Total and Formal Syntheses of Fostriecin

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Total and Formal Syntheses of Fostriecin

Gao Dong, [a, †] Bohui Li [b, †] and George O'Doherty [b,*]

Two formal syntheses and one total synthesis of fostriecin (**1**) have been achieved, as well as, the synthesis of its related congener dihydro-dephospho-fostriecin. All the routes use the Sharpless dihydroxylation to set the absolute stereochemistry at *C*-8/9 positions and a Leighton allylation to set the *C*-5 position of the natural product. In the formal syntheses a Noyori transfer hydrogenation of an ynone was used to set the *C*-11 position while the total synthesis employed a combination of asymmetric dihydroxylation and Pd-π-allyl reduction to set the *C*-11 position. Finally in the total synthesis, a trans-hydroboration of the *C*-12/13 alkyne was used in combination with a Suzuki cross coupling to establish the *Z,Z,E*-triene of fostriecin (**1**).

Introduction

The phosphorylated polyketide natural products, represented by fostriecin (**1**, CI-920),[1] are typified by polyene-, polyol- and pyranone functionalities. Since the isolation of fostriecin (**1**) from *Steptomyces pulveraceus* in 1983, additional members of this unique class of natural products have been discovered. Not surprisingly, this group of natural products has been the subject of significant synthetic efforts. [2] The synthetic studies of fostriecin (**1**) began with a synthesis of the *C*-9 diastereomer by Just, [3] then the full stereochemical assignment (1997) [4] and subsequent total synthesis by Boger.[5] A short time after the Boger synthesis of fostriecin (**1**), a second total synthesis was reported by Jacobsen. [6] In the subsequent years, there have been thirteen additional total or formal syntheses of fostriecin (**1**)[7] and related approaches.[8] The last of these was an effort reported by us in 2010[7l] and then again in 2019 (Scheme 1).[7m]
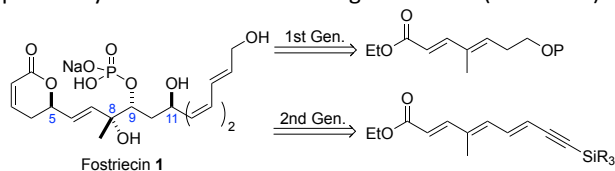

Figure 1 Two generations of synthesizing fostriecin (**1**)

The unique ability of fostriecin (**1**) to inhibit several protein phosphatases (aka, PP1, PP2A and PP4) has also inspired studies of its mechanism-of-action (MOA).[9] Of particular interest is the potency and selectivity of fostriecin's inhibition (*e.g.*, IC$_{50}$ = 45 nM; PP2A, IC$_{50}$ = 1.5 nM; PP4 IC50 = 3.0 nM),[10] and the resulting broad ranging cancer cell cytotoxicity (*e.g.*, leukemia, lung cancer, breast cancer, and ovarian cancer). [11 , 12] In fact, fostriecin (**1**) has been explored as a potential anti-cancer

therapy, having advanced to the clinical trial stage at the National Cancer Institute. [13] Our interest in a synthesis of fostriecin (**1**), as well as, its related congener dihydro-dephospho-fostriecin **2** arose from our general interest in the synthesis of 1,3-polyol and pyranone natural products for stereochemical-structure activity relationship (S-SAR) studies.[14] Herein we disclose the full account of our synthetic efforts which involved two distinct approaches to fostriecin (**1**) and resulted in two formal syntheses and one total synthesis of the natural product.

