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Synthesis of Homoallylic Chiral Tertiary Alcohols via Chelation-Controlled Diastereoselective Nucleophilic Addition on α-Alkoxyketones: Application for the Synthesis of the C_1–C_{11} Subunit of 8-*epi*-Fostriecin

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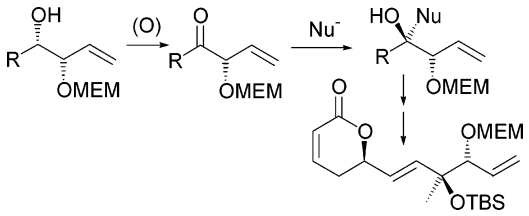
ABSTRACT



Chiral *β-syn*-alkoxyhomoallylic alcohols derived from alkoxyallylboration of aldehydes upon oxidation provided the corresponding chiral ketones. Chelation-controlled nucleophilic addition to these ketones occurred in a highly stereoselective manner to afford *anti*-homoallylic tertiary alcohols. This methodology has been applied for the synthesis of the C_1–C_{11} subunit of C_8-*epi*-fostriecin.

Homoallylic alcohols are extremely versatile synthetic intermediates that have been extensively utilized for the stereoselective synthesis of complex natural products.[1] Due to their importance, there have been several methods reported in the literature for the stereoselective synthesis of homoallylic alcohols,[2] and allylboration[3] is a widely used procedure. For the past two decades, we have been developing various α-pinene-based reagents for asymmetric "allyl" boration, and these reagents have found wide acceptance among the synthetic organic community.[4] One such reagent is *B*-γ-alkoxyallyldiisopinocampheylborane for the syn-selective alkoxyallylboration of aldehydes.[5] Although this reagent provides very high levels of ee and de for aldehydes, ketones fail to provide similar results, probably due to less favorable stereoelectronic factors.

Stereoselective synthesis of homoallylic tertiary alcohols is very important since they can be used as building blocks for the synthesis of complex natural products. There has been no general procedure for the preparation of homoallylic tertiary alcohols in high de and ee. We envisaged that oxidation of β-alkoxy homoallylic alcohol to the correspond-

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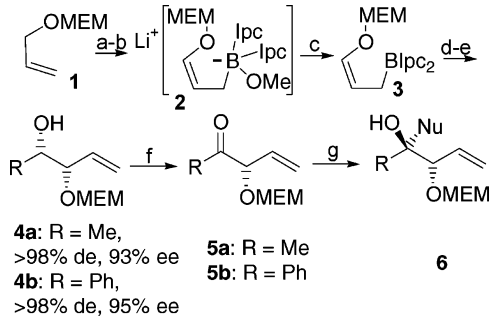
ing ketone, followed by nucleophilic addition, would furnish homoallylic tertiary alcohols. Chelation-controlled diastereoselective nucleophilic additions on α-alkoxyketones[6] are well-known. On this basis, we undertook a project involving diastereoselective nucleophilic additions on α-alkoxyketones derived from *syn*-alkoxy homoallylic alcohols.

We started with *syn*-monoalkoxy homoallylic alcohols **4a** and **4b** derived from reaction of *B*-*γ*-methoxyethoxymethoxyallyldiisopinocampheylborane[7] **3** with acetaldehyde and benzaldehyde, respectively. The alcohols **4a** and **4b** were oxidized to the corresponding ketones **5a** and **5b** using Dess−Martin periodinane (DMP).[8] We chose various nucleophiles as representative examples for the present study. Reduction of ketones **5a** and **5b** with $Zn(BH_4)_2$ at −78 °C afforded *anti*-homoallylic 2°-alcohols **6a** and **6e** in 50 and 95% de, respectively. Addition of organometallic reagents took place very smoothly, and the product *anti*-homoallylic tertiary alcohols were obtained in very high de (Scheme 1 and Table 1). In all of these cases, metal coordination with carbonyl oxygen and alkoxy oxygen atom leads to a five-membered transition state followed by nucleophilic addition from the opposite face providing the anti products.

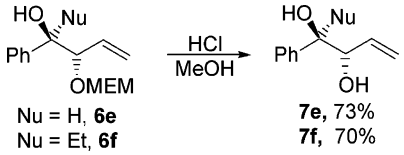
Scheme 1[a]



[a] Conditions: (a) *sec*-BuLi, THF, −78 °C, 0.5 h. (b) (+)-Ipc_2BOMe, −78 °C, 1 h. (c) $BF_3.Et_2O$, −78 °C, 5 min. (d) RCHO, −78 °C, 10 h. (e) $NaOH/H_2O_2$, rt, 6 h. (f) DMP, CH_2Cl_2, (g) Nu^-.

To demonstrate the utility of this procedure, we converted the *anti*-alcohols **6e** and **6f** into *anti*-diols **7e** and **7f**, respectively, in good yields by cleaving the MEM group under acidic conditions (Scheme 2).

