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Formal Total Synthesis of Fostriecin

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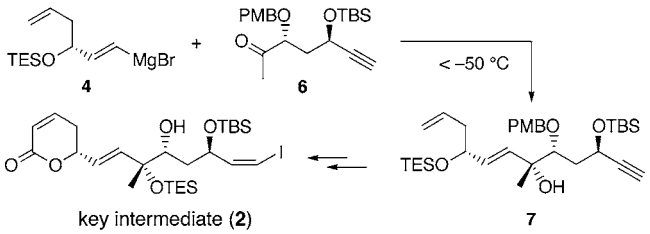
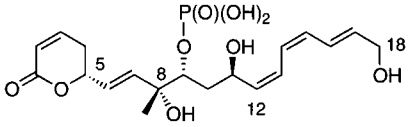
ABSTRACT

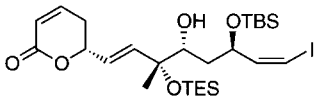


Addition of magnesium anion 4 (M = MgBr, R^1 = TES) to ketone 6 (R^2 = PMB) at −78 °C in THF proceeded under chelation control to provide alcohol 7, which possesses the full set of the chiral centers of fostriecin. Subsequently, 7 was transformed successfully to the known key intermediate 2.

After its isolation in 1983,[1] the antitumor activity of fostriecin against a broad range of cancerous cell lines and its inhibitory activity against protein serin/threonine phosphatases have attracted much interest among both biological and pharmaceutical researchers.[2] In 1997, the relative and absolute stereochemistry of fostriecin was established by the Boger group,[3] which made investigation at the molecular level possible. However, a few years passed before the first total synthesis of fostriecin (**1**) was reported by Boger in 2001.[4] Since then, three total syntheses have been reported.[5] The conjugated triene unit has been synthesized by joining two parts at the C(12) and C(13) carbons with a palladium catalyst. The vinyl halides such as **2** are those which belong to a partner containing the highly congested



fostriecin (**1**)



key intermediate **2**

C(5)−C(11) functionality and another partner is the organometallic corresponding to the remaining C(13)−C(18) diene. This strategy for the construction of the triene unit is efficient and straightforward, and thence synthesis of the central moiety is of much interest at present.[6] Although elegant syntheses of this complex moiety have been published, we examined another approach to this moiety in order not only to establish a route to **1** but also to provide a potentially versatile route to the analogues.

Illustrated in Scheme 1 is our approach to **2**, in which the key reaction is chelation-controlled addition of anion **4** to α-alkoxy ketone **6** furnishing the adduct **7** with the full set of the chiral centers. The metal for the chelation is MgX,[7]

(1) (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot*. **1983**, *36*, 1595−1600. (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot*. **1983**, *36*, 1601−1605. (c) Leopold, W. R.; Shillis, J. L.; Mertus, A. E.; Nelson, J. M.; Roberts, B. J.; Jackson, R. C. *Cancer Res*. **1984**, *44*, 1928−1932.

(2) (a) Jackson, R. C.; Fry, D. W.; Boritzki, T. J.; Roberts, B. J.; Hook, K. E.; Leopold, W. R. *Adv. Enzyme Regul*. **1985**, *23*, 193−215. (b) de Jong, R. S.; de Vires, E. G. E.; Mulder, N. H. *Anti-Cancer Drugs* **1997**, *8*, 413−418.

(3) Boger, D. L.; Hikota, M.; Lewis, B. M. *J. Org. Chem*. **1997**, *62*, 1748−1753.

(4) Boger, D. L.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc*. **2001**, *123*, 4161−4167.

(5) (a) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2001**, *40*, 3667−3670. (b) Reddy, Y. K.; Falck, J. R. *Org. Lett*. **2002**, *4*, 969−971. (c) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. *Chem. Commun*. **2002**, 742−743.