Results and discussion
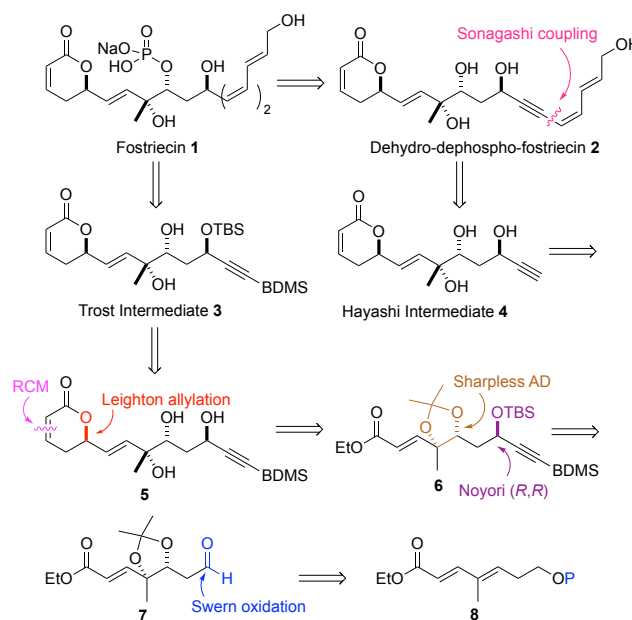
Scheme 1 1st generation retrosynthesis of fostriecin (**1**)

The retrosynthesis for our initial approach to fostriecin (**1**) was based on a desire to access both fostriecin (**1**) and its dehydro-fostriesin congener **2** (Scheme 1).[7m] At the outset, the approach was developed, fully cognizant of the approaches of Trost and Hayashi. More specifically, we envisioned that both target
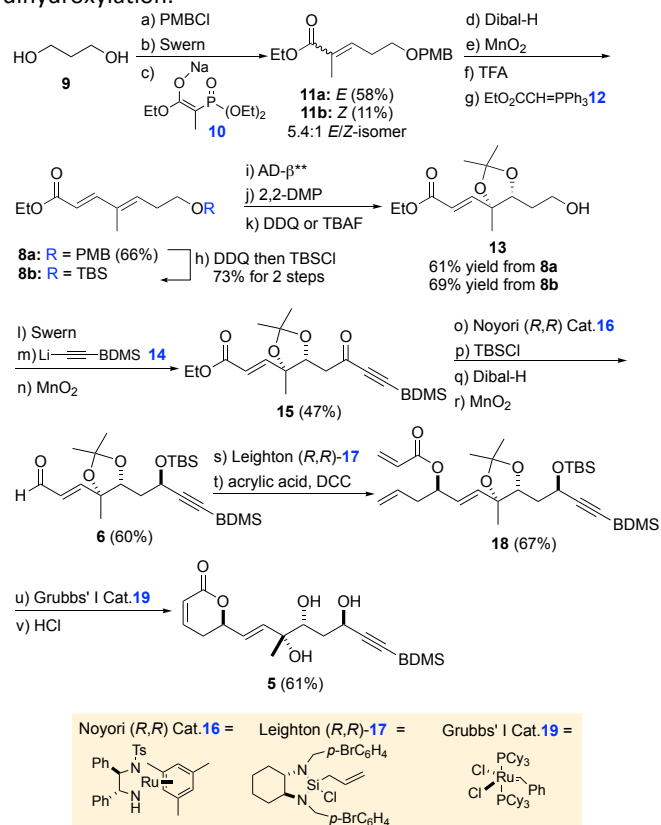
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molecules **1** and **2** could be derived from the Trost fostriecin intermediate **3** with a terminal BDMS-protected alkyne and the Hayashi intermediate **4**, respectively.[7g,i] Both intermediates **3** and **4** could be derived from triol **5**, which could be prepared by pyranone annulation of enone **6** with the requisite *C*-8,9,11-triol stereochemistry installed. We envisioned the *C*-11-propargyl alcohol of **6** being installed by an alkyne addition to aldehyde **7**. Finally, the chirality of **7** could be prepared from a suitably protected achiral enoate **8** by a Sharpless asymmetric dihydroxylation.[15]
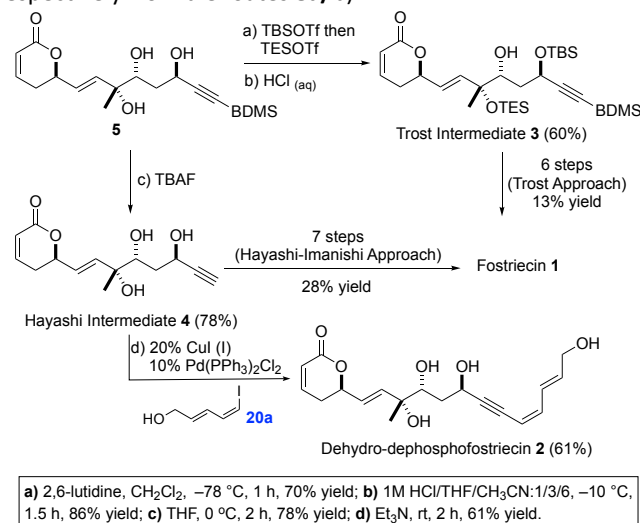

