

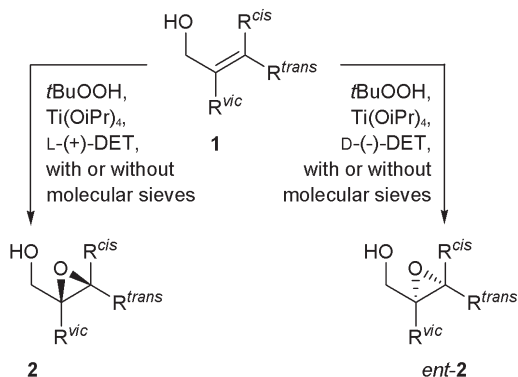
Asymmetric Epoxidation of Pentadienols

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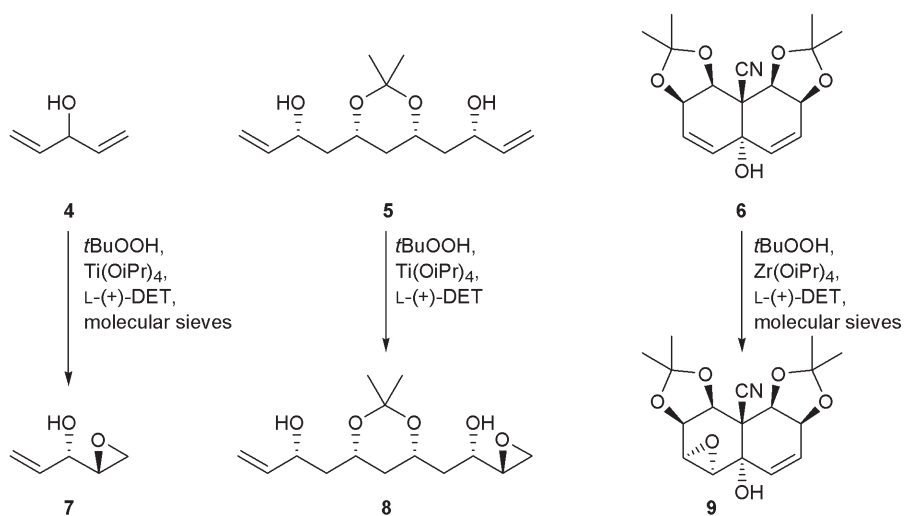
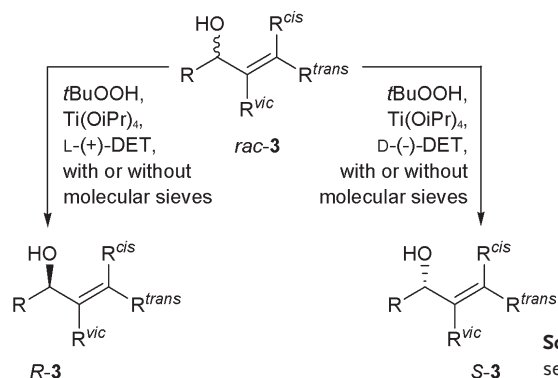
Background

The asymmetric epoxidation of allylic alcohols – or Sharpless asymmetric epoxidation (“SAE”) or Sharpless-Katsuki epoxidation – was a breakthrough in asymmetric synthesis [1]. Arguably it is one of the top ten transformations of organic chemistry [2R]. Indeed, it became a Nobel Prize winning reaction [3]. SAEs of achiral primary allylic alcohols **1** lead to glycidols of controllable configuration **2** or *ent*-**2** (Scheme 1a). These compounds can be carried on to an abundance of follow-up species by elaborating any or all of the *three* functionalities at C¹, C² or C³ [4]. In contrast, SAEs of racemic secondary allylic alcohols *rac*-**3** affect one enantiomer of the substrate and enrich the other, i.e. *R*-**3** or *S*-**3**, accomplishing a kinetic resolution (Scheme 1b).

