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A Concise Synthesis of the Fully Functional Lactide Core of Cycloviracin B with Implications for the Structural Assignment of Related Glycolipids

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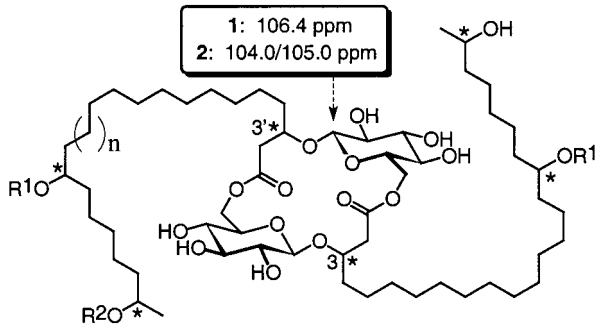
The paucity of effective medication against viral infections together with the increasing resistance toward approved drugs renders the search, optimization, and clinical development of novel antiviral agents highly desirable. Two families of natural products called cycloviracins[1] and fattiviracins[2] constitute promising new lead compounds in this regard. These conspicuous glycolipids exhibit potent activity i.a. against the herpes simplex and human immunodeficiency viruses, most likely by protecting the host cells against invasion by these pathogens.[3] As can be seen from the *proposed* structures of two prototype members **1** and **2**, they *seem* to differ only in the length of the lateral fatty acid residues and the substituents at the remote centers while sharing a common lactide core.[4] The absolute stereochemistry of the chiral centers (*) along the alkyl chains is currently unknown.



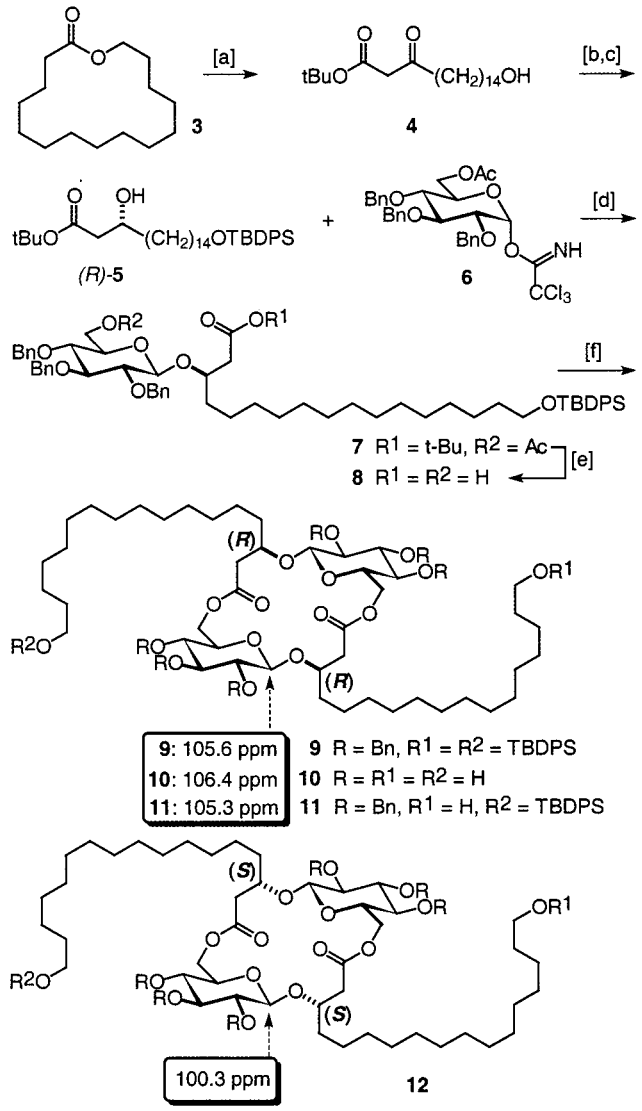
1 ***Cycloviracin B 1*** $n = 5$, $R^1 = R^2 =$ 2-*O*-Me-β-D-Glc

2 ***Fattiviracin FV-8*** $n = 1$, $R^1 =$ β-D-Glc, $R^2 = H$

As part of a long-term project on bioactive glycoconjugates,[5,6] we ventured into the synthesis and biological evaluation of these targets. Our goals are the unambiguous assignment of their actual structure and the development of a preparative approach that is flexible enough to enable their total synthesis as well as a mapping of the pharmacophore. These objectives must be seen in the light of a previous study directed toward **1** which (i) provided only a truncated version of the core that cannot be elaborated any further, (ii) is prohibitively lengthy to allow for systematic variations, and (iii) remained inconclusive with respect to the absolute stereochemistry at the branching points C-3/C-3′.[7] Therefore, we pursued an entirely different approach based on the perception that the specific array of O atoms within the central region might endow **1** and congeners with some degree of ionophoric character. This could allow the assembly of the target by a template-directed cyclodimerization process which, in turn, should minimize the preparative efforts.[8,9]

The building block required to test this hypothesis (Scheme 1) is prepared by a ring-opening Claisen condensation of penta-

Scheme 1 [a]



3 **4** **(*R*)-5** **6** **7** R^1 = t-Bu, R^2 = Ac **8** $R^1 = R^2 = H$ **9** R = Bn, $R^1 = R^2$ = TBDPS **10** $R = R^1 = R^2 = H$ **11** R = Bn, $R^1 = H$, R^2 = TBDPS **12**