Scheme 2 Synthesis of pyranone **5**

The synthesis of the key triol intermediate **5** commenced with commercially available 1,3-propane diol (**9**) (Scheme 2). Mono-PMB-protection, Swern oxidation and Horner-Wadsworth-Emmons olefination afforded a 5.4:1 *E/Z*-mixture of the PMB-protected enoates **11a/b** in a 58% yield (3 steps).[16,17] A Dibal-H reduction of the mixture of esters **11a/b** followed by MnO$_2$ oxidation yielded a similar *E/Z*-mixture of enals, with the undesired *Z*-isomer being easily isomerized into the *E*-isomer

upon exposure to TFA (80%). Finally, exposure of the diastereomerically pure enal to a olefination the a stabilized Wittig reagent **12** selectively yielded the *E,E*-dienoate **8a** (66 % yield for 4 steps).[18] Because we worried about the oxidative stability of the PMB group to the dihydroxylation condition, we decided to also prepare a TBS-protected version of dienoate **8a** (*i.e.*, **8b**). Thus, the PMB-protecting group was removed (DDQ) and replaced with a TBS-protecting group to give dienoate **8b** in 73% yield for the 2 steps. To our delight, both dienoates **8a** and **8b** reacted cleanly upon being subjected to our typical dienoate variant Sharpless asymmetric dihydroxylation conditions (for **8a**, 1% OsO$_4$, 2% (DHQD)$_2$PHAL for **8b**, 2% OsO$_4$, 4% (DHQD)$_2$PHAL) to regioselectively form diols, which after acetonide formation and TBS-/PMB-deprotection to form primary alcohol **13** in high enantiopurity (98% *ee*)[19] and excellent yield (61% and 69%, respectively from dienoates **8a/b**).

a) 2,6-lutidine, CH$_2$Cl$_2$, –78 °C, 1 h, 70% yield; b) 1M HCl/THF/CH$_3$CN:1/3/6, –10 °C, 1.5 h, 86% yield; c) THF, 0 °C, 2 h, 78% yield; d) Et$_3$N, rt, 2 h, 61% yield.

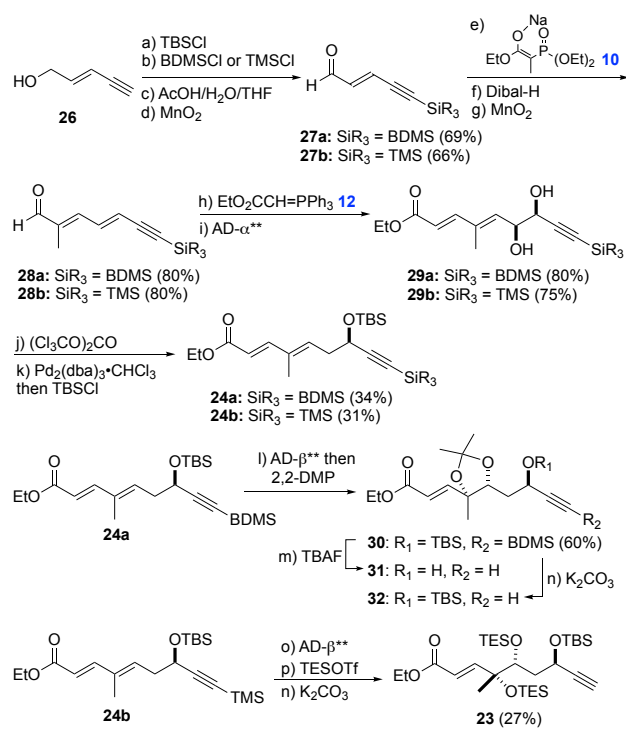**Scheme 3** Two formal syntheses of fostriecin (**1**)