Conceptually most intriguing are the desymmetrizing SAEs depicted in Scheme 2. Divinylcarbinol (**4**), a prochiral alcohol, and bis(allylic alcohol) **5**, a *meso* alcohol, provided epoxyalcohols **7** with > 99.7% *ee* [5] and **8** with “> 99.99999% *ee* expected” [6], respectively. These enantioselectivities distinctly surpass those found for achiral primary allylic alcohols. Interestingly, this outcome could be predicted by Schreiber’s insightful analysis [5a]. The tertiary *meso*-dialkenylcarbinol **6** was desymmetrized similarly, albeit only when Zr(OiPr)₄ was used and not Ti(OiPr)₄ [7].

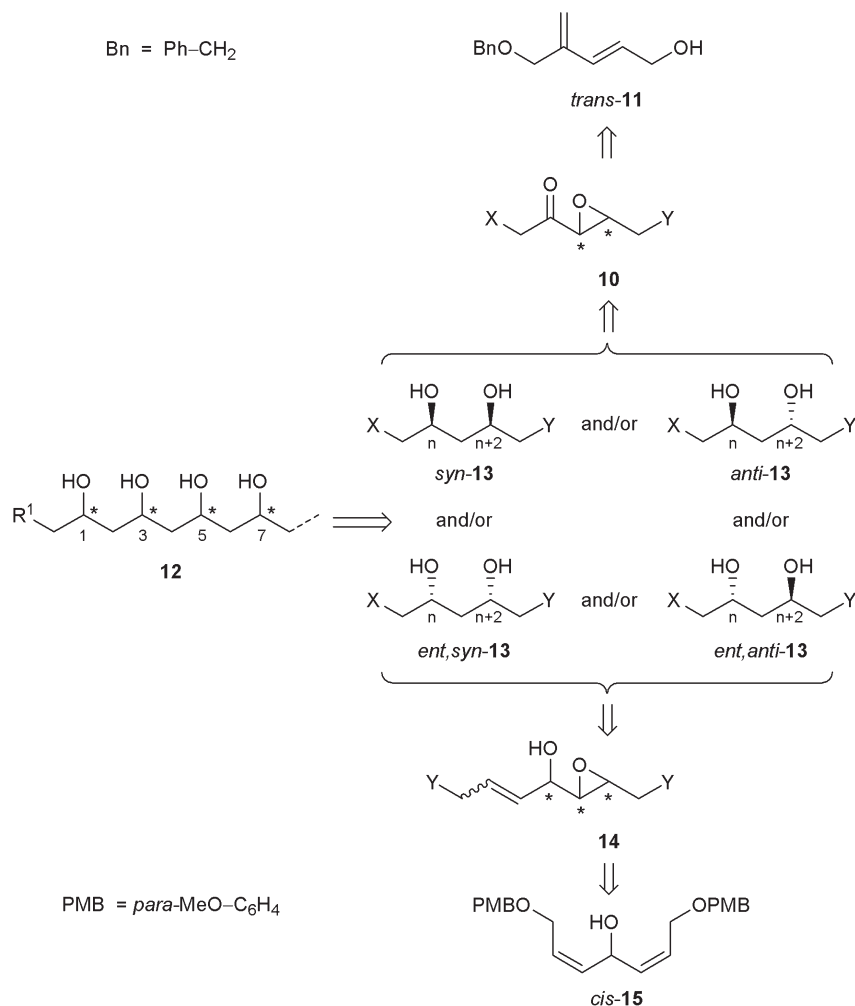


Scheme 1a SAEs of achiral primary allylic alcohols **1**.



Objective: Making Building Blocks for the Synthesis of 1,3,5,7,...-Polyols from Epoxyalcohols

Polyol/polyene macrolide antibiotics contain extended stretches of unbranched 1,3,5,7,...polyols **12** (Scheme 3). The latter are neither “isotactically” nor “syndiotactically” configured but comprise, rather, random sequences of *syn*- and *anti*-configured 1,3-diol subunits. This feature suggests that a set of 1,3-diol building blocks **13** of all four conceivable configurations would be useful for constructing such polyols. We accessed two sets of such molecules **13** via SAEs: one from the conjugated dienol *trans-11* and one starting from the nonconjugated dienol *cis-15*. In both substrates, one C=C bond was oxidized and one preserved – initially, namely until its presence allowed follow-up transformations.

