Enantio- and stereoselective route to the phoslactomycin family of antibiotics: formal synthesis of (+)-fostriecin and (+)-phoslactomycin B†

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A general methodology applicable for the synthesis of the phoslactomycin family of antibiotics, potent and selective protein phosphatase inhibitors, has been developed starting from a β-isocupreidine-catalyzed asymmetric Baylis–Hillman reaction of 3-(4-methoxybenzyloxy)propanal with hexafluoroisopropyl acrylate, and thereby formal syntheses of (+)-fostriecin and (+)-phoslactomycin B have been accomplished.

Phoslactomycins A–F and I, produced by the soil bacteria species *Streptomyces*, constitute the phoslactomycin family of antifungal and antitumor antibiotics together with phosphazomycins C1 and C2, leustroducsins A–C and H, PD113,2714 and fostriecin.[1] These compounds are highly potent and selective inhibitors of protein serine/threonine phosphatase 2 A, which is proposed to be responsible for their antitumor activity.[1,2] Due to their intriguing molecular architectures and their potential as lead compounds for anticancer drugs as well as their importance as biological tools, this family of compounds has attracted much attention in the chemical and biological communities. Thus, there have been a number of synthetic studies including formal and total syntheses of phoslactomycin A[3] and B,[4] leustroducsin B,[5] fostriecin,[6,7] and PD113,271 (Fig. 1).[8] However, in spite of similarities, previously reported synthetic methods are not of general utility to prepare the entire members of this family. Herein, we report the formal asymmetric syntheses of (+)-fostriecin (**1**) and (+)-phoslactomycin B (**2**) from a common precursor, demonstrating a general approach to the phoslactomycin family for the first time.

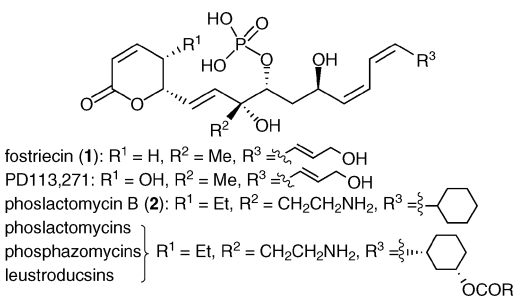

Fig. 1

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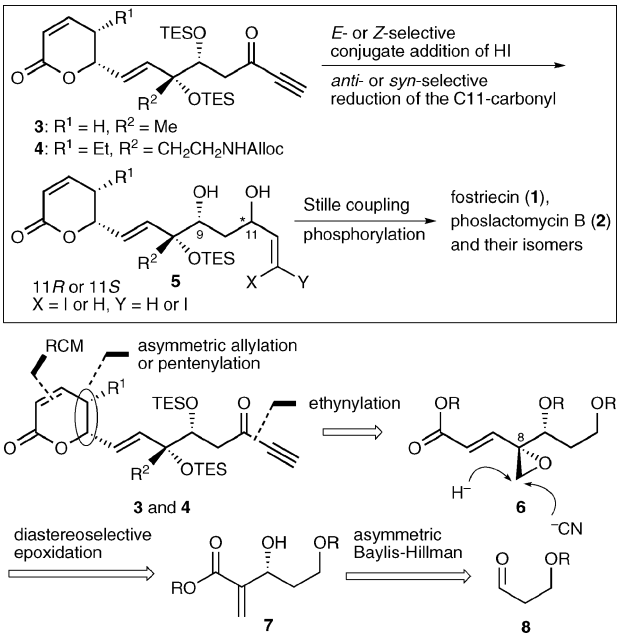
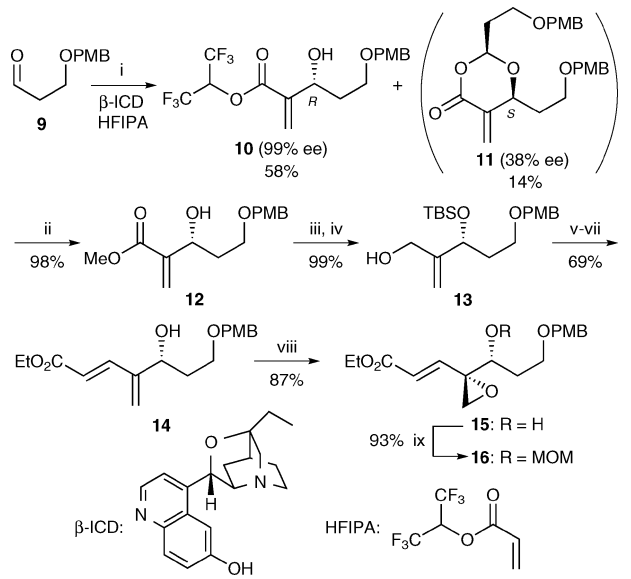
† Electronic supplementary information (ESI) available: Experimental details and spectral data (^{1}H and ^{13}C NMR, IR, HRMS, $[\alpha]_D$). See DOI: 10.1039/b912267b



