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A carbohydrate-based approach for the total synthesis of strictifolione

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Abstract—A chiral pool approach starting with D-glucose, using the Yamaguchi protocol and a *Z*-selective HWE reaction followed by lactonization, has been applied to execute the total synthesis of strictifolione.

Strictifolione **1** belongs to the family of 5,6-dihydro-δ-pyrone derivatives having an alkyl side chain at the C6 position.[1] The broad range of biological activities reported for this class of compounds has been ascribed to their inherent tendency to act as good Michael acceptors. Strictifolione was isolated by Aimi and co-workers from the stem bark of *Cryptocarya strictifolia* that grows in the Indonesian tropical rainforests.[2] The relative and the absolute configuration of strictifolione were revised by the same group after accomplishing its first total synthesis.[3] Later, asymmetric syntheses, primarily with a RCM as one of the key reactions, have been reported.[4]

As a part of our longstanding interest in the synthesis of bioactive natural products using the chiron approach,[5] we have taken up the total synthesis of strictifolione **1**. As shown in Figure 1, the disconnection process began with two bonds at C(3)–C(4) and C(2′)–C(3′), each of which could be realized by a cis-HWE reaction and a Yamaguchi approach, respectively. This led to the key intermediate **2** whose preparation by a convergent approach would involve the intermediates **3** and **4**. The intermediate **3** was envisaged from D-glucose, while the chiral propargyl alcohol **4** could be produced from the epoxy chloride **6** by a double elimination protocol.

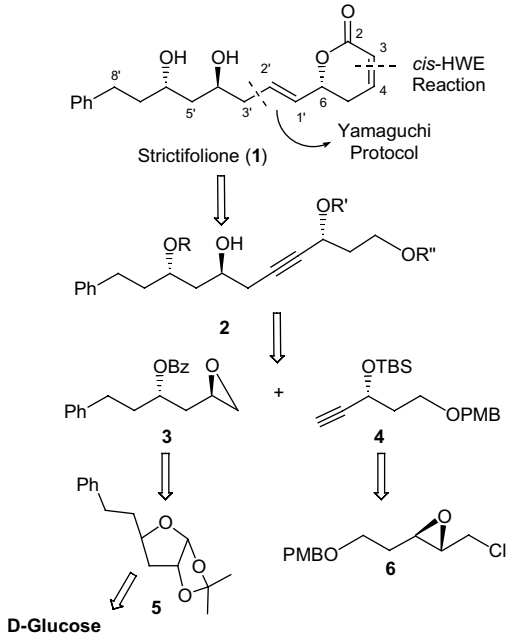

Figure 1. Retrosynthetic analysis for strictifolione.

The synthesis of fragment **3** began by following the literature procedure[6] to prepare 3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose **7** from D-glucose. Selective deprotection of the 5,6-*O*-isopropylidene group, sodium periodate mediated oxidative cleavage and Wittig olefination with benzyltriphenylphosphorane furnished an impure mixture of the styrene derivative **8**. Subsequent hydrogenation of **8** in the presence of Raney-Ni and ethanol at 60 psi gave **5**, whose spectral and analytical data were in agreement with the assigned

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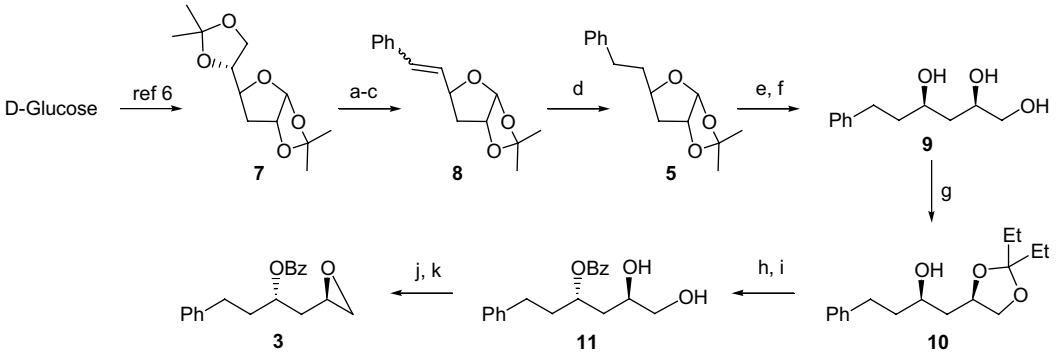
structure.[7a] Cleavage of the 1,2-*O*-isopropylidene group of **5** in refluxing 30% aq AcOH followed by reduction with $LiAlH_4$ in THF provided the triol **9** (Scheme 1).