[a] Conditions: (a) lithio *tert*-butyl acetate, THF, −78 °C, 61%; (b) [(*R*)-BINAP·$RuCl_2]_2$·NEt_3 catalytic, H_2 (15 atm), MeOH, 70 °C, 88%; (c) TBDPSCl, imidazole, DMF, 81%; (d) BF_3·Et_2O, MS 4 Å, CH_2Cl_2, −78 °C → r.t., 62%; (e) (i) F_3CCOOH, CH_2Cl_2, (ii) NH_3/MeOH, 74%; (f) 2-chloro-1,3-dimethylimidazolinium chloride, DMAP, KH, CH_2Cl_2, 71%.

decanolide **3**[10] with lithio *tert*-butyl acetate to give β-keto ester **4** which is hydrogenated under Noyori's conditions.[11] Silylation of the primary −OH group of the resulting diol with TBDPSCl delivers alcohol (*R*)-**5** (ee = 98%) ready for glycosylation with trichloroacetimidate **6**.[12,13] Since the benzyl ethers in **6** provide no anchimeric assistance, β-selectivity must be ensured by the proper choice of the promoter and the solvent.[14] BF_3·Et_2O in CH_2Cl_2 turned out to

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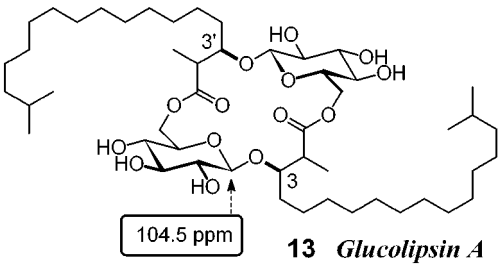
be optimal, providing the desired glycoside **7** in 62% isolated yield (α:β = 1:6).[15] Subsequent cleavage of the *tert*-butyl ester with trifluoroacetic acid followed by saponification of the residual acetate with NH_3/MeOH leads to hydroxy acid **8** in 74% yield over both steps and sets the stage for the envisaged cyclodimerization reaction.

In line with our expectations, this macrocyclization is highly responsive to admixed alkali metal cations. While exposure of compound **8** to 2-chloro-1,3-dimethylimidazolinium chloride[16] and DMAP in CH_2Cl_2 (0.02 M) at 0 °C in the absence of any further additive furnished a mixture of cyclic monomer (28%), the desired cyclic dimer **9** (37%), and several other oligomeric products (35%), the addition of KH led not only to an increased reaction rate but also to a significant improvement of the product distribution in favor of **9**. Under optimized conditions, product **9** is obtained in 71% isolated yield. Since the effect exerted by NaH or Cs_2CO_3 is much less pronounced,[12] this outcome is deemed to reflect the ability of the K^+ cation to preorganize the cyclization precursor for directed macrodilactonization. Importantly, this convergent approach is inherently flexible and favorably compares with the previously published route[7] to a more truncated version of the cycloviracin core in all relevant respects.

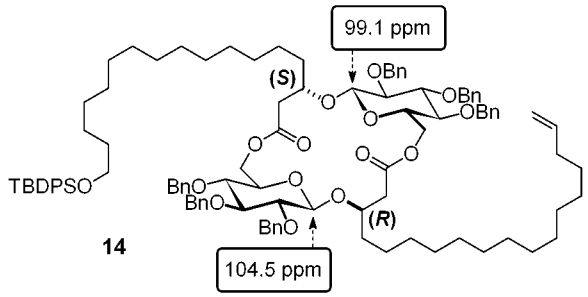
The NMR spectra of **9**, the deprotected compound **10**, and the unsymmetrical derivative **11** ($R^1 \neq R^2$) match those reported for **1**, suggesting that the absolute stereochemistry of cycloviracin B is (3*R*,3′*R*). To corroborate this notion, the analogous (3*S*,3′*S*)-configured lactide **12** was prepared following the same sequence of reactions (the required aglycone (*S*)-**5** is easily obtained by Noyori reduction of **4** using (*S*)-BINAP as the ligand).[11] Notably, the spectral data of **12** are significantly altered, with the high-field shift of the anomeric C-atoms at δ = 100.3 ppm being particularly diagnostic.[12] These marked shift differences between lactides **9** and **12** allow the *unambiguous assignment of the stereochemistry at the branching points in the cycloviracin core as 3R,3′R*. We believe that they also pertain to the closely related glucokinase activator glucolipsin A **13**, the anomeric center of which resonates at δ = 104.5 ppm.[17] Therefore, we confidently ascribe the (3*R*,3′*R*)-configuration to this molecule as well.



13 ***Glucolipsin A***

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 lactide, all members of the fattiviracin family invariably show inequivalent subunits.[2,4] Although the presence of an (3*R*,3′*S*)-configured core which might explain this phenomenon would be highly surprising from the biosynthesis viewpoint, we could not rigorously exclude this possibility except by synthesis. Since a cyclodimerization approach is obviously unsuitable for this purpose, a stepwise macrocyclization protocol had to be pursued en route to **14** comprising a highly productive Yamaguchi macrolactonization as the key step.[7,12,18]

The anomeric centers in the unsymmetrical lactide **14** resonate at δ = 104.5/99.1 ppm,[12] showing that the differently configured subunits can be reliably distinguished by NMR. These values, however, do not correlate at all with those reported for **2**. Therefore,



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one can *exclude* that **2** contains a lactide unit similar to the one found in **1** or **13**, independent of whether one assumes an (*R*,*R*)-, (*S*,*S*)-, or (*R*,*S*)-configuration at the branching points. Hence, *the structure proposed for the fattiviracins clearly needs revision*. One possibility might be a different connectivity pattern involving an −OH group farther down the lateral chain of the compound to form an expanded macrolactone ring.[19]

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Supporting Information Available: Experimental details and full set of NMR data (PDF). This material is available free of charge via the Internet at http:pubs.acs.org.

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