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1,4-Induction in aldol reactions of (tertiary α′-alkoxy)methyl ketones: synthesis of the C_8–C_{11} stereotriad of *ent*-fostriecin

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ABSTRACT

A diastereoselective, boron-mediated aldol process inspired by the natural product fostriecin is described. Using a tertiary α′-stereocenter as the induction element, aldol adducts are provided with high yields, good to excellent levels of diastereoselection, and broad substrate scope. An Evans–Tischencko reduction of the aldol adduct from cinnamaldehyde resulted in the C_8–C_{11} stereotriad of *ent*-fostriecin.

Introduction

Isolated in 1983 from *Streptomyces pulveraceus* by scientists at Warner–Lambert/Parke–Davis,[1] fostriecin (**1**, Fig. 1) has attracted considerable attention from the medical community due to its broad in vitro and in vivo antitumor activities.[2] The accepted mechanism of action of this interesting natural product is linked to potent and selective inhibition of protein serine/threonine phosphatases PP2A and PP4, with the C_9 phosphate acting as an important recognition element.[3]

Although the planar structure was determined in the context of the original isolation, it was not until 1997 that Boger and coworkers determined the relative and absolute stereochemistry of the natural product via degradation studies,[4] and then completed the first total synthesis five years later.[5] Over the course of the last decade, numerous total syntheses[6,7] and synthetic studies[8,9] have appeared in the chemical literature.

The aldol reaction, while a powerful synthetic tool for the construction of polyketide stereoarrays, is under-represented in the fostriecin prior art. The only examples, in the Trost[7h] and Shibasaki[7g] syntheses, involve chiral catalyst or stoichiometric modifier control to construct the C_9–C_{10} bond and set the C_9 stereochemistry. We were interested in investigating a fundamentally different approach (Fig. 1): the C_{10}–C_{11} is targeted and the C_{11} stereochemistry is controlled by induction from the α′-tertiary alkoxy stereocenter of the methyl ketone reaction partner.

Discussion

Prior to this work, the only (α′-tertiary alkoxy) methyl ketone substrate which had demonstrated the ability to control the stereochemical course of an aldol process involved a sterically-encumbered and conformationally rigid camphor-based auxiliary.[10] Nonetheless, we found inspiration for our planned disconnection through the combination of two loosely related aldol processes (Fig. 2). Urpi has previously shown that secondary α′-alkoxy groups provide good to excellent levels of 1,4-induction in titanium aldol reactions (Eq. 1).[11] Carda and Marco have shown that the α′-alkoxy protecting group can lead to reversal of stereoinduction in a poly-oxygenated enolate (Eq. 2).[12] Combining elements of these two studies, we hoped that a ketone possessing an α′-tertiary alkoxy group and β′-oxygenation would be successful in controlling the stereochemical course of our desired process

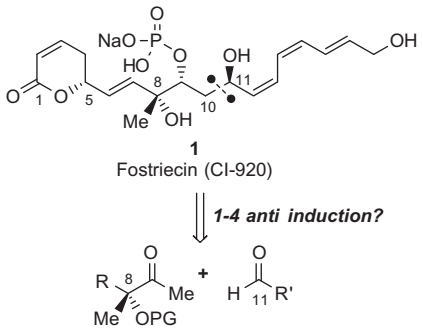

Figure 1. The structure of fostriecin and the planned bond disconnection.

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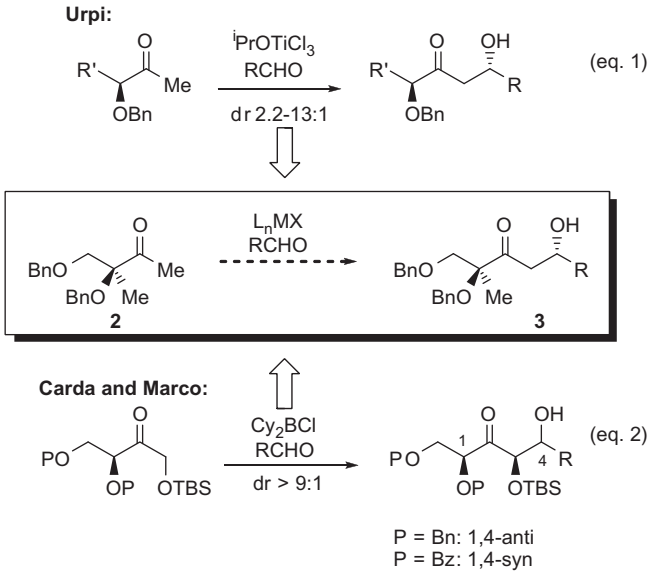