Our next target was to invert the center at C-4 for which the selective protection of the 1,2-glycol unit of **9** was first carried out using 3-pentanone and catalytic CSA. The expected dioxolane derivative **10** was obtained exclusively leaving the 4-hydroxy group free. The Mitsunobu reaction of **10** in the presence of TPP, DEAD, and benzoic acid followed by hydrolysis of dioxolane ring gave the diol **11**. This was treated with TsCl, Bu_2SnO, and triethylamine in CH_2Cl_2, which resulted in the formation of the monotosyl derivative whose exposure to NaH in THF afforded the desired epoxy derivative **3**.[7b]

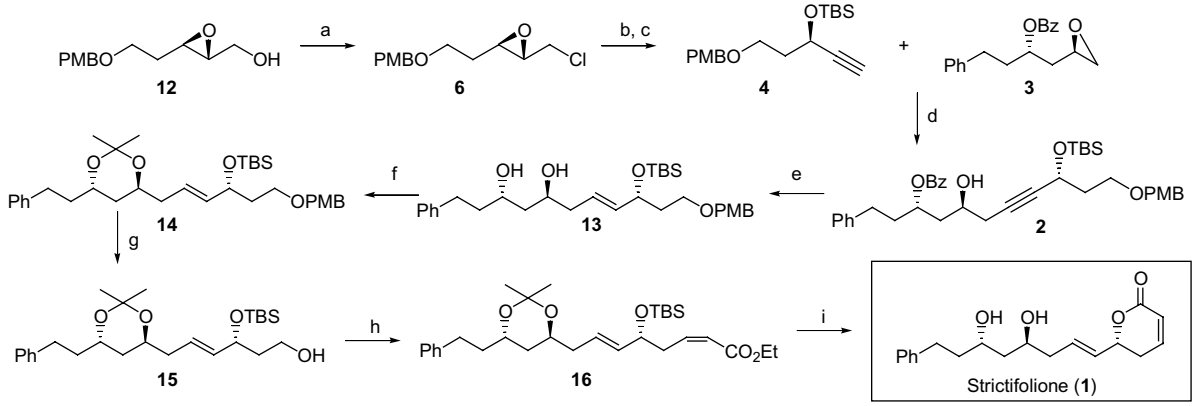
The synthesis of alkyne **4** began with the known[8] epoxide **12**, which upon chlorination[9] in refluxing CCl_4 and TPP gave the chloroepoxide **6**. This was subjected to double elimination reaction[10] by using excess *n*-BuLi in THF at −40 °C and the resulting propargyl alcohol was protected as the TBS-ether **4** (Scheme 2).

Having now access to both the fragments **3** and **4**, the Yamaguchi protocol[11] for C–C bond formation was investigated in the presence of *n*-BuLi, $BF_3{\cdot}Et_2O$ in THF at −78 °C. This protocol resulted in the formation of the advanced intermediate **2**. The spectral and analytical profiles of **2** were in agreement with the assigned structure.[12] The reduction of C≡C to the corresponding *E*-olefin with concomitant de-benzoylation occurred when **2** was treated with Redal-H[13] in ether at −20 °C. The required product **13** was isolated and consequently transformed into the isopropylidene derivative **14** with 2,2-dimethoxypropane-catalytic CSA.[14] In the ^{13}C NMR of **14**, the acetonide methyl groups resonated together at 24.9 ppm indicating a 1,3-*anti*-relationship.[15] This was further substantiated by the appearance of the quaternary carbon in the downfield region (100.3 ppm).