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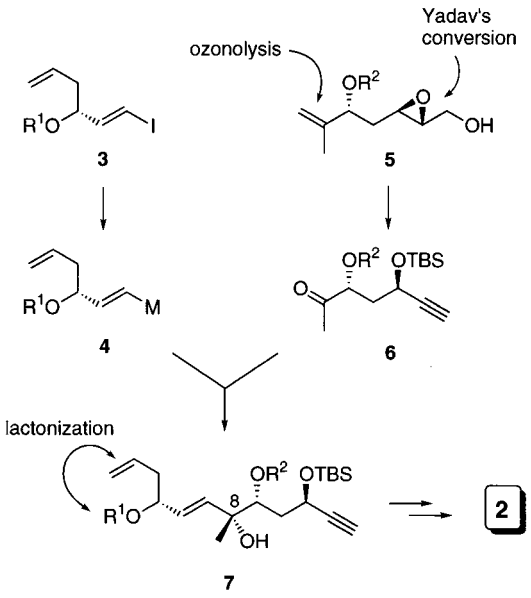
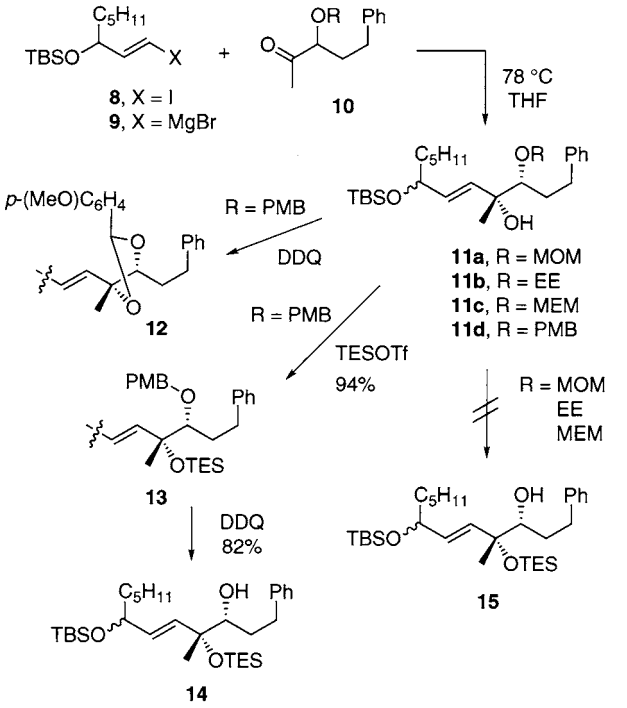
Scheme 1. A Strategy for Synthesis of the Key Intermediate **2**



and this anion is expected to be generated from iodide **3** through lithiation followed by transmetalation with MgX_2. On the other hand, a transformation of **5** illustrated in Scheme 1 was envisioned for synthesis of ketone **6**. Herein, we disclose the successful result of this approach, where the asymmetric chiral centers of **3** and **5** were created by using the Sharpless asymmetric epoxidation.[8]

First, we studied a protective group at the C(9) hydroxyl group which should be removed at a later stage after the chelation-controlled addition. Ketones **10** with different protective groups (R = MOM, EE, MEM, PMB) were chosen as model compounds of **6** and submitted to the reaction with magnesium anion **9** derived from **8** [(1) *n*-BuLi; (2) $MgBr_2$] to afford the addition products **11a**−**d** in good yields (Scheme 2). As expected,[7] the protective groups we examined furnished high stereoselectivity of >20:1 by ^{1}H NMR spectroscopy (300 MHz), and thence deprotection was studied with these products under the following conditions: PPTS/MeOH, PPTS/*n*-PrOH,[9a] $MgBr_2/Et_2O$,[9b] CBr_4/*i*-PrOH[9c] for MOM ether **11a**; PPTS/MeOH for EE ether **11b**; $ZnBr_2/CH_2Cl_2$,[9d] $TiCl_4$[9d] in CH_2Cl_2 or hexane for MEM ether **11c**; DDQ in wet CH_2Cl_2[9e] for PMB ether **11d**. However, these conditions resulted in recovery of the ethers, production of Me ether (from **11b**/MeOH), formation of acetal **12** (from **11d**), or production of mixtures. On the contrary, reaction