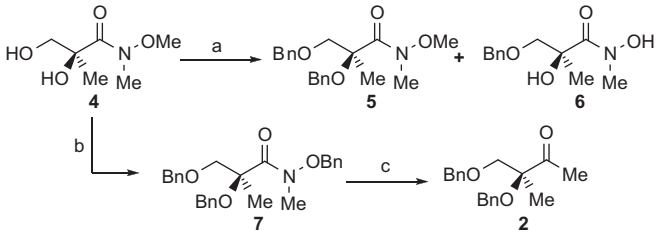
Figure 2. Merger of Urpi and Carda/Marco strategies.

through judicious selection of protecting groups and enolization conditions. To this end, we targeted ketone **2** for the first iteration of aldol studies.

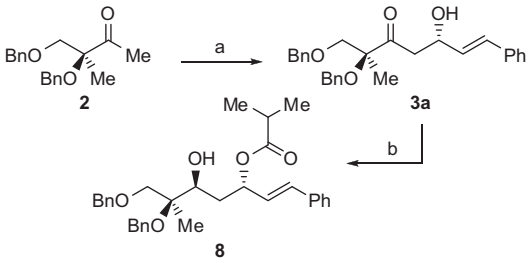
Due to the commercial availability of only one enantiomer of Weinreb amide **4** (Scheme 1), we chose to target the antipode of the fostriecin stereotriad.[13] Despite the availability of this advanced intermediate, however, synthesis of ketone **2** was not straightforward. Treatment of **4** with sodium hydride and benzyl bromide provided low and variable levels of the desired dibenzyl ether **5**.[14] Careful analysis of the reaction mixture from these conditions revealed the formation of a significant quantity of demethylation product **6**. This observation allowed us to find an acceptable solution: subjection of **4** to forcing benzylation conditions provided tribenzyl derivative **7**. Treatment of **7** with methyl lithium provided desired ketone **2**, demonstrating that the *O*-benzyl Weinreb analog is an acceptable surrogate for the traditional *N,O*-dimethyl variant.

With a scalable synthesis of ketone **2** in place, we were prepared to test the key aldol process (Scheme 2). *Trans*-cinnamaldehyde was selected as the initial reaction partner in order to provide a potential synthetic handle for future modifications. To our delight, enolization of ketone **2** with dicyclohexylboron chloride, followed by addition of the aldehyde coupling partner, provided a quantitative yield of the aldol adduct **3a** as a 7.4:1 mixture of diastereomers. By contrast, lithium enolate conditions resulted in an unselective aldol process.[15]

Stereochemical determination through Mosher ester formation was not possible at this stage due to concomitant elimination of the activated β-acyloxy group. As an alternative, formation of the final stereocenter of the triad was first accomplished via an Evans–Tischencko reduction[16] to alcohol **8**. This operation, which



Scheme 1. Reagents and conditions: (a) 2.2 equiv NaH, 2.2 equiv BnBr, 0.2 equiv TBAI, DMF, 0–15% **5**; (b) 5 equiv NaH, 4 equiv BnBr, 2 equiv 15-crown-5, 0.2 equiv KI, THF, 75%; (c) MeLi, Et_2O, 58% (84% br s m).



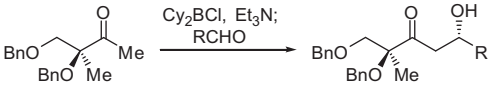
Scheme 2. Reagents and conditions: (a) 1.8 equiv Cy_2BCl, 2.0 equiv Et_3N, Et_2O, 0 °C then cinnamaldehyde, 7.8:1 dr, 99%; (b) 5 equiv ^{i}PrCHO, 0.15 equiv SmI_2, THF, −10 °C, >20:1 dr, 87%.

