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Dinuclear Asymmetric Zn Aldol Additions: Formal Asymmetric Synthesis of Fostriecin

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Direct asymmetric aldol reactions constitute a powerful methodology for the synthesis of biologically active compounds. With the use of our dinuclear asymmetric zinc complexes we recently demonstrated the feasibility of using alkynyl methyl ketones as donors.[1] One of the advantages of using terminal benzyldimethylsilyl alkynes as donors in this reaction is the potential for employing the resultant adducts directly in subsequent cross-coupling reactions.[2] The strategic potential offered by these reactions led us to target fostriecin (CI-920, **1**), a cytotoxic phosphate ester isolated from *Streptomyces pulveraceus*.[3] The natural product displays potent anticancer activity against leukemia and many other cell lines.[4] The cytotoxic properties of **1** are attributed to its selective inhibition of protein phosphatase 2A (PP2A).[5] The absolute and relative stereochemistry of **1** was established by Boger,[6] who also disclosed the first total synthesis of the natural product[7] as well as preliminary SAR studies of this molecule.[8] Several total syntheses have been published,[9] as well as a number of synthetic approaches.[10] Herein we report our efforts in this area, which culminated in a short and efficient synthesis of dephospho-fostriecin **2**.

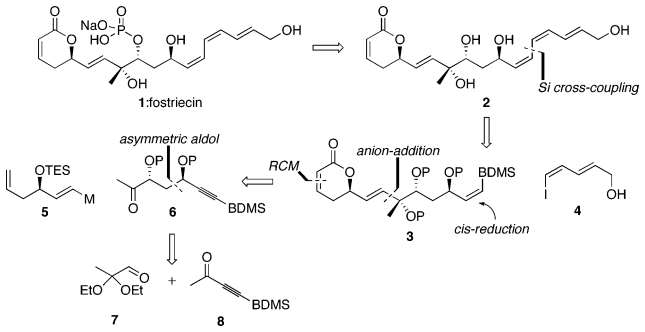
As shown in Scheme 1, we targeted the tetraol **2**, a key intermediate in Boger's synthesis.[7] We envisioned that **2** could be disconnected between C13 and C14 to give silane **3** and iodide **4**. In the synthetic direction, an alkenylsilane cross-coupling reaction would be employed to forge the labile triene unit.[2,11] Further disconnection at the C7−C8 bond gives a vinyl metal species **5** and ketone **6**. Finally, ketone **6** would be derived from the aldehyde **7** and ynone **8**, utilizing the direct Zn-catalyzed asymmetric aldol reaction developed in this group.[1]

Our synthesis commenced with the preparation of the metalation precursor of **5**. Thus, ethyl propiolate was converted to the *β*-*E*-iodoacrolein **10** according to literature procedures (Scheme 2).[12] The labile aldehyde **10** was allylated according to Brown's procedure,[13] giving the allylic alcohol in high yield and ee (81% and 95%, respectively). Finally, silylation under standard conditions afforded the target vinyl iodide **11**.

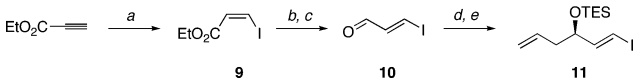
With an efficient route to **11** in hand, attention shifted to the preparation of the C8−C13 portion of fostriecin (**1**) (Scheme 3).

Here we wished to establish the C9 stereochemistry by enantioselective direct aldol reaction as reported recently.[1] Thus, the requisite alkynyl ketone **8** was prepared by the addition of ethynylmagnesium bromide to benzyldimethylchlorosilane (BDMSCl) followed by deprotonation and subsequent acylation. Ketone **12** was treated with aldehyde **7** under our standard Zn-catalyzed direct aldol reaction (3 mol % **13**, 6 mol % Et_2Zn), affording the aldol adduct **14** in an excellent ee (99%). It is worth noting that this reaction could routinely be performed on 50 mmol scale with no deterioration in yield or ee. Use of 5 mol % catalyst bumped the yield to 73%. Next, a diasteroselective reduction was envisaged. Unfortunately, various substrate-controlled methods failed to deliver the desired *anti*-diol in useful yield. Reduction under Noyori's Ru-catalyzed transfer hydrogenation conditions[14] (cf. **15**) gave the desired alcohol **16** in high yield and selectivity. Selective silylation and hydrolysis of the ketal furnished ketone **17**, which was protected as the DMBO-acetal[15] **18** in high yield with no detectable epimerization at the α-stereocenter. Thus, the stage was set for the introduction of vinyl metal species **5**. A chelation-controlled addition

Scheme 1. Retrosynthetic Analysis

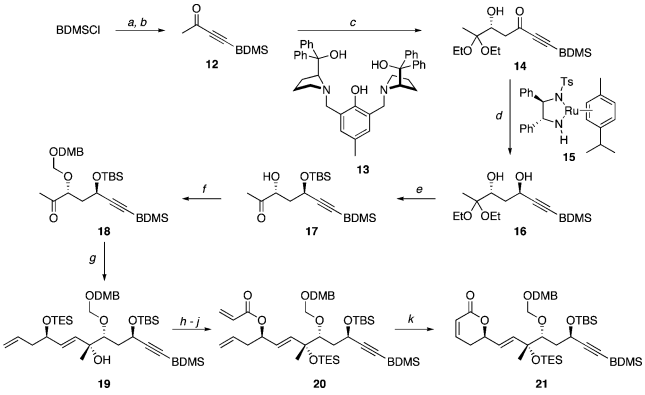


Scheme 2. Synthesis of Vinyl Iodide 11[a]



[a] Reagents and conditions: (a) NaI, AcOH, 70 °C, (77%); (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, (95:5 *E*:*Z*); (d) (+)-Ipc_2BOMe, allylmagnesium chloride, Et_2O, −90 °C, (49% over 3 steps, 95% ee); (e) TESCl, imidazole, DMF, (95%).

