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Asymmetric Synthesis of (3R, 5R)-3-((tert-Butyldimethylsily)oxy)-5-((Z)-2-Bromovinyl)-Tetrahydro-Furan-2-one, an Intermediate for the Synthesis of Fostriecin

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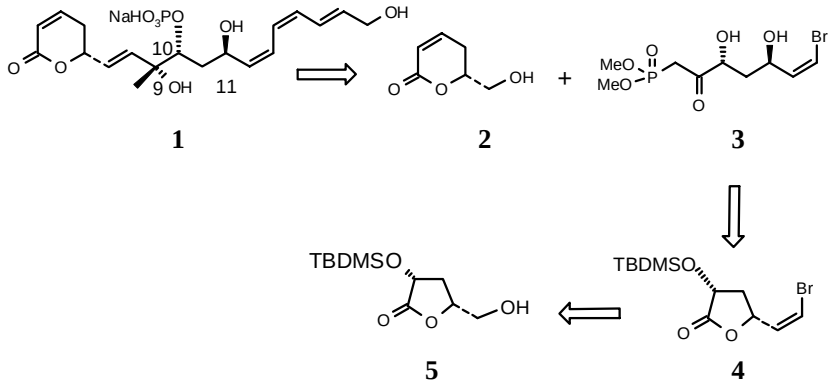
Abstract: (3R,5R)-3-((tert-Butyldimethylsily)oxy)-5-((Z)-2-bromovinyl)-tetrahydro-furan-2-one, an intermediate for the synthesis of Fostriecin was achieved by intramolecular asymmetric induction in propene addition of (-)-8-phenylmenthyl glyoxylate followed by inversion of C_3-hydroxyl group and Sharpless asymmetric dihydroxylation with simultaneous cyclization to give lactone **5**. Then protection of C_3-hydroxyl group and oxidation of the C_6-primary hydroxyl group which reacted with Wittig reagent to yield the target compound **4**.

Keywords: Fostriecin, dihydroxylation, (-)-8-phenylmenthol asymmetric synthesis.

Fostriecin(CI-920) **1**[1] a potential anticancer agent presently in phase I clinical trials at NCI is a novel phosphate ester produced by *Streptomyces pulveraceus.*

Scheme 1



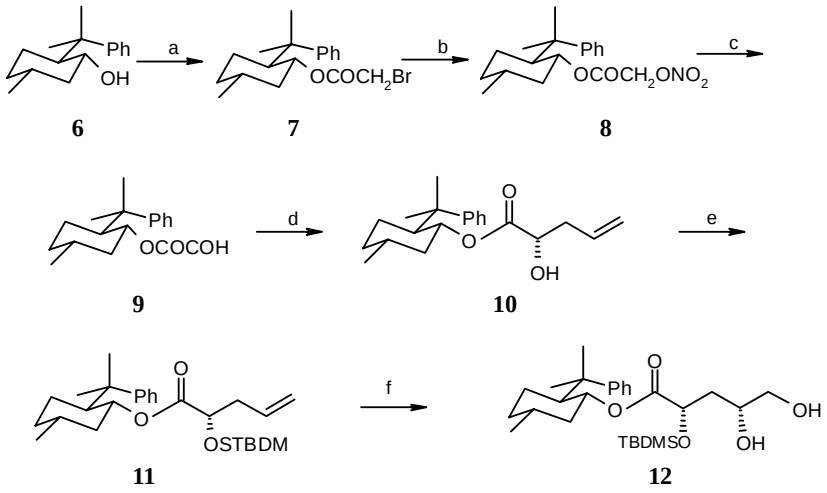
1 **2** **3**

5 **4**

Synthesis of C_{10} epimer of compound **1** had been reported by Just G[2]. during the determination of its structure. On the basis of Just's synthesis, a revised retro-asymmetric synthetic route of Fostriecin (**scheme 1**) was designed here of which compound **3** was synthesized from **5** with C_3 in R configuration corresponding to C_{10} of **1** instead of glucofuranose derivative used for its epimer by Just. The synthetic routes of compound **4** were listed in **scheme 2** and **scheme 3**. Compound **10** was prepared from **6** by the

procedures detailed by Whitesell[3]. The yields and ^{1}HNMR data of these compounds (**6**, **7**, **8** and **9**) checked nicely with what have been reported except the $[\alpha]_D$ and ^{1}HNMR of **10**[8a] which had not been mentioned in the original paper. The C_2-OH of compound **10** was protected and followed by asymmetric dihydroxylation of compound **11** with AD-mix-β [4] to give the compound **12** as a yellowish oil (**Scheme 2**). Cyclization of **12** failed

