comparison of these derivatives with the natural product allowed us to establish the as yet unknown absolute stereochemistry of 6 chiral centers of **1** as (3*R*,19*S*,25*R*,3′*R*,-17′*S*,23′*R*). Thereby, the ^{13}C NMR shifts of the anomeric position of the β-glycosides residing at those positions turned out to be excellent probes for the absolute configuration of the attached aglycones. The concise set of data thus obtained also makes clear that the proposed structure of the fattiviracins, a seemingly closely related family of glycoconjugates, is not matched by the published data. Finally, the biological activity of synthetic **1** and some of the key intermediates obtained en route to this natural product was investigated, showing that the entire construct is necessary for appreciable and selective antiviral activity.

Introduction

The paucity of effective medication against viral infections together with the increasing resistance toward approved drugs render the search, optimization, and clinical development of novel antiviral agents highly desirable. In this context, two families of natural products called cycloviracins[1] and fattiviracins[2] isolated from the soil microorganisms *Kibdelosporangium albatum* so. nov. (R761-7)[3] and *Streptomyces microflavus* No 2445, respectively, deserve attention as potential new lead compounds because they have been reported to exhibit activity against the human pathogens herpes simplex virus type 1 (HSV-1), influenza A virus, varicella-zoster virus, and human immunodeficiency virus type 1 (HIV-1). Although less potent than acyclovir[4] (50% antivirally effective concentration of **1** against HSV-1: $\sim$5 μg/mL), the known biological and physical properties of these complex glycolipids prompt more detailed investigations. The lack of cytotoxicity against Vero cells (50% cytotoxic concentration, >400 mg/mL) and the lack of activity against bacteria, yeasts, and fungi at concentrations of 100 μg/mL suggest antiviral specificity. Preliminary data indicate that these compounds diminish the infectivity of the viruses by inhibiting their entry into the host cells;[5] importantly, this specific mode of action is complementary to that of most approved antiviral drugs. Finally, the good solubility of these glycoconjugates in aqueous media constitutes an additional bonus.

Although the constitutions of the cycloviracins and fattiviracins have been elucidated by extensive NMR spectroscopic investigations, several structural details remain unclear and even somewhat puzzling. As can be seen from the proposed structures

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(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. Anitbiot.* **1992**, *45*, 1472. (c) Tsunakawa, M.; Yamasaki, T.; Tomita, K.; Osamu, T. EP 0 472 005 A1 (1991−07−26).

(2) (a) Uyeda, M.; Yokomizu, K.; Miyamoto, Y.; Habib, E.-S. E. *J. Antibiot.* **1998**, *51*, 823. (b) Yokomizo, K.; Miyamoto, Y.; Nagao, K.; Kumagae, E.; Habib, E.-S. E.; Suzuki, K.; Harada, S.; Uyeda, M. *J. Antibiot.* **1998**, *51*, 1035. (c) Habib, E.-S. E.; Yokomizo, K.; Murata, K.; Uyeda, M. *J. Antibiot.* **2000**, *53*, 1420. (d) Habib, E.-S. E.; Yokomizo, K.; Suzuki, K.; Uyeda, M. *Biosci., Biotechnol., Biochem.* **2001**, *65*, 861.

(3) For information on the producing strain, see: Tomita, K.; Hoshino, Y.; Miyaki, T. *Int. J. Syst. Bacteriol.* **1993**, *43*, 297.

(4) (a) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* **1978**, *272*, 583. (b) Elion G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U S. A.* **1977**, *74*, 5716. (c) Whitley, R. J.; Gnann, J. W. *N. Engl. J. Med.* **1992**, *327*, 782.

(5) Habib, E.-S. E.; Yokomizo, K.; Nagao, K.; Harada, S.; Uyeda, M. *Biosci., Biotechnol., Biochem.* **2001**, *65*, 683.

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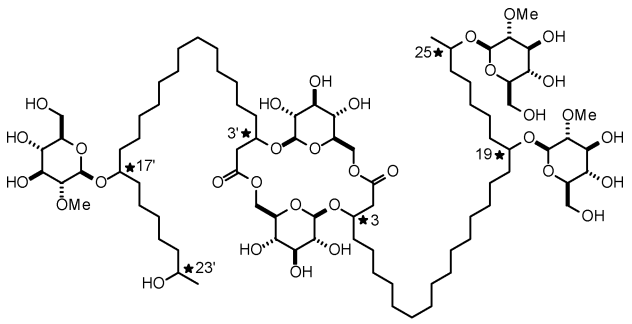
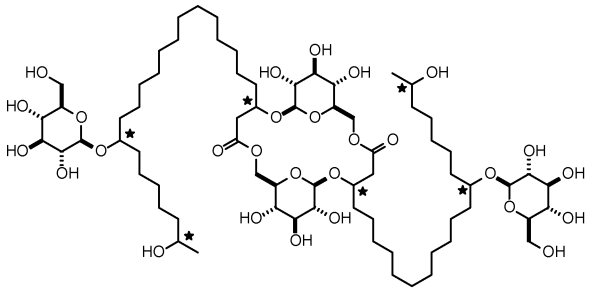


Cycloviracin B_1 (**1**)

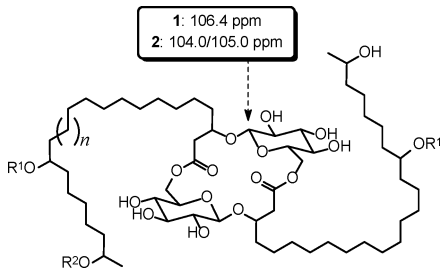


proposed structure of **Fattiviracin FV-8** (**2**)

of the two prototype members **1** and **2**, these compounds *seem* to differ only in the length and glycosylation pattern of the lateral fatty acid residues while sharing a common macrodiolide core. A closer look at the reported NMR data, however, reveals a rather suspicious detail: in contrast to the cycloviracins, which give rise to only one set of signals for both units forming this central motif, all members of the fattiviracin family invariably show inequivalent subunits (cf. generalized structure in Scheme 1).[6] *This difference can hardly be explained in view of the overall resemblance of both series*. Therefore, it is an imperative prelude to any further study to clarify this structural ambiguity and to determine the as yet unknown absolute stereochemistry of the six chiral centers (*) along the alkyl chains of either **1** or **2**.

As part of a long-term project on bioactive glycoconjugates,[7−9] we initiated an extensive program addressing these issues. Our initial goal was the unambiguous determination of their actual structure by a preparative approach that should ultimately enable total synthesis. As will be shown below, this project was largely successful. It has not only led to the elucidation of the previously unknown stereostructure of cycloviracin B_1 **1,** but also allowed us to conquer this demanding glycolipid by a straightforward and high-yielding route.[10] However, the highly consistent picture derived from these studies reveals a serious mismatch between the proposed constitution of the fattiviracins and the published

Scheme 1 [a]



[a] Common structural motif of the cycloviracins and the proposed structure of all fattiviracins known to date.

data. Finally, cycloviracin B_1 itself and some of the key synthetic intermediates obtained during its total synthesis were evaluated for their antiviral activities. From the results obtained, it must be concluded that neither a stripped-down macrodiolide core nor the segments representing the lateral chains exhibit any appreciable activity, while specific antiviral effects for the entire construct are corroborated by these preliminary investigations.

Results and Discussion

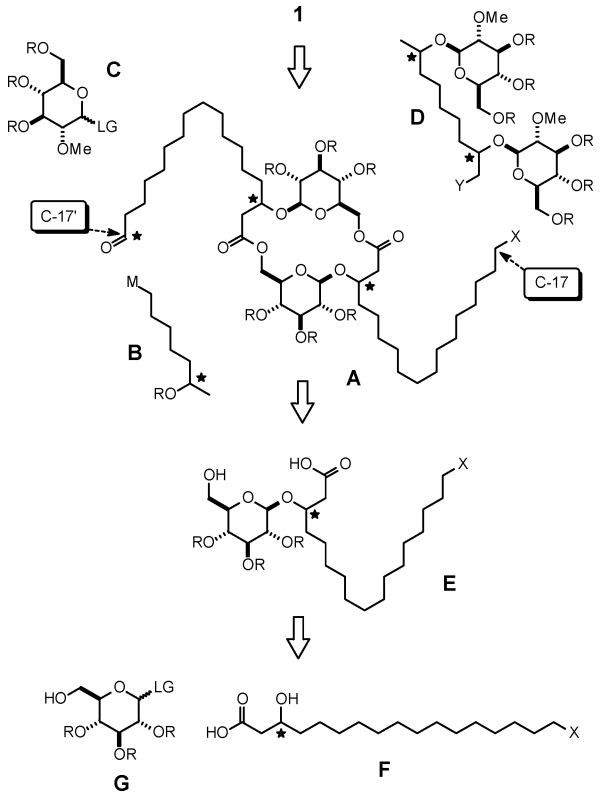
Retrosynthetic Analysis and Strategic Considerations. In view of the size and complexity of the targets as well as the structural ambiguities at the outset of the project, it was clear that only a highly convergent and inherently flexible approach might allow to reach the objectives set forth above.

