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Asymmetric Tandem Wittig Rearrangement/Aldol Reactions

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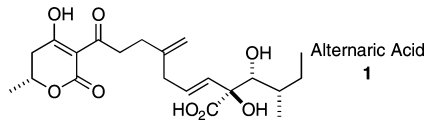
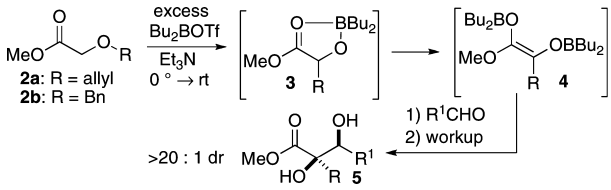
Substituted α-alkyl-α,β-dihydroxy carboxylic acids and esters are important building blocks for organic synthesis and are displayed in many biologically active molecules, such as the antifungal agent alternaric acid (**1**).[1,2] The enantioselective construction of these groups is often achieved through asymmetric dihydroxylation of α-alkyl-α,β-unsaturated esters. However, this approach requires a multistep stereoselective synthesis of the trisubstituted enoate starting material, and the presence of other alkenes appended to the substrate is usually not tolerated by the highly electrophilic oxidant.[2b,3] Asymmetric aldol reactions have been used to prepare derivatives bearing protected hydroxyl groups that can be deprotected in subsequent steps.[4] However, only a single study of asymmetric aldol reactions that directly afford α-alkyl-α,β-dihydroxy esters has appeared in the literature. The selectivity for formation of syn as opposed to anti diols varied widely from substrate to substrate, and syn diol products were obtained with little or no enantioselectivity.[5,6]



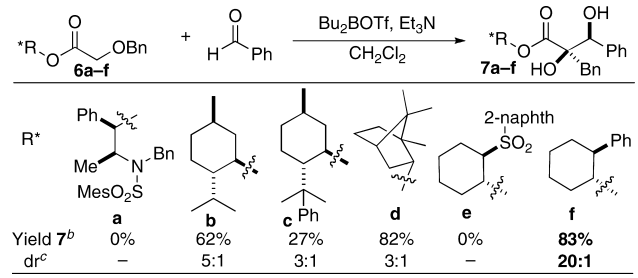
We recently reported a new method for the conversion of methyl *O*-allylglycolate (**2a**) or methyl *O*-benzylglycolate (**2b**) into α-alkyl-α,β-dihydroxy esters via a tandem 1,2-Wittig rearrangement/aldol reaction sequence (Scheme 1).[7] For example, treatment of **2** with excess Bu_2BOTf and Et_3N at 0 °C followed by warming to room temperature (rt) effects ester enolate 1,2-Wittig rearrangement to provide **3**.[8,9] Chelation between the ester carbonyl and the boron alkoxide in intermediate **3** facilitates the highly stereoselective formation of doubly borylated *E* enolate **4**, which undergoes aldol reaction upon addition of an aldehyde electrophile. This tandem reaction sequence constructs two C−C bonds and two stereocenters, one of which is quaternary, to afford syn diol products **5** with excellent stereocontrol. Moreover, the generation of **4** by way of **3** provides a means for controlling the enolate geometry that is difficult to achieve through direct deprotonation of α-alkyl-α-hydroxy esters.[5,10]

Scheme 1. Tandem Wittig Rearrangement/Aldol Reaction



In this communication, we describe the development of asymmetric tandem Wittig rearrangement/aldol reactions that provide enantiomerically enriched α-alkyl-α,β-dihydroxy esters. These are the first examples of tandem reactions involving enolate [1,2]-Wittig rearrangements that afford nonracemic products and are also the first asymmetric aldol reactions of α-alkyl-α-hydroxy ester enolates that generate unprotected diol products with both high syn/anti selectivity and high ee. In addition, this new method provides a significantly improved route to a key intermediate in the synthesis of alternaric acid.[2b]

Table 1. Chiral Auxiliary Screen[a]

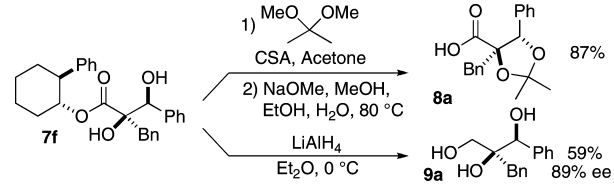


[a] Conditions: 1.0 equiv of **6**, 1.5 equiv of PhCHO, 3.2 equiv of Bu_2BOTf, 4 equiv of Et_3N, CH_2Cl_2, 0 °C → rt → 0 °C. [b] Isolated yield (average of two or more experiments). [c] Diastereomeric ratios were determined by ^1H NMR analysis.

In our preliminary studies, we sought to achieve asymmetric induction through the use of esters derived from chiral alcohols (Table 1). Although the Masamune auxiliary has been shown to provide excellent results in aldol reactions of trisubstituted ester enolates,[11] an *O*-benzylglycolate ester bearing this group (**6a**) failed to undergo [1,2]-Wittig rearrangement. In contrast, promising results were obtained with menthyl ester **6b**, and further experiments indicated that the *O*-benzylglycolate ester prepared from commercially available 2-phenylcyclohexanol[12,13] (**6f**) was transformed to **7f** with excellent stereoselectivity.[14]

Removal of the chiral auxiliary from **7f** was accomplished using one of two methods (Scheme 2). A two-step sequence involving conversion of **7f** to an acetonide followed by hydrolysis of the ester afforded carboxylic acid **8a** in good yield. Alternatively, treatment of **7f** with $LiAlH_4$ afforded enantiomerically enriched triol **9a**.