Our next concern was to install the dihydropyran ring. The PMB group was cleaved using DDQ in CH_2Cl_2–H_2O and then the free hydroxyl group of **15** was successively subjected to Swern oxidation and HWE reaction with ethyl (di-*o*-tolylphosphono)acetate[16] and NaH in THF to obtain the *Z*-unsaturated ester **16** exclusively.[17] Among a few reagents examined, PPTS in ethanol[18] at 55 °C effectively deprotected both the TBS and the acetonide groups. Moreover, the lactonization step also took place to complete the total synthesis of strictifolione **1**. The physical and spectroscopic data of the synthetic



Scheme 1. Reagents and conditions: (a) 30% AcOH, rt, 75%; (b) $NaIO_4$ on silica gel, CH_2Cl_2, 96%; (c) $C_6H_5CH_2P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C → rt, 67%; d) Raney-Ni, ethanol, 60 psi, 98%; (e) 30% AcOH, reflux, 72%; (f) $LiAlH_4$, THF, rt, 92%; (g) 3-pentanone, CSA, 85%; (h) DEAD, TPP, benzoic acid, THF, 91%; (i) PTSA, methanol, 74%; (j) TsCl, Bu_2SnO, triethylamine, CH_2Cl_2, rt, 89%; (k) NaH, THF, 0 °C, 94%.



Scheme 2. Reagents and conditions: (a) TPP, CCl_4, reflux, 87%; (b) *n*-BuLi, THF, −40 °C, 79%; (c) TBSCl, imidazole, CH_2Cl_2, rt, 81%; (d) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, then **3**, 85%; (e) red-Al, ether, −20 °C, 73%; (f) 2,4-DMP, CSA, acetone, 95%; (g) DDQ, DCM–water (9:1), 86%; (h) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (ii) ethyl (di-*o*-tolylphosphono)acetate, NaH, THF, 0 → −78 °C, overall 81%; (i) PPTS, ethanol, 55 °C, 67%.

sample **1** were in good agreement with the reported data of natural strictifolione {$[\alpha]_D^{25}$ +61 (*c* 0.6, $CHCl_3$); lit.[2] $[\alpha]_D^{25}$ +81.5 (*c* 0.52, $CHCl_3$); lit.[4c] $[\alpha]_D^{25}$ +54.1 (*c* 0.33, $CHCl_3$)}.

In summary, the total synthesis of strictifolione using a combination of chiral pool approach and an asymmetric epoxidation reaction has been accomplished.

