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ENANTIOENRICHED FORMATION OF SYNTHONS OF 1,5-HEXADIENE BIS-EPOXIDES FOR CONSTRUCTION OF NONRACEMIC CIS- AND TRANS-2,5-DISUBSTITUTED TETRAHYDROFURANS[1]

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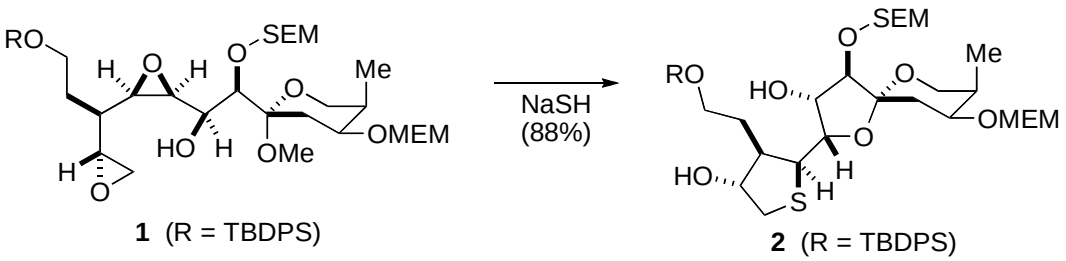
Abstract – A pathway for the synthesis of enantioenriched *bis*-epoxides derived from 2,6-heptadien-1-ol is described. Use of the Katsuki titanium salalen catalyst affords high asymmetric induction for mild epoxidation of the monosubstituted alkene as the key step. Regioselective nucleophilic additions to these chiral *bis*-epoxides lead to a stereocontrolled preparation of nonracemic *cis*- and *trans*-2,5-disubstituted tetrahydrofurans.

In the course of our studies for natural product total synthesis, we have previously developed a number of strategies for the stereocontrolled formation of substituted tetrahydrofurans (THF's), which are frequently embedded within the molecular architectures of microbial and marine metabolites.[1] Unabated interest in the stereoselective synthesis of THF's continues,[2] and these activities have, in part, been encouraged by studies of biomimetic cascade reactions from polyepoxide precursors to give complex THF's and related oxacyclic systems.[3] Our studies leading to the total synthesis of (+)-breynolide documented an early example of this concept by formation of the *bis*-epoxide **1** for sequential ring-opening reactions to produce the advanced intermediate tetrahydrothiophene-ketal **2** using sodium hydrogen sulfide.[4] However, issues of enantiofacial and diastereofacial control in the formation of polyepoxide precursors remains a particularly challenging problem. The reagents and the conditions required for the preparation of nonracemic polyepoxides present a number of difficulties owing to the inherent reactivity of these oxirane systems with Lewis acids and nucleophilic Lewis bases. Previous studies have focused on strategies for the enantiocontrolled preparation of 1,5-hexadiene *bis*-epoxides as synthons toward

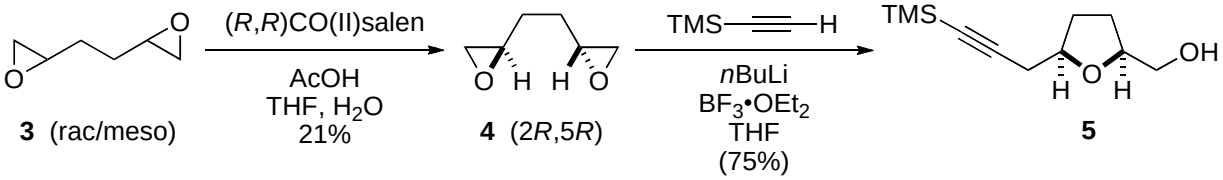
[1] *Dedicated to Dr. Albert Padwa in celebration of his 75th birthday.*

the construction of nonracemic THF's.[5] For example, the Jacobsen hydrolytic kinetic resolution of 1,5-hexadiene *bis*-epoxide **3** has provided (2*R*,5*R*)-**4** in 21% yield with >95% ee.[6,7] The corresponding (2*S*,5*S*)-**ent-4** is available from the chiral pool via a seven-step route using D-mannitol.[8]



