Pergamon

Tetrahedron Letters 43 (2002) 2435–2438

TETRAHEDRON LETTERS

A stereoselective synthesis of the C13–C19 fragment of sanglifehrin A

Mukund K. Gurjar* and Siddhartha Ray Chaudhuri

National Chemical Laboratory, Pune 411008, India

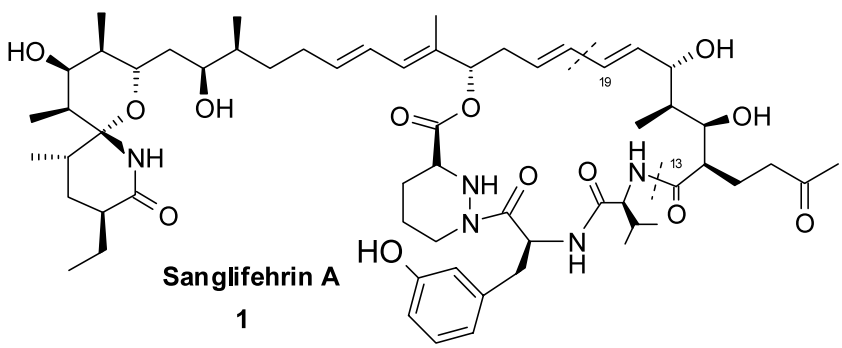
Received 6 November 2001; revised 17 January 2002; accepted 24 January 2002

Abstract—A stereo-controlled radical C–C bond formation involving a 5-chloro-5-deoxy-L-idofurano-6,3-lactone derivative and allyltri-*n*-butyltin/AIBN is described. Further elaboration led to the synthesis of the C13–C19 segment of sanglifehrin A. © 2002 Published by Elsevier Science Ltd.

A large number of immunosuppressive agents represented by cyclosporin A, FK- 506, ISP-1, pironetin, etc have become focal points of investigations.[1] These compounds, except pironetin, are involved in T-lymphocyte inhibition. However, there is a demand to discover immunosuppressants such as pironetin,[2] which can inhibit both T- and B-lymphocytes simultaneously. But, pironetin is associated with cytotoxicity. The recently isolated[3] natural product sanglifehrin A (**1**) showed immunosuppressive activity against both T- and B-lymphocytes. This bio-activity coupled with the structural ingenuity of **1** has attracted much attention[4] towards synthetic investigations leading to its total synthesis. As a part of our long standing interest[5] in immunosuppressive agents, the synthesis of sanglifehrin A (**1**) was chosen for investigation and this report communicates a synthesis of the C13–C19 segment starting from 1,2-*O*-isopropylidene-α-D-glucurono-6,3-lactone.

Our strategy to the above segment of sanglifehrin A (**1**) was founded on the study of stereoselective C–C bond formation through a radical mediated reaction of the 5-chloro-5-deoxy-glucurono-6,3-lactone derivative (**2**) with carbon electrophiles. This step was envisaged to stereochemically control the installation of the crucial side-chain present at C-14 of **1**. The stereochemical correlation of the remaining C_2–C_4 segment of **2** with C15–C17 of the natural product should be amenable by the virtue of well-defined transformations of carbohydrate chemistry. More importantly, the 1,2-acetonide backbone of **2** inherently blocked non-participating hydroxy groups, thus circumventing to a large extent, protection–deprotection protocols.