The key design element of this plan exploits the hidden symmetry of these glycolipids. The fact that the individual subunits of the macrodiolide core of cycloviracin B_1 are indistinguishable by NMR at 600 MHz is best explained by assuming a C_2-symmetric structure in this part of the molecule. This then suggests to implement a two-directional synthesis strategy[11] en route to **1** to minimize the preparative efforts and to ensure maximum flexibility during fragment coupling (Scheme 2). Given the different length of its two lateral chains and their discrete hydroxylation pattern, however, this plan bears a considerable risk for the final assembly stages. While established methodology should allow to control the configuration of the −OH group at C-17′ generated by coupling of fragments **A** and **B** (M = metal), 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 maneuver 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 (i.e., at C-2 and/or C-2′) easily engenders 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.

Despite this considerable uncertainty, the strategic disconnections shown in Scheme 2 are tempting for the significant overall decrease in complexity which they entail. Thus, lactide **A** as the key component of this synthesis plan might be assembled by a template-directed cyclodimerization process[12,13] if one assumes that the specific array of *O*-atoms in the core

(6) This applies to all 13 individual fattiviracins known to date, cf. refs 2 and 5.
(7) (a) Fürstner, A.; Jeanjean, F.; Razon, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2097. (b) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem. Eur. J.* **2003**, *9*, 307. (c) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem. Eur. J.* **2003**, *9*, 320.
(8) (a) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (b) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424. (c) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758. (d) Lehmann, C. W.; Fürstner, A.; Müller, T. *Z. Kristallogr.* **2000**, *215*, 114.
(9) (a) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072. (b) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.
(10) For preliminary communications, see: (a) Fürstner, A.; Albert, M.; Mlynarski, J.; Matheu, M. *J. Am. Chem. Soc.* **2002**, *124*, 1168. (b) Fürstner, A.; Mlynarski, J.; Albert, M. *J. Am. Chem. Soc.* **2002**, *124*, 10274.
(11) (a) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9. (b) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167.

Scheme 2

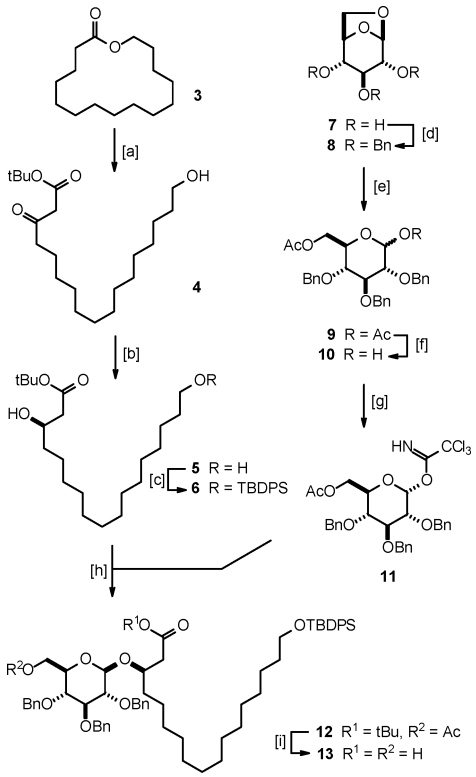


region endows the molecule with some degree of ionophoric character.[14] This then allows to deconvolute the target to a single precursor **E** which derives from a β-selective glycosylation of the rather simple aldol derivative **F** with a suitably protected glucosyl donor **G** (LG = leaving group).

The appeal of this convergent synthesis plan becomes apparent on comparison with a stepwise and hence linear construction of the macrodiolide core as the alternative scenario which must come into play should any of the premises described above prove invalid. In this context, a previous study directed toward **1** has to be mentioned which pursued such a stepwise route.[15] It may not come as a surprise that this approach ultimately turned out to be prohibitively lengthy to allow for systematic variations, provided only a highly truncated version of the cycloviracin core that cannot be elaborated any further, and therefore remained inconclusive with respect to the absolute stereochemistry at the branching points C-3/C-3′.[15]

C2-Symmetrical Core Structures by Template-Directed Macrodilactonization. To reduce the synthesis blueprint shown in Scheme 2 to practice, it is necessary to develop an efficient approach to the common aldol synthon **F** which derives from the envisaged disconnection of the nonequivalent lateral fatty

Scheme 3 [a]



[a] Conditions: [a] lithio *tert*-butyl acetate, THF, −78 °C, 61%; [b] [(*R*)-BINAP·$RuCl_2]_2$·NEt_3 cat., H_2 (15 atm), MeOH, 70 °C, 88%; [c] TBDPSCl, imidazole, DMF, 81%; [d] NaH, BnBr, DMF, 77%; [e] Ac_2O, NaOAc, H_2SO_4 cat., 95%; [f] H_2NNH_2·HOAc, DMF, r.t., 81%; [g] NaH, CH_2Cl_2, Cl_3CCN, 74%; [h] BF_3·Et_2O, MS 4 Å, CH_2Cl_2, −78 °C → r.t., 62%; [i] (i) F_3CCOOH, CH_2Cl_2; (ii) NH_3/MeOH, 74%.

acid chains of **1** at the glycosidic bond and the symmetry related C-17/C-17′ positions. A ring-opening Claisen condensation of well-accessible pentadecanolide **3**[16] with lithio *tert*-butyl acetate solves this problem very well, giving rise to β-keto ester **4** in 61% yield on a 15 g scale together with small amounts of the corresponding tertiary alcohol formed by double addition of the nucleophile to the lactone (Scheme 3).[17] Subsequent hydrogenation of **4** in the presence of Noyori's catalyst [((*R*)-BINAP)-$RuCl_2]_2$·NEt_3[18] affords the corresponding diol **5** in excellent yield, which is regioselectively silylated at the terminal position with TBDPSCl in the presence of imidazole to give the (*R*)-configured product **6** (ee = 98%) ready for subsequent glycosylation.[19]

After some experimentation with different glycosyl donors, trichloroacetimidate **11**[20] was selected as a suitable precursor

(12) Fürstner, A. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 2000; pp 249−273.
(13) (a) For recent studies on the synthesis of macrodiolides by nontemplated cyclodimerization reactions, see the following leading references and a comprehensive compilation of pertinent literature: Su, Q.; Beeler, A. B.; Lobkovsky, E.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett*. **2003**, *5*, 2149. (b) For the synthesis of a natural product from our laboratory by an RCM-based cyclodimerization process, see: Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett*. **2001**, *3*, 449.
(14) For a study on cyclic oligosaccharides acting as crown ethers, see: Shizuma, M.; Kadoya, Y.; Takai, Y.; Imamura, H.; Yamada, H.; Takeda, T.; Arakawa, R.; Takahashi, S.; Sawada, M. *J. Org. Chem*. **2002**, *67*, 4795 and literature cited therein.
(15) Velarde, S.; Urbina, J.; Pena, M. R. *J. Org. Chem*. **1996**, *61*, 9541.
(16) For a shortcut synthesis, see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, 61, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (c) Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc*. **2001**, *123*, 9000.
(17) Only very few examples of ring-opening Claisen condensations are known using four- to six-membered lactones as the substrates, cf: (a) Bone, E. A.; Davidson, A. H.; Lewis, C. N.; Todd, R. S. *J. Med. Chem.* **1992**, *35*, 3388. (b) Yamaguchi, M.; Nakamura, S.; Okuma, T.; Minami, T. *Tetrahedron Lett.* **1990**, *31*, 3913. (c) Shimizu, M.; Ishii, K.; Fujisawa, T. *Chem. Lett.* **1997**, *8*, 765.
(18) For comprehensive treatises, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1; pp 199−246.
(19) The order of silylation and hydrogenation can also be inversed. In this case, however, the overall yield of product **6** is somewhat lower due to partial cleavage of the terminal TBDPS group during the asymmetric reduction step.
(20) Wang, Y.; Mao, J.; Cai, M. *Synth. Commun*. **1999**, *29*, 2093.