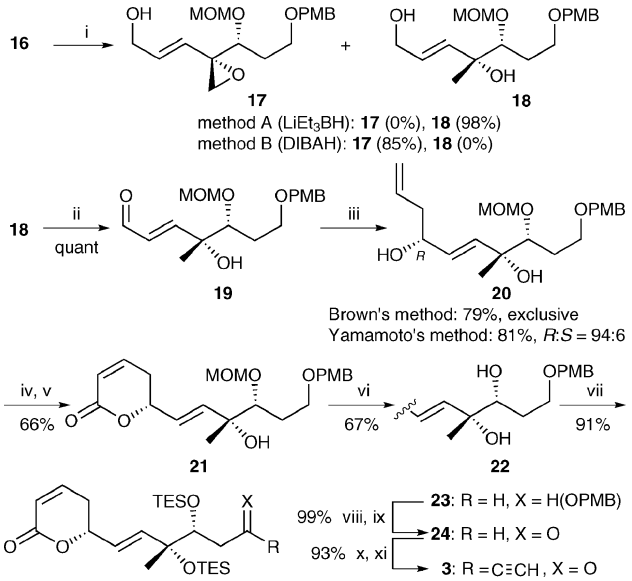
Scheme 1

Recently we have demonstrated[4c,9] that ynones **3** and **4** effectively served as pivotal intermediates for the synthesis of **1** and **2** as well as their various isomers *via* *Z*- or *E*-selective conjugate addition of hydroiodic acid, C9-hydroxy directed *anti*- or *syn*-selective reduction of the C11-carbonyl group, Stille coupling and phosphorylation as major transformations (Scheme 1). From the retrosynthetic perspective based on the methodology we have previously established,[4c,9] we envisioned epoxide **6** as a common precursor of **3** and **4** by the disconnection *via* ethynylation, ring closing metathesis, and asymmetric allylation or pentenylation. We expected that either the methyl group or the aminoethyl group on the C8-quaternary center could be installed *via* nucleophilic opening of the epoxide with a hydride or cyanide ion. To access **6** we envisaged the approach from aldehyde **8** involving an asymmetric Baylis–Hillman (BH) reaction[10] giving **7** and diastereoselective epoxidation. We came up with this strategy because we have developed a highly enantioselective asymmetric BH reaction of an aldehyde using β-isocupreidine (β-ICD) as a catalyst and hexafluoroisopropyl acrylate (HFIPA) as an activated ester (β-ICD–HFIPA method).[11]

Our synthesis thus began with application of the β-ICD–HFIPA method to aldehyde **9**[4c] (Scheme 2). When **9**



Scheme 2 *Reagents and conditions*. (i) β-ICD (0.1 equiv.), HFIPA (1.3 equiv.), DMF, −55 °C; (ii) Et_3N, MeOH, 0 °C to rt; (iii) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, −78 °C; (iv) DIBAH, CH_2Cl_2, −78 °C; (v) Dess–Martin periodinane, CH_2Cl_2; (vi) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 to 0 °C; (vii) *n*-Bu_4NF, THF; (viii) $VO(acac)_2$ (0.2 equiv.), *t*-BuOOH, CH_2Cl_2, −20 °C to rt; (ix) $MeOCH_2Cl$, *i*-Pr_2EtN, CH_2Cl_2, 45 °C.

