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Enantioselective Synthesis of *syn*- and *anti*-1,3-Diols via Allyltitanation of Unprotected β-Hydroxyaldehydes

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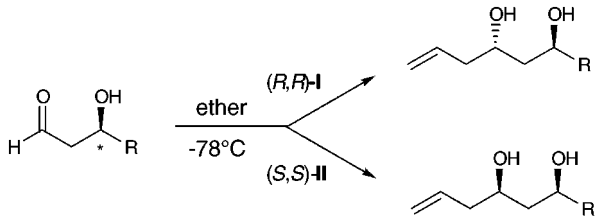
ABSTRACT



***syn*- or *anti*-1,3-diols units were synthesized with excellent diastereomeric excess from unprotected chiral β-hydroxyaldehydes by using an enantioselective allyltitanation.**

The 1,3-diol subunit is commonly found in many natural products.[1] The presence of alternating hydroxy groups on a contiguous carbon chain can be found in a variety of bioactive organic compounds, including macrolide antibiotics such as Roxaticin (Figure 1).[1b] A great variety of methodologies have been developed to synthesize these 1,3-diols. An important way to access these compounds is through a diastereoselective reduction of β-hydroxyketones since *syn*- or *anti*-diols are obtained depending on the reducing agent used.[2,3] In the case of the reductive decyanation of cyanohydrin acetonides, *syn*-1,3-diols are exclusively formed.[4] *anti*-1,3-Diols are formed by regioselective reductive opening of the epoxy ring of *trans*-α-epoxyalcohols.[5]

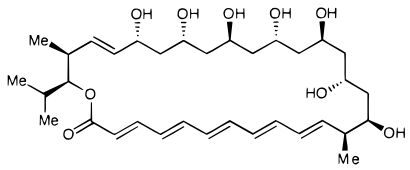


Figure 1. Roxaticin.

The other methods that allow the synthesis of 1,3-diol subunits are C−C bond-forming reactions. Depending on the substrates, reagents, and conditions, *syn*- or *anti*-1,3-diols can be synthesized. For example, the reductive lithiation of *O*,*S*-acetals gives lithioethers, which can be alkylated to provide *anti*-1,3-diols at low temperature and *syn*-1,3-diols when they are alkylated at 0 °C.[6,7] The stereocontrolled homologation of chiral *O*-glycosylated alkyl radicals by ethyl trifluoroacetoxyacrylate can result in the clean formation of *syn*- and *anti*-1,3-diols depending on the glycosyl auxiliary.[8]

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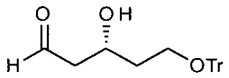
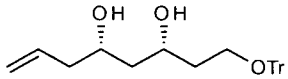
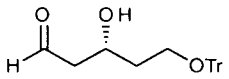
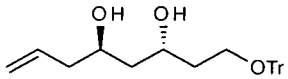
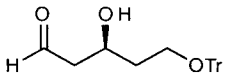
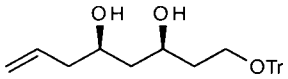
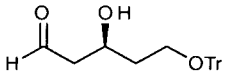
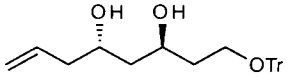
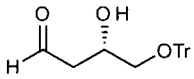
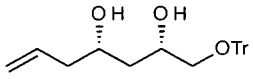
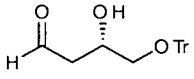
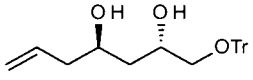
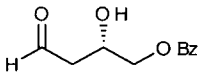
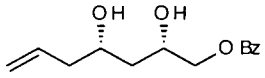
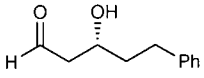
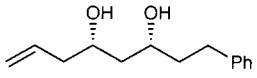
Table 1. Preparation of Optically Active *syn*- or *anti*-1,3-Diols from β-Hydroxyaldehydes

Entry	Aldehydes	Complex	Major 1,3-diols	de %	yield %
1	 **10**	(*R*, *R*)-**I**	 **15**	93	79
2	 **10**	(*S*, *S*)-**II**	 **16**	93	83
3	 **11**	(*S*, *S*)-**II**	 **17**	93	85
4	 **11**	(*R*, *R*)-**I**	 **18**	93	75
5	 **12**	(*R*, *R*)-**I**	 **19**	94	78
6	 **12**	(*S*, *S*)-**II**	 **20**	93	81
7	 **13**	(*R*, *R*)-**I**	 **21**	96	79
8	 **14**	(*R*, *R*)-**I**	 **22**	95	80