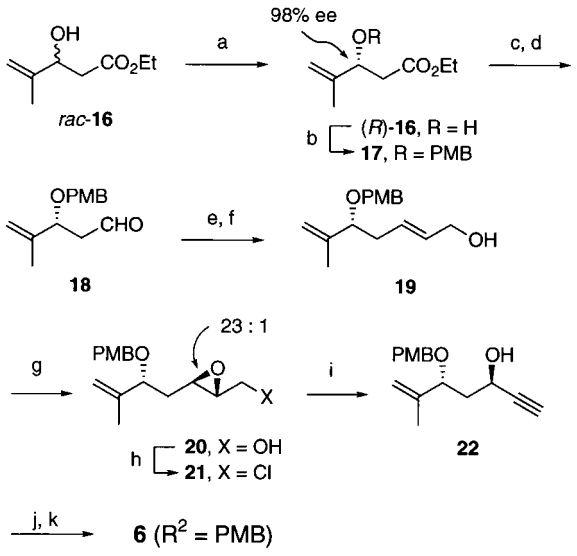
Scheme 2. Preliminary Study



of TES ether **13**, derived from **11d**, with DDQ furnished alcohol **14** in 82% yield.

With these preliminary results in mind, synthesis of fostriecin was performed as depicted in Schemes 3−5.

Scheme 3. Synthesis of C(8)−C(12) Intermediate **6**[a]



[a] Reagents and conditions: (a) *t*-BuOOH (1.0 equiv), L-(+)-DIPT (0.35 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.30 equiv), 4A MS, 49%; (b) PMBOC-(CCl_3)=NH, CSA, CH_2Cl_2, 93%; (c) $LiAlH_4$, 93%; (d) $(COCl)_2$, DMSO then Et_3N; (e) LiCl, DBU, $(EtO)_2P(=O)CH_2CO_2Et$, 99% (two steps); (f) DIBAL (2.5 equiv), 92%; (g) *t*-BuOOH (1.5 equiv), D-(−)-DIPT (0.24 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.20 equiv), 4A MS, 92%; (h) CCl_4, PPh_3, $NaHCO_3$ (cat.), 83%; (i) *n*-BuLi, THF, 91%; (j) TBSCl, 94%; (k) O_3, *n*-PrOH, 85%.

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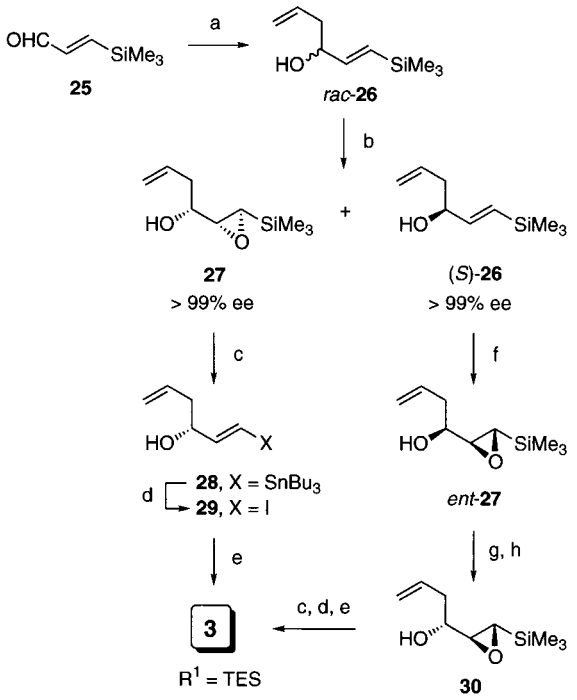
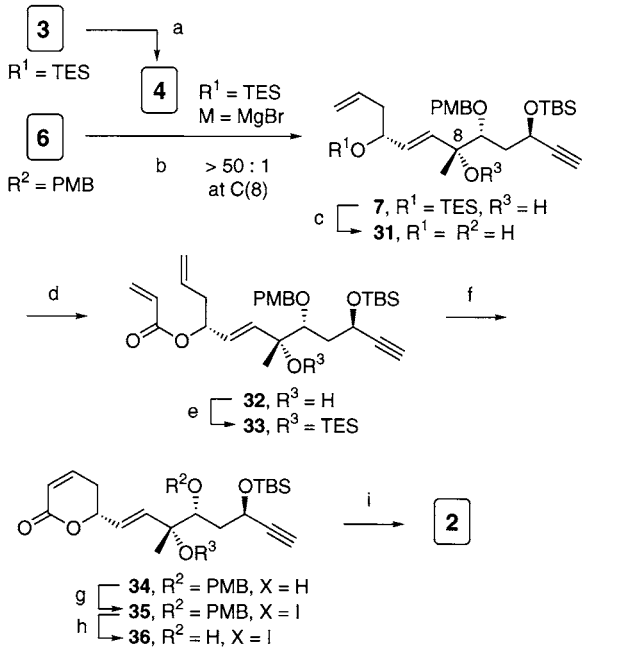
Scheme 4. Synthesis of C(3)−C(7) Intermediate **7**[a]