Scheme 2

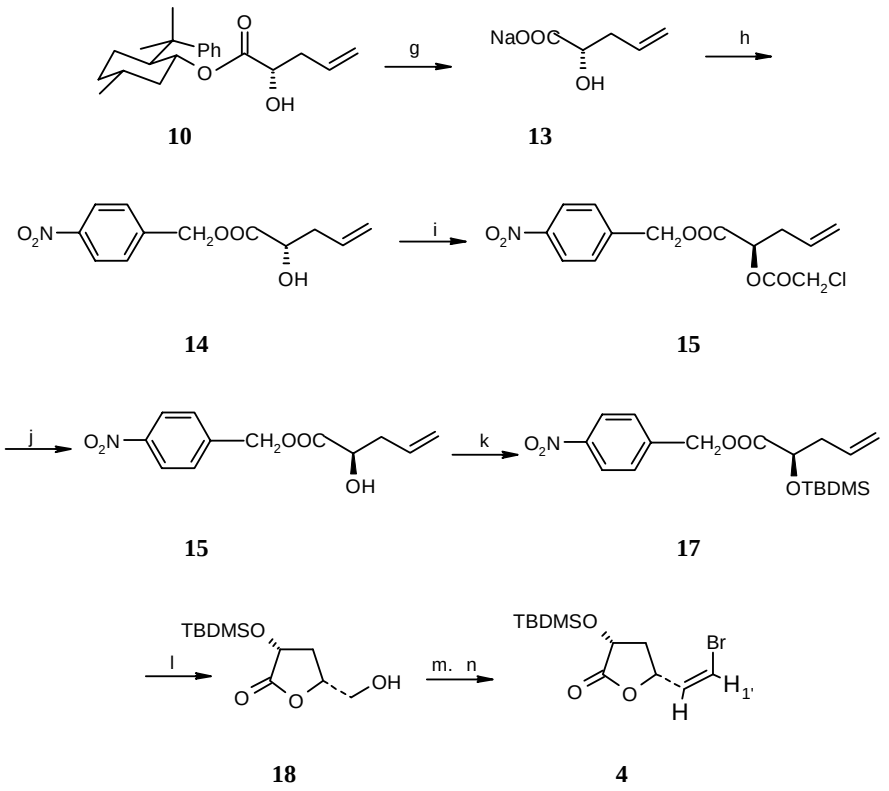


Regents and conditions: (a) $BrCH_2COOH$/p-Toluenesulfonic acid/benzene, 97%; (b) $AgNO_3/CH_3CN$, 93%; (c) DMSO/NaOAc, 93%; (d) propene/$SnCl_4/CH_2Cl_2$, -78℃, 98%; (e) tert-Butyldimethylsilyl chloride/imidazole/DMF, 96%; (f) AD-mix-β /H_2O, tert-BuOH, 0℃**,** 86%.

possibly due to the steric effect of 8-phenylmenthol. Attempt to cyclize of the free acid was not satisfactory. Therefore the menthyl group was replaced by less bulky *p*-nitrobenzyl group and which has strong fluorescence, easy to monitor the reaction by TLC. The 8-phenylmenthyl group of compound **10** was removed with 5% sodium hydroxide as shown in **scheme 3** and the sodium salt was treated directly with *p*-nitrobenzyl bromide. Ester **14** was an oil ($[\alpha]_D^{19}$ -18.13 (c 2.46 $CHCl_3$)) which failed to crystallize on standing. Inversion of C_2 configuration from the undesired "S" to "R" was achieved through Mitsunobu reaction[5] followed by treatment of the intermediate **15** with thiourea to give compound **16** ($[\alpha]_D^{20}$ +18.09 (c 2.86 $CHCl_3$)). Protection of hydroxy group with tert-butyldimethylsilyl group and asymmetric dihydroxylation with AD-mix-β gave directly the cyclized furanone **18** (m.p.66.7~68.1℃) with strong peaks at 1770 cm^{-1} in IR. After Swern oxidation[6] of **18**, the aldehyde was treated with the bromomethyl ylide[7]. The bromoethenyl furanone **4** was obtained as a white solid (m.p.53.3~55.5℃, ^{1}H-NMR δ , 6.41(d, J 7.2Hz, $C_{1'}$-H), 6.30(t, J 7.2, $C_{2'}$-H)) in 51%

yield[8].

Scheme 3



Regents and conditions: g) 5% NaOH, h) *p*-Nitrobenzylbromide/DMF, 70%; i) $ClCH_2COOH$/TPP/DEAD/Toluene, 90%; j) Thiourea/EtOH, 89%; k) tert-Butyldimethylsilyl chloride/imidazole/DMF, 96%; l) AD-mix-β /H_2O,t-BuOH, 0℃, 79%; m) Oxalyl chloride/Et_3N/DMSO, -78℃; n) Ph_3P^+=CHBr.Br^-/t-BuOK/THF, -78℃, 51%

^{1}H-NMR, ^{13}C-NMR EI-MS and IR data of compound **10**, **12**, **14**, **15**, **16**, **18** and **4** were listed in note 8. The synthesis of Fostriecin (CI-920) is on going.