Table 1. Effect of Different Additives on the Product Distribution in the Macrodilactonization Reaction of Hydroxy Acid **13**. Product Distributions Were Determined by HPLC without Correction for the Response Factors of the Different Compounds

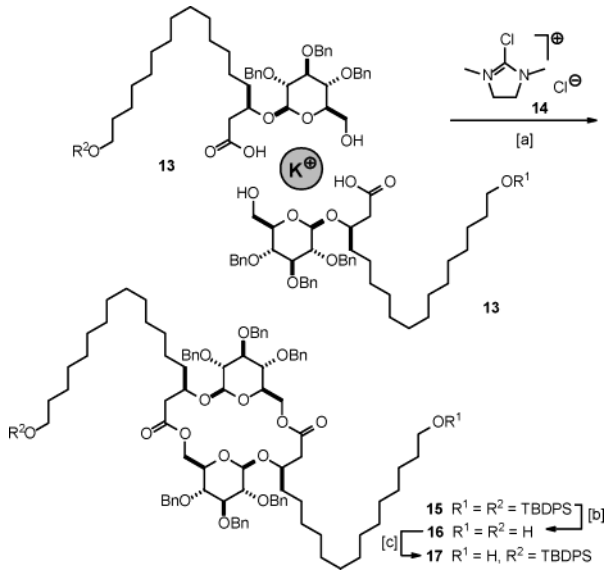
no.	molarity	additive	**18**	**15**	other (total)
1	20 mM		28%	37%	35%
2	20 mM	NaH	24%	52%	24%
3	20 mM	KH	20%	75%	5%
4	30 mM	KH	24%	68%	8%
5	50mM	KH	23%	68%	9%
6	20 mM	Cs_2CO_3	24%	48%	28%

for the glucose units to be embedded into the lactide core. This compound bears orthogonal protecting groups and is readily available in only four high-yielding operations from commercial laevoglucosane **7** as shown in Scheme 3.[21] Since the benzyl group at the C-2 position of **11** will not exert anchimeric assistance in the glycosylation event,[22,23] high selectivity in favor of the required β-glucoside must be ensured by the proper choice of promotor and solvent. Specifically, exposure of **6** and **11** in CH_2Cl_2 at low temperature to $BF_3{\cdot}Et_2O$ in the presence of molecular sieves provides β-glucoside **12** in an appreciable 62% isolated yield (87% based on recovered starting material), with the α/β-ratio being 1:6; the anomers are readily separable by flash chromatography. A similar result (68% yield, $\alpha/\beta = 1{:}5$) is obtained by performing the reaction with TMSOTf in CH_2Cl_2/MeCN (1:1) by taking advantage of the β-directing effect of the nitrile cosolvent.[24] Subsequent cleavage of the *tert*-butyl ester in **12** with trifluoroacetic acid followed by saponification of the residual acetate with NH_3/MeOH leads to hydroxy acid **13** in 74% yield over both steps and sets the stage for the envisaged cyclodimerization reaction.

Preliminary experiments using DCC/DMAP as the activating agent in dilute CH_2Cl_2 solution were unsuccessful. In this context it is also important to note that Peña et al. reported on attempted cyclodimerizations of model compounds with the aid of biocatalyts which were so unrewarding that they opted for a stepwise approach en route to the truncated cycloviracin core model mentioned above.[15]

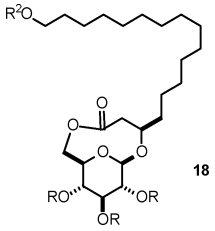
Despite these pitfalls, however, the original plan was pursued further in the hope that a more efficient activator than DCC would allow to effect the desired esterification/lactonization tandem of the hydroxy acid **13**. Encouraging observations were made when compound **13** was exposed to 2-chloro-1,3-dimethylimidazolinium chloride **14**, a commercially available dehydrating agent.[25−27] Specifically, reaction of **13** with **14** in

Scheme 4 [a]



[a] Conditions: [a] 2-chloro-1,3-dimethylimidazolinium chloride **14**, DMAP, KH, CH_2Cl_2, 71%; [b] TBAF, THF, 92%; [c] *t*$BuPh_2SiCl$, Et_3N, CH_2Cl_2, 85%.

the presence of DMAP at 0 °C affords a separable mixture of cyclic monomer **18** (28%), the desired cyclic dimer **15** (37%), and several oligomeric byproducts (combined yield ca. 35%, cf. Table 1, entry 1).

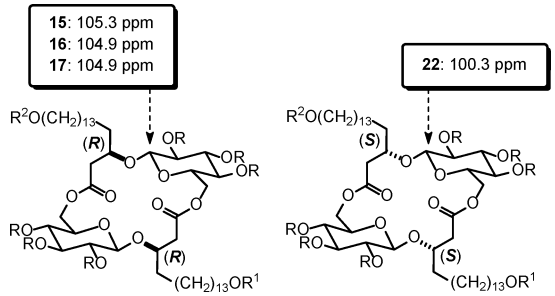


Although this product distribution is far from optimal, it shows that the cyclodimer can be formed in a single step. Therefore, systematic investigations were carried out to improve on this result by templating the cyclization reaction with the aid of suitable additives.[12] In line with our expectations, this process was found to be highly responsive to admixed alkali metal cations (Scheme 4 and Table 1). Gratifyingly, the addition of KH not only led to a substantially increased reaction rate but also to a significant improvement of the product distribution in favor of **15**; under optimized conditions, this product is obtained in 71% isolated yield (75% HPLC, cf. Table 1, entry 3). Since the effect exerted by NaH or Cs_2CO_3 is much less pronounced, this outcome is deemed to reflect the ability of the K^+ cation to preorganize the cyclization precursor **13** for directed macrodilactonization. Representative results are summarized in Table 1.

The NMR spectra of **15**, the desilylated alcohol **16**, as well as the unsymmetrical derivative **17** ($R^1 \neq R^2$) all match those reported for **1**[1] very well, suggesting that the absolute stereochemistry of cycloviracin B_1 is (3*R*,3′*R*). To corroborate this notion, however, it was necessary to prepare the analogous (3*S*,3′*S*)-configured lactide **22** and to compare its spectroscopic properties with those of the natural product. The synthesis of compound **22** is highly straightforward. It follows the route

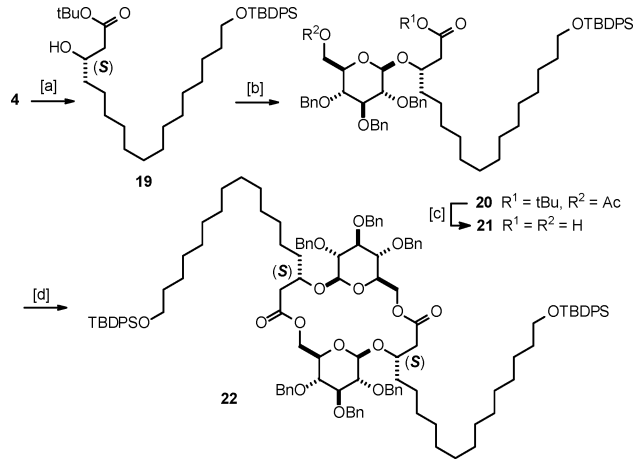
(21) (a) Bourke, D. G.; Collins, D. J.; Hibberd, A. I.; McLeod, M. D. *Aust. J. Chem.* **1996**, *49*, 425. (b) Hoch, M.; Heinz, E.; Schmidt, R. R. *Carbohydr. Res.* **1989**, *191*, 21.
(22) General discussions: (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl*. **1982**, *21*, 155. (b) Schmidt, R. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6; pp 33−61. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
(23) Pertinent reviews on the trichloroacetimidate method: (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 212. (b) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem*. **1994**, *50*, 21.
(24) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694.
(25) (a) Isobe, T.; Ishikawa, T. *J. Org. Chem*. **1999**, *64*, 5832. (b) Isobe, T.; Ishikawa, T. *J. Org. Chem*. **1999**, *64*, 6984. (c) Isobe, T.; Ishikawa, T. *J. Org. Chem*. **1999**, *64*, 6989. (d) See also: Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett*. **1982**, 1891.
(26) For a related cyclotrimerization en route to the glycolipid anthrobacilin A, see: Garcia, D. M.; Yamada, H.; Hatakeyama, S.; Nishizawa, M. *Tetrahedron Lett*. **1994**, *35*, 3325.
(27) For an application of these reagents in organometallic chemistry, see: Fürstner, A.; Seidel, G.; Kremzow, D.; Lehmann, C. W. *Organometallics* **2003**, *22*, 907.

Scheme 5 [a]



[a] Comparison of the shifts of the anomeric carbon atoms of the (3*R*,3′*R*) and the (3*S*,3′*S*)-configured core structures.