The synthesis started with the radical C–C bond formation of the known[6] 5-chloro-5-deoxy-1,2-*O*-isopropylidine-α-L-idofurano-6,3-lactone (**2**) with various electrophiles[7] shown in Table 1. Surprisingly, methyl



Sanglifehrin A

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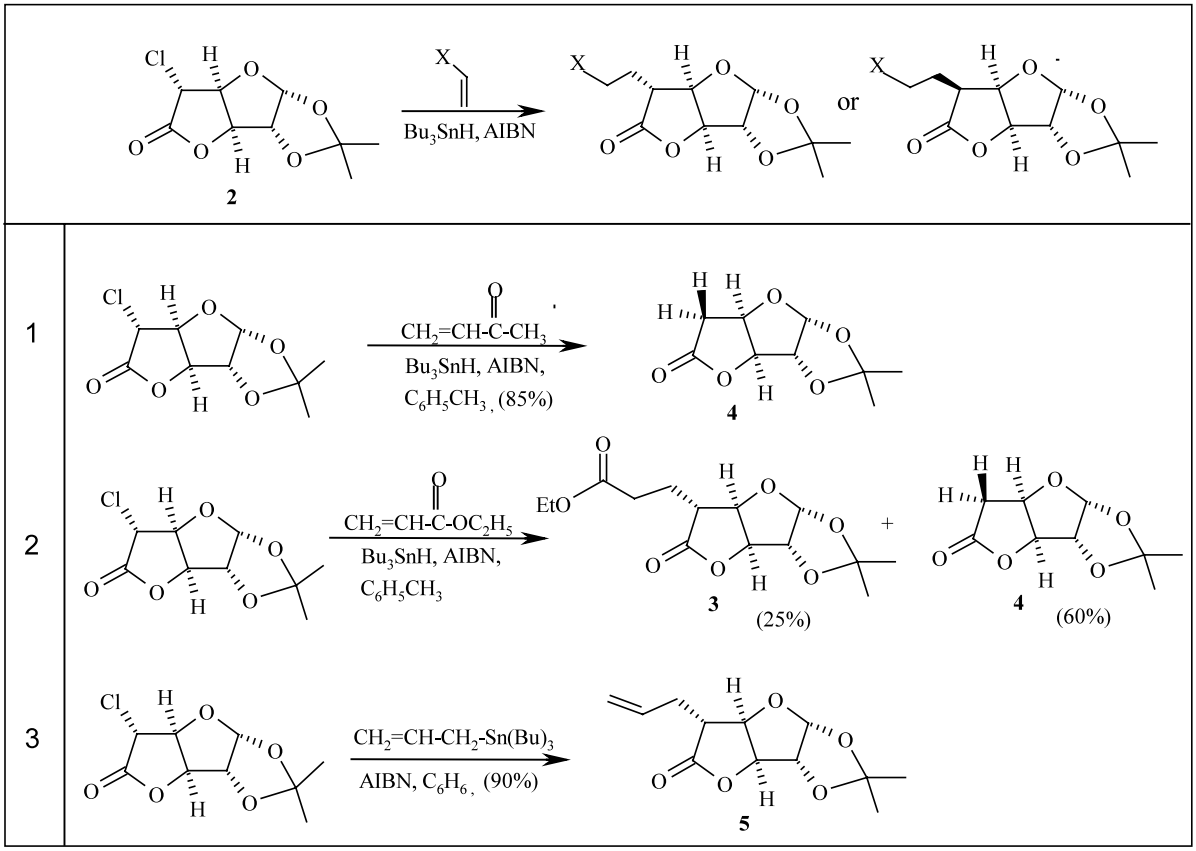
* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00191-0

Table 1.



vinyl ketone (entry 1), was found to be a poor electrophile, the reaction generating predominantly the hydrodechlorination product (**4**). The reaction with ethyl acrylate (entry 2) gave the desired product (**3**) in only 25% yield. The most promising results were obtained from the reaction of **2** with allyltri-*n*-butyltin in the presence of AIBN in refluxing benzene.

From these observations it was apparent that the competitive dechlorination reaction, due to the presence of Bu_3SnH (entries 1–2), was a major stumbling block. The next objective was to ascertain the stereochemistry at C-5. For example, the ^1H NMR spectrum of compound **3** (entry 2) was amenable to first order splitting which clearly revealed signals due to H-1, H-2, H-3 and H-4 as doublets at δ 6.00 ($J=3.4$ Hz), 4.83 ($J=3.4$ Hz), 4.84 ($J=3.2$ Hz) and 4.71 ($J=3.2$ Hz). The lack of any coupling between H-4/H-5 confirmed the *trans* relationship and the structure as **3**. In addition, the triplet due to H-5 appeared at δ 2.76 ($J=8.7$ Hz). Similarly the ^1H NMR spectrum of **5** was useful proving its structure beyond any doubt.