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7. (a) *Spectral data of compound* **5**: mp = 71–72 °C. $[\alpha]_D^{25}$ −7.7 (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30–7.19 (m, 5H), 5.83 (d, *J* = 3.7 Hz, 1H), 4.72 (br dd, *J* = 5.0, 3.7 Hz, 1H), 4.26–4.17 (m, 1H), 2.79 (ddd, *J* = 13.8, 10.3, 5.8 Hz, 1H), 2.69 (ddd, *J* = 13.8, 9.7, 6.7 Hz, 1H), 2.09 (dd, *J* = 13.2, 4.1 Hz, 1H), 2.01–1.77 (m, 2H), 1.50–1.43 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.1 (q), 26.5 (q), 32.3 (t), 35.9 (t), 38.8 (t), 77.1 (d), 80.5 (d), 105.2 (s), 110.7 (s), 125.8 (d), 128.3 (d), 141.0 (s). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.23; H, 7.95; (b) *Spectral data of compound* **3**: $[\alpha]_D^{25}$ −12.7 (*c* 1, $CHCl_3$). IR: 3109, 1714, 1602, 1275, 756 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.05 (br dd, *J* = 7.8, 1.4 Hz, 2H), 7.57 (br tt, *J* = 7.4, 1.4 Hz, 1H), 7.46 (br d, *J* = 7.8, 1H), 7.45 (br d, *J* = 7.8, 1H), 7.27–7.24 (m, 2H), 7.18–7.15 (m, 3H), 5.37 (tt, *J* = 7.7, 4.8 Hz, 1H), 3.03–3.0 (m, 1H), 2.75 (ddd, *J* = 13.8, 10.0, 5.8 Hz, 1H), 2.72 (br dd, *J* = 5.0, 4.0 Hz, 1H), 2.60 (ddd, *J* = 13.7, 9.9, 6.7 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.16–2.03 (m, 2H), 1.98–1.88 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.7 (t), 36.2 (t), 37.8 (t), 46.8 (t), 49.1 (d), 72.0 (d), 125.9 (d), 128.3 (d), 128.3 (d), 128.4 (d), 129.5 (d), 130.2 (d), 132.9 (q), 141.1 (q), 165.9 (q). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.84; H, 7.02.
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14. *Spectral data of compound* **14**: $[\alpha]_D^{25}$ 10.3 (*c* 1.1, $CHCl_3$). IR: 3027, 1613, 1586, 1248, 1092, 836 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.25–7.23 (m, 4 H), 7.19–7.14 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.52 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.45 (dd, *J* = 15.4, 6.2 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.24 (br q, *J* = 6.2 Hz, 1H), 3.83–3.78 (m, 1H), 3.79 (s, 3H), 3.76–3.70 (m, 1H), 3.51 (dt, *J* = 9.2, 6.8 Hz, 1H), 3.44 (dt, *J* = 9.2, 6.2 Hz, 1H), 2.75 (ddd, *J* = 13.7, 9.3, 5.3 Hz, 1H), 2.60 (ddd, *J* = 13.7, 8.9, 7.2 Hz, 1H), 2.20 (dt, *J* = 13.7, 6.5 Hz, 1H), 2.12 (dt, *J* = 13.7, 6.5 Hz, 1H), 1.86–1.78 (m, 1H), 1.76–1.69 (m, 3H), 1.58–1.55 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.8 (q), −4.2 (q), 18.2 (s), 24.9 (q), 25.9 (q), 31.7 (t), 37.5 (t), 38.2 (t), 38.4 (t), 38.6 (t), 55.1 (q), 65.7 (d), 66.3 (d), 66.4 (t), 70.4 (d), 72.6 (t), 100.3 (q), 113.7 (s), 125.7 (d), 128.3 (d), 128.4 (d), 129.2 (d), 130.6 (d), 135.9 (d), 141.9 (s), 159.1 (s). Anal. Calcd for $C_{34}H_{52}O_5Si$: C, 71.79; H, 9.21. Found: C, 71.93; H, 9.47.
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17. *Spectral data of compound* **16**: $[\alpha]_D^{25}$ +16 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.28–7.25 (m, 2H), 7.19–7.15 (m, 3H), 6.28 (dt, *J* = 11.5, 7.2 Hz, 1H), 5.80 (dt, *J* = 11.5, 1.3 Hz, 1H), 5.58 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.48 (dd, *J* = 15.4, 6.2 Hz, 1H), 4.23 (br q, *J* = 5.9 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.8 (br tt, *J* = 8.2, 6.8 Hz, 1H), 3.76–3.71 (m, 1H), 2.85–2.82 (m, 2H), 2.75 (ddd, *J* = 13.8, 9.3, 5.3 Hz, 1H), 2.61 (ddd, *J* = 13.8, 9.1, 7.2 Hz, 1H), 2.22 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.12 (dt, *J* = 13.7, 6.6 Hz, 1H), 1.86–1.79 (m, 1H), 1.74–1.67 (m, 1H), 1.59–1.55 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.8 (q), −4.4 (q), 14.3 (q), 18.2 (s), 24.9 (q), 24.9 (q), 25.8 (q), 31.6 (t), 37.5 (t), 37.5 (t), 38.1 (t), 38.5 (t), 59.8 (t), 65.8 (d), 66.3 (d), 72.3 (d), 100.3 (s), 120.8 (d), 125.7 (d), 126.2 (d), 128.3 (d), 128.4 (d), 135.1 (d), 141.9 (s), 146.3 (d), 166.4 (s). Anal. Calcd for $C_{30}H_{48}O_5Si$: C, 69.72; H, 9.36. Found: C, 69.87; H, 9.49.
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