Scheme 6 [a]



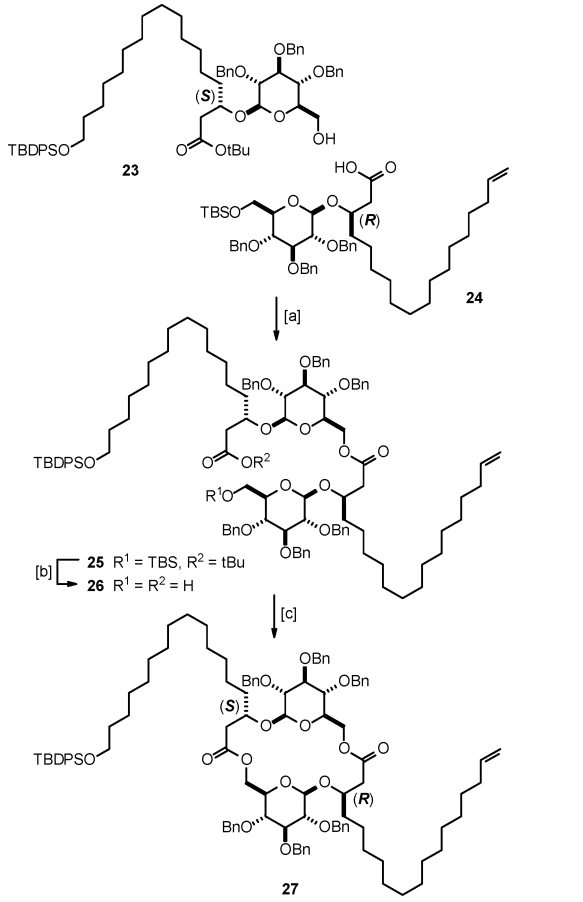
[a] Conditions: [a] (i) [(*S*)-BINAP·$RuCl_2$]$_2$·NEt_3 cat., H_2 (15 atm), MeOH, 70 °C, 92%; (ii) TBDPSCl, Et_3N, CH_2Cl_2, 97%; [b] imidate **11**, TMSOTf cat., MeCN/CH_2Cl_2 (1:1), −50 °C → r.t., 63% (+ 19% of the α-anomer separated by flash chromatography); [c] (i) NH_3 in MeOH, 83%; (ii) F_3CCOOH, CH_2Cl_2; [d] 2-chloro-1,3-dimethylimidazolinium chloride **14** (2.5 equiv), DMAP (3 equiv), KH (2.5 equiv), CH_2Cl_2, 41%.

described above, simply using (*S*)-BINAP instead of (*R*)-BINAP as the ligand in the hydrogenation of keto ester **4** (Scheme 6). The glycosidation of the resulting aglycone **19** with trichloroacetimidate **11** is best achieved with TMSOTf in CH_2Cl_2/MeCN (1:1) at −50 °C. As expected, the subsequent cyclodimerization of the diastereomeric hydroxy acid **21** derived thereof occurs smoothly in the presence of 2-chloro-1,3-dimethylimidazolinium chloride **14**,[25] DMAP, and KH, albeit the isolated yield of lactide **22** is somewhat lower (41%).

Notably, however, the spectral data of **22** are significantly different, with the high-field shift of the anomeric C-atoms at $\delta_C = 100.3$ ppm being particularly diagnostic. These marked shift differences of the anomeric carbon atoms in lactides **15**−**17** on one hand and compound **22** on the other hand ($\Delta\delta \sim 5$ ppm, cf. Scheme 5) allow the *assignment of the stereochemistry at the branching points in the cycloviracin core as 3R,3′R.*[10a,28]

In short, the convergent approach to the C_2-symmetrical macrodiolides outlined above is not only highly productive but also inherently flexible and therefore allowed to determine the previously unknown configuration of the branching points in cycloviracin B_1 **1** without undue preparative efforts. It favorably compares with the previously published route[15] to a more truncated version of the core in all relevant respects, in particular with regard to its inherent "economy of steps" as a prime indicator for high efficiency.[29]

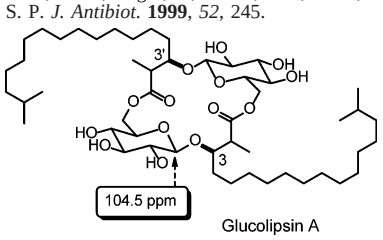
Scheme 7 [a]



[a] Conditions: [a] Diisopropyl carbodiimide (DIC), DMAP, CH_2Cl_2, 83%; [b] F_3CCOOH/CH_2Cl_2 (1:10), 77%; [c] 2,4,6-trichlorobenzoic acid chloride, Et_3N, THF; then DMAP, toluene, reflux, 89%.

Fattiviracin Problem. Preparation of the (3R,3′S)-Configured Macrodiolide. In view of the foregoing, however, a rather puzzling situation as to the actual structure of the fattiviracins ensues. In contrast to the cycloviracins, which give rise to only one set of signals for both units forming the macrodiolide ring,[1] all members of the fattiviracin family invariably show inequivalent subunits (cf. Scheme 1).[2,6] Specifically, the anomeric positions for fattiviracin FV-8 **2** as a prototype example resonate at 104.0 and 105.0 ppm, respectively, a fact that seems neither consistent with the situation found in cycloviracin (i.e. 3*R*,3′*R*) nor with a (3*S*,3′*S*) configuration at the branching points. To complicate matters even

(28) Although the closely related shift values of the glucokinase activating macrodiolide glucolipsin A seem to suggest that this particular compound—*which contains an extra methyl branch at the adjacent position*—might also be (3*R*,3′*R*) configured, a recent total synthesis by our group shows that glucolipsin incorporates in fact a (2*R*,3*S*)-configured syn aldol entity. For the isolation of glucolipsin, see: Qian-Cutrone, J.; Ueki, T.; Huang, S.; Mookhtiar, K. A.; Ezekiel, R.; Kalinowski, S. S.; Brown, K. S.; Golik, J.; Lowe, S.; Pirnik, D. M.; Hugill, R.; Veitch, J. A.; Klohr, S. E.; Whitney, J. L.; Manly, S. P. *J. Antibiot.* **1999**, *52*, 245.

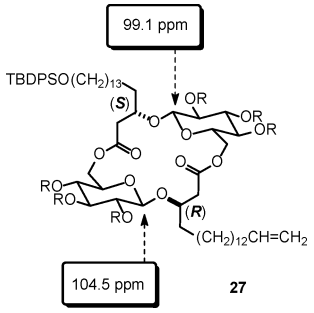


(29) For a discussion, see: Fürstner, A. *Synlett* **1999**, 1523.

further, these data also seem to exclude the only remaining option of a (3*R*,3′*S*)-configured core. Although such a stereochemical hermaphrodite would be highly surprising from a biosynthetic viewpoint as well, we saw no way except synthesis to rigorously exclude this possibility. Since a cyclodimerization approach is obviously unsuitable in this case, a stepwise macrocyclization protocol had to be pursued (Scheme 7).

For this purpose, the acetate group in **20** is cleaved with NH_3/MeOH to give the (3*S*)-configured alcohol **23,** which is esterified in 83% yield with the (3*R*)-configured synthon **24**[30] in the presence of DIC/DMAP. Subsequent treatment of compound **25** with F_3CCOOH in CH_2Cl_2 leads to the concomitant cleavage of the *tert*-butyl ester (= R^2) and the *tert*-butyldimethylsilyl ether (= R^1) while leaving the *tert*-butyldiphenylsilyl group at the terminus of one of the lipidic chains intact. The resulting hydroxy acid **26** is then cyclized to the desired lactide **27** by a Yamaguchi lactonization.[31]

The anomeric centers in the unsymmetrical lactide **27** thus formed resonate at $\delta = 99.1$ and 104.5 ppm, respectively, thus showing that the differently configured subunits can be clearly distinguished by NMR. More important, however, is the *striking mismatch* with the data reported for **2** ($\delta = 104.0$ and 105.0).[2] They are not consistent with the proposed constitution implying a lactide unit similar to the one found in cycloviracin **1**, independent of whether one assumes an (*R*,*R*)-, (*S*,*S*)-, or (*R*,*S*)-configuration at the branching points. It must be concluded that either the proposed structure of the fattiviracins or the reported set of data are erroneous and need revision in the future.

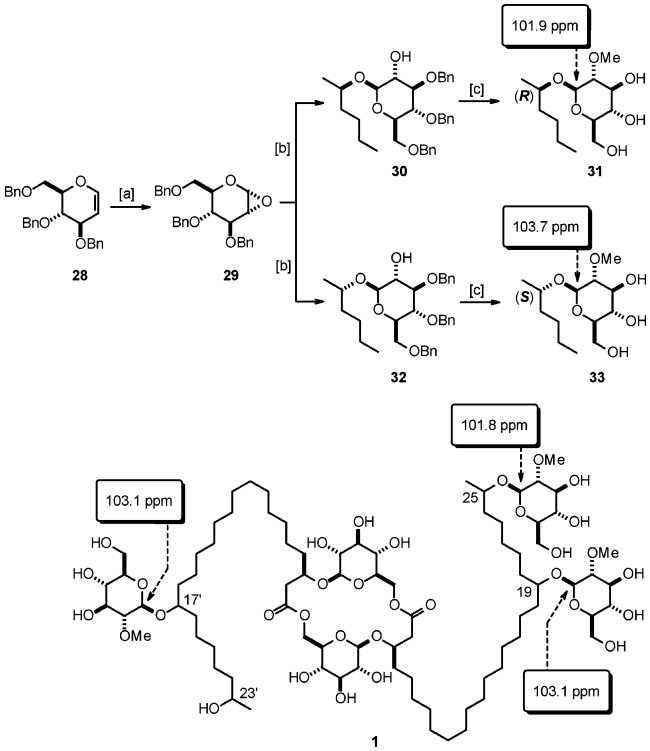


27

Although a conclusive answer to this puzzle will require further preparative and spectroscopic studies, one may speculate about a different connectivity pattern of the individual subunits involving an −OH group further down the fatty acid chain to form an expanded macrolactone ring, which might perhaps explain the observed data. Interestingly, a new family of glycolipids with antiviral properties was recently disclosed in the patent literature which contains such a giant entity (e.g., BA-2836, also called "macroviracin").[32] The possible relationship between these intriguing macrocycles and the fattiviracins is subject to further investigations in our laboratory.