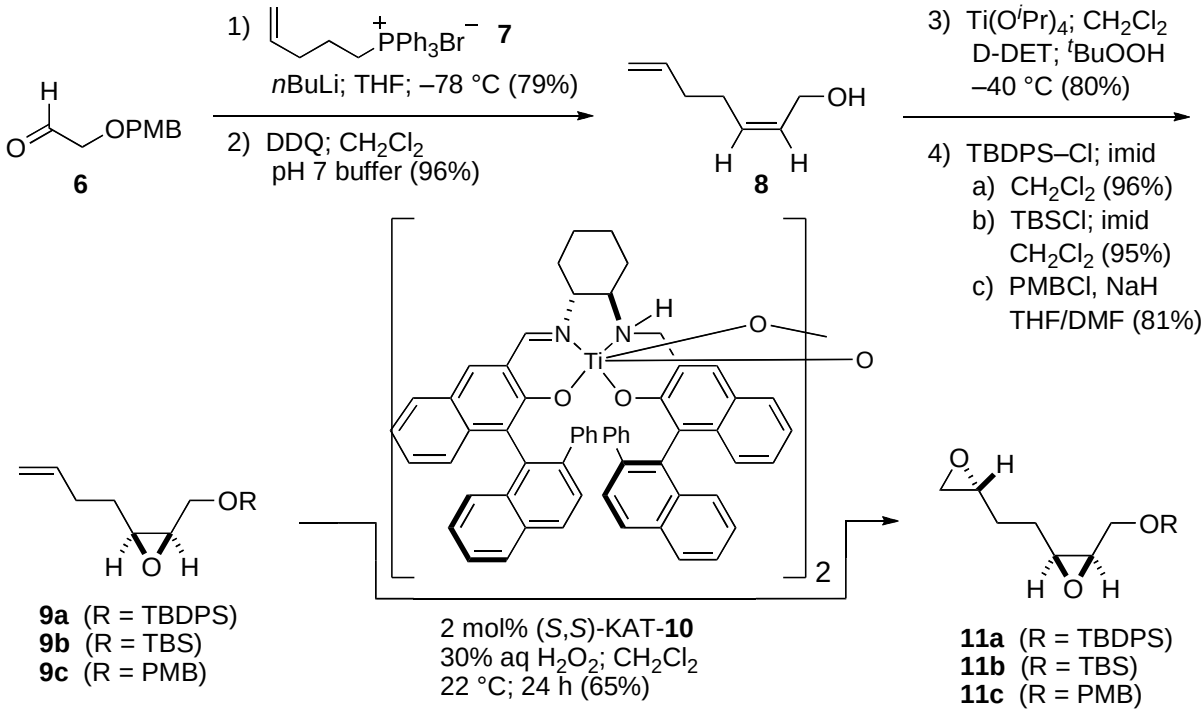
1 (R = TBDPS) **2** (R = TBDPS)

In these cases, direct methods resulting in asymmetric induction via reagent-controlled epoxidations have generally been problematic for monosubstituted aliphatic alkenes.[9] This aspect is a significant barrier for successful applications leading to nonracemic *cis*- and *trans*-2,5-disubstituted THF's because a generalized synthetic solution relies upon the selective nucleophilic opening of a terminal oxirane. The intermediate, alkoxide initiates the cascading internal backside displacement leading to tetrahydrofuran formation as illustrated in **5**.[6] Herein, we describe an effective means for the preparation of enantioenriched *bis*-epoxides of 2,6-heptadien-1-ol and subsequent reactions leading to the selective formation of 2,5-disubstituted THF's.



3 (rac/meso) **4** (2*R*,5*R*) **5**

For our purpose, we required the use of (*Z*)-2,6-heptadien-1-ol (**8**), which was readily prepared via the low temperature Wittig reaction of aldehyde **6** and phosphonium salt **7** followed by DDQ deprotection (Scheme 1). Sharpless asymmetric epoxidation of **8** with D-(–)-diethyl tartrate (DET) provides the expected epoxyalcohol as the major product of a 91:9 ratio of enantiomers. The ratio of enantiomers was determined by a modified Mosher ester analysis.[10] Protection of the primary alcohol as the corresponding *tert*-butyldiphenylsilyl (TBDPS) or *tert*-butyldimethylsilyl (TBS) ethers **9a** and **9b** proceeded in high yields, as well as conversion into the p-methoxybenzyl (PMB) ether **9c** (NaH; PMBCl; TBAI; THF/DMF; (4:1 by volume), 81% yield), and this step provided materials with favorable solubility for subsequent manipulations. Asymmetric oxidation of the terminal alkene of each of the derivatives **9a, b, c**, was accomplished using 2 mol% of the Katsuki titanium salalen catalyst,[11] (*S*,*S*)-KAT-**10**, in methylene chloride by the dropwise addition of 30% aq. H_2O_2 (1.5 eq) at room temperature. The reaction proceeds over 24 h with continuous stirring, and results in a stereoselective epoxidation with production of the nonracemic *bis*-epoxide **11** as the principle component of a highly enriched mixture of epoxide isomers (65% yield), without the formation of other byproducts.



