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Formal synthesis of fostriecin by a carbohydrate-based approach☆

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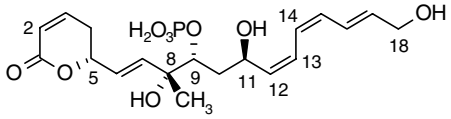
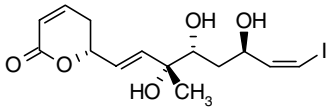
Abstract—The formal synthesis of fostriecin starting from D-glucose, involves chelation-controlled addition, Wittig rearrangement, ring closing metathesis and iodomethylenation, as described.

Fostriecin (CI-920) **1**, a cytotoxic phosphate ester natural product isolated from *Streptomyces pulveraceus*, possesses potent anticancer activity against leukaemia and many other cell lines.[1,2] The cytotoxic properties of **1** are attributed to its selective inhibition of protein phosphatase 2A (PP2A).[3] The relative and absolute stereochemistry of **1** was established by Boger,[4] who also disclosed the first synthesis of the natural product,[5] as well as by preliminary SAR studies.[6] A number of total syntheses[7] as well as synthetic approaches to fostriecin have been reported in the literature.[8] However, it continues to be a challenging endeavor to synthesize this molecule using inexpensive and readily available raw materials via shorter routes.



Fostriecin (CI - 920) **1**



Key intermediate **2**

Figure 1.

Herein, we disclose a chiral pool approach to the C1–C13 fragment **2**, a key intermediate in the Imanishi synthesis of fostriecin (Fig. 1).[7d] The C14–C18 fragment has been prepared in a straightforward fashion,[9] and has also been attached to the C1–C13 fragment.[7a,f,d]

Our approach to **2** is illustrated in Scheme 1, in which the key fragment **8** obtained from D-glucose, plays a central role, serving not only as the source of the C-9 and C-11 stereocentres, but also sets the stage for introducing the C-8 and C-5 stereocentres through chelation-controlled addition[10] of anion **9** (M = MgBr) and Wittig rearrangement.[11] Asymmetric allylation and generation of the *Z*-olefin by iodomethylenation[12] completed the synthesis of **2** (Scheme 2).

Elimination of the triflate derived from glucose diacetonide **3**[13a] by treatment with DBU afforded olefin **4**.[14] Subsequent hydrogenation of **4** in the presence of Raney-Ni in ethanol at 40 psi gave **5**, whose spectral and analytical data were in agreement with the assigned structure.[15a]

Selective deprotection of the 5,6-*O*-isopropylidene group, followed by sodium periodate mediated oxidative cleavage of diol **6** and Grignard reaction of the resulting aldehyde with methylmagnesium iodide in ether at 0 °C, gave a diastereomeric mixture of alcohol **7**, which was oxidized using PCC and NaOAc in CH_2Cl_2 to give the ketone **8**.[15b] Following the above sequence, a higher overall yield of ketone **8** (59%) was obtained from **3** as compared to earlier routes (44%) using the same starting material.[13]

Keywords: D-Glucose; Raney-Ni; Chelation-controlled addition; Wittig rearrangement; Wittig olefination; Chiral allylation; Ring closing metathesis, Iodomethylenation.