Configuration of the Distal Chiral Centers in Cycloviracin. Model Studies. After having established the absolute configuration of the branching points in cycloviracin as (3*R*,3′*R*), model studies were undertaken to gain further insights into the stereostructure of this target prior to launching the actual total synthesis. Since the shift of the anomeric positions of the glucosides were found to be highly diagnostic for the configuration of the attached lipidic aglycones (see above), it was envisaged to use this effect[33] also for investigating the more distal sites residing on the lateral fatty acid appendices in **1**.

Scheme 8 [a]



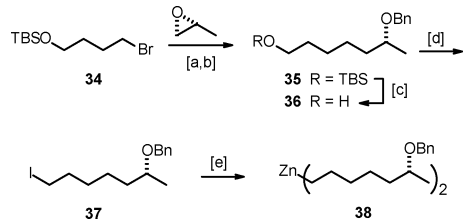
[a] Conditions: [a] *m*-chloroperbenzoic acid, KF, CH_2Cl_2, cf. ref. 34; [b] (2*R*)- or (2*S*)-hexanol, $ZnCl_2$, THF, 32−36%; [c] (i) MeI, NaH, DMF; (ii) H_2, Pd/C, EtOH, 66−70% (over both steps).

For this purpose, glycal epoxide **29**[34] was reacted with (2*R*)- and (2*S*)-hexanol in the presence of $ZnCl_2$ as the promoter to give glycosides **30** and **32**, respectively, albeit in moderate yield.[35] Both compounds were *O*-methylated under standard conditions at the liberated O-2 site prior to hydrogenolytic cleavage of the benzyl ether groups. As can be seen from Scheme 8, the resulting glycosides **31** and **33** differing only in the configuration of their aglycone are easily distinguished by NMR. Most notable is the fact that the anomeric center of **31** linked to the (*R*)-configured alcohol resonates at $\delta_C = 101.9$ ppm, a shift which correlates exceedingly well with that of the distal 2-*O*-methyl glucoside of cycloviracin B_1 ($\delta_C = 101.8$ ppm), thus making a (25*R*)-configuration in the natural product highly likely. Moreover, the comparison between **33** and **1** provides a first indication that the chiral centers at C-17′ and C-19 of the latter might be (*S*)-configured.

It seemed appropriate, however, to corroborate this notion by further model studies since these stereocenters reside within the most "symmetrical" segments of the hydrocarbon chains,

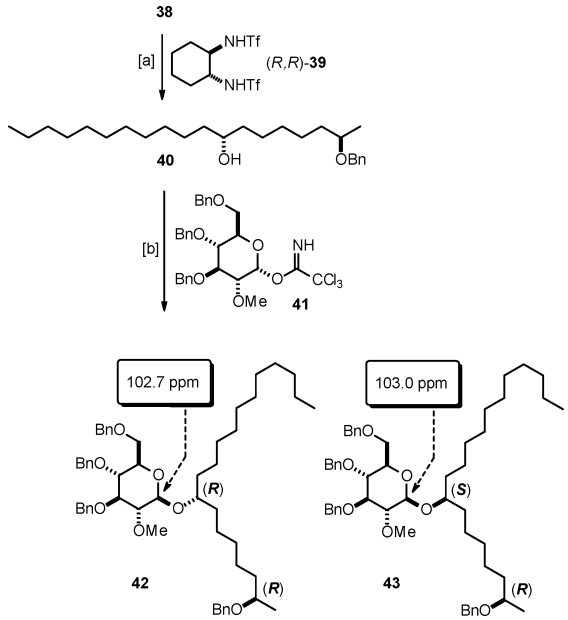
(30) The synthesis of this compound is outlined in the Supporting Information.
(31) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(32) (a) Hyoda, T.; Tsuchira, Y.; Sekine, A.; Amano, T. Jpn. Kokai Tokkyo Koho Jpn. Pat. 11246587 (1999−09−14). (b) See also: Takahashi, S.; Hosoya, M.; Koshino, H.; Nakata, T. *Org. Lett.* **2003**, *5*, 1555.
(33) For methods allowing the determination of the configuration of secondary alcohols by using sugar derivatives as derivatizing agents, see the following for leading references and literature cited therein: (a) Trujillo, M.; Morales, E. Q.; Vazquez, J. T. *J. Org. Chem*. **1994**, *59*, 6637. (b) Kobayashi, M. *Tetrahedron* **2002**, *58*, 9365.
(34) Bellucci, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron: Asymmetry* **1995**, *6*, 221.
(35) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1989**, *111*, 6661. (b) Review: Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1380.

Scheme 9 [a]



[a] Conditions: [a] (i) Mg, THF; (ii) CuCl(COD) cat., (*R*)-propene oxide, 70%; [b] BnBr, NaH, 73%; [c] TBAF, THF, 93%; [d] I_2, imidazole, PPh_3, 89%; [e] Et_2Zn (excess) CuCN cat.

Scheme 10 [a]

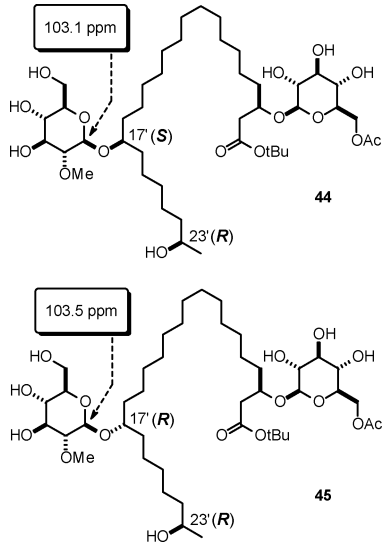


[a] Conditions: [a] dodecanal, $Ti(OiPr)_4$, (*R*,*R*)-**39**, toluene, 65%; [b] TMSOTf cat., CH_2Cl_2/MeCN (1:1), 92%.

with the stereochemical determinants being *five* CH_2 units away from the sites in question.

Specifically, reaction of the Grignard reagent derived from the protected 4-bromo-1-butanol derivative **34** with enantiomerically pure (*R*)-propene oxide[36] in the presence of catalytic amounts of CuCl(COD) leads to efficient ring opening (Scheme 9). Protection of the resulting secondary −OH group as a benzyl ether followed by cleavage of the TBS group of **35** with TBAF provides alcohol **36** in good overall yield, which is converted into the primary iodide **37** under standard conditions. This compound affords the functionalized diorganozinc derivative **38** on prolonged exposure to neat Et_2Zn and catalytic amounts (3 mol %) of CuCN.[37] Addition of this donor to dodecanal in the presence of $Ti(OiPr)_4$ and (*R*,*R*)-**39** as the controlling ligand[38] furnishes the corresponding (*R*)-configured alcohol **40** in 65% yield with excellent optical purity (de ≥ 99%). Reaction of this material with trichloroacetimidate **41** mediated by TMSOTf in CH_2Cl_2/MeCN gives the corresponding β-glycoside **42** in 92% isolated yield (Scheme 10).

Scheme 11



The anomeric center of this compound resonates at δ_C = 102.7 ppm, while the shift of the corresponding (*S*)-configured analogue **43** is δ_C = 103.0 ppm. The more advanced models **44** and **45** prepared along similar lines[30] can also be clearly distinguished by NMR ($\Delta\delta_C$ = 0.4 ppm). Although the observed differences are small, they are significant and likely characteristic. Most important is the fact that in all pairs of stereoisomers investigated (**31/33**, **42/43**, **44/45**) the anomeric center of the compound bearing the (*S*)-configured aglycone invariably resonates at a shift that is (almost) identical to the corresponding signal in **1** (δ_C = 103.1).[39] Moreover, an NMR inspection of a 1:1 mixture of **42/43** or **44/45** showed that the individual compounds can be clearly discerned. Therefore, it is highly likely that a direct comparison of the spectra of synthetic **1** with (19*S*,17′*S*)-configuration[40] with that of authentic cycloviracin B_1 will result in a visible mismatch of the patterns if the stereochemistry at those centers does not correspond to that of the natural product.