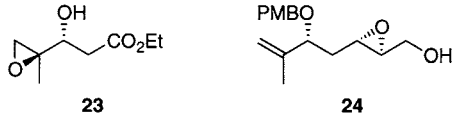
[a] Reagents and conditions: (a) CH_2═$CHCH_2MgCl$, THF, 100%; (b) *t*-BuOOH (1.5 equiv), D-(−)-DIPT (0.35 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.30 equiv), 4A MS, 46% and >99% ee of **27**, 45% and >99% ee of (*S*)-**26**; (c) LDA, Bu_3SnH; (d) I_2, Et_2O, 98% from **27**, 84% from **30**; (e) TESCl, 93−100%; (f) *t*-BuOOH (2.0 equiv), L-(+)-DIPT (0.35 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.30 equiv), 4A MS, 95%; (g) 3,5-$(NO_2)_2C_6H_3CO_2H$, DIAD, PPh_3, 93%; (h) NaOH, 94%.

Scheme 5. Final Stage Leading to the Key Intermediate **2**[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C then $MgBr_2$; (b) −78 to −50 °C, 91%; (c) HF, 98%; (d) CH_2═$CHCOCl$, DIPEA, 85%; (e) TESOTf, 89%; (f) $(PCy_3)_2RuCl_2$(═CHPh) (0.1 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.3 equiv), CH_2Cl_2, 83%; (g) NIS (1.2 equiv), $AgNO_3$ (2 equiv), acetone, 83%; (h) DDQ, rt, 2 h, CH_2Cl_2/H_2O (18:1), 82% from **34**; (i) *o*-$(NO_2)C_6H_4SO_2N$═NH (1.2 equiv), Et_3N (2 equiv), 88%.

Racemic alcohol *rac*-**16**, prepared by aldol reaction of methacrolein and the anion derived from ethyl acetate (LDA, THF, −78 °C) in 91% yield, was submitted to kinetic resolution through the Sharpless asymmetric epoxidation[8b,c] to furnish (*R*)-**16** with 98% ee by ^1H NMR spectroscopy of the corresponding MTPA ester (Scheme 3). The isolated yield after chromatography on silica gel was 49% based on *rac*-**16**. The corresponding epoxide **23** produced by the epoxidation (checked by TLC) was quite unstable during workup (10% tartaric acid and NaF), and thus isolation of (*R*)-**16** by chromatography on silica gel was performed easily. Protection of the hydroxyl group of (*R*)-**16** furnished PMB (PMB = $CH_2C_6H_4$(OMe)-*p*) ether **17** in 93% yield, which was converted into allylic alcohol **19** by the standard sequence of reactions through aldehyde **18** in good overall yield. A catalytic version of the Sharpless asymmetric epoxidation[8c] of **19** proceeded efficiently to produce epoxide **20** in 92% yield with a 23:1 ratio of **20** (^1H NMR two peaks at 4.42 and 4.46 ppm: doublet, J = 12 Hz) and **24** (two peaks at 4.44 and 4.48 ppm: doublet, J = 12 Hz). Although the mixture (**20** and **24**) was not separated at this stage, transformation of the mixture by the Yadav protocol[10] furnished acetylenic alcohol **22** in 76% yield after chromatography on silica gel without contamination of the diastereomer. Finally, TBS protection of **22** followed by ozonolysis afforded ketone **6** (R^2 = PMB), the C(8)−C(13) intermediate, in good yield.