Scheme 3. Synthesis of Alkynyl Silane[a]



[a] Reagents and conditions: (a) ethynylmagnesium bromide, THF, 0 °C (99%); (b) *n*BuLi, MeCON(Me)OMe, THF, −78 to −15 °C (90%); (c) **13** (3 mol %), Et_2Zn (6 mol %), 4 Å MS, **7**, rt (58−67%, 99% ee); (d) **15** (1 mol %), *i*PrOH, rt (88%, >10:1 dr); (e) TBSCl, Im, DMF, then CSA, Me_2CO (77% 2 steps); (f) $DMBOCH_2Cl$, TBAI (14 mol %), DIEA, DMF, 40 °C (97%); (g) $MgBr_2$, THF, rt, then **11**, *i*PrMgCl, *s*BuLi, THF, −78 °C (75%, >20:1 dr); (h) HF, MeOH, MeCN, rt (91%); (i) acryloyl chloride, DIEA, CH_2Cl_2 (99%); (j) TESOTf, DIEA, CH_2Cl_2 (99%); (k) Grubbs 1 (10 mol %), CH_2Cl_2, reflux (93%).

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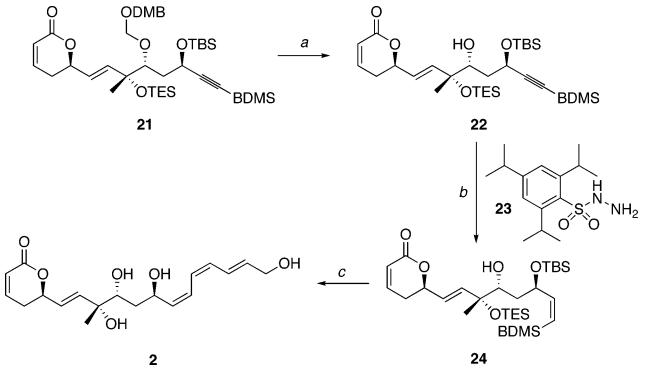
Scheme 4. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) DDQ, CH_2Cl_2:H_2O (10:1) (94%); (b) **23**, $NaHCO_3$, MeOH, rt (53%, 72% brsm); (c) **4**, $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), TBAF (4 equiv slow addition), THF, 0 °C to room temperature (54%).

of the corresponding magnesiate species[16] of **11** afforded **19** as a single diastereomer in very good yield (75%). The unsaturated lactone moiety was installed by selective removal of the allylic TES-group, followed by acylation with acrolyl chloride giving **20**, which was subsequently exposed to Grubbs first-generation catalyst, yielding key intermediate **21** (83% over three steps).

With an ample supply of **21** in hand, the stage was set for examination of the final steps toward the target, fostriecin precursor, tetraol **2**. Thus, the acetal protecting group was removed by the addition of DDQ, providing alkyne **22** in 94% yield (Scheme 4).

A *cis* reduction was required to install the vinyl silane. Attempts to effect this transformation were hampered by either poor yield and/or over-reduction. Eventually, using diimide precursor **23**[17] under mildly basic conditions afforded the *cis*-vinyl silane **24**. Finally the assembly of the triene unit called upon a Pd-catalyzed vinyl silane cross-coupling reaction. The susceptibility of the unsaturated lactone toward base complicated this cross-coupling. After much experimentation, it was found that the sensitive triene functionality could be assembled by adding TBAF slowly to a combination of vinyl silane **24**, vinyl iodide **4**,[18] and catalytic amounts of $Pd_2(dba)_3$·$CHCl_3$ in THF. As expected, the cross-coupling also led to concomitant deprotection of the silicon protecting groups, giving the dephosphofostriecin **2** in good yield. The conversion of **2** to fostriecin (**1**) has been demonstrated by Boger.[7]

In conclusion, we have completed the synthesis of dephosphofostriecin **2**, and thereby a formal synthesis of fostriecin **1**, in 14 steps for the longest linear sequence and 8.5% overall yield. This work illustrates for the first time the use of the direct asymmetric Zn-catalyzed aldol reaction, and the utility of the corresponding aldol adducts as building blocks for complex molecule synthesis. It also exemplifies the extraordinary utility of the Pd-catalyzed vinyl silane cross-coupling as an alternative to more mainstream Pd-catalyzed cross-coupling reactions, in the synthesis of complex molecules.

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Supporting Information Available: Experimental details and characterization for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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(18) Vinyl iodide **4** was prepared from ester **9**, via DIBAL-H reduction, Horner−Wadsworth−Emmons reaction and subsequent DIBAL-H reduction, which afforded **4** in 33% overall yield, see Supporting Information for more details.

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