Oxidation of alcohol **13** via a Swern type DMSO oxidation, followed by addition of lithium acetylide **14** (BDMS-acetylene plus *n*-BuLi) to the resulting aldehyde afforded a 1:1 mixture of diastereomeric propargylic alcohols. A MnO$_2$ oxidation of the crude mixture of alcohols gave ynone **15** (47%, 3 steps). The reagent controlled, diastereoselective reduction of ketone **15** was accomplished using the Noyori catalyzed (1% **16**, Et$_3$N•HCO$_2$H) to give a single diastereomeric propargyl alcohol (dr >20:1).[20] A subsequent TBS-protection, ester reduction with Dibal-H and MnO$_2$ oxidation formed aldehyde **6**. A highly diastereoselective allylation of aldehyde **6** was accomplished with the (*R,R*)-Leighton reagent **17** (–10 °C, 2 days) to give a homoallylic alcohol with near perfect stereocontrol (88%).[21,22] A DCC-promoted esterification (4 equiv of acrylic acid, DCC) gave trienyne **18** (78%). Exposure of a refluxing CH$_2$Cl$_2$ solution of the trienyne **18** to the Grubbs I catalyst **19** resulted in a clean cyclization into a pyranone,[23] which after acetonide deprotection gave the desired triol **5** (61%, 2 steps).

a) NaH, THF, TBAI, 0 °C to rt, 8 h, 74% yield; b) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, –78 °C, 2 h, then Et$_3$N, –78 °C to rt, 6 h, 83% yield; c) THF, 0 °C to rt, 3 h, 94% yield (5.4:1 *E/Z*-isomer); d) CH$_2$Cl$_2$, –78 °C to rt, 3 h, 93% yield; e) CH$_2$Cl$_2$, rt, 24 h, 89% yield; f) CH$_2$Cl$_2$ rt, 80% yield; g) THF, rt, 48 h, 99% yield; h) CH$_2$Cl$_2$/H$_2$O: 10/1, rt, 3 h, then imid., DMF, rt, 12 h; i) AD-β** = 1% OsO$_4$, 2% (DHQD)$_2$PHAL, 3 equiv K$_3$Fe(CN)$_6$, 3 equiv K$_2$CO$_3$, 1 equiv MeSO$_2$NH$_2$ in 1:1 *t*-BuOH/H$_2$O, 81% yield for **10a** and AD-β** = 2% OsO$_4$, 4% (DHQD)$_2$PHAL, 3 equiv K$_3$Fe(CN)$_6$, 3 equiv K$_2$CO$_3$, 1equiv MeSO$_2$NH$_2$ in 1:1 *t*-BuOH/H$_2$O, 82% yield for **10b**; j) CSA, acetone, rt, 1 h, 92% yield (for PMB), and 88% yield (for TBS); k) CH$_2$Cl$_2$/H$_2$O: 10/1, rt, 3 h, 82% yield (for PMB); or THF, 0 °C, 2 h. 95% yield (for TBS); l) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, –78 °C, 2 h, then Et$_3$N, –78 °C to rt, 6 h.76% yield; m) THF, –78 °C, 2 h. 82% yield; n) CH$_2$Cl$_2$, rt, 24 h. 76% yield. o) 1 % Noyori (*R,R*) Cat., Et$_3$N, HCOOH, rt, 4 h, 78% yield; p) imid., rt, 3 h, 89% yield; q) CH$_2$Cl$_2$, –78 °C to rt, 3 h, 97% yield; r) CH$_2$Cl$_2$, rt, 24 h, 89% yield; s) –10 °C, 48 h, 88% yield; t) DMAP, rt, 5 h, 78% yield; u) 10% Grubbs' I Cat., reflux 2 h. 87% yield; v) 10% HCl, 65 °C, 0.5 h. 70% yield.