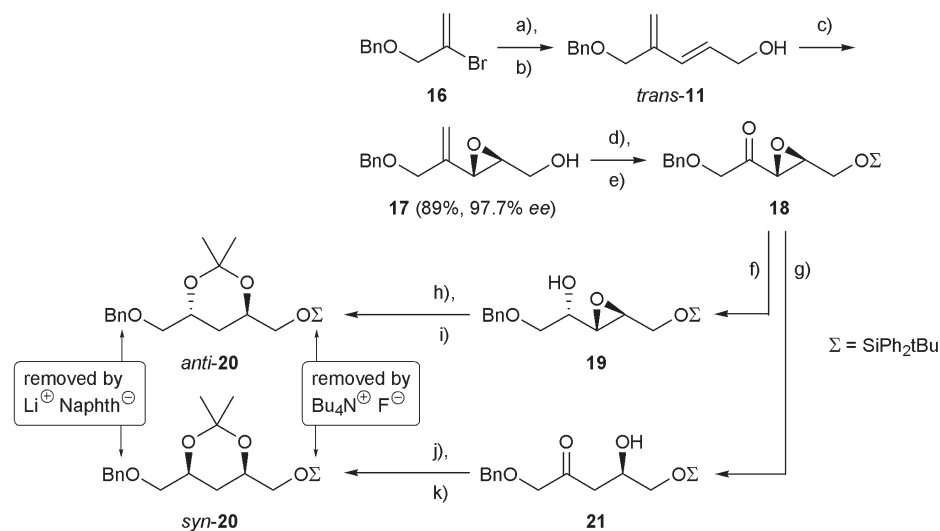


Scheme 3 Tracing back 1,3,5,7,...-polyols (**12**) via 1,3-diol building blocks (**13**) to epoxidized allylic alcohols.

Results

Asymmetric Epoxidation of a Conjugated Pentadienol [8]

SAE of pentadienol *trans*-**11** functioned best (89% yield/97.7% *ee*) with near-stoichiometric [1a] rather than catalytic [1b] amounts both of L-(+)-diisopropyl tartrate and Ti(OiPr)₄ (Scheme 4). Epoxyalcohol **17** was silylated, the C=C bond ozonolyzed, and the resulting epoxyketone **18** reduced, either by chelation-controlled hydride addition (\rightarrow **19**) or by electron transfer (\rightarrow **21**). Renewed reduction followed by transacetalization yielded acetone *anti*-**20** and *syn*-**20**, respectively. Their protecting groups were selectively removable. Accordingly, these species are realizations of the 1,3-diol building blocks *syn*-, *anti*-, *ent,syn*-, and *ent,anti*-**13**.



Scheme 4 a) $\text{H}_2\text{C}=\text{CH}-\text{CO}_2\text{Me}$, $\text{Pd}(\text{OAc})_2$ (cat.), LiCl , Bu_4NCl , K_2CO_3 , DMF ; 57 %. b) DIBAL, CH_2Cl_2 ; 85 %. c) *tert*BuOOH, $\text{Ti}(\text{OiPr})_4$ (56 mol %), *L*-(+)-diisopropyl tartrate (64 mol %), CH_2Cl_2 , molecular sieves 4 Å. d) *tert*BuPh₂SiCl, imidazole, THF; 90 %. e) O_3 , CH_2Cl_2 ; PPh_3 ; 81 %. f) $\text{Zn}(\text{BH}_4)_2$, toluene; 73 %. g) Zn , Cp_2TiCl_2 , 1,4-cyclohexadiene; 60 %. h) Same as (g); 67 %. i) $\text{Me}_2\text{C}(\text{OMe})_2$, camphor sulfonic acid (cat.), acetone; 79 %. j) Et_2BOMe , MeOH , THF; NaBH_4 ; 73 %. k) Same as (j); 85 %. (Ref. [8].)