Synthesis of another key intermediate **3** (R^1 = TES) was accomplished by a sequence delineated in Scheme 4. Kinetic resolution[11] of racemic alcohol *rac*-**26**, derived from aldehyde **25**, by using the Sharpless asymmetric epoxidation[8b,c] with D-(−)-DIPT as a chiral source afforded epoxide **27** and (*S*)-**26** in 46% yield with >99% ee (by the MTPA method) and in 45% yield with >99% ee, respectively. Both products were converted into the target compound **3** (R^1 = TES) by using the literature procedure.[12] Thus, epoxide **27** after separation by chromatography was transformed into iodide **29** through vinyl stannane **28** in 98% yield. On the other hand, four-step conversion of (*S*)-**26** [(1) asymmetric epoxidation with L-(+)-DIPT, (2) Mitsunobu inversion,[13] (3) Bu_3SnLi, (4)

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(13) Mitsunobu, O. *Synthesis* **1981**, 1−28.

iodination] afforded iodide **29** in good yield. Finally, TES protection of iodo alcohol **29** furnished the key intermediate **3** with R^1 = TES.

To combine the above two pieces **3** (R^1 = TES) and **6** (R^2 = PMB) by the chelation-controlled addition, 2 equiv of magnesium anion **4** (R^1 = TES, M = MgBr), generated from **3**, was submitted to reaction with ketone **6** in THF at $-78 \sim -50$ °C (Scheme 5) for 1 h to produce **7** (R^1 = TES, R^2 = PMB) in 91% yield with the ratio of **7** and the C(8) epimer (structure not shown) being > 50:1 by ^{1}H NMR spectroscopy (δ 1.26 and 1.29 ppm, respectively). Additionally, reaction of lithium anion **4** (M = Li, R^1 = TES) and ketone **6** was also examined under the same reaction conditions to afford a mixture of **7** and the C(8) epimer in a 45:55 ratio.

The TES group of **7** was removed with HF and MeOH in 98% yield without concomitant loss of the TBS group at the C(11) oxygen. Regioselective esterification of the resulting diol **31** with CH_2=CHCOCl afforded ester alcohol **32** in 85% yield, and subsequent protection with TESOTf produced the TES ether **33** in good yield. Ring-closing metathesis (RCM)[14] of **33** was accomplished with the Grubbs' 1st-generation catalyst[15] (0.1 equiv) in the presence of Ti(O-*i*-Pr)$_4$ (0.3 equiv) in refluxing CH_2Cl_2 overnight to afford lactone **34** in 83% yield. Without Ti(O-*i*-Pr)$_4$, the RCM was sluggish as stated by Ghosh,[16] producing **34** only in 62% yield with recovery of the starting **33** after 24 h. Iodination of lactone **34** with NIS and $AgNO_3$ proceeded selectively at the terminal position of the acetylene moiety and subsequent removal of PMB on **35** and reduction of **36** with *o*-$(NO_2)C_6H_4SO_2N$=NH[17] furnished the target key intermediate **2** in 60% yield from **34** (3 steps). The ^{1}H and ^{13}C NMR spectra of synthetic **2** were coincident with those kindly provided by the authors of ref 5c.

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Supporting Information Available: Detailed description of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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