From triol **5** we were able to link it to two formal syntheses offostriecin (Scheme 3). A selective TBS-protection and TES-deprotection was used in a three-step protecting group manipulation strategy to give the Trost intermediate **3**. Thus, exposure of triol **5** to one equiv of TBSOTf and excess 2,6-lutidine selectively protected the *C*-11 propargyl alcohol. Upon disappearance of the starting material, 2 equiv of TESOTf was added to the reaction mixture to form the persilylated material. Selective deprotection of the *C*-9 secondary TES-ether with aqueous HCl afforded the known Trost intermediate **3** (60%, 2 steps), which Trost et al. converted into fostriecin (**1**) in 6 steps with 13% yield.[7g] In an attempt to discover an alternative approach to fostriecin and analogues, we came interested in preparing dihydro-dephospho-fostriecin **2**.[7m,24] This desire led us to the synthesis of the terminal alkyne **4**, an intermediate in Hayashi's fostriecin synthesis that was completed using Imanishi's end game.[7b, 25] Thus, upon treatment of BDMS-protected alkyne **5** with TBAF, the terminal alkyne **4** was prepared in 78% yield. Exposure of alkyne **4** to the Sonogashira cross coupling conditions with 5-iodo-butan-*E*,*Z*-dien-1-ol **20a** afforded a 61% yield of dihydro-dephospho-fostriecin **2**. [26] Unfortunately, all efforts to selectively reduce the alkyne in **2** were unsuccessful (*e.g.*, dissolving metal reductions, Red-Al, etc.). As a result, we turned our attention to an alternative route to fostriecin (**1**).
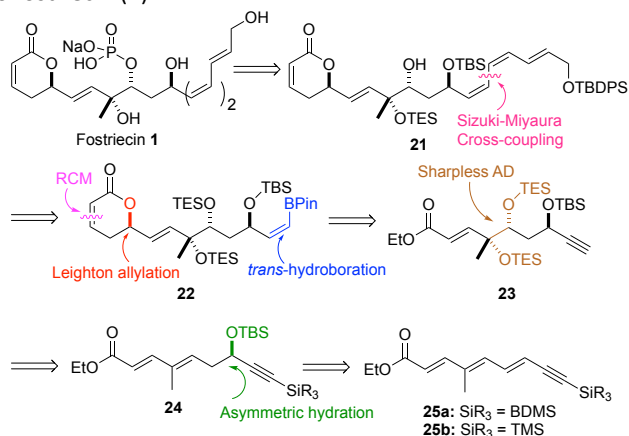
Scheme 4 Our 2nd generation approach to fostriecin (**1**)

Concurrent with the approach outlined above, we explored an alternative route to fostriecin (**1**). Our retrosynthetic analysis for this alternative approach was focused upon our interest in using an iterative asymmetric hydration[27] and dihydroxylation of achiral polyene **25** to address the *C*-8,9,11-triol positions (Scheme 4). Key to the approach is the reliance on the polarizing effect of ester conjugation to control the regioselectivity of two Sharpless dihydroxylation and formic acid reduction of a Pd-π-allyl intermediate (*vide infra*). An additional unique feature to this approach is the use of a *trans*-selective hydroboration/Suzuki cross-coupling reaction to install the *E*,*Z*,*Z*-triene functionality of fostriecine (**1**). As with the previous approach this approach would rely on a Leighton allylation and ring-closing metathesis to install the pyranone ring.