Sequential ring openings of the C_2-symmetric bis-epoxide through organometallics led to an elegant synthesis of enantiopure *anti*-1,3-diols,[9−11] and the attack of organometallic reagents on the epoxy ring of β-hydroxyepoxides led to *syn*-1,3-diols.[12] When 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydrazones are α,α'-bis-alkylated, precursors of *anti*-1,3-diols are obtained.[13] In the case of O-protected β-hydroxyaldehydes, which are well-suited for the chelation-controlled addition of organometallic reagents, a wide variety of anti-configurated 1,3-diols can be obtained.[14] Unprotected β-hydroxyaldehydes can also be transformed into *anti*-1,3-diols via allylboration.[15] Syn-selective additions to O-protected or unprotected β-hydroxyaldehydes are not generally possible unless one exploits addition reactions with reagent control of diastereoselectivity.[16] Here, we would like to report that *syn*- or *anti*-1,3-diols can be obtained with good to excellent enantiomeric excess by allyltitanation of nonprotected β-hy-

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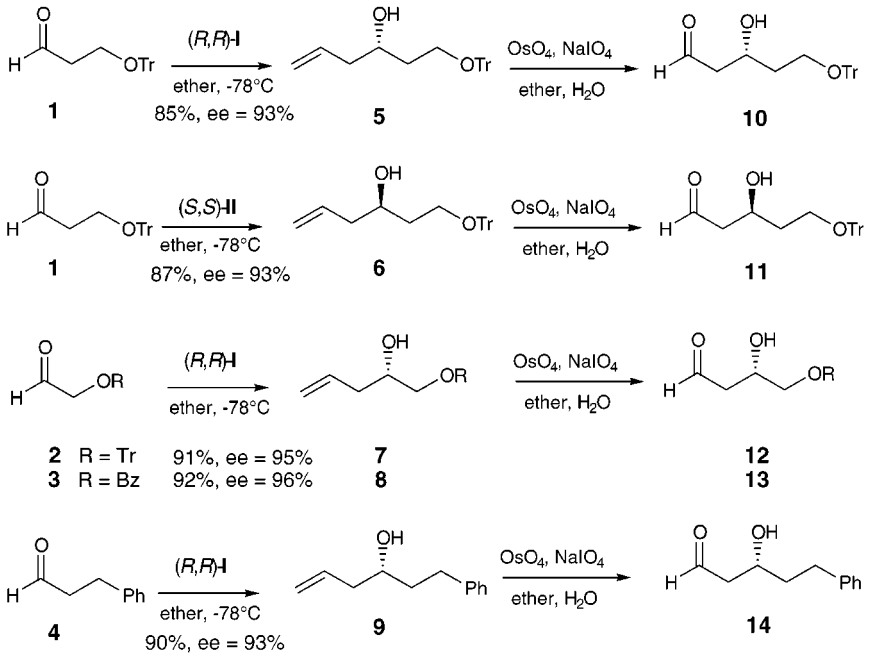
Scheme 1. Preparation of Optically Active Homoallylic Alcohols and β-hydroxyaldehydes



droxyaldehydes of type **B** with cyclopentadienyldialkoxyallyltitanium complexes (*R*,*R*)-**I** or (*S*,*S*)-**II**[17] (Figure 2).

β-Hydroxyaldehydes **10**−**14** were prepared in two steps by allyltitanation of aldehydes of type **A**. Treatment of aldehydes **1**−**4** with either complexe (*R*,*R*)-**I** or (*S*,*S*)-**II** in ether at − 78 °C afforded homoallylic alcohols **5**−**9** with good enantiomeric excess (ee = 93−96%)[18,19] and in high yield (85−92%). The transformation of these homoallylic alcohols to the corresponding β-hydroxyaldehydes **10**−**14** was achieved by using sodium periodate in the presence of a catalytic amount of osmium tetraoxide.[20]

These β-hydroxyaldehydes were unstable and were treated directly with the allytitanium complexes. When the unprotected β-hydroxyaldehydes **10**−**14** were treated with the (*R*,*R*)-**I**, or (*S*,*S*)-**II** complexes, the *syn*-1,3-diols **15**, **17**, **19**, **21**, and **22** were obtained in high yield (78−85%) and with diastereoisomeric excesses up to 93%. When β-hydroxyaldehydes **10**, **11**, and **12** were treated with the same allyltitanium complexes (*R*,*R*)-**I** or (*S*,*S*)-**II**, the *anti*-1,3-diols **16**, **18**, and **20** were isolated in high yield (75−83%) and with diastereoisomeric excesses up to 93%. The formation of *syn*- or *anti*-1,3-diols from unprotected β-hydroxyaldehydes of type **B**, by using complex (*R*,*R*)-**I** or (*S*,*S*)-**II**, is general and the results are summarized in Table 1.

