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Synthesis of the C1–C12 Fragment of Fostriecin

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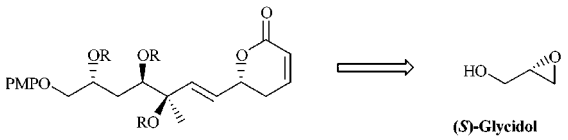
ABSTRACT



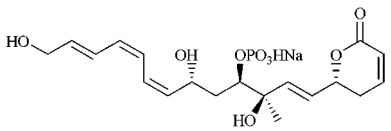
C1-C12 Fragment of Fostriecin

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[1,2] 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_{50} 0.46 μM), lung, breast, and ovarian cancer and displays efficacious in vivo antitumor activity against L1210 and P338 leukemia.[3,1c] Currently, fostriecin is under evaluation as an antitumor drug in clinical trials. (+)-Fostriecin inhibits DNA, RNA, and protein synthesis[4] 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*.[5] However, fostriecin is distinctly different from previously described inhibitors of topoisomerase II in that it does not cause protein-associated DNA strand breaks.[5]

Instead, it inhibits the mitotic entry checkpoint,[6] potentially through inhibition of protein phosphatases 1 and 2A (IC_{50} 4 μM and 40 nM respectively).[7−9] 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[10] (Figure 1).

Recently, the first total synthesis of fostriecin has been reported.[11] 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 enantioselective 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).



Fostriecin

Figure 1.

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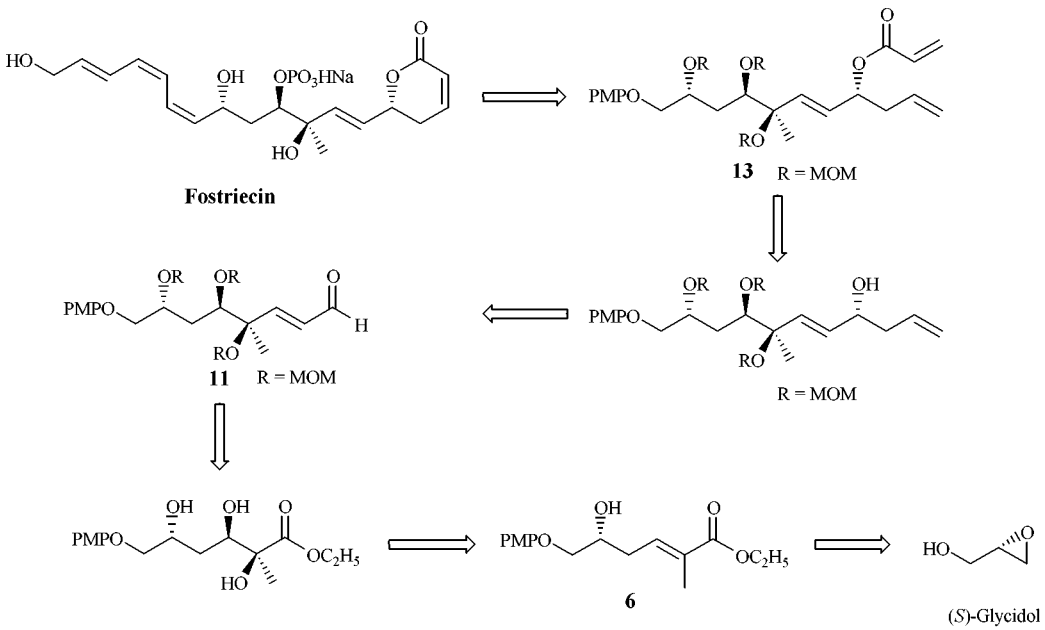
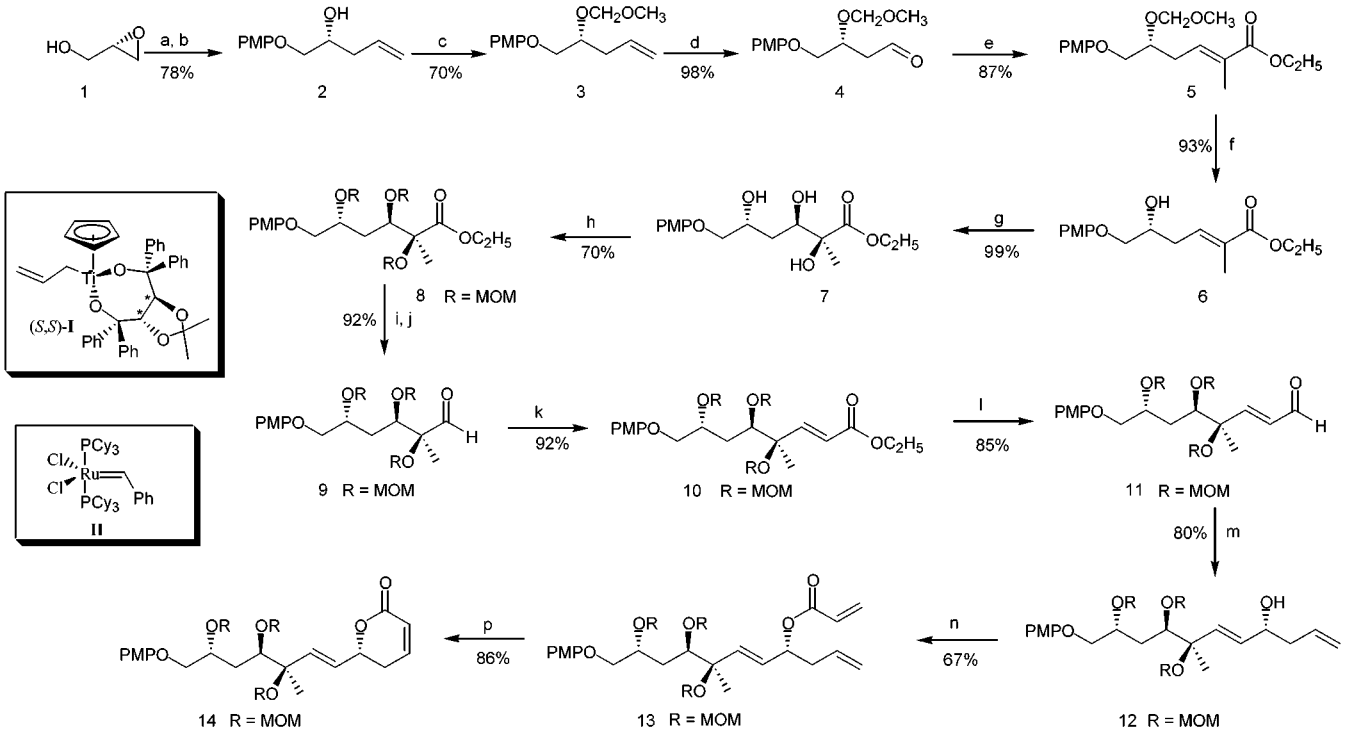
Scheme 1