Scheme 5 Synthesis and asymmetric hydration/oxidation of tri-enynoate **24**

The revised approach began with the synthesis of trienynes **25a/b** with a BDMS and TMS-protected alkyne, respectively, from commercially available enynol **26**. A TBS-ether protection of the allylic alcohol was followed by protection of the alkyne as a TMS and BDMS alkyne. An acid catalyzed deprotection of the silyl-ether followed by a MnO$_2$ oxidation of the allylic alcohol to form enals **27a/b** (69%/66%, 4 steps). Exposure of aldehydes **27a** and **27b** separately to the Horner-Wadsworth-Emmons olefination gave respective enoates, which were reduced with two equiv of Dibal-H to form two allylic alcohols. A MnO$_2$ oxidation of the allylic alcohols gave the two enals **28a/b** (80%/80%, 3 steps). Wittig olefinations of **28a/b** with the stabilized Wittig reagent **12** gave enynols **25a/b**, which were then regio- and enantio-selectively dihydroxylated (OsO$_4$/(DHQ)$_2$PHAL) to give diols **29a/b** (80%/75%, from **28a/b**). The allylic alcohols in **29a** and **29b** were selectively reduced over the propargylic by a two-step cyclic carbonate formation and formic acid reduction with catalytic Pd(0)/PPh$_3$ to form two propargyl alcohols, which after TBS-protection formed **24a/b** (34%/31%, 2 steps). At this stage the routes diverged at BDMS-

alkynes **24a** and **24b**. The BDMS-alkyne **24a** was diastereoselectively dihydroxylated (OsO$_4$/(DHQD)$_2$PHAL) to give a crude diol, which was protected as an acetonide **30** (60%). Subsequently, the BDMS group was removed with K$_2$CO$_3$ in methanol to give **32** (85%). In a related sequence, the TMS-protected alkyne **24b** was regioselectively oxidized under the Sharpless conditions gave a diol, which was protected as a bis-TES ether. Finally, the TMS-alkyne was deprotected with K$_2$CO$_3$ in methanol to give **23** (27%, 3 steps).
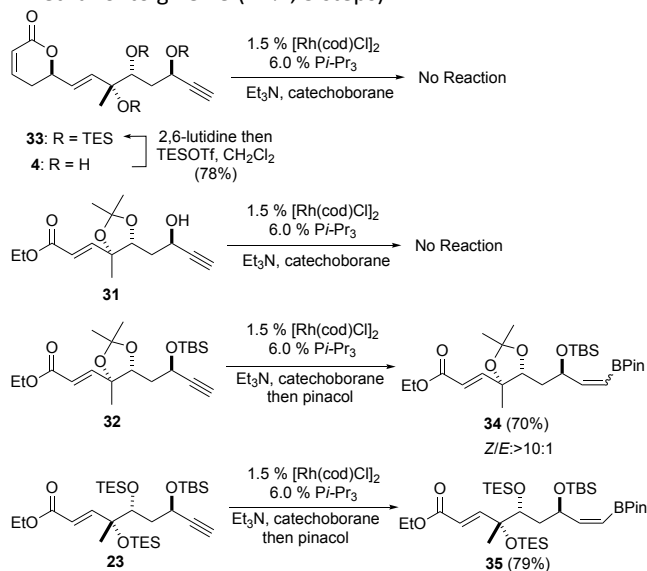
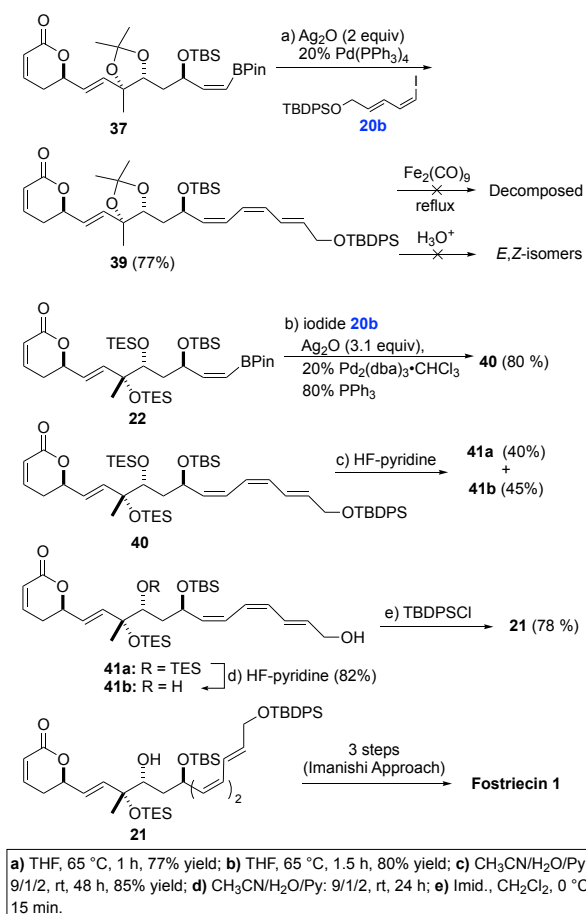**Scheme 6** *Trans*-hydroboration of alkynes **23** and **30**