Biosynthetic considerations also strongly advocate an (*S*)-configuration at those sites. It is known that the lipidic segments of these antiviral glycolipids derive from acetate units via the usual polyketide pathway.[2d] Therefore, the most probable product is the one in which any leftover hydroxyl groups reside on the same side of the aliphatic chain.[40]

On the basis of these results and considerations, one can (i) assign the (*R*)-configuration to the branching points at C-3 and C-3′ in cycloviracin B_1, (ii) ascribe the (*R*)-configuration to the distal sites at C-23′ and C-25, and (iii) make the (*S*)-configuration for the remaining stereocenters at C-17′ and C-19 highly probable. These conclusions set the basis for the total synthesis of this bioactive target molecule summarized below.

(36) Enantiopure propene oxide is commercially available or can be conveniently prepared on a large scale in optically active form using Jacobsens's excellent HKR method, cf.: (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

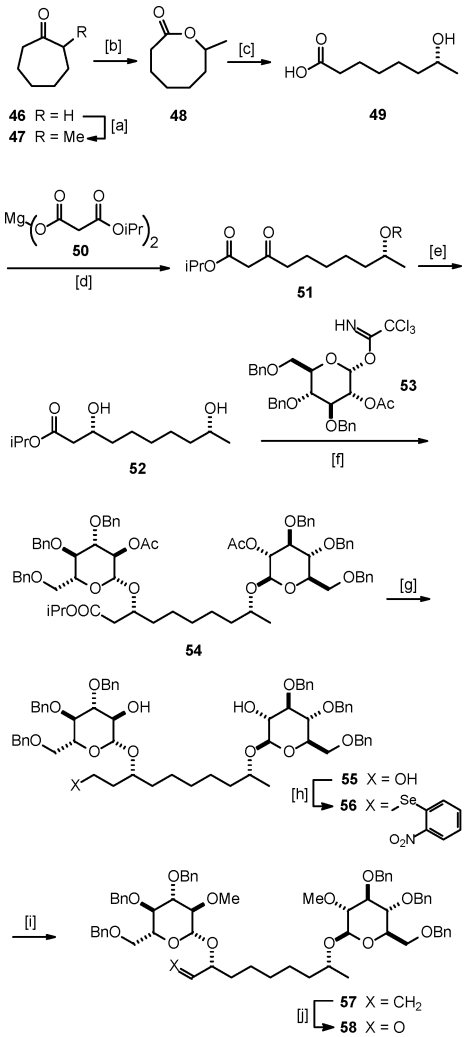
(37) Rozema, M. J.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 3115.

(38) (a) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691. (b) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013. (c) Knochel, P. *Synlett* **1995**, 393.

(39) Similar effects are visible in the ^1H NMR spectra which are also distinctly different for the pairs of stereoisomers **31/33**, **42/43**, **44/45**. Particularly diagnostic is the shift of the terminal methyl group of the fatty acid chain which resonates at δ = 1.34 ppm in the 17*S*-configured compounds but at δ = 1.31 ppm in the 17*R*-configured products. The pertinent shift in the natural product is δ = 1.34 ppm.

(40) 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.

Scheme 12 [a]

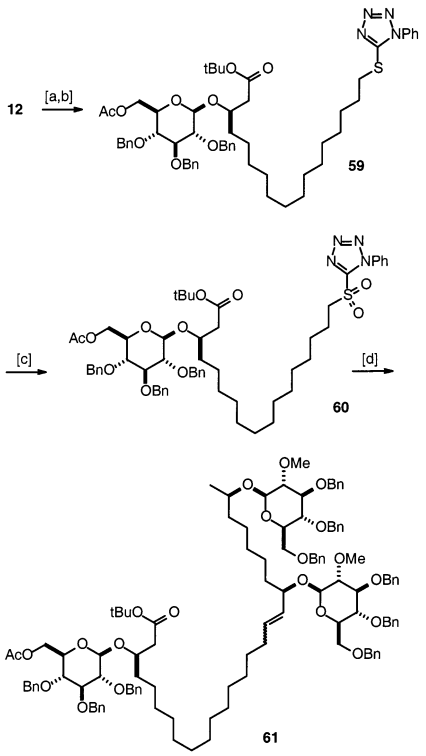


[a] Conditions: [a] LDA, THF, −78 °C, then MeI, 84%; [b] mCPBA, CH_2Cl_2, 74%; [c] porcine liver esterase, pH 7.2, 40%, ee = 95%; [d] (i) carbonyl diimidazole, reagent **50**, THF; (ii) NaOH, THF/H_2O, 74%; [e] H_2 (10 atm), [((*R*)-BINAP)$RuCl_2$]$_2$·NEt_3, MeOH/THF, 70 °C, 99%, de = 99%; [f] trichloroacetimidate **53**, TMSOTf cat., MS 4 Å, CH_2Cl_2, 82%; [g] $LiAlH_4$, THF, 82%; [h] Bu_3P, *o*-nitrophenyl selenocyanate, THF; [i] (i) H_2O_2, THF, 90%; (ii) NaH, MeI, DMF, 78%; [j] O_3, CH_2Cl_2, −78 °C, then Me_2S, 95%.

Preparation of the Missing Building Blocks and Model Studies on Fragment Coupling. The next interim goal en route to cycloviracin B_1 was the preparation of adequate building blocks for its glycosylated fatty acid appendices and the assessment of proper methodology for the attachment of these lateral segments to the central macrodiolide ring. While the successful application of the diorganozinc derivative **38** in the model studies strongly recommends the use of this reagent for the construction of the C-18′−C-24′ region of the final target, a suitable surrogate for the other terminus ranging from C-18 through C-26 remains to be developed. The chosen approach is summarized in Scheme 12.

The synthesis starts with the α-methylation of cycloheptanone **46**[41] followed by a Baeyer−Villiger oxidation of the resulting product **47**. It is known that hydrolysis of lactone **48** thus formed catalyzed by pig liver esterase (PLE) results in an efficient kinetic resolution leaving the (*S*)-configured lactone behind which is essentially enantiomerically pure (ee > 95%).[42] For the purpose of our study, however, an (*R*)-configured building block is required.[43] Since an assay of 19 different commercially available enzymes did not show any hit for a biocatalyst with such a reversed preference, the hydrolysis reaction was optimized for the preparation of the resulting hydroxy acid. Keeping the pH constant at 7.2 and stopping the PLE-catalyzed reaction after 40% conversion furnishes acid **49** with an ee = 95% in 38% yield on a multigram scale. This compound is then activated with carbonyl diimidazole and reacted with the magnesium carboxylate **50** developed by Masamune et al.[44,45] to give keto ester **51a** (R = H) together with small amounts of imidazolyl carbamate **51b** (R = C(O)imidazolyl); simple workup of the crude material with aq. NaOH in THF effectively cleaves the carbamate group and allows for a convenient isolation of product **51a** in 74% isolated yield. Asymmetric hydrogenation of this material in the presence of [((*R*)-BINAP)$RuCl_2$]$_2$·NEt_3 [18] affords diol **52** in almost quantitative yield, which was found to be optically pure (de = 99%). Subsequent glycosylation with trichloroacetimidate **53** prepared as previously described by our

Scheme 13 [a]



[a] Conditions: [a] TBAF, THF, 92%; [b] 1-phenyl-5-mercapto tetrazole, PPh_3, DIAD, 85%; [c] $(NH_4)_6Mo_7O_{24}$·$4H_2O$, aq. H_2O_2, EtOH, 97%; [d] LiHMDS, DME, −78 °C, then aldehyde **58**, 45%.

(41) (a) Liu, H.-J.; Wang, D.-X.; Kim, J. B.; Browne, E. N. C.; Wang, Y. *Can. J. Chem.* **1997**, *75*, 899. (b) Dave, V.; Warnhoff, E. W. *J. Org. Chem.* **1983**, *48*, 2590.