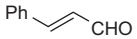
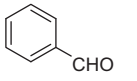
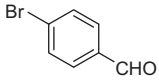
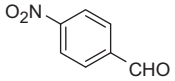
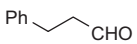
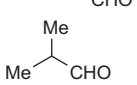
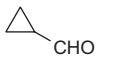
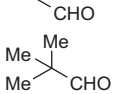
results in a 1,3-*anti*-hydroxy relationship, provides the added benefit of leaving the directing hydroxyl protected as an ester while leaving the newly formed center unprotected. Mosher ester formation on this hydroxyl allowed establishment of the overall stereochemistry, which proved to be the desired 1,2-*syn*/1,4-*anti* relationship present in fostriecin.[17]

With a synthesis of the fostriecin stereotriad completed, we were interested to investigate the substrate scope of the aldol process. As Table 1 shows, synthetically useful yields and levels of diastereoselection can also be achieved with aryl (entries **b**–**d**) and alkyl aldehydes (entries **e**–**h**). In general, diastereoselectivity is marginally improved for electron poor aromatics, and selectivity improves slightly as steric hindrance increases in the alkyl series.

To explain the sense of induction observed, we examined the Zimmerman–Traxler transition states[18] possible for the two potential aldol adducts. Houk has determined computationally that twist-boat cyclic transition states are preferred for unsubstituted boron enolates, contrary to the chair transition state commonly accepted for ethyl ketone enolates.[19] Four possible transition structures, two for each diastereomeric product, are provided in

Table 1
Substrate scope for the diastereoselective aldol process



Entry	Aldehyde	Diastereoselection[a]	Isolated yield[b]
a		7.4:1	>95%
b		5.8:1	>95%
c		8.2:1	>95%
d		8.4:1	73%
e		5.7:1	84%
f		6.2:1	86%
g		6.6:1	92%
h		6.4:1	>95%

[a] Determined by integration of the methyl singlet from a 500 MHz ^{1}H NMR spectrum (see Supplementary data for further details).
[b] Yield of the purified mixture of diastereomers.

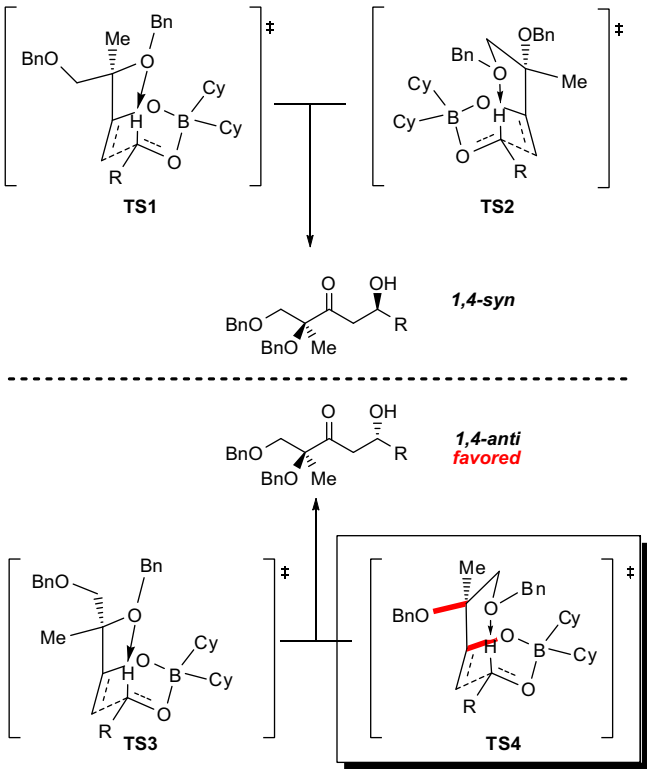


Figure 3. Transition structures explaining the observed sense of induction.

Figure 3. Only one of these structures (TS4) has the possibility to combine three stabilizing features: orientation of the methyl stereocenter away from the reacting center, minimization of the dipole moment of the α′-alkoxy and enolate oxygens (red bonds in TS4), and formation of a stabilizing formyl hydrogen bond with the β′-alkoxy group as the acceptor.[20]

In conclusion, a general diastereoselective aldol process has been developed, using a tertiary α′-alkoxy group as the stereochemical control element. This process has been applied to the synthesis of the C_8–C_{11} stereotriad of *ent*-fostriecin. Future work will involve modification of the protecting group scheme to validate the proposed transition state model, and to explore if the sense of induction can be reversed.

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Supplementary data

Supplementary data (general reaction conditions for the diastereoselective aldol process are provided, as well as details of the stereochemical analysis of **8** and images of ^{1}H NMR for the methyl singlet used in determination of diastereoselectivity for examples in Table 1) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.130.

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