Asymmetric Epoxidation of a Nonconjugated Pentadienol [9, 10]

The substrate of this approach to 1,3-diol motifs of variable stereostructure was the bis(*cis*-alkenyl)carbinol *cis*-15 (readily obtained from propargyl ether **22** and ethyl formate; Scheme 5). SAE in the presence of molecular sieves [1b] and stoichiometric $\text{Ti}(\text{OiPr})_4$ /diisopropyl tartrate [1a] proceeded with 95–96 % *ee*. Since SAE of the analogous mono-PMB ether of *cis*-2-butene-1,4-diol gives only 85–88 % *ee*, the “Schreiber effect” is likely to have intervened. Whereas epoxyalcohols *anti*- and *ent,anti*-**23** formed with only ~75:25 *ds*, the epimers *syn*- and *ent,syn*-**23** resulted diastereopure from the $\text{Zr}(\text{OiPr})_4$ -mediated AE of the same pentadienol *cis*-15 [7]. In these conditions, we raised the *ee* of epoxyalcohol *syn*-**23** up to 99 % by allowing for some over-oxidation, and *proved* that this over-oxidation consumes most of the initially present minor enantiomer, furnishing bisepoxyalcohol *syn*, *syn*-**24** (Figure 1).

Scheme 6 depicts the extraction of stereodefined 1,3-diol building blocks from the pentadienol oxides **23** for a representative enantiomer from both the *anti*- and the *syn*-series: through reduction by Red-Al™ at 60 °C. The reagent effects two transformations in a single operation, namely regioselective opening of the epoxide and chemoselective cleavage of the allylic ether (by what we believe to be an OH-directed $\text{S}_{\text{N}}2'$ reaction).

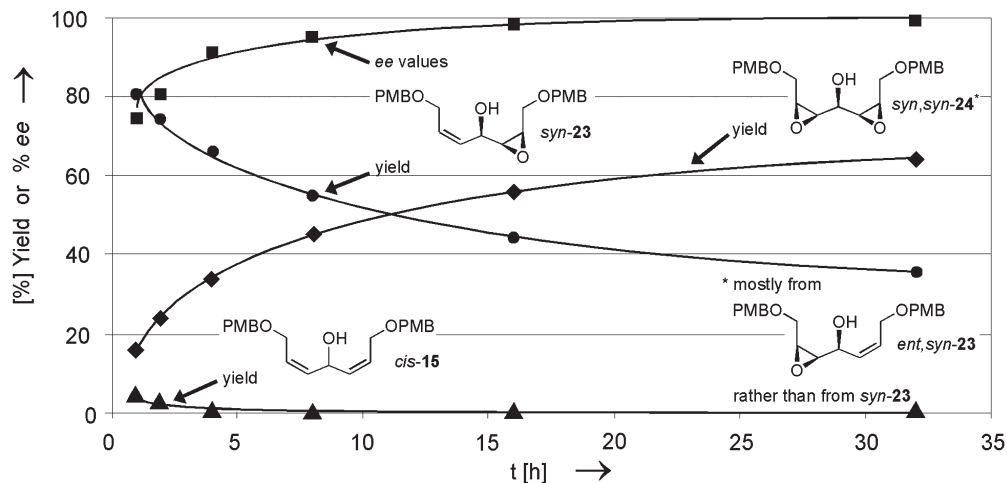
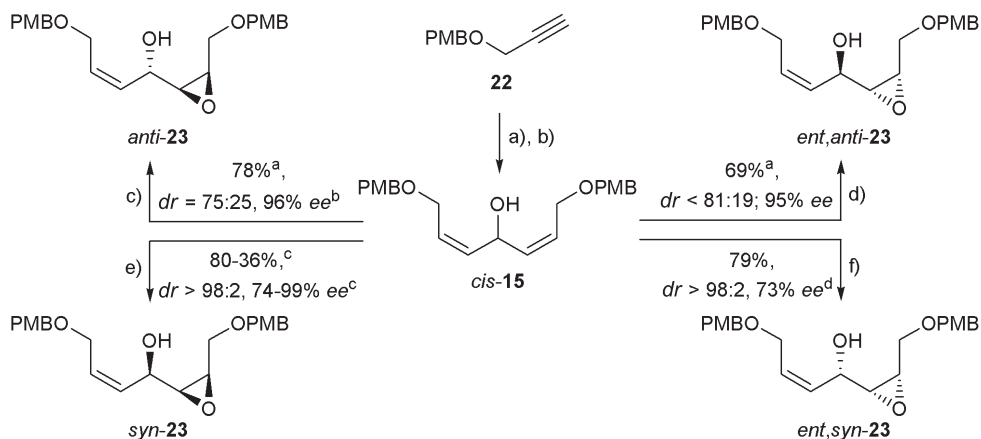
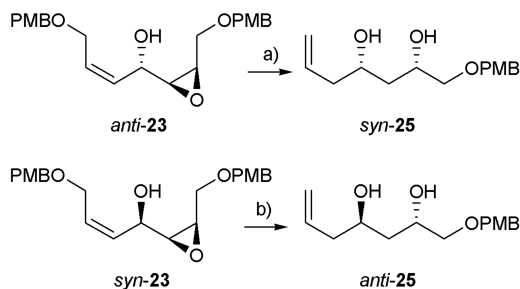


