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A short access to the macrocyclic core of cycloviracin and glucolipsin

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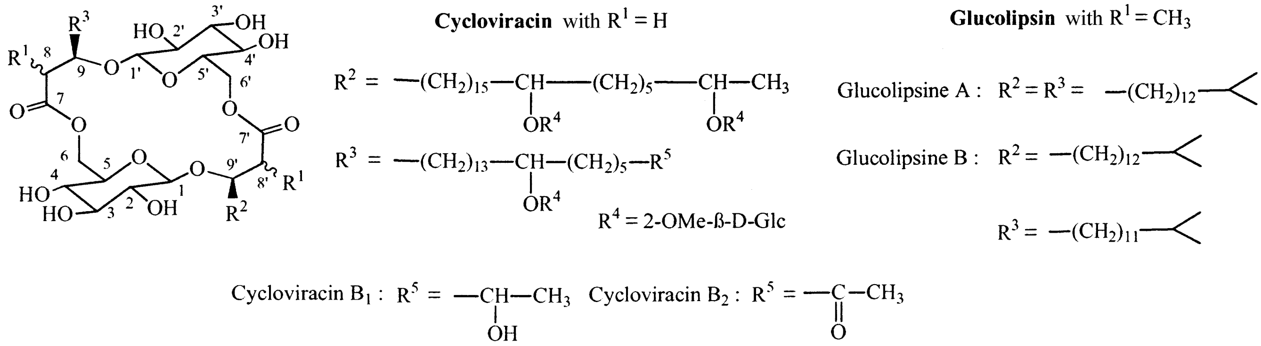
Abstract—The macrocyclic core of cycloviracin and glucolipsin has been synthesised in ten steps from levoglucosan and (*S*)-(−)-dimethyl malate. The limited number of steps to obtain this macrolide makes it a valuable procedure for the synthesis of analogues of cycloviracin and glucolipsin.

A few years ago, cycloviracin[1] was isolated from an actinomycete strain found in a soil sample collected in Mindanao Island in the Philippines (Scheme 1). This natural product exhibits a very interesting antiviral activity against herpes simplex virus type I. The development of new antiviral agents is necessary for fighting these diseases owing to the appearance of resistant mutant strains. Two major components have been isolated: cycloviracins B_1 and B_2. These natural products are eighteen-membered macrolides which include two molecules of D-glucose and carry two side chains. The structural difference involves the constitution of their side chains.

The closely related structure of glucolipsin[2] can also be connected to this family of molecules (Scheme 1). Two substances, called glucolipsin A and B have been isolated from the culture broth of *Streptomyces purpurogenisscleroticus* and *Nocardia vaccinii*, respectively, relieving the inhibition of glucokinase by long chain acyl CoA esters (FAC).[3] Glucokinase is one of the principal enzymes of glucose phosphorylation in glucose sensitive cells. Glucose phosphorylation influences circulating blood glucose levels, making glucokinase regulation one of the main points for possible therapeutic intervention in diabetes.

Due to the original structure and interesting biological activity of these natural products, several groups have attempted their total syntheses. A partial synthesis of cycloviracin has been achieved by Velarde and coworkers.[4] Recently, the total synthesis of cycloviracin B_1 has been described by Fürstner and co-workers.[5] It is also worthy of note that Nishizawa and co-workers



Cycloviracin with $R^1 = H$

$R^2 = -(CH_2)_{15}-\underset{OR^4}{CH}-(CH_2)_5-\underset{OR^4}{CH}-CH_3$

$R^3 = -(CH_2)_{13}-\underset{OR^4}{CH}-(CH_2)_5-R^5$

R^4 = 2-OMe-ß-D-Glc

Glucolipsin with $R^1 = CH_3$

Glucolipsine A : $R^2 = R^3 = -(CH_2)_{12}-$

Glucolipsine B : $R^2 = -(CH_2)_{12}-$

$R^3 = -(CH_2)_{11}-$

Cycloviracin B_1 : $R^5 = -\underset{OH}{CH}-CH_3$ Cycloviracin B_2 : $R^5 = -\underset{\overset{\|}{O}}{C}-CH_3$

Scheme 1. Structures of cycloviracin and glucolipsin.