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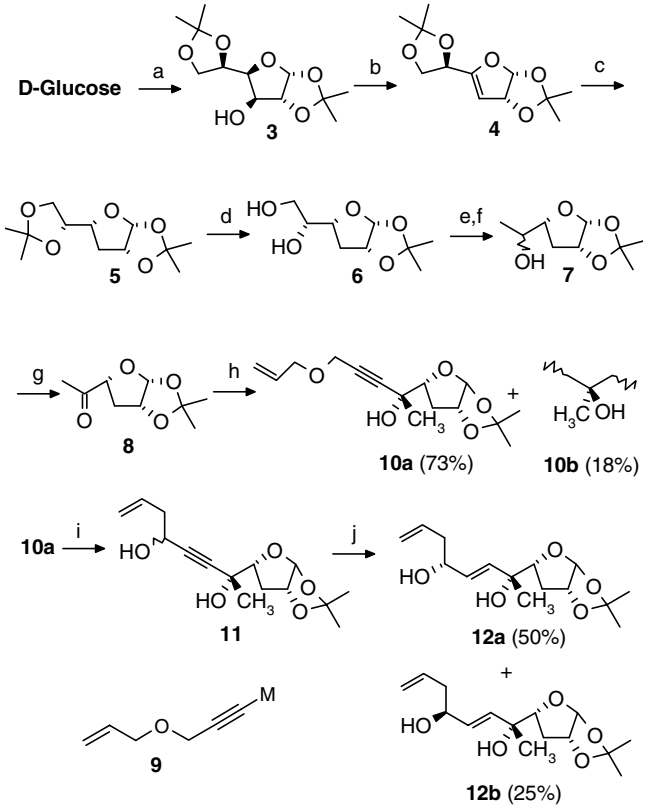
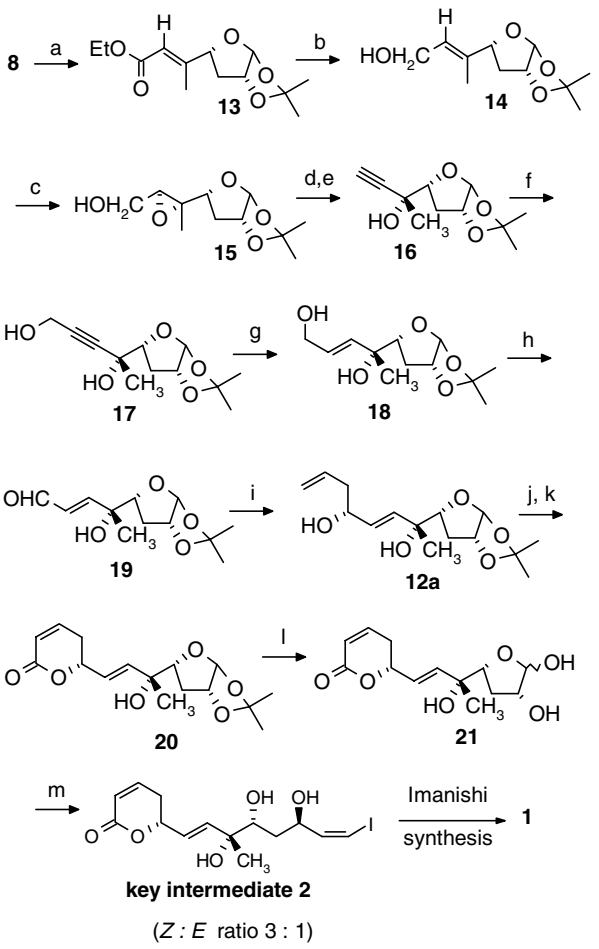


Scheme 1. Reagents and conditions: (a) Ref. 12a; (b) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 0.5 h, then DBU, rt, 16 h, 94%; (c) Raney-Ni, H_2, ethanol, 40 psi, 6 h, 98%; (d) 40% AcOH, rt, 6 h, 83%; (e) $NaIO_4$ on silica gel, CH_2Cl_2/H_2O (8:2), 1 h; (f) MeMgI, ether, 0 °C, 2 h, 88% (for two steps); (g) PCC, NaOAc, CH_2Cl_2, rt, 12 h, 89%; (h) **9**, −78 to −50 °C, 3 h, 91% (**9a** alone 73%); (i) *n*-BuLi (5 equiv), THF, −100 °C, 3 h; (j) $LiAlH_4$, THF, 0 °C to rt, 2 h; 75% (for two steps, **12a** alone 50%).