Figure 1 Time-resolved product analysis of the epoxidation of pentadienol *cis*-15a with tert-BuOOH (2.0 equiv.), $\text{Zr}(\text{OiPr})_4$ (1.0 equiv.), L-(+)-diisopropyl tartrate (1.1 equiv.), and molecular sieves (4 Å) in CH_2Cl_2 at -20°C .



Scheme 6 a) Red-AlTM, toluene; 83% (analogous reduction of *ent,anti*-23: 95%) (Ref. [9].

b) Same as (a); 51% (Ref. [10].

CV of Reinhard Brückner

Reinhard Brückner (born 1955) studied chemistry at the Universität München, acquiring his doctoral degree with Rolf Huisgen (1984). After post-doctoral studies with Paul A. Wender (Stanford University), he realized a habilitation under the auspices of Reinhard W. Hoffmann (Universität Marburg). Brückner has been a Professor of Organic Chemistry at the Universities of Würzburg (1990–92), Göttingen (1992–98), and Freiburg (since 1998) and a Visiting Professor at the Universities of Wisconsin (Madison), Santiago de Compostela (Spanien), Indiana (Bloomington), and Tokyo (Tokyo University). He received the Literature Prize of the Fonds der Chemischen Industrie for his textbook on organic reaction mechanisms and the Chemistry Prize of the Akademie der Wissenschaften Göttingen.

Selected Publications

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- 2R. (a) T. Katsuki, V. S. Martín, *Org. React.* **1996**, *48*, 1–299. *Asymmetric Epoxidation of Allylic Alcohols: The Katsuki-Sharpless Epoxidation Reaction.* (b) R. A. Johnson, K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, I. Ojima (Ed.), Wiley-VCH, Weinheim, 2nd edn., **2000**, pp. 231–286. *Catalytic Asymmetric Epoxidation of Allylic Alcohols.*
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6. S. L. Schreiber, M. T. Goulet, G. Schulte, *J. Am. Chem. Soc.* **1987**, *109*, 4718–4720. *Two-Directional Chain Synthesis: The Enantioselective Preparation of Syn-Skipped Polyol Chains from Meso Presursors.*
7. A. C. Spivey, S. J. Woodhead, M. Weston, B. I. Andrews, *Angew. Chem. Int. Ed.* **2001**, *40*, 769–771. *Enantioselective Desymmetrization of meso-Decalin Diallylic Alcohols by a New Zr-Based Sharpless AE Process: A Novel Approach to the Asymmetric Synthesis of Polyhydroxylated Celastraceae Sesquiterpene Cores.*
8. S. Weigand, R. Brückner, *Synlett* **1997**, 225–228. *Building Blocks for the Sterecontrolled Synthesis of 1,3-Diols of Various Configurations.*
9. T. Berkenbusch, R. Brückner, *Synlett* **2003**, 1813–1816. *Concise Synthesis of Optically Pure syn-1,3-Diols by Stereoselective Desymmetrization of a Divinylcarbinol.*
10. R. Kramer, R. Brückner, *Synlett* **2006**, 33–38. *Desymmetrizing Asymmetric Epoxidations of Bis(cis-Configured) Divinylcarbinols: Unusual syn-Selectivity Combined with ee-Enhancement through Kinetic Resolution.*