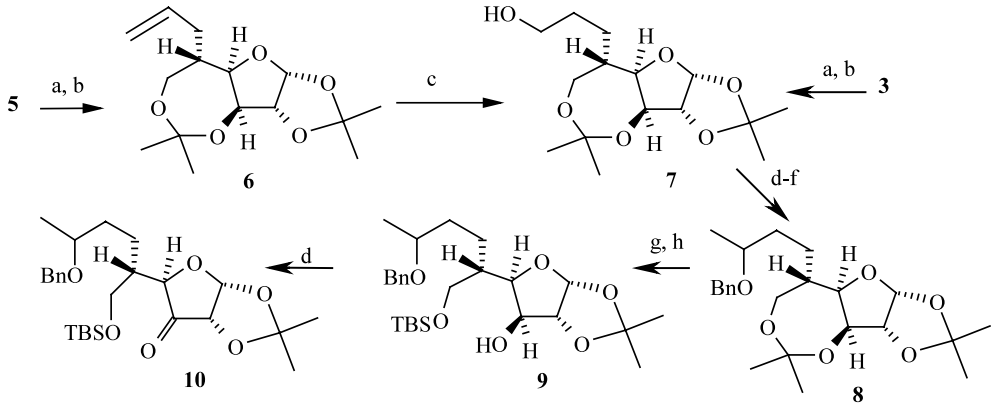
The lithium aluminium hydride (LAH) reduction of **3** in THF gave a triol which was protected as its seven-membered acetonide derivative (**7**) whose successive oxidation, Grignard reaction with MeMgI and benzylation gave **8**.[8]

In another sequence, compound **5** was reduced with LAH in THF and then subjected to a hydroboration–oxidation sequence to afford **7** which had already been transformed into **8**. The conversion of **8** into the corresponding 3-ulose derivative (**10**) via **9** was accomplished in three high yielding steps (Scheme 1).

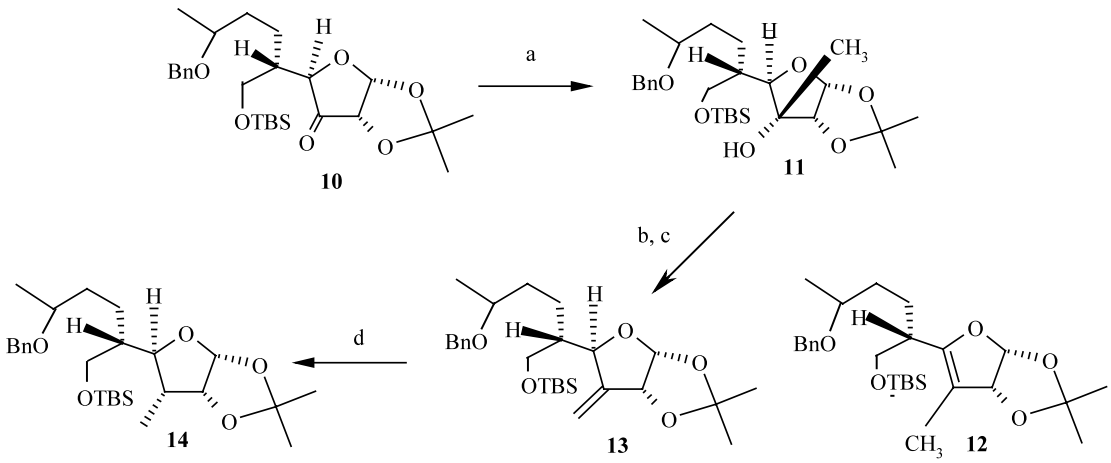
Our next concern was to introduce the methyl group at C-3 with concomitant epimerization at C-4 via the intermediate **12**. Grignard reaction of **10** with MeMgI furnished the carbinol derivative (**11**). We believe based on literature precedents[9] that the methyl group approaches from the top face leading to **11** as the exclusive product.