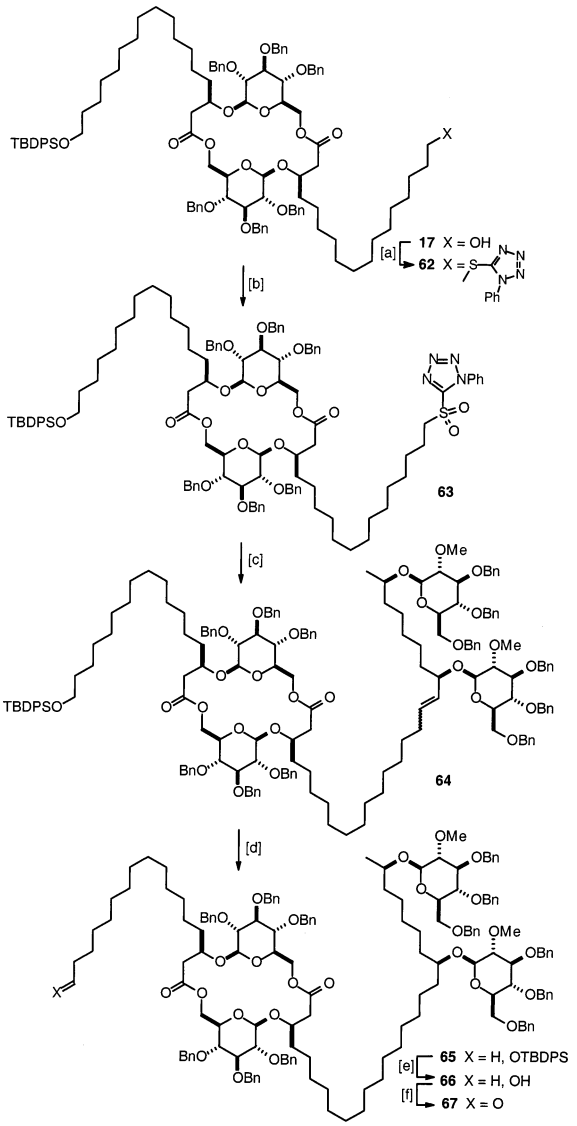
(42) Fouque, E.; Rousseau, G. *Synthesis* **1989**, 661.

(43) Note again the formalism of the Chan−Ingold−Prelog nomenclature. The use of the (2*R*)-configured aldehyde **58** will ultimately result in a (19*S*)-configured cycloviracin derivative due to change in priorities of the substituents at that center.

(44) (a) Brooks, D. W.; Lu, L. D. L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72. (b) For an advanced application, see the total synthesis of thienamycin reported by the Merck Laboratories: Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

(45) For a convenient preparation of the magnesium carboxylate, see: Page, P. C. B.; Moore, J. P. G.; Mansfield, I.; McKenzie, M. J.; Bowler, W. B.; Gallagher, J. A. *Tetrahedron* **2001**, *57*, 1837.

Scheme 14 [a]

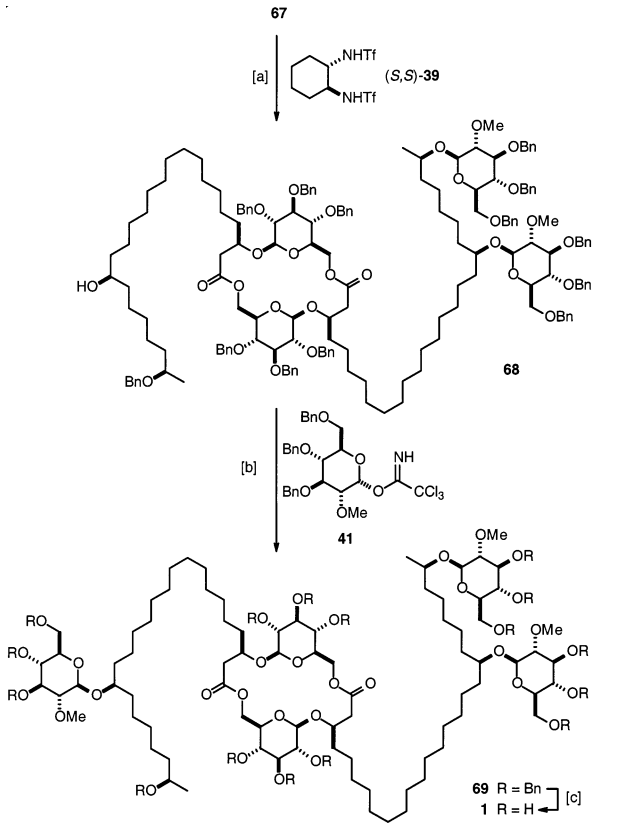


[a] Conditions: [a] 1-phenyl-5-mercapto tetrazole, PPh_3, DIAD, 91%; [b] $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, aq. H_2O_2, EtOH/CH_2Cl_2, 67%; [c] LiHMDS, DME, −78 °C, aldehyde **58**, 61% (*E*:*Z* = 1:1); [d] H_2 (1 atm), Pd/C, EtOAc, 72%; [e] TBAF, THF, 95%; [f] PCC, CH_2Cl_2, 83%.

group[46] in the presence of TMSOTf in CH_2Cl_2 is not only highly effective but also completely selective for the β-glycoside due to the anchimeric assistance of the 2-*O*-acetyl group in the donor. Interestingly, however, the inspection of the mixture shows that the reaction initially leads to the rather selective formation of the corresponding ortho esters, which only slowly rearrange to the desired glycosides on prolonged reaction at −78 °C for 2 h. A similarly advanced ortho ester → β-glycoside rearrangement[47] was recently exploited in the final steps of our total synthesis of woodrosin I, a macrocyclic glycolipid belonging to the resin glycoside family.[7]

Further elaboration of product **54** thus formed starts with an exhaustive $LiAlH_4$ reduction of the three ester moieties to give triol **55**. Only its primary alcohol reacts with *o*-nitrophenylselenocyanate in the presence of Bu_3P to give the corresponding selenide **56,** which is oxidized with aq. H_2O_2 to the corresponding selenoxide;[48] this compound undergoes a rather slow but clean elimination with formation of the corresponding alkene in 90% yield. *O*-Methylation of the remaining two hydroxyl groups on the sugar moieties under standard conditions to give **57** followed by ozonolysis of the alkene affords the desired aldehyde **58,** which constitutes a fully functional surrogate of synthon **D** depicted in the retrosynthetic Scheme 2.

Scheme 15 [a]

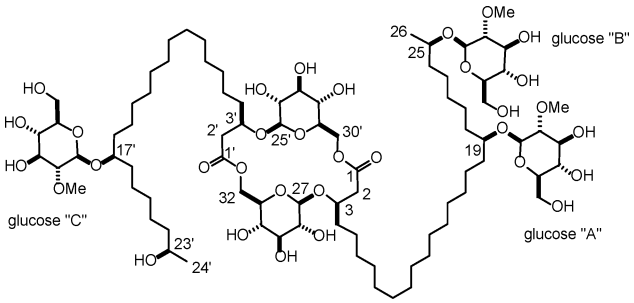


[a] Conditions: [a] compound **38**, $Ti(OiPr)_4$, (*S*,*S*)-**39**, toluene, 87%; [b] imidate **41**, TMSOTf cat., CH_2Cl_2, MeCN (1:1), 87%; [c] H_2 (1 atm), Pd/C, EtOH/EtOAc (4:1), 88%.

As outlined in the Introduction, a successful end game of the envisaged total synthesis critically depends on the ability to convert the intact macrodiolide ring **A** into a suitable C-nucleophile (X = metal). Importantly, this reactive intermediate must kinetically resist a possible intramolecular attack onto its own lactone groups as well as a destructive deprotonation of the C−H acidic sites adjacent to those lactones. Moreover, its reaction with aldehyde **58** must not entail any racemization of the chiral center α to the carbonyl. Because only a highly stabilized and weakly basic nucleophile, if any, might meet these stringent criteria, recourse was taken to the venerable Julia olefination[49] in the powerful modification developed by Kocienski.[50] It was expected that the somewhat higher kinetic

(46) Fürstner, A.; Konetzki, I. *Tetrahedron Lett.* **1998**, *39*, 5721.
(47) (a) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron Lett.* **1964**, *5*, 289. (b) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron* **1967**, *23*, 693. (c) For the use of TMSOTf as promotor in Kochetkov-type ortho ester rearrangements, see: Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6.
(48) (a) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947. (b) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(49) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175.
(50) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. (b) For a recent review, see: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

Table 2. Comparison of the ^{13}C NMR Data Recorded in Pyridine-d_5 for the Synthetic Sample of Cycloviracin B_1 (150 MHz) with Those Reported for the Natural Product (100 MHz).[1] As Can Be Seen, the $\Delta\delta$ Is $\leq$0.1 ppm, Which Is within Experimental Accuracy. Arbitrary Numbering Scheme as Shown in the Insert



position	literature	synthetic sample
1,1	171.7	171.7
2,2	42.4	42.5
3,3	78.9	78.9
19	79.3	79.3
25	74.2	74.2
26	19.5	19.5
27,25	106.4	106.5
28,26	75.1	75.2
29,27	78.3	78.3
30,28	72.1	72.1
31,29	74.5	74.6
32,30	65.3	65.4
17	79.3	79.3
22	40.1	40.2
23	67.0	67.0
24	24.3	24.3
1A	103.1	103.1
2A	85.3	85.3
3A	77.7	77.8
4A	71.8	71.9
5A	78.0	78.0
6A	62.9	62.9
2A-OMe	60.7	60.8
1B	101.8	101.8
2B	85.0	85.1
3B	77.6	77.7
4B	71.7	71.8
5B	78.0	78.0
6B	62.8	68.9
2B-OMe	60.6	60.6
1C	103.1	103.2
2C	85.3	85.4
3C	77.7	77.8
4C	71.8	71.9
5C	78.1	78.1
6C	62.9	62.9
2C-OMe	60.7	60.8

acidity together with the better accessibility of a terminal tetrazolyl sulfone should allow for a selective deprotonation by means of a sterically encumbered base without damaging the C−H acidic groups on the lactide ring; the stabilized nature of lithiated sulfones in general is well documented in the literature.[51]