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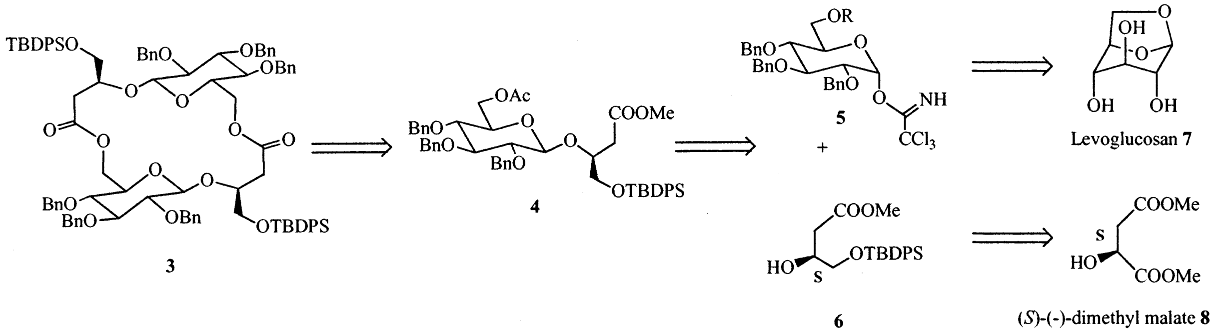
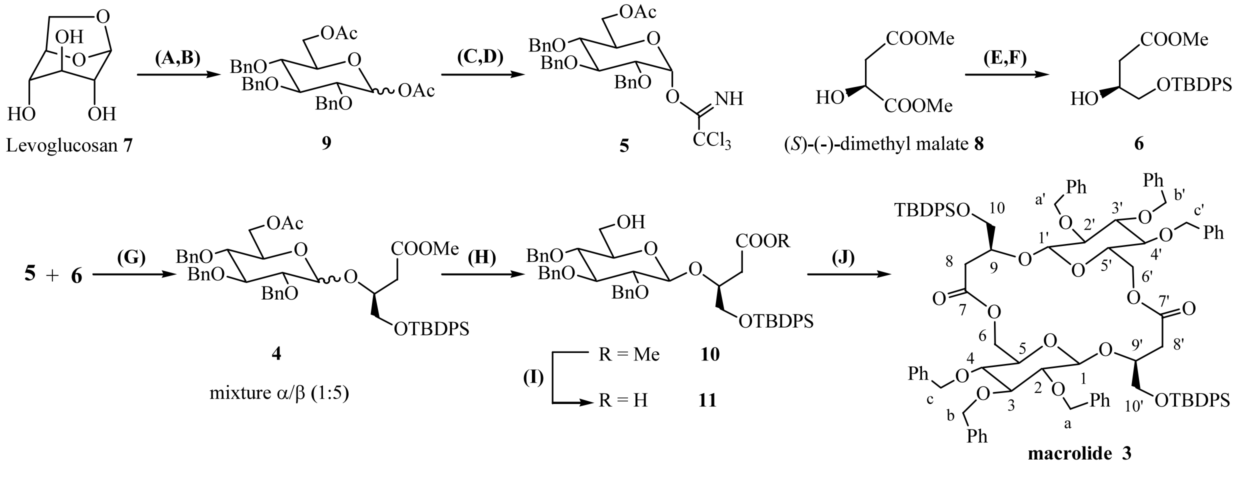
have obtained a closely related structure during their total synthesis of arthrobacilin A.[6] The absolute stereochemistry of the 9 and 9′ carbons was not elucidated when these natural products were isolated. The completed syntheses have established the (*R*,*R*) configuration of these carbons.[4–6] The results described by Fürstner and co-workers, prompted us to disclose our own results based on an approach allowing ready access to analogues.

We were interested in finding a simple and rapid access to macrolide **3** allowing the easy introduction of various types of side-chains (Scheme 2). In fact, the macrocyclisation step was envisaged by cyclodimerisation of intermediate **4**, prepared from the building blocks **5** and **6** by Schmidt glycosidation.[7] Compounds **5** and **6** could easily be obtained from levoglucosan **7** and commercially available (*S*)-(−)-dimethyl malate **8**, respectively. Recently, we described an easy preparation of levoglucosan **7** via a solid-supported, solvent-free, microwave-assisted procedure.[8]

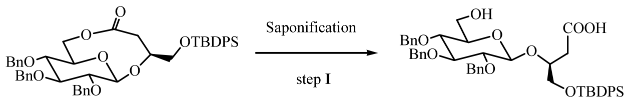
The synthesis of **5** began with the benzylation of the hydroxy groups in levoglucosan **7**, followed by acetolysis to afford **9** (Scheme 3). Subsequent selective cleavage of the anomeric acyl group with benzylamine,[9] followed by formation of the corresponding trichloroacetimidate gave the desired compound **5** in 56% overall yield (from **7**). Starting from commercially available (*S*)-(−)-dimethyl malate **8**, we have synthesised compound **6** in two steps and in 67% overall yield, according to the procedure described by Moriwake.[10] The glycosyl donor **5** (1.5 equiv.) was reacted with alcohol **6** in acetonitrile: dichloromethane (1:1) at −40°C, in the presence of trimethylsilyl triflate, to give **4** in 85% yield (α:$\beta = 1$:5) as an inseparable mixture. The deacetylation of **4** was achieved under Zemplen conditions[11] to give **10** in 86% yield. At this stage, a partial separation of the anomeric mixture by flash chromatography on silica gel was accomplished. After saponification of **10**, **11** was obtained in 83% yield. The cyclodimerisation was performed under Fürstner's conditions from **11**; we obtained the macrolide **3**[12] in 37% yield along with the cyclic monomer **12** in 56% yield (and cyclic oligomers in 6% yield). These compounds could be separated by flash chromatography. The overall yield could be improved by recycling **12** to **11** by saponification (Scheme 4).