The elimination step was carried out by reacting **11** with triflic anhydride in Py/CH_2Cl_2 at -15°C. The ^1H NMR spectrum of the newly formed product did not correspond to the expected structure **12**. However, based on the ^1H and ^{13}C NMR spectroscopic data, the presence of an *exo*-methylene group was noted and structure **13** is proposed. The structure was further supported when **13** was hydrogenated over Pd/C to produce **14** whose ^1H NMR spectrum was consistent with the assigned structure (Scheme 2).

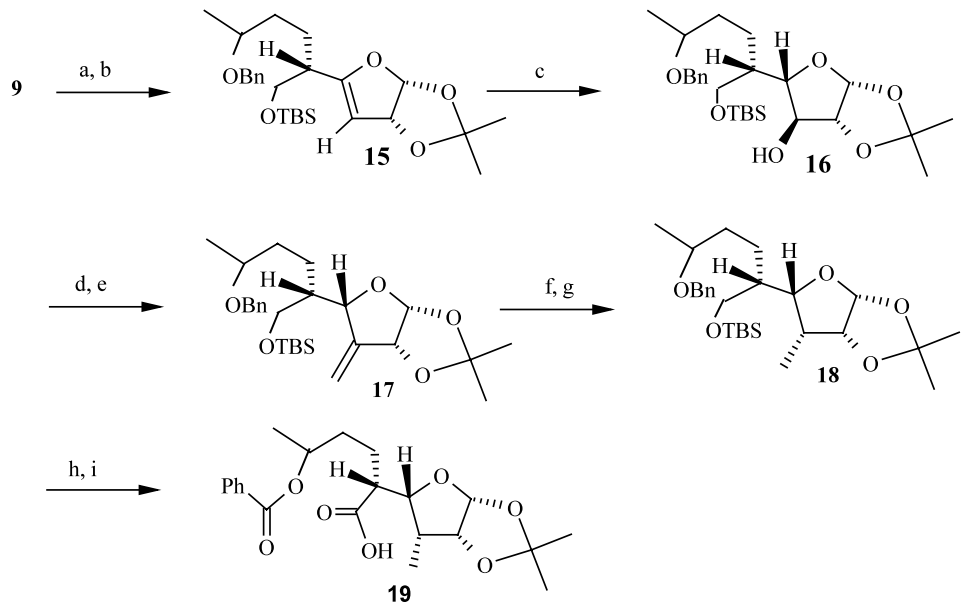
In order to circumvent the above problem, we revised our initial strategy according to which **9** was subjected



Scheme 1. *Reagents and conditions*: (a) LAH, THF, 0°C–rt, 2 h (90%); (b) 2,2-dimethoxypropane, PTSA, CH_2Cl_2, 3 h (70%); (c) BH_3:DMS, NaOAc, H_2O_2 (75%); (d) $(COCl)_2$, DMSO, ET_3N, CH_2Cl_2, −78°C; (e) CH_3MgI, Et_2O, THF, rt, 2 h (75%, two steps); (f) BnBr, NaH, DMF, rt (80%); (g) 0.8% H_2SO_4, MeOH (85%); (h) TBS-Cl, imidazole, CH_2Cl_2, rt (90%).



Scheme 2. *Reagents and conditions*: (a) CH_3MgI, Et_2O, THF, 0–rt, 2 h (75%, from **10**); (b) TF_2O, Py, CH_2Cl_2, 1.5 h, −15°C; (c) DBU, Et_2O; 12 h (75%, two steps); (d) 10% Pd/C, H_2, MeOH, 3 h (95%).