Scheme 2. Cleavage of Auxiliary



As shown in Table 2, the asymmetric Wittig rearrangement/aldol reactions were effective for the conversion of *O*-benzyl- and *O*-allylglycolate esters **6f** and **10**, respectively, to a number of different diol products. A wide range of aldehydes were transformed in good yield, and all of the reactions proceeded with at least 20:1 syn/anti selectivity of the diol. In seven of eight cases examined, the ratio of (2′*R*,3′*S*)/(2′*S*,3′*R*) diol stereoisomers was ≥20:1,[15] and cleavage of the auxiliary from these products with $LiAlH_4$ afforded enantiomerically enriched triols with 89−95% ee.

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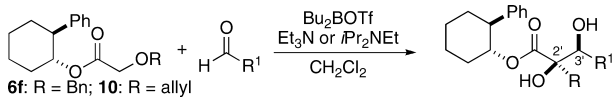
Table 2. Asymmetric Wittig Rearrangement/Aldol Reactions[a]



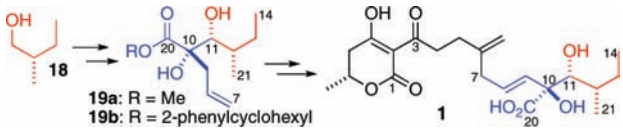
6f: R = Bn; **10**: R = allyl

Entry	R	R^1	Product	Yield[b]	(2′*R*,3′*S*):[c] (2′*S*,3′*R*)	ee after $LiAlH_4$ reduction[d]
1	Bn	Ph	**7f**	83%	20:1	89%
2	Bn	C_9H_{19}	**11**	88%	>20:1	95%
3	Bn	Cy	**12**	71%	20:1	91%
4	Bn		**13**	81%	>20:1	93%
5	Allyl	Ph	**14**	83%	20:1	90%
6	Allyl	C_9H_{19}	**15**	79%	8:1	75%
7	Allyl	*i*Pr	**16**	68%	20:1	89%
8	Allyl		**17**	59%	>20:1	95%

[a] Conditions: 1.0 equiv of **6f** or **10**, 1.5−2 equiv of R^1CHO, 3.2 equiv of Bu_2BOTf, 4 equiv of Et_3N (R = Bn) or $iPrNEt_2$ (R = allyl), CH_2Cl_2, 0 °C → rt → 0 °C. [b] Isolated yield (average of two or more experiments). [c] Ratios were determined by ^1H NMR analysis. All products were obtained with >20:1 syn/anti selectivity. [d] Enantiomeric excess was determined by chiral HPLC or Mosher ester analysis after reduction to the corresponding triol with $LiAlH_4$.

In order to illustrate the synthetic utility of this transformation, we sought to prepare **19b**, which is closely related to a key intermediate (**19a**) in Trost's synthesis of alternaric acid (Scheme 3).[2b] Ester **19a** was previously generated from commercially available (*S*)-2-methyl-1-butanol (**18**) in seven steps (longest linear sequence).[2b] The C10,C11 diol functionality was introduced via Sharpless asymmetric dihydroxylation (AD) of a trisubstituted enoate, and the pendant terminal alkene was installed in subsequent steps.

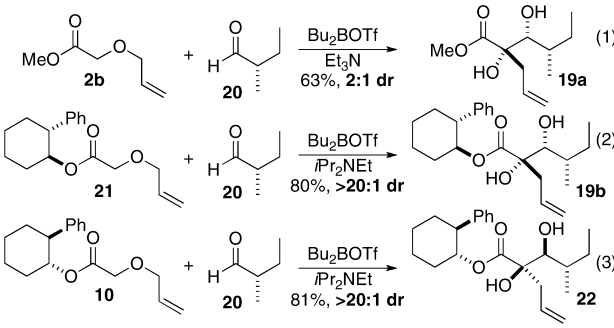
Scheme 3. Key Intermediate in Alternaric Acid Synthesis[2b]



In principle, **19a** could be generated through a Wittig rearrangement/aldol reaction sequence between methyl ester **2b** and enantiopure aldehyde **20** (prepared in one step from **18**).[16] However, addition reactions of nucleophiles to **20** are known to occur with poor diastereoselectivity because of the similar steric properties of the aldehyde C2 substituents (Me vs Et). As anticipated, the coupling of **2b** with **20** proceeded with modest Felkin selectivity to afford **19a** with only 2:1 dr (eq 1). In contrast, the (1*S*,2*R*)-2-phenylcyclohexyl ester **21** was transformed to **19b** in 80% yield as a single stereoisomer (eq 2). Overall, our synthesis of **19b** required only three steps in the longest linear sequence, as ester **21** was prepared in two steps from commercially available materials. Importantly, our strategy complements Sharpless AD chemistry, as the Wittig rearrangement/aldol reaction allows for preparation of α,β-dihydroxy esters bearing relatively nucleophilic alkenes that would not tolerate typical dihydroxylation conditions.[2b,3]

In view of the high selectivity observed in reactions of achiral aldehydes with glycolate esters derived from 2-phenylcyclohexanol, it seemed likely that the chiral auxiliary could override the slight preference for Felkin selectivity typically observed with chiral aldehyde **20**. This hypothesis proved to be correct, as the tandem Wittig rearrangement/aldol reaction of (1*R*,2*S*)-**10** with **20** provided **22** in 81% yield with >20:1 dr (eq 3).

In conclusion, we have developed an asymmetric tandem Wittig rearrangement/aldol reaction sequence that affords enantiomerically



enriched α-alkyl-α,β-dihydroxy esters in good yield with excellent stereoselectivity. These transformations provide a new means for the enantioselective construction of quaternary carbon stereocenters and allow for straightforward preparation of compounds that are cumbersome to access via existing methods. Further studies involving extensions and applications of this chemistry are currently underway.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and descriptions of stereochemical assignments with supporting crystallographic structural data for **7f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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