Scheme 2. Reagents and conditions: (a) $Ph_3PCHCOOEt$ (3 equiv), C_6H_5COOH (cat), toluene, reflux, 16 h, 91% (*E*-isomer alone 83%); (b) DIBAL-H, THF, −78–0 °C, 2 h, 92%; (c) (+)-DIPT, Ti(O-*i*-Pr)$_4$, TBHP, 4 Å molecular sieves, CH_2Cl_2, −23 °C, 24 h, 90%; (d) TPP, CCl_4, reflux, 6 h; (e) *n*-BuLi, THF, −23 °C, 84% (two steps, 76%, **16**); (f) EtMgBr, THF, 0 °C, 1 h then $(CH_2O)_n$, reflux, 3 h, 79%; (g) $LiAlH_4$, THF, 0 °C to rt, 2 h, 91%; (h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 94%; (i) (+)-Ipc$_2$BOMe, allylmagnesium bromide, Et_2O, −100 to 23 °C, 1.5 h; 30% H_2O_2, pH 7 buffer, 23 °C, 12 h, 79%; (j) acryloyl chloride, DIPEA, CH_2Cl_2, 0 °C, 2 h; (k) $(PCy_3)_2RuCl_2$(=CHPh) (0.1 equiv), Ti(*O-i*-Pr)$_4$ (0.3 equiv), CH_2Cl_2, reflux, 12 h, 92% (for two steps); (l) 30% AcOH, 50 °C, 2 h, 92%; (m) $Ph_3P^+CHI\ I^-$, NaHMDS, HMPT, −78 °C to rt, 2 h, 63% (*Z*:*E* ratio = 3:1).

The stereocentre at C-8 of fostriecin was introduced by the chelation-controlled addition[10] of **9** (M = MgBr), generated from allyl propargyl ether and EtMgBr in THF at 0 °C to ketone **8** in THF at −78 to −50 °C for 3 h to afford a chromatographically separable mixture of diastereomers **10a** and **10b** in 91% yield in a ratio of 8:2. Additionally, the reaction of the lithium anion of **9** (M = Li) with ketone **8** was also examined under the same reaction conditions, which gave a mixture of **10a** and **10b** in a 3:7 ratio.

Compound **10a** was subjected to Wittig rearrangement[11] by treatment with excess *n*-BuLi at −100 °C for 3 h to afford **11**. Reduction of the triple bond using $LiAlH_4$ in THF afforded a separable mixture of diastereomers **12a** and **12b** in a 2:1 ratio (Scheme 1).

The stereocentres at C-8 and C-5 were also confirmed by establishing another route, for which ketone **8** was subjected to Wittig olefination with (carboethoxymethylidene)triphenylphosphorane and catalytic benzoic acid in refluxing toluene to afford *E*-ester **13** in 83% yield. The ester was reduced to allylic alcohol **14** using DIBAL-H in THF. Sharpless asymmetric epoxidation[16] of **14** proceeded efficiently to produce epoxide **15** in 90% yield in a 10:1 ratio. Although the mixture was not separated at this stage, transformation by our methodology[17] furnished acetylenic alcohol **16** in 76% yield after chromatography on silica gel, without contamination by the other diastereomer. Compound **16** when subjected to formylation gave **17** in 79% yield, which upon protection as its allyl ether, gave spectral and analytical data in agreement with the assigned structure of **10a**.[18a]

Triple bond reduction of **17** with $LiAlH_4$ in THF provided allylic alcohol **18**. Oxidation of **18** with Dess–Martin periodinane gave aldehyde **19**, which underwent asymmetric allylation[19] using (+)-β-methoxydiisopinocamphenyl borane and allylmagnesium bromide at low temperature to afford **12a** in 79% yield.

Chemoselective esterification of diol **12a** with acryloyl chloride and DIPEA in CH_2Cl_2 at 0 °C gave an ester alcohol, which was subjected to ring-closing metathesis[20] (RCM) with Grubbs' 1st generation catalyst (0.1 equiv) in the presence of Ti(O-*i*-Pr)$_4$ (0.3 equiv) in refluxing CH_2Cl_2 for 12 h to afford lactone **20** in 92% yield. Cleavage of the 1,2-*O*-isopropylidene group of **20** by heating at 50 °C in 30% aq AcOH afforded the lactol **21**. Iodomethylenation of lactol **21** gave the *Z*-isomer of **2** as the major product (*Z*:*E* = 3:1; Scheme 2).

In conclusion, we have disclosed the synthesis of the key intermediate **2** in the formal synthesis of fostriecin using a carbohydrate-based approach, which would be of great use for the synthesis of various fostriecin congeners.