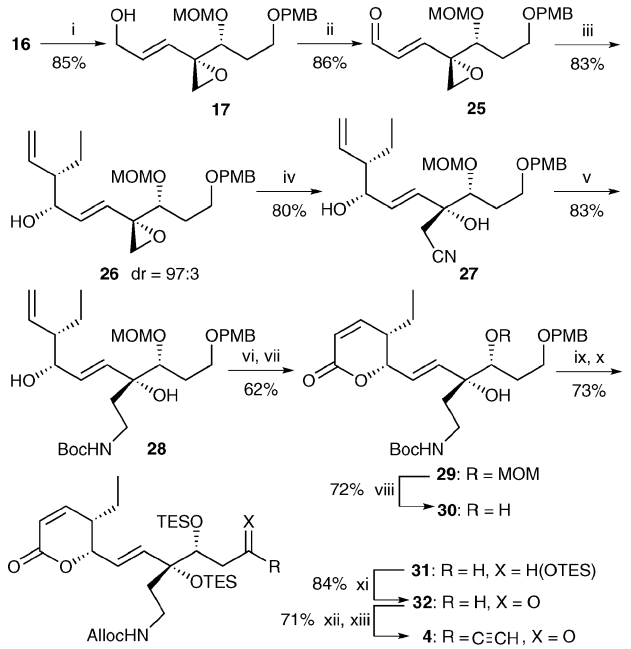


Scheme 3 *Reagents and conditions*. (i) Method A: $LiEt_3BH$, THF, −78 to 0 °C, method B: DIBAH, THF, −78 °C; (ii) Dess–Martin periodinane, CH_2Cl_2; (iii) Brown and co-worker's method: (+)-Ipc_2BOMe, $CH_2{=}CHCH_2MgBr$, THF-Et_2O, −78 °C to rt, then 30% H_2O_2, 3 M NaOH, THF, Yamamoto and co-worker's method: $(MeO)_3SiCH_2CH{=}CH_2$, (*R*)-*p*-tol-BINAP (0.2 equiv.), AgF (0.2 equiv.), MeOH, −20 °C; (iv) $ClCOCH_2CH{=}CH_2$, *i*-Pr_2EtN, CH_2Cl_2, 0 °C; (v) Grubbs' 2nd (0.1 equiv.), CH_2Cl_2, reflux; (vi) $ZrCl_4$ (0.8 equiv.), *i*-PrOH; (vii) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (viii) DDQ, CH_2Cl_2, 0 °C; (ix) Dess–Martin periodinane, CH_2Cl_2; (x) HCCMgBr, $CeCl_3$, THF, −50 °C; (xi) Dess–Martin periodinane, CH_2Cl_2.

was reacted with 1.3 equiv. of HFIPA in the presence of 0.1 equiv. of β-ICD in DMF at −55 °C, **10** was obtained in excellent enantiomeric purity‡ (99% ee) in 58% yield together with **11** (38% ee, 14% yield). It is important to note that this reaction can be easily carried out on a multi-gram scale. After methanolysis of **10**, methyl ester **12** was then converted to **14** in 68% overall yield by a five-step sequence involving silylation, DIBAH reduction, Dess–Martin oxidation, Horner–Emmons reaction and desilylation. Gratifyingly, vanadium-catalyzed epoxidation[12] of **14** turned out to proceed with complete diastereoselectivity to furnish **15** in excellent yield. The hydroxy group of **15** was then protected as its methoxymethyl ether to give **16**.

Having prepared our envisaged key intermediate **6** as **16** in enantiomerically pure form, we then investigated the synthesis of ynone **3**, a precursor of fostriecin (**1**). The crucial reductive opening of the epoxide of **16** was examined using $LiEt_3BH$, DIBAH and $LiAlH_4$ under various conditions (Scheme 3).§ It was found that $LiEt_3BH$ was the reducing agent of choice and the desired **18** was obtained almost quantitatively. Interestingly, reaction of **16** with DIBAH at −78 °C allowed the selective reduction of the ester group without affecting the epoxy group to give **17** in 85% yield. The $LiAlH_4$ reduction gave a complex mixture including **17** and **18**. After Dess–Martin oxidation of **18**, using Brown and co-workers' asymmetric allylation[13] on **19** afforded **20** as a single diastereomer in good yield. Alternatively, using Yamamoto and co-workers' asymmetric allylation[14] on **19** turned out to proceed with high diastereoselectivity (dr = 94 : 6) to give **20** again in good yield. It should be noted that, compared with the former, the latter allylation was more beneficial for large scale production of **20** due to the ease of purification in spite of its lower diastereoselectivity. Acryloylation of **20** followed by ring closing metathesis[15] of the resulting acrylate using Grubbs' second generation catalyst led to the clean formation of **21**. However, in the next deprotection of the methoxymethyl group, we unexpectedly met with difficulty under standard acidic conditions. After exploring various conditions, we eventually found that $ZrCl_4$-promoted alcoholysis[16] was effective in this particular case to give **22** in an acceptable yield. Upon silylation, oxidative removal of the *p*-methoxybenzyl group and Dess–Martin oxidation, **22** afforded **24** in good overall yield. Finally, addition of acetylene followed by Dess–Martin oxidation converted **24** to ynone **3** almost quantitatively, the synthesis of which constitutes a formal synthesis of (+)-fostriecin (**1**).[9]