Acknowledgment

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References and notes

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8. a). Compound **10**: colorless oil, $[\alpha]_D^{12}$ +2.2 (c 2.14, CH_3OH); ^{1}H-NMR ($CDCl_3$ 300MHz) δ
   ppm: 7.27 (m, 4H), 7.18 (m, 1H), 5.61 (m, 1H), 5.05 (m, 2H), 4.88 (dt, J 10.5Hz, 4.5Hz, 1H), 3.26 (m, 1H), 2.18 (m,2H), 2.06 (m, 1H), 1.29 (s, 3H), 1.19 (s, 3H), 0.89 (d, J 6..3Hz, 3H), 1.99~0.90 (m, 8H); EI-MS: *m/z* 330 (M^+) 119 (100%) 105 (30%) 91 (24%) .
   b). Compound **12:** yellowish oil, ^{1}H-NMR ($CDCl_3$ 300MHz) δ ppm: 7.29~7.13 (m 5H), 4.75 (m, 1H), 3.73 (m, 1H), 3.54 (m, 1H), 3.36 (m, 1H), 2.10 (m, 2H), 1.24 (s, 3H), 1.18 (s, 3H), 0.92 (s, 9H), 0.87 (d, J 6.6Hz, 3H), 0.14 (s, 3H), 0.08 (s, 3H), 2.0~0.8 (m, 8H).
   c). Compound **14:** yellowish oil $[\alpha]_D^{19}$ -18.13 (c 2.46 $CHCl_3$), ^{1}H-NMR ($CDCl_3$ 300MHz) δ ppm: 8.24 (d, J 8.4Hz, 2H), 7.52 (d, J 8.4Hz, 2H), 5.79 (m, 1H), 5.30 (s, 2H), 5.11 (m, 2H), 4.36 (dd, J 7.0Hz, 4.8Hz, 1H), 2.66 (m, 2H), 2.50 (m, 1H).
   d). Compound **15:** yellowish oil $[\alpha]_D^{21}$ +9.83 (c 1.76 $CHCl_3$), ^{1}H-NMR ($CDCl_3$ 300MHz) δ ppm: 8.25 (d, J 8.5Hz, 2H), 7.52 (d, J 8.5Hz, 2H), 6.74 (m, 1H), 5.28 (s, 2H), 5.18 (m, 1H), 5.12 (m, 2H), 4.15 (s, 2H), 2.68 (m, 2H).
   e). Compound **16:** yellowish oil; $[\alpha]_D^{20}$ +18.09 (c 2.86 $CHCl_3$); ^{1}H-NMR ($CDCl_3$ 300MHz) δ ppm: 8.24 (d, J 8.4Hz, 2H), 7.52 (d, J 8.4Hz, 2H), 5.76 (m, 1H), 5.30 (s, 2H), 5.11 (m, 2H), 4.36 (t, J 5.7Hz, 1H), 2.87 (s, 1H), 2.63 (m, 1H), 2.47 (m, 1H).
   f). Compound **18:** colorless crystals, m.p.66.7~68.1℃ (EtOAc); ^{1}H-NMR ($CDCl_3$ 500MHz) δ ppm: 4.52 (t, J 9.1Hz, 1H), 4.47 (m, 2H), 3.89 (dd, J 2.6Hz, 12.5Hz, 1H), 3.68 (dd, J 5.3Hz, 12.5Hz, 1H), 2.50 (m, 1H), 2.12 (m, 1H). 1.85 (s, 1H), 0.92 (s, 1H), 0.18 (s, 1H), 0.15 (s, 1H); IR υ (KBr cm^{-1}) 3446, 2953, 2927, 2858, 1779, 1334, 1273, 1265, 1212, 1165, 1092, 1019, 963, 890, 845, 780, 723, 613.
   g). Compound **4:** yellowish crystals, m.p.53.3~55.5℃ (EtOAc); ^{1}H-NMR ($CDCl_3$ 300MHz) δ ppm: 6.41 (d, J 7.2 Hz, 1H), 6.3 (t, J 7.2Hz, 1H), 5.23 (m, 1H), 4.50 (m, 1H), 2.79 (m, 1H), 2.00 (m, 1H), 0.92 (s, 9H), 0.19 (s, 3H), 0.15, (s, 3H), IR υ (KBr cm^{-1}): 3080, 2958, 2927, 2856, 1770, 1630, 1470, 1361, 1326, 1292, 1252, 1205, 1158, 1068, 996, 864, 839, 779, 731, 687, 623.

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