Having exhaustively explored Sonogashira type approaches, we next decided to investigate the possibility of using Miyaura's Rh-catalyzed *trans*-hydroboration of alkynes[28] for the generation of cross-coupling compatible organometallic species capable of delivering the requisite *Z,Z,E*-triene of fostriecin. Our initial efforts to explore the Miyaura's conditions (catecholborane, 1.5% [Rh(cod)Cl]$_2$, 6.0% P(*i*-Pr)$_3$ then pinacol) for the *trans*-hydroboration of the terminal alkyne with substrates that contained free alcohols or pyranones (*e.g.*, **33**, **4** and **31**) led to less than desirable outcomes. For example, exposure of pyranone containing alkyne **33** to the reaction conditions led to no reaction. Similar negative results were seen when alkyne **31** with a free propargyl alcohol was used. This lack of reactivity was overcome by exploring substrates devoid of free alcohol and pyranone functionalities. For instance, excellent yields of pinacolboranes **34** and **35** were stereoselectivity obtained when terminal alkynes **32** and **23** were exposed to the reaction conditions.
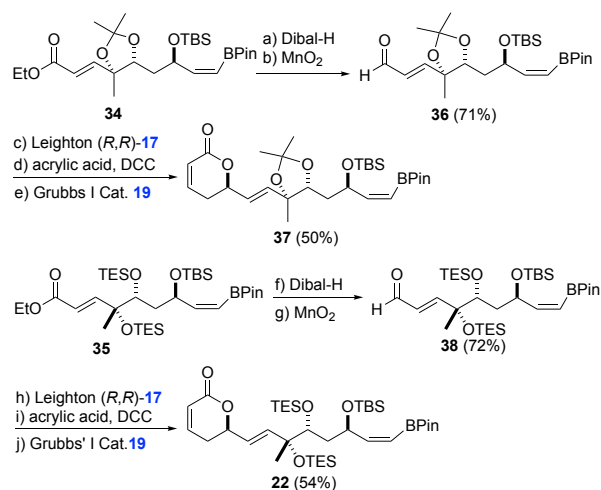
Scheme 7 The installation of the pyranone ring

The pinacol boronate products **34** and **35** were remarkably stable to silica gel chromatography as well as to several reaction conditions. For instance, vinyl borane **34** survived exposure to excess Dibal-H and MnO$_2$ oxidation to give aldehyde **36** (71%, 2 steps). Interestingly the stability of the vinyl borane was stereospecific as only the *Z*-vinyl borane was isolated after the MnO$_2$ oxidation, as the minor *E*-isomer did not survive the reaction conditions. The stability to the vinyl borane unique to a *Z*-isomer was similarly on display as it survived the Leighton allylation of **36** and a subsequent DCC coupling reaction (DCC/acrylic acid) and ring-closing metathesis with the Grubbs I catalyst **29** to give **37** (50%, 3 steps). The *Z*-vinyl borane **35**, with a *C*-8/9 bis-TES ether protection group instead of an acetonide, similarly survived the Dibal-H reduction and allylic alcohol oxidation to form **38** (72%, 2 steps). Once again, the vinyl borane functionality of **38** survived the Leighton allylation, acrylation and ring-closing metathesis to form **22** (53%, 3 steps).[23,29]