Next, we investigated the synthesis of ynone **4**, a precursor of phoslactomycin B (**2**) from the above-mentioned intermediate **16**. Since the first attempt to open the epoxide with cyanide ion under various conditions gave us disappointing results because of the high reactivity of the ester group, we decided to implement asymmetric pentenylation before cyanation (Scheme 4). Thus, by taking advantage of the method described above, **16** was chemoselectively reduced with DIBAH to **17** which, upon Dess–Martin oxidation, gave **25**. According to the procedure we have previously developed,[4c] **25** was then subjected to asymmetric pentenylation using the reagent prepared from (*Z*)-2-pentenylpotassium and (+)-$(Ipc)_2BOMe$ to give *syn*-isomer **26** in excellent diastereoselectivity (dr = 97 : 3) in 83% yield. In this particular case, silver-catalyzed pentenylation of **25** using trimethoxy((*Z*)-pent-2-enyl)silane under Yamamoto and co-worker's asymmetric allylation conditions[14a] did not proceed at all.



Scheme 4 *Reagents and conditions.* (i) DIBAH, THF, −78 °C; (ii) Dess–Martin periodinane, CH_2Cl_2; (iii) (*Z*)-2-pentene, *t*-BuOK, *n*-BuLi, THF, −78 °C, then (+)-$(Ipc)_2BOMe$, $BF_3{\cdot}Et_2O$, THF–Et_2O, −78 to −50 °C, then 1 M NaOH; (iv) LiCN·acetone, THF, reflux; (v) $LiAlH_4$, Et_2O, then Boc_2O, $NaHCO_3$, H_2O–MeOH; (vi) $ClCOCH_2CH{=}CH_2$, *i*-Pr_2EtN, CH_2Cl_2, 0 °C; (vii) Grubbs' 2nd (0.1 equiv.), CH_2Cl_2, reflux; (viii) $ZrCl_4$ (0.8 equiv.), *i*-PrOH, 50 °C; (ix) 5 M HCl, THF, then $CH_2{=}CHCH_2OCOCl$, $NaHCO_3$; (x) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (xi) $(COCl)_2$, DMSO, CH_2Cl_2, −78 to −40 °C then Et_3N, 0 °C; (xii) HCCMgBr, $CeCl_3$, THF, −50 °C; (xiii) Dess–Martin periodinane, CH_2Cl_2.

The crucial nucleophilic opening of the epoxide turned out to be low yielding under the common conditions using KCN, Et_2AlCN and TMSCN. However, we were pleased to find that LiCN·acetone complex promoted this reaction effectively. Thus, according to the procedure developed by Ciaccio *et al.*,[17] **26** was reacted with LiCN·acetone complex at 40 °C in THF to afford **27** in good yield. Reduction of **27** with $LiAlH_4$ followed by *tert*-butoxycarbonylation gave **28**. Upon acryloylation followed by ring closing metathesis using Grubbs' second generation catalyst, **28** gave **29** in almost the same yield as that of **21**, indicating that the *N*-Boc-aminoethyl group did not hamper the ring closing metathesis.

In the same manner as described above for the synthesis of **3**, ynone **4** was successfully synthesized from **29**. Thus, $ZrCl_4$-promoted deprotection of the methoxymethyl group of **29** again afforded **30** cleanly, which, upon successive acidic hydrolysis, allyloxycarbonylation and silylation, gave **31** in good yield. Exposure of **31** to Swern oxidation conditions[18] allowed the direct production of **32** *via* selective cleavage of the primary triethylsilyl ether group. Finally, addition of acetylene followed by Dess–Martin oxidation converted **32** to ynone **4**. At this stage, a formal synthesis of (+)-phoslactomycin B (**2**)[4c] was also accomplished.

In conclusion, we have achieved the formal asymmetric synthesis of **1** and **2** from the common intermediate **16**. This represents a significant improvement of our previous synthesis in the selectivity issues. The present work illustrates a new methodology of general value for the synthesis of the entire members of the phoslactomycin family. In addition, this work exemplifies the synthetic utility of our β-ICD–HFIPA method.

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Notes and references

‡ The absolute configuration and the enantiomeric purity of **10** and **11** were determined by chiral HPLC analysis and ^1H NMR analysis of the *R*- and *S*-Mosher's esters after converting them to methyl ester **12**, respectively.

§ Reductive opening of the epoxide of **15** failed under various conditions and always gave a complex mixture.

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