To probe the viability of this concept, a model study was carried out commencing with compound **12** (Scheme 13). Deprotection of its terminal TBDPS−ether with TBAF in THF is followed by conversion of the resulting primary alcohol into sulfide **59,** which is then oxidized to the required sulfone **60**.[50] Selective deprotonation of **60** at the sulfone site with LiHMDS at −78 °C in DME as the best solvent followed by addition of aldehyde **58** at that temperature furnishes the desired alkene **61** in 45% isolated yield as an inseparable mixture of both stereoisomers (*E:Z* = 1:1). This result shows that the ester groups and the acidic protons adjacent to them can survive under the chosen reaction conditions. Not surprisingly though, any excess of the base must be strictly avoided. Moreover, it was found that the use of either NaHMDS or KHMDS for the deprotonation of sulfone **60** leads to significantly larger amounts of unidentified byproducts. Although the outcome of this experiment is not fully satisfactory in terms of yield, it suggests that a Julia−Kocienski olefination should qualify for the delicate assembly of cycloviracin B_1 from the individual building blocks.

Completion of the Total Synthesis. Encouraged by the results of this exploratory study, the (3*R*,3′*R*)-configured lactide **15** was desymmetrized by cleavage of both terminal silyl groups followed by introduction of a single OTBDPS group (**15** → **16** → **17**, cf. Scheme 4). This protocol turned out to be more productive than attempts to remove only one silyl ether from **15**. Conversion of alcohol **17** to sulfide **62** on treatment with commercial 1-phenyl-1*H*-tetrazole-5-thiol and PBu_3[52] proceeds with excellent yield, whereas the subsequent oxidation to the corresponding sulfone **63** turned out to be somewhat more difficult than expected (Scheme 14). Due to the poor solubility of **62** in EtOH as the preferred solvent, the oxidation with H_2O_2 in the presence of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$[53] had to be carried out in a mixed solvent system ($EtOH/CH_2Cl_2$) which significantly retards the reaction and occasionally leads to incomplete conversions. Under optimized conditions, however, sulfone **63** is obtained in 67% yield.

With this compound in hand, the crucial Julia−Kocienski olefination[49−51] was investigated. Gratifyingly, addition of aldehyde **58** to a solution of the lithio sulfone derived from **63** by deprotonation with LiHMDS in DME at −78 °C and stirring of the mixture at that temperature for 60 min delivers the corresponding alkene **64** in 61% yield (*E:Z* ∼ 1:1), which was hydrogenated over Pd/C in EtOAc to give product **65** in order to facilitate the analysis of the NMR spectra. We are unaware of any precedence for Julia-type olefination reactions involving sulfones bearing such base-labile and electrophilic β-hydroxy ester motifs as those present in compound **63**.

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Table 3. Cytotoxicity and Antiviral Activity of Various Glycolipids in HEL Cell Cultures

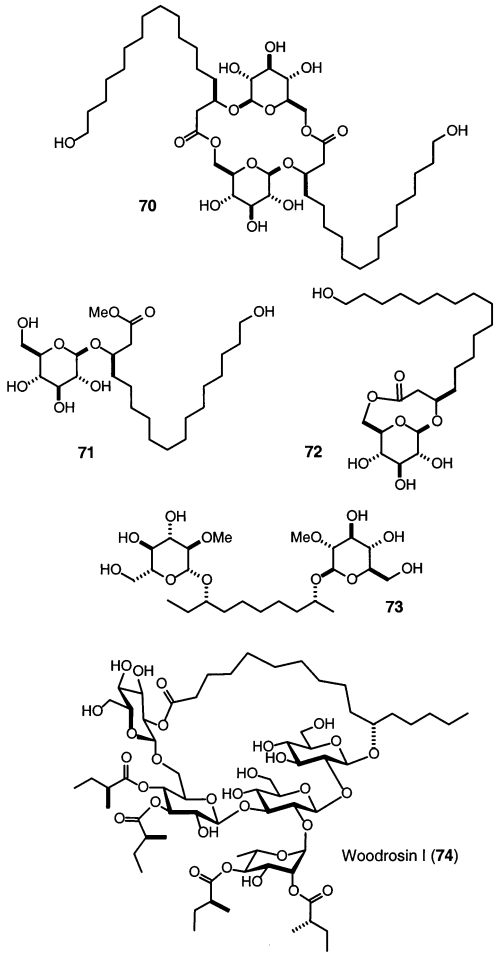
		min virus inhibitory conc[b] (μg·mL^{-1})				
compd	min. cytotoxic conc[a] (μg·mL^{-1})	HSV-1 (KOS strain)	HSV- 2 (G strain)	vaccinia virus	vesicular stomatitis virus	HSV-1 (TK$^-$ KOS ACV^r strain)[c]
1	>200	24	120	24	>200	6.4
70	≥16	>16	>16	>16	>16	>16
71	>200	>200	>200	120	>200	120
72	≥400	>80	>80	>80	>80	>80
73	≥400	>80	>80	>80	>80	>80
woodrosin (**74**)	≥8	4.8	≥6.4	4.8	>8	4.8

[a] Required to cause a microscopically detectable alteration of normal cell morphology. [b] Required to reduce virus-induced cytopathogenicity by 50%. [c] TK$^-$: tymidine kinase deficient; ACV^r: resistant to acyclovir.

Standard deprotection of the residual silyl ether in **65** followed by oxidation of the resulting alcohol **66** with PCC affords the rather labile aldehyde **67,** which readily reacts at low temperature (−50 → −20 °C) with the diorganozinc reagent **38** in the presence of a catalyst formed in situ from $Ti(OiPr)_4$ and the (*S*,*S*)-configured bistriflate **39** as the controller ligand[38] to give alcohol **68** in 81% yield as a single diastereomer after flash chromatography (Scheme 15). Beyond doubt, this transformation constitutes one of the most advanced applications of ligand-controlled dialkylzinc addition reactions to aldehydes known to date and bears witness for the maturity of this method.[38,54] Subsequent β-selective glucosidation of **68** with trichloroacetimidate **41** was promoted by TMSOTf in CH_2Cl_2/MeCN. Exhaustive debenzylation of product **69** thus formed by hydrogenolysis over Pd/C cleanly provided cycloviracin B_1 **1** and completes the first total synthesis of an antiviral glycoconjugate of this type. Not only are all analytical and spectroscopic data in excellent agreement with those reported in the literature (Table 2), but—most importantly—the pattern signature of its NMR spectrum is perfectly superimposable to that of authentic cycloviracin B_1[1] recorded at the same magnetic field. Knowing from the model studies that any diastereoisomer is clearly discernible by high-field NMR, we therefore assign the absolute stereochemistry of the six chiral centers residing on the fatty acid residues as (3*R*,19*S*,25*R*,3′*R*,17′*S*,23′*R*).

Antiviral Assays. As an ultimate proof of the structural integrity of synthetic cycloviracin B_1 obtained by the route outlined above, the cytotoxicity as well as the antiviral activity of this compound against herpes simplex virus-1 (HSV-1, strain KOS), HSV-1 (strain TK$^-$ KOS ACV^r), HSV-2 (strain G), vaccinia virus, and vesicular stomatitis virus have been determined. Moreover, a few selected intermediates obtained en route to **1** were fully deprotected by standard hydrogenolysis, and the resulting compounds **70**−**73** representing various subunits of the natural product were subjected to the same antiviral assays. Moreover, the complex glycolipid woodrosin I (**74**) previously prepared by our group was also screened for antiviral activity.

While these data confirm a specific antiviral activity for **1** (i.e., the minimal antivirally effective concentration is ≥5-fold lower than the minimal cytotoxic contentration), none of the derivatives was found to exhibit similar effects. This also includes compound **70** representing the intact macrodiolide core of **1** which is rather cytotoxic and not antivirally active at subtoxic concentrations. HSV-1 (strain TK$^-$ KOS ACV^r) shows the highest sensitivity against **1** in an assay using cultured human embryonic lung (HEL) cells, with a minimum inhibitory concentration of about 6.4 μg·mL^{-1}. While woodrosin I is effective at similar concentrations, its cytotoxicity is much more pronounced than that of cycloviracin B_1. Representative data



are compiled in Table 3. Compound **1** has also been evaluated—but found inactive at subtoxic concentrations—against Coxsackie B4 virus, respiratory syncytial virus, parainfluenza type 3 virus, reovirus type 1, Sindbis virus, and Punta Toro virus.

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Supporting Information Available: Full experimental details together with the analytical and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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