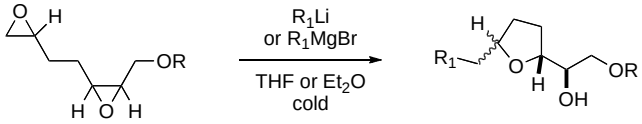
Scheme 1. Preparation of *bis*-epoxides **11**

Starting alkene is routinely recovered by flash chromatography (20–25% yield) and is recycled with additional catalyst **10** and oxidant to provide an 80% overall conversion to **11** after two cycles. The Katsuki catalyst is slowly degraded during the oxidation, and at 24 h, sluggish reactions are not revived by the introduction of small quantities of **10** and aqueous hydrogen peroxide. The level of asymmetric induction achieved by the Katsuki catalyst was evaluated via the ^{13}C NMR data of the *bis*-epoxide products and displayed a 90:10 ratio of diastereomers (based on a measure of signal peak intensities).[12] Additionally, we have used the Jacobsen hydrolytic kinetic resolution (HKR)[13] employing (*R*,*R*)-Co(II)(salen)OAc with **11a** to enrich the diastereomeric purity (dr 94:6).[12]

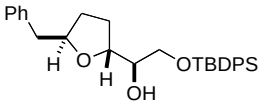
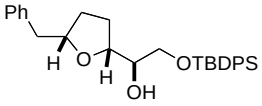
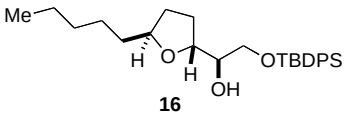
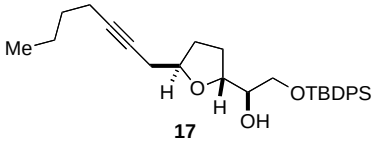
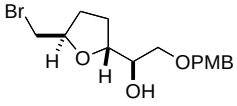
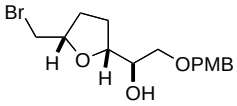
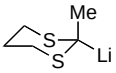
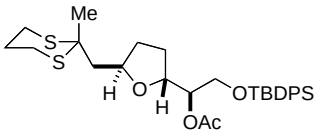
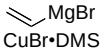
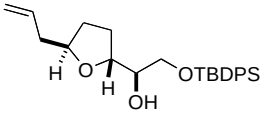
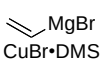
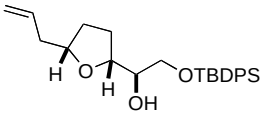
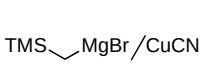
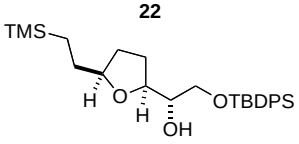
We note that the order of the epoxidation steps is significant. In this regard, our studies have also examined opportunities for the asymmetric epoxidation of optically active (*R*,*Z*)-5-(oxiran-2-yl)pent-2-en-1-ol which was prepared from D-malic acid (Aldrich). Directed oxidations via the Sharpless asymmetric epoxidation or $VO(acac)_2$ and ^{t}BuOOH led to rapid decomposition owing to the Lewis acidity of these reagents. The Jacobsen epoxidation[14] of ether derivatives of this substrate using the (*R*,*R*)-salen-Mn(III) catalyst led to the desired *bis*-epoxides in low yield with poor diastereoselectivity.