Scheme 2. Retrosynthetic scheme for macrolide **3**.



Scheme 3. *Reagents and conditions*: (A) NaH, BnBr, DMF, rt, 4 h, 90%; (B) CF_3COOH, Ac_2O, rt, 5 h, 92%; (C) $BnNH_2$, rt, 3 h, 90%; (D) NaH (0.2 equiv.), Cl_3CCN, CH_2Cl_2, rt, 1 h then NaH (0.2 equiv.), 2 h, 75%; (E) $BH_3{\cdot}Me_2S$, THF then $NaBH_4$, 4 h, 75%; (F) TBDPSCl, imidazole, DMF, rt, 12 h, 90%; (G) **6** (1 equiv.), **5** (1.5 equiv.), TMSOTf (0.1 equiv.), CH_3CN: CH_2Cl_2 (1:1), −50°C, 1.5 h then rt, 30 min, 85%; (H) MeONa (20 mol%), MeOH, CH_2Cl_2, rt, 3 h, 86%; (I) LiOH aq., Et_2O, MeOH, reflux, 1 h, 83%; (J) KH (2 equiv.), DMC (2.5 equiv.), DMAP (4 equiv.), CH_2Cl_2, rt, 15 h, 37%.



monomer 12 **11**

Scheme 4.

In conclusion, we have synthesised the macrocyclic core of cycloviracin and glucolipsin in ten steps. This short access makes it a valuable procedure for the synthesis of analogues of cycloviracin and glucolipsin.

Acknowledgements

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12. Characteristic data for macrolide **3**: colorless oil; R_f 0.52 (30% ethyl acetate in heptane); $[\alpha]_D^{20}$ +31 (c 1.9, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$), $\delta = 7.58–7.65$ (m, 8H, H-Ar), 7.12–7.40 (m, 42H, H-Ar), 4.90 (d, 2H, H-b, H-b′, $J = 11$ Hz), 4.83 (d, 2H, H-c, H-c′, $J = 11$ Hz), 4.82 (d, 2H, H-a, H-a′, $J = 11$ Hz), 4.76 (d, 2H, H-b, H-b′, $J = 11$ Hz), 4.63 (d, 2H, H-a, H-a′, $J = 11$ Hz), 4.50 (d, 2H, H-c, H-c′, $J = 11$ Hz), 4.45 (d, 2H, H-1, H-1′, $J = 7.8$ Hz), 4.34 (dd, 2H, H-6, H-6′, $J = 2.2$, 11.8 Hz), 4.19 (qt, 2H, H-9, H-9′, $J = 5.3$ Hz), 4.01 (dd, 2H, H-6, H-6′, $J = 4.9$, 11.8 Hz), 3.80 (dd, 2H, H-10, H-10′, $J = 5.2$, 10.5 Hz), 3.67 (dd, 2H, H-10, H-10′, $J = 6.2$, 10.5 Hz), 3.59 (t, 2H, H-3, H-3′, $J = 9$ Hz), 3.51 (m, 2H, H-4, H-4′), 3.39 (m, 2H, H-5, H-5′), 3.37 (dd, 2H, H-2, H-2′, $J = 7.8$, 9 Hz), 2.78 (dd, 2H, H-8, H-8′, $J = 6.3$, 16.4 Hz), 2.69 (dd, 2H, H-8, H-8′, $J = 5$, 16.4 Hz), 1.00 (s, 18H, 2×*t*-Bu); (qt: quintuplet). ^{13}C NMR (150 MHz, $CDCl_3$), $\delta = 171.3$ (C-7, C-7′), 138.5, 138.2, 137.8, 135.6, 135.5, 129.8, 129.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (C-Ar), 104.6 (C-1, C-1′), 84.5 (C-3, C-3′), 82.1 (C-2, C-2′), 78.0 (C-9, C-9′), 77.5 (C-4, C-4′), 75.6 (C-b, C-b′), 75.0 (C-c, C-c′), 74.7 (C-a, C-a′), 72.2 (C-5, C-5′), 65.3 (C-10, C-10′), 63.2 (C-6, C-6′), 38.0 (C-8, C-8′), 26.8 (CH_3, *t*Bu), 19.2 (C-quaternary, *t*Bu). HRMS (ESI-pos.) calcd for $C_{94}H_{104}O_{16}NaSi_2$ $(M+Na)^+$ 1567.6777. Found: 1567.6761.