The relative stereochemistry of the 1,3-diols was determined on compounds **15**−**22** by converting them to acetonides and analyzing their ^{13}C NMR chemical shifts.[21] For example, the *syn*-1,3-diol acetonide **23**, synthesized from **15**, displays acetal methyl resonances at 19.6 and 30.1 ppm and the acetal carbon resonates at 98.3 ppm, while the methyl resonances of the *anti*-1,3-diol acetonide **24**, synthesized from **16**, are at 24.8 ppm and the acetal carbon resonates at 100.1 ppm (Scheme 2).

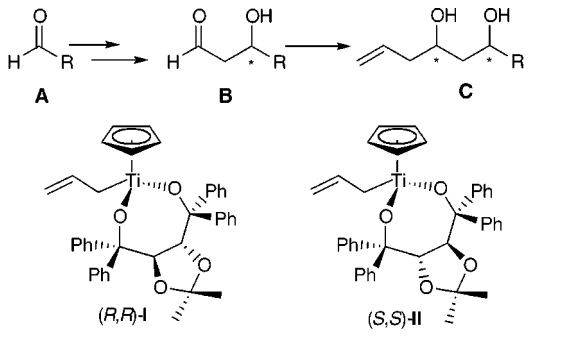
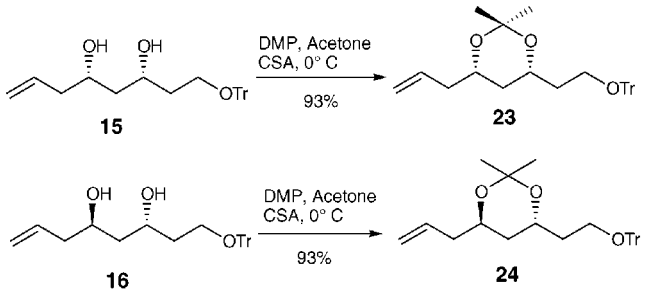


Figure 2. Formation of 1,3-diols.

Scheme 2. Formation of Acetonides



It is noteworthy that this methodology affords 1,3-diols with good to excellent chemical yields and with excellent diastereomeric excesses regardless of the starting β-hydroxyaldehydes. The yield in 1,3-diols depends on the success of

the formation of β-hydroxyaldehydes of type **B**. Sensitive protecting groups, such as benzoyl and trityl groups, are tolerated due to the mild reaction conditions and to the neutral aqueous conditions employed in the workup. Furthermore, the chiral ligand, TADDOL, can be recovered and recycled to synthesize the titanium complexes (*R*,*R*)-**I** and (*S*,*S*)-**II**.[17]

The formation of 1,3-diols from unprotected β-hydroxyaldehydes indicates that during this allyltitanation reaction, the titanium complexes were not chelated to a hydroxy group since the formation of *syn*- and *anti*-1,3-diols depends only on the (*R*,*R*)- or (*S*,*S*)-allyltitanium complexes used and not on the (*R*)- or (*S*)-configuration of β-hydroxyaldehydes of type **B**. This enantioselective allyltitanation of unprotected β-hydroxyaldehydes allows an efficient preparation of *syn*- or *anti*-1,3-diols without any protective and deprotective steps, which enhances the synthetic potential of this organometallic allylation.

Acknowledgment. The authors are indebted to Dr. R. O. Duthaler for a generous gift of chiral cyclopentadienyldialkoxyallyltitanium complexes and C. Ferroud and A. Falguières for HPLC analysis.

Supporting Information Available: Spectroscopic and analytical data for **15**−**24** as well as representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The enantiomeric excess of homoallylic alcohols was determined by HPLC analysis, Chiralcel-AD$_2$ column (hexane/2-propanol).

(19) All new homoallylic alcohols exhibited satisfactory spectroscopic data (^{1}H and ^{13}C NMR, IR, MS).

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