Acknowledgement

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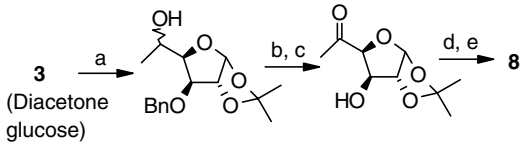

Reagents and conditions: (a) Ref. 12b; (b) PCC, NaOAc, CH_2Cl_2, rt, 12 h, 89%; (c) Pd/C, H_2, rt, 12 h, 98%; (d) MsCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C–rt, 3 h, then DBU, rt, 12 h, 94%; (e) Raney-Ni, H_2, *n*-hexane, 98%.

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15. (a) *Spectral data of compound* **5**: mp = 78–80 °C $[\alpha]_D^{25}$ −28.4 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (d, J = 3.8 Hz, 1H), 4.70–4.65 (m, 1H), 4.42–4.32 (m, 1H), 4.11–4.05 (m, 1H), 4.00 (td, J = 7.7, 1.5 Hz, 1H), 3.60 (dd, J = 8.5, 7.0 Hz, 1H), 2.24–2.09 (m, 1H), 1.82 (dd, J = 14.0, 3.8 Hz, 1H), 1.55 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.6, 109.8, 106.3, 81.3, 80.3, 77.5, 65.9, 33.4, 27.2, 26.6, 26.1, 25.2. Mass (ESI-MS) *m*/*z*: 267 $(M+Na)^+$. HRMS calcd for $C_{12}H_{20}O_5Na$: 267.1203 $(M+Na)^+$. Found: 267.1208; (b) *Spectral data of compound* **8**: $[\alpha]_D^{25}$ +5.8 (*c* 3.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (d, J = 4.5 Hz, 1H), 4.67–4.64 (m, 1H), 4.31 (dd, J = 9.8, 1.5 Hz, 1H), 2.69 (d, J = 14.3 Hz, 1H), 2.32 (s, 3H), 2.11–2.02 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.8, 111.6, 106.5, 84.4, 79.5, 33.4, 26.5, 25.6, 25.3. Mass (ESI-MS) *m*/*z*: 209 $(M+Na)^+$. HRMS calcd for $C_9H_{14}O_4Na$: 209.0734 $(M+Na)^+$. Found: 209.0738.
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18. (a) *Spectral data of compound* **9a**: $[\alpha]_D^{25}$ −28.5 (*c* 3.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.93–5.78 (m, 1H), 5.71 (d, J = 4.5 Hz, 1H), 5.29 (dd, J = 17.3, 1.5 Hz, 1H), 5.18 (dd, J = 10.5, 1.5 Hz, 1H), 4.77–4.71 (m, 1H), 4.15 (s, 2H), 4.07 (dd, J = 8.3, 7.5 Hz, 1H), 4.04–4.01 (m, 2H), 2.92 (br s, OH), 2.22 (dt, J = 13.5, 7.5 Hz 1H), 2.09 (ddd, J = 13.5, 11.3, 3.7 Hz, 1H), 1.56 (s, 3H), 1.40 (s, 3H),

1.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.9, 117.6, 113.4, 105.7, 88.5, 86.0, 80.6, 80.3, 70.3, 68.3, 57.2, 32.0, 27.5, 26.8, 25.1. IR (Neat): 3417, 2987, 2936, 1619, 1445, 1376, 1218, 1164, 1082, 931, 860 cm^{-1}. Mass (ESI-MS) *m/z*: 305 $(M+Na)^+$. HRMS calcd for $C_{15}H_{22}O_5Na$: 305.1363 $(M+Na)^+$. Found: 305.1364; (b) *Spectral data of compound* **9b**: $[\alpha]_D^{25}$ +46 (*c* 3.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92–5.77 (m, 1H), 5.70 (d, $J = 3.77$ Hz, 1H), 5.27 (dd, $J = 16.8$, 1.5 Hz, 1H), 5.19 (dd, $J = 9.8$, 1.5 Hz, 1H), 4.74–4.69 (m, 1H), 4.13 (s, 2H), 4.07 (t, $J = 7.55$ Hz, 1H), 4.01–3.99 (m, 2H), 3.06 (br s, OH), 2.34–2.30 (m, 2H), 1.52 (s, 3H), 1.43 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 117.5, 113.5, 106.1, 87.4, 85.8, 80.5, 80.4, 70.3, 69.1, 57.2, 33.0, 27.1, 26.8, 26.5.

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