This strategy offers a modular approach for the synthesis of THF units which is amenable to the preparation of all stereochemical isomers within a series of nonracemic compounds by simple variations of: (a) the *E*/*Z*-geometry of the starting allylic alcohol; (b) the choice of D/L-tartrate; and (c) the use of the (*R*,*R*)- or (*S*,*S*)-Katsuki catalyst. As a proof of principle, we have also prepared the

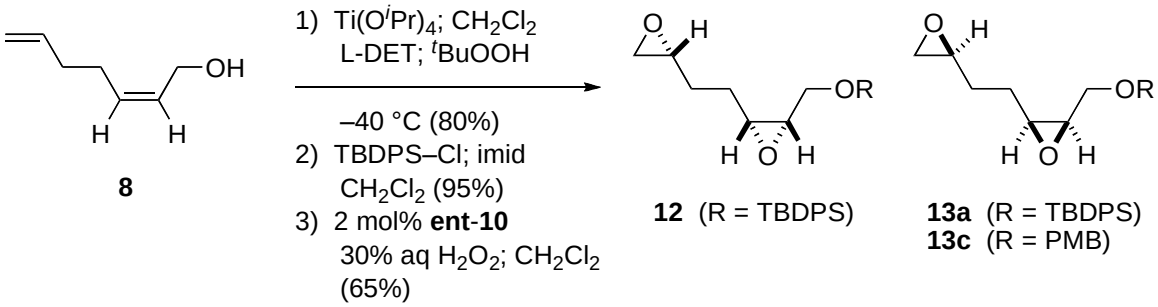
Table 1. Formation of nonracemic 2,5-*cis*- and *trans*-THF's



Bis-epoxides **11** – **13** **14** – **23**

Entry	Reagent[a]	Bis-epoxide	Major Product[b]	Yield (optical rotation)
1	PhMgBr/CuI	**11a**	 **14**	55% $[\alpha]_D^{25}$ –6.0 (c 2.29, $CHCl_3$)
2	PhMgBr/CuI	**13a**	 **15**	53% $[\alpha]_D^{25}$ –2.3 (c 2.83, $CHCl_3$)
3	*n*BuLi/BF_3•OEt_2	**11a**	 **16**	56% $[\alpha]_D^{25}$ –2.0 (c 2.58, $CHCl_3$)
4	Me–$(CH_2)_3$–C≡C–Li BF_3•OEt_2	**11a**	 **17**	52% $[\alpha]_D^{25}$ +22 (c 1.96, $CHCl_3$)
5	LiBr/BF_3•OEt_2	**11c**	 **18**	42% $[\alpha]_D^{25}$ –6.0 (c 0.22, $CHCl_3$)
6	LiBr/BF_3•OEt_2	**13c**	 **19**	40% $[\alpha]_D^{25}$ –17.1 (c 0.6, $CHCl_3$)
7		**11a**	 **20**[c]	60% $[\alpha]_D^{25}$ +1.8 (c 0.45, $CHCl_3$)
8		**11a**	 **21**	56% $[\alpha]_D^{25}$ –2.0 (c 0.85, $CHCl_3$)
9		**13a**	 **22**	54% $[\alpha]_D^{25}$ –7.0 (c 1.61, $CHCl_3$)
10		**12**	 **23**	59% $[\alpha]_D^{25}$ +11.0 (c 1.64, $CHCl_3$)

[a] Reaction conditions: The *bis*-epoxides were introduced into a solution of the nucleophilic reagent at –78 °C under nitrogen atmosphere, and reaction mixtures were slowly warmed to a suitable temperature where product formation was observed. Entries 3, 4, 5 and 6 proceeded rapidly in anhydrous ether at –78 °C with the addition of (3.0 equiv) BF_3•OEt_2. For entries 1, 2, 8, 9 and 10, reactions were undertaken in dry THF solvent and proceeded at –40 °C to 0 °C in the presence of copper(I) additives. CuI (10 mol%) was used for entries 1 and 2, and CuBr•DMS (10 mol%) was used in entries 8 and 9. One equivalent CuCN was used in entry 10. The 2-methyl-2-lithio-1,3-dithiane reagent of entry 7 was prepared by deprotonation of the parent dithiane upon treatment with nBuLi and $(nBu)_2Mg$ in THF solvent at –60 °C with addition of *bis*-epoxide and warming to 22 °C. [b] Major products are purified by flash silica gel chromatography and are fully characterized. *Cis*- and *trans*-2,5-THF's are distinguished and assigned by ^1H NMR spectroscopy. [c] Product **20** results from acetylation of the initially formed secondary alcohol (AcCl, pyr, CH_2Cl_2 22 °C) using the crude reaction product. Yield (60%) is given for the two-step process and purification of **20**.