Scheme 3. *Reagents and conditions*: (a) TF_2O, Py, CH_2Cl_2, −15°C, 1.5 h; (b) DBU, Et_2O; rt, 12 h (75%, two steps); (c) BH_3:DMS, NaOAc, H_2O_2 (75%); (d) $(COCl)_2$, DMSO, ET_3N, CH_2Cl_2, −78°C; (e) $PhP_3{\equiv}CH_2$, THF, −15°C–rt (80%, two steps); (f) BH_3:DMS, NaOAc, H_2O_2, THF; (g) NaH, THF, 0–rt, CS_2, rt, MeI; Bu_3SnH, AIBN, toluene, reflux, 3 h (50%, three steps); (h) TBAF, THF, rt, 1 h; (i) $RuCl_3{\cdot}H_2O$, CH_3CN:CCl_4:H_2O, $NaIO_4$, 2 h (50%).

to an elimination reaction to give **15** which on hydroboration–oxidation gave the alcohol **16** in which the stereochemistry at C-4 had been reversed. The ^{1}H NMR spectrum of **16** when compared with **9** supported the assigned structure. The derived *exo*-methylene derivative (**17**) was transformed into the C-3 methyl derivative (**18**) in two steps involving hydroboration–oxidation and Barton-radical deoxygenation reactions.[10,11] The stereocentres at C-3 and C-4 of **18** were compatible with C16 and C15 of **1**, respectively. Removal of the silyl protecting group and oxidation with $RuCl_3/NaIO_4$ in CH_3CN–CCl_4–H_2O gave **19** in which the benzyl group was also oxidised to the benzoate.

In the ^{1}H NMR spectrum of **19**, signals due to H-8 appeared at 5.12 ppm as a multiplet indicating the presence of a benzoate group at this carbon. The double-doublet ($J=2.0$, 4.8 Hz) due to H-2 appeared at 4.57 ppm and was indicative of its coupling with H-1 and H-3 and therefore the *syn* relation between H-2/H-3. In addition H-4 revealed a double–doublet ($J=8.0$, 10.0 Hz) at 4.13 ppm. The MS, ^{13}C NMR and elemental analysis of **19** were in support of the assigned structure (Scheme 3).[12]

In conclusion, this communication reports a highly stereo-controlled radical C–C bond formation on glucurono-6,3-lactone and elegant synthetic manoeuvering to complete the C-13 to C-19 segment of sanglifehrin A (**1**). Our next strategy is to couple the peptide segment with the carboxylic acid portion of **19** followed by synthetic elaboration at C-1.