(*S*)-Glycidol was transformed to the corresponding *p*-methoxyphenol ether by using a Mitsunobu reaction (*p*-methoxyphenol, DEAD, PPh_3, 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

Scheme 2[a]



[a] (a) *p*-$CH_3OC_6H_4OH$, PPh_3, DEAD, THF, 0 °C; (b) vinylMgCl, CuI, THF, −40 °C; (c) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C; (d) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25 °C; (e) $Ph_3PC(CH_3)CO_2C_2H_5$ **15**, benzene, 80 °C; (f) $BF_3{\cdot}Et_2O$, Me_2S, 0 °C; (g) AD-mix-β, *t*-BuOH/H_2O/toluene, 0 °C; (h) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C; (i) $LiAlH_4$, THF, 25 °C; (j) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, Et_3N, 25 °C; (k) $PPh_3CHCO_2C_2H_5$ **16**, toluene, 80 °C; (l) DIBAL-H, toluene, −78 °C; (m) (*S*,*S*)-**I**, ether, −78 °C, 4 h; (n) acryloyl chloride, CH_2Cl_2, Et_3N −78 °C; (p) Grubbs' catalyst **II**, CH_2Cl_2, 55 °C.

methoxymethyl ether **3** (MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C, 70% yield) followed by oxidative cleavage of the double bond led to aldehyde **4** (OsO_4, NMO, acetone/H_2O; $NaIO_4$; 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_2S at 0 °C, alcohol **6** was isolated in 93% yield and subjected to asymmetric dihydroxylation (ADmix-β, $NaHCO_3$, $CH_3SO_2NH_2$, $K_2OsO_2(H_2O)_2$, *t*-BuOH/H_2O: 1/1, toluene, 0 °C, 48 h) to provide triol **7** in 99% yield and with an excellent diastereoselectivity of up to 95%.[12] 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 $^{i}Pr_2NEt$ 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 [$(COCl)_2$, DMSO, CH_2Cl_2, −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,[13] homoallylic alcohol **12** was produced and esterified with acryloyl chloride in the presence of Et_3N and a catalytic amount of 4-DMAP (CH_2Cl_2, −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)[14] provided after 5 h the desired lactone **14** in 86% yield (Scheme 2).[14]

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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