diastereomeric *bis*-epoxide **12** from **8** by using L-DET for the Sharpless asymmetric epoxidation, and the use of the (*S*,*S*)-Katsuki catalyst, **ent-10**, with alkenes **9a** and **9c** afforded *bis*-epoxides **13a** and **13c**. These epoxides were obtained with similar stereoselectivity and yield as described in Scheme 1. A number of results featuring the formation of chiral, nonracemic THF's by the anticipated 5-exo-tet cyclization initiated by site-selective nucleophilic attack are shown in Table 1. In each instance, a small quantity of THF diastereomer (5–8%) was separated from the major product by flash silica gel chromatography.[15] The examples of Table 1 are chosen to illustrate the extension of the concept to a variety of common nucleophiles, including alkynyl, alkenyl and alkyl carbanions which lead to the preparation of THF's **14**–**23**. Yields of these products have not been optimized, and in some cases, small quantities of epoxyalcohol have been identified as side products stemming from incomplete cyclizations. However, in the examples of copper(I)-catalyzed reactions (entries 1, 2, 8 and 9), we have noted the formation of byproducts arising from nucleophilic opening at C_3 of the epoxy TBDPS ether in addition to the desired attack at the terminal oxirane. Deprotection of the products **14**–**23** provides for the formation of 1,2-diols which may undergo oxidative cleavage to yield the corresponding tetrahydrofuran carboxaldehydes as substrates for subsequent nucleophilic additions. Thus, our chiral *bis*-epoxides serve as nonracemic synthons of 1,5-hexadiene *bis*-epoxides which afford regiocontrolled introduction of the nucleophilic attack leading to THF formation.

In summary, the Katsuki oxidation facilitates the asymmetric epoxidation of monosubstituted alkene in the presence of nonracemic titanium salalen catalyst. This key transformation allows for the preparation of sensitive, enantioenriched *bis*-epoxides derived from 2,6-heptadien-1-ol following the Sharpless asymmetric epoxidation of the allylic alcohol moiety. We have shown that *bis*-epoxides **11**, **12** and **13** are useful in the synthesis of nonracemic *cis*- and *trans*-2,5-disubstituted tetrahydrofurans via initial site-selective nucleophilic attack at the less hindered oxirane. In this fashion, our *bis*-epoxides serve as chiral synthons that provide a flexible and general strategy toward the formation of substituted THF's for efficient incorporation into more complex molecular arrays.

ACKNOWLEDGEMENTS

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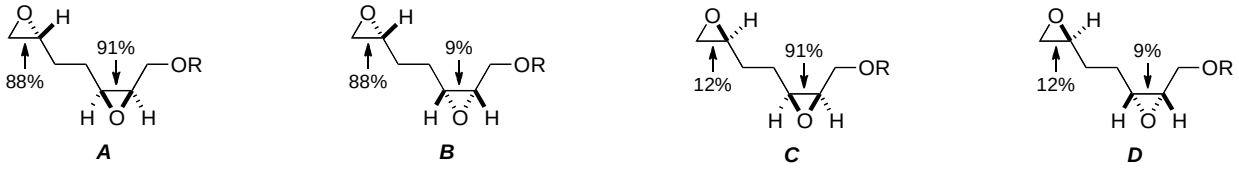
12. Our reaction pathway independently introduces two elements of chirality and produces two pairs of enantiomeric diastereoisomers **A**, **B**, **C** and **D**, shown below. A ratio of isomers (**A**:**B**:**C**:**D** ratio 80:8:11:1) is estimated based upon the enantiofacial selectivity of the Sharpless epoxidation (91:9 er) and a diastereofacial preference of the Katsuki oxidation (88:12). This calculation predicts a

diastereomer ratio (**A**+**D**:**B**+**C**) of dr 81:19. Our experimental observations (dr 90:10) may reflect the degree of uncertainty introduced in the measurement of peak heights in the decoupled ^{13}C NMR spectrum or unintended enrichment as a result of flash chromatography of the *bis*-epoxide. On the other hand, the NMR determination of the **A**:**B** ratio following the application of HKR to the *bis*-epoxides of **11a** is in close agreement with prediction (dr 91:9). Based on this assessment, the optical purity of **11a** (**A** and **D** are enantiomers) is 98% ee.



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15. The modified Mosher ester analysis was used to evaluate the optical purity of our products **14**–**23** and these NMR experiments showed no evidence for the presence of enantiomeric material. Based on the limitations of detection, we assume an er ≥ 96:4. The amount of the minor diastereomer THF is in line with our expectations (see reference 12) based on similar yields as in Table 1.