Scheme 2



Application of this methodology was further demonstrated by the synthesis of the C_8 epimer of the C_1-C_{11} subunit of fostriecin (Figure 1). Fostriecin is a natural product isolated from *Streptomyces pulveraceus* exhibiting potent anti-cancer properties against a wide range of cell lines.[9] Accordingly, there have been several reports of the synthesis of this molecule in the recent past.[10] We have employed a strategy similar to our ongoing program on "allyl"boration−ring-closing metathesis for the synthesis of biologically active natural products.[11]

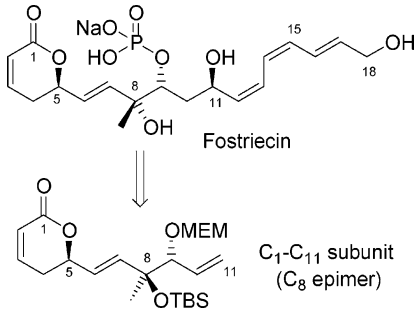
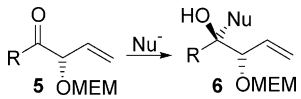


Figure 1.

Table 1.



compd	R	Nu	yield	de
6a	Me	$Zn(BH_4)_2$	90	50
6b	Me	EtMgBr	85	>95
6c	Me	$(CH_2{=}CH)MgBr$	78	>95
6d	Me	$CH_3{-}C{\equiv}CMgBr$	75	85
6e	Ph	$Zn(BH_4)_2$	92	>95
6f	Ph	EtMgBr	88	>95
6g	Ph	$(CH_2{=}CH)MgBr$	81	>95
6h	Ph	$CH_3{-}C{\equiv}CMgBr$	77	>95

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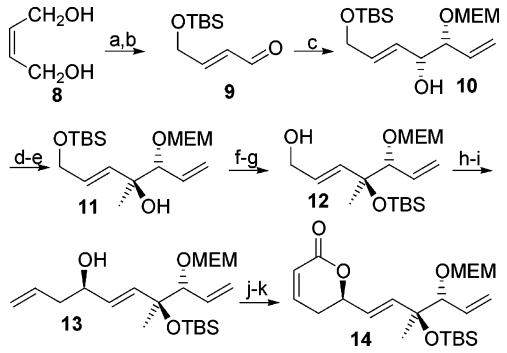
Monoprotection of *cis*-2-butene-1,4-diol **8**, with TBSCl, followed by PCC oxidation, provided the *trans*-aldehyde **9**.[12] This, upon alkoxyallylboration with (−)-*B*-γ-methoxyethoxymethoxyallyldiisopinocampheylborane **3**, furnished the homoallylic alcohol **10** in >98% de and 94% ee. DMP oxidation provided the α-alkoxyketone, and addition of methylmagnesium bromide took place stereoselectively to provide the anti tertiary alcohol **11** in >90% de. Protection of this alcohol as its TBS ether and subsequent deprotection of the primary TBS group yielded the alcohol **12**. DMP oxidation, followed by allylboration of the resulting aldehyde with *B*-allyldiisopinocampheylborane,[13] gave the homoallylic alcohol **13** in 87% de. Treatment with acryloyl chloride and ring-closing metathesis of the resulting acrylate with Grubbs' first-generation ruthenium catalyst[14] provided the C_8-epimer of the C_1-C_{11} subunit of fostriecin **14** (Scheme 3).

In conclusion, we have developed an efficient procedure for the highly stereoselective synthesis of *anti*-β-alkoxy and β-hydroxy homoallylic 3°-alcohols. We have also applied this procedure for the synthesis of the C_8-epimer of the C_1-C_{11} subunit of fostriecin. Further exploration of this methodology is in progress, and we believe that this protocol for preparing chiral homoallylic 3°-alcohols and diols will find major applications in organic synthesis.

Scheme 3[a]



[a] Conditions: (a) TBSCl, imidazole, 72%. (b) PCC, CH_2Cl_2, 81%. (c) $CH_2{=}CHCH_2OMEM$, *sec*-BuLi, (−)-Ipc_2BOMe, $BF_3.Et_2O$, NaOH, H_2O_2,69%. (d) DMP, 92%. (e) MeMgBr, −78 °C. (f) TBSOTf, 2,6-lutidine, 79% overall. (g) AcOH, THF, H_2O, 72%. (h) DMP, 88%. (i) (+)-Ipc_2BAll, NaOH, H_2O_2, 65%. (j) Acrylic acid, DCC, DMAP, 84%. (k) Grubbs first-generation generation catalyst, CH_2Cl_2, 78%.

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Supporting Information Available: Experimental and spectral data along with ^1H and ^{13}C NMR spectra for various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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