a) THF, 65 °C, 1 h, 77% yield; b) THF, 65 °C, 1.5 h, 80% yield; c) CH$_3$CN/H$_2$O/Py: 9/1/2, rt, 48 h, 85% yield; d) CH$_3$CN/H$_2$O/Py: 9/1/2, rt, 24 h; e) Imid., CH$_2$Cl$_2$, 0 °C, 15 min.

Scheme 8 End game of fostriecin (**1**)

We first explored the Suzuki-Miyaura cross coupling *Z*-vinyl borane **37** with *Z*-vinyl iodide **20b**, using Ag$_2$O and Pd(PPh$_3$)$_4$ as a catalyst to form the *E*,*E*,*Z*-triene **39** in good overall yield and triene selectivity.[30] Unfortunately, we were unable to find condition to deprotect the acetonide protecting group without isomerizing the triene. Our efforts to protect the polyene as an Fe(CO)$_3$ complex also led to isomerization. When we turned to cross-coupling of the persilyl protected vinyl borane **22**, we found the Pd(PPh$_3$)$_4$/Ag$_2$O system failed to give any product. Fortunately, excellent yields of cross coupling reactions could be obtained, when we increased the catalyst loading and switched to alternative Pd(0) source while the Pd/PPh$_3$ ratio was maintained at a 1:2 ratio (20% Pd$_2$(dba)$_3$•CHCl$_3$/80% PPh$_3$). Under these optimal conditions the *Z*-vinyl boranate **22** and *Z*-vinyl iodide **20b** coupled to form the *Z*,*Z*,*E*-triene **40** in an 80% yield and with excellent triene *E*/*Z*-stereoselectivity (>20:1).

In triene **40** all the carbon atoms and stereocenters of fostriecin (**1**) have been successfully installed. To complete the synthesis

all that was required was the adjustment of the silyl protecting groups to match the protecting group pattern used by Imanishi (*i.e.*, **21**). The selective deprotection of the *C*-9 TES-silyl ether in **40** to **21** was not straightforward, as it always occurred with concomitant deprotection of the TBDPS group. After considerable experimentation, a practical three step solution was found that began with deprotection of the TBDPS group in **40** with HF•Py to give **41a** along with an equal amount of **41b** with the *C*-9 TES-group already removed. After chromatographic separation, re-exposure of **41a** to HF•Py selectively removed the *C*-9 TES-group to cleanly provide **41b**. A subsequent re-protection of the primary hydroxyl group of **41b** with TBDPSCl/imidazole afforded the desired fostriecin precursor **21**. Finally, carefully following the Imanishi protocol, a three-step sequence converted precursor **21** into fostriecin **1** (~ 0.5 mg) whose ^{1}HNMR, HRMS date matched those of the natural material.

Conclusions

In summary, three distinct enantioselective routes for the synthesis of fostriecin (**1**) have been developed. The two formal syntheses used a combination of Noyori ynone reduction, Sharpless dihydroxylation and a Leighton allylation to install all the stereochemistry required to converge with the syntheses established by Trost and Hiyashi. The formal approach also enabled a route to a dihydro-dephospho-congener **2**. An alternative total synthesis of fostriecin was also described which used a combination of highly regioselective asymmetric dihydroxylations and Pd-π-allyl-mediated reductions of an achiral **25** trieneyne to install the *C*-8,9,11-triol portion of the molecule. Finally, a *trans*-selective hydroboration and cross coupling sequence along with a staged protection/deprotection sequence was used to complete the synthesis.

Notes and references

1   Citations should appear here in the format A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523; A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523.

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