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8. The Grignard reaction gave predominantly (>95%) of a single diastereomer based on its ^{1}H and ^{13}C NMR spectroscopic data. The newly formed stereo-centre of **8** is of no consequence as it will finally be transformed into a ketone functionality.
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11. Pd–C-catalysed hydrogenation of **17** even at 250 psi was found to be very sluggish perhaps due to steric reasons.
12. Spectroscopic data of some selected compounds: **3**: ^{1}H NMR (500 MHz, $CDCl_3$): 1.27 (t, 3 H, $J=7.6$ Hz), 1.35 (s, 3 H), 1.54 (s, 3 H), 1.94 (m, 2 H), 2.52 (m, 2 H), 2.76 (t, 1 H, $J=8.7$ Hz), 4.18 (q, 2 H, $J=7.6$ Hz), 4.71 (d, 1 H, $J=3.2$ Hz), 4.83 (d, 1 H, $J=3.4$ Hz), 4.84 (d, 1 H, $J=3.2$ Hz), 6.0 (d, 1 H, $J=3.4$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 14.3, 23.2, 26.5, 27.0, 31.3, 46.5, 60.8, 82.3, 82.9, 84.2, 106.0, 112.7, 172.0, 175.9; MS: 285 (M^+–15). Compound **5**: ^{1}H NMR (200 MHz, $CDCl_3$): 1.34 (s, 3 H), 1.50 (s, 3 H), 2.32 (dt, 1 H, $J=8.0$, 14.0 Hz), 2.49 (dt, 1 H, $J=6.0$, 14.0 Hz), 2.81 (dd, 1 H, $J=6.0$, 8.0 Hz), 4.71 (d, 1 H, $J=2.0$ Hz), 4.75 (d, 1 H, $J=4.0$ Hz), 4.81 (d, 1 H, $J=4.0$ Hz), 5.20 (m, 2 H), 5.78 (m, 1 H), 5.94 (d, 1 H, $J=4.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 25.9, 26.0, 31.6, 46.4, 81.7, 82.0, 83.7, 105.4, 111.8, 118.0, 132.8, 175.7; MS: 225 (M^+–15). Anal. calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.52; H, 6.75. Compound **16**: ^{1}H NMR (200 MHz, $CDCl_3$): 0.06 (s, 6 H), 0.90 (s, 9 H), 1.19 (d, 3 H, $J=6.5$ Hz), 1.33 (s, 3 H), 1.49 (s, 3 H), 1.55 (m, 4 H), 1.85 (m, 1 H), 3.49 (m, 1 H), 3.76 (m, 3 H), 4.08 (m, 1 H), 4.44, 4.57 (ABq, 2 H), 4.51 (dd, 1 H, $J=2.0$, 4.0 Hz), 5.75 (d, 1 H, $J=4.0$ Hz), 7.3 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.5, 18.3, 19.7, 21.5, 25.9, 26.8, 27.6, 29.7, 34.0, 42.3, 62.2, 70.3, 74.9, 76.8, 87.0, 87.7, 104.2, 113.1, 127.4, 128.3, 138.9. Anal. calcd for $C_{26}H_{44}O_6Si$: C, 64.95; H, 9.23. Found: C, 64.87; H, 9.66. Compound **17**: ^{1}H NMR (200 MHz, $CDCl_3$): 0.06 (s, 6 H), 0.89 (s, 9 H), 1.21 (d, 3 H, $J=6.5$ Hz), 1.33 (s, 3 H), 1.50 (s, 3 H), 1.51–1.71 (m, 4 H), 1.77 (m, 1 H), 3.49 (m, 1 H), 3.78 (m, 2 H), 4.50 (m, 3 H), 4.85 (d, 1 H, $J=4.0$ Hz), 5.16 (br. s, 1 H), 5.42 (br. s, 1 H), 5.77 (d, 1 H, $J=4.0$ Hz), 7.3 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$): −5.6, 18.1, 19.3, 19.5, 22.6, 25.8, 26.8, 33.5, 44.7, 60.9, 69.9, 74.8, 81.6, 82.5, 104.7, 112.4, 113.3, 127.0, 128.0, 139.0, 146.4; MS: 461 (M^+–15). Anal. calcd for $C_{27}H_{44}O_5Si$: C, 68.01; H, 9.31. Found: C, 67.56; H, 9.03. Compound **19**: ^{1}H NMR (200 MHz, $CDCl_3$): 1.0–2.0 (m, 10 H), 1.34 (s, 3 H), 1.65 (s, 3 H), 2.43 (m, 1 H), 3.10 (m, 1 H), 4.13 (dd, 1 H, $J=8.0$, 10.0 Hz), 4.57 (dd, 1 H, $J=2.0$, 4.8 Hz), 5.12 (m, 1 H), 5.76 (d 1 H, $J=2.0$ Hz), 7.43 (m, 3 H), 8.02 (d, 2 H, $J=7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 9.7, 20.1, 25.6, 25.8, 33.6, 39.5, 48.8, 70.9, 71.4, 83.2, 105.2, 112.6, 128.3, 129.5, 130.7, 132.8, 166.2, 177.0, MS: 377 (M^+–15). Anal. calcd for $C_{21}H_{28}O_7$: C, 64.26; H, 7.20. Found: C, 65.42; H, 7.99.