## Synthesis of the C1–C12 Fragment of Fostriecin

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The synthesis of the  $C_1-C_{12}$  fragment of fostriecin was achieved from (*S*)-glycidol in 15 steps by using an enantioselective allytitanation reaction and a ring-closure metathesis as the key steps.

In 1984, several articles<sup>1,2</sup> were published describing CI-920, a structurally novel antibiotic isolated from a fermentation broth of a new actinomycetes (*Streptomyces pulveraceus*). This compound is active in vitro against leukemia (L1210, IC<sub>50</sub> 0.46  $\mu$ M), lung, breast, and ovarian cancer and displays efficacious in vivo antitumor activity against L1210 and P338 leukemia.<sup>3,1c</sup> Currently, fostriecin is under evaluation as an antitumor drug in clinical trials. (+)-Fostriecin inhibits DNA, RNA, and protein synthesis<sup>4</sup> and was shown to block cells in the G2 phase of the cell cycle and to have inhibition effects on partially purified type II topoisomerase from Ehrlich *ascites carcinoma.*<sup>5</sup> However, fostriecin is distinctly different from previously described inhibitors of topoisomerase II in that it does not cause protein-associated DNA strand breaks.<sup>5</sup>

Instead, it inhibits the mitotic entry checkpoint,<sup>6</sup> potentially

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through inhibition of protein phosphatases 1 and 2A (IC<sub>50</sub> 4  $\mu$ M and 40 nM respectively).<sup>7–9</sup> Inhibition of the mitotic entry checkpoint and protein phosphatase are novel properties for a potential clinical antitumor agent. Despite its intriguing biological properties, the complete relative and absolute stereochemistry of fostriecin was only determined in 1997<sup>10</sup> (Figure 1).

Recently, the first total synthesis of fostriecin has been reported.<sup>11</sup> Here, we report the synthesis of the C1–C12 fragment of fostriecin from (*S*)-glycidol (the C2 of which corresponds to the C11 of fostriecin) by using an enantio-selective allyltitanation applied to **11** to control the C5 center, an enantioselective osmylation of unsaturated ester **6** to control the C9 and C8 centers, and a ring-closing metathesis (RCM) reaction applied to the unsaturated ester **13** to build up the lactone moiety (Scheme 1).





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(S)-Glycidol was transformed to the corresponding pmethoxyphenol ether by using a Mitsunobu reaction (pmethoxyphenol, DEAD, PPh<sub>3</sub>, THF, 0 °C, 15 h, yield 82%) and then treated with vinylmagnesium cuprate in THF at -40 °C to afford the corresponding homoallylic alcohol **2** in 95% yield. Transformation of **2** to the corresponding



<sup>*a*</sup> (a) *p*-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>OH, PPh<sub>3</sub>, DEAD, THF, 0 °C; (b) vinylMgCl, CuI, THF, -40 °C; (c) MOMCl, <sup>*i*</sup>Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (d) OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O, NaIO<sub>4</sub>, 25 °C; (e) Ph<sub>3</sub>PC(CH<sub>3</sub>)CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub> **15**, benzene, 80 °C; (f) BF<sub>3</sub>·Et<sub>2</sub>O, Me<sub>2</sub>S, 0 °C; (g) AD-mix $\beta$ , *t*-BuOH/H<sub>2</sub>O/ toluene, 0 °C; (h) MOMCl, <sup>*i*</sup>Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (i) LiAlH<sub>4</sub>, THF, 25 °C; (j) (COCl)<sub>2</sub>, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, Et<sub>3</sub>N, 25 °C; (k) PPh<sub>3</sub>CHCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub> **16**, toluene, 80 °C; (l) DIBAL-H, toluene, -78 °C; (m) (*S*,*S*)-I, ether, -78 °C, 4 h; (n) acryloyl chloride, CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N -78 °C; (p) Grubbs' catalyst **II**, CH<sub>2</sub>Cl<sub>2</sub>, 55 °C.

methoxymethyl ether **3** (MOMCl, <sup>*i*</sup>Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 70% yield) followed by oxidative cleavage of the double bond led to aldehyde **4** (OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O; NaIO<sub>4</sub>; 98% yield). Aldehyde **4** was treated with the phosphonium salt **15** to give the unsaturated ester **5** (refluxing benzene, 15 h, 87% yield).

After deprotection of **5** using  $BF_3 \cdot EtO_2$  in Me<sub>2</sub>S at 0 °C, alcohol 6 was isolated in 93% yield and subjected to asymmetric dihydroxylation (ADmix-β, NaHCO<sub>3</sub>, CH<sub>3</sub>SO<sub>2</sub>-NH<sub>2</sub>, K<sub>2</sub>OsO<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>, t-BuOH/H<sub>2</sub>O: 1/1, toluene, 0 °C, 48 h) to provide triol 7 in 99% yield and with an excellent diastereoselectivity of up to 95%.<sup>12</sup> It is worth noting that, when the unsaturated ester 5 was dihydroxylated under the same conditions that were used previously, the monoprotected triol was obtained with a low diastereoselectivity (de = 80:20). The protection of triol 7 using MOMCl in  ${}^{i}Pr_{2}$ -NEt as solvent (MOMCl, 6 equiv; 0 °C; 15 h) led to compound 8 (70% yield) which was transformed to aldehyde 9 in two steps. After reduction of ester 8 by LAH (THF, rt), the alcohol was directly oxidized to aldehyde 9 using a Swern oxidation [(COCl)<sub>2</sub>, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C]. Aldehyde 9 was isolated with an overall yield of 92%, and its subsequent treatment with phosphonium ester 16 (refluxing toluene, 15 h) cleanly provided the unsaturated ester 10 (E/Z > 30/1) in 92% yield.

Ester **10** was then reduced to aldehyde **11** (85% yield) using Dibal-H in toluene at -78 °C for 30 min. When aldehyde **11** was treated with the (*S*,*S*)-**I** allyltitanium complex according to the reported procedure,<sup>13</sup> homoallylic alcohol **12** was produced and esterified with acryloyl chloride in the presence of Et<sub>3</sub>N and a catalytic amount of 4-DMAP (CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to 0 °C, 2 h). The corresponding ester **13** 

was produced in 53% yield (for the two steps). Ring-closing metathesis (RCM) was then attempted on 13. Treatment of 13 with the Grubbs' catalyst II (in refluxing  $CH_2Cl_2$ )<sup>14</sup> provided after 5 h the desired lactone 14 in 86% yield (Scheme 2).<sup>14</sup>

The C1-C12 fragment of fostriecin was prepared from (S)-glycidol in 15 steps with an overall yield of 9.8% by using three key steps: an enantioselective allyltitanation applied to an aldehyde, an enantioselective dihydroxylation of an unsaturated ester, and a ring-closure metathesis reaction.

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