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Stereocomplementary Desymmetrizations of Divinylcarbinols by Zirconium(IV)- *vs.* Titanium(IV)-Mediated Asymmetric Epoxidations

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Dedicated to Professor Andreas Pfaltz on the occasion of his 60th birthday

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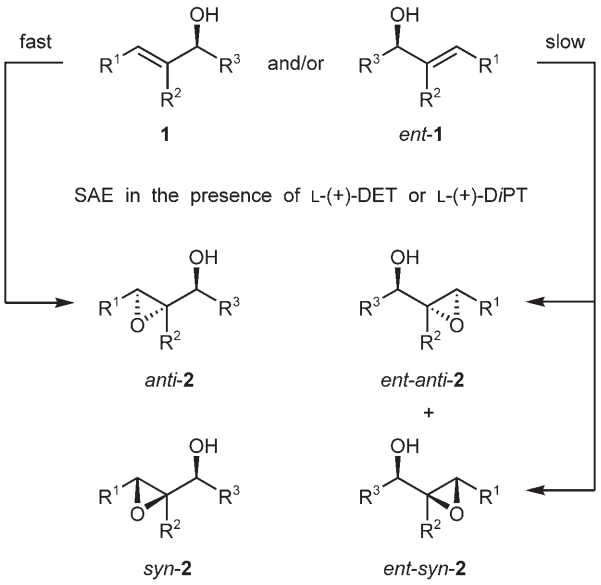
Abstract: Substituted C_s-symmetric penta-1,4-dien-3-ols ("divinylcarbinols") containing *cis*- or *trans*-disubstituted C=C bonds were desymmetrized by asymmetric monoepoxidations. Sharpless conditions gave *anti*-configured monoepoxides. For *cis*,*cis*-divinylcarbinols this was unprecedented. Oxidation with *tert*-butyl hydroperoxide (*t*-BuOOH) in the presence of zirconium tetraisopropoxide [Zr(O-*i*-Pr)$_4$] and a dialkyl tartrate led to the corresponding *syn*-configured monoepoxides. Under the reaction conditions the *ee* of monoepoxide *syn*-**12** increased with time from 75 to 99% *ee*. The reason is the preferential overoxidation of its minor enantiomer. The ease of preparation and multitude of functional groups make epoxides **12**–**14** worthwhile building blocks for the synthesis of non-racemic structures.

Keywords: diastereoselectivity; enantioselectivity; epoxy alcohols; kinetic resolution; Sharpless asymmetric epoxidation

Introduction

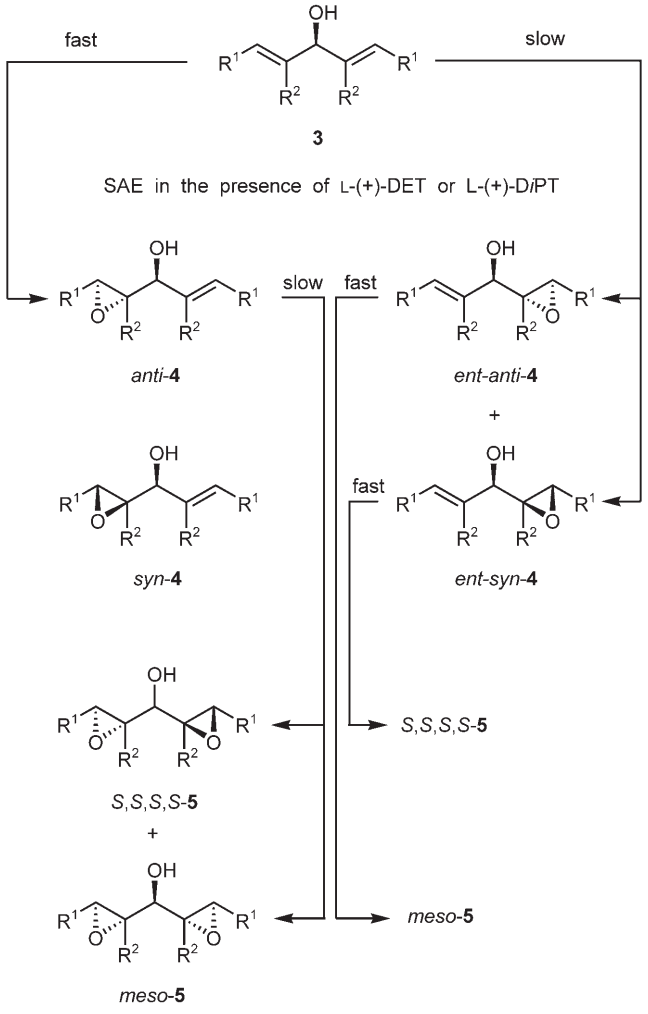
The conversion of allyl alcohols into non-racemic epoxy alcohols by Sharpless' asymmetric epoxidation[1] (SAE) is an almost universally possible transformation.[2] Accordingly, it has gained tremendous importance in synthesis.[3]

Most SAEs affect achiral primary allyl and racemic secondary allyl alcohols. In the latter case SAEs perform a kinetic resolution of the substrate. To this end, such an SAE is stopped after slightly more than 50% conversion. This is because at this moment the more reactive enantiomer **1** of the substrate has been epoxidized completely while the less reactive enantiomer *ent*-**1** has hardly begun to react (*cf.* Scheme 1). As a consequence, the remaining allyl alcohol (*ent*-**1**) is enantiomerically purer than the major diastereomer (*anti*-**2**/*ent*-*anti*-**2**) of the epoxy alcohol mixture (*anti*-**2**/*ent*-*anti*-**2**+*syn*-**2**). It should be noted that the enantio- and the diastereoselectivity, with which epoxy alcohol *anti*-**2** emerges from the SAE of Scheme 1 are highest at the onset of the reaction and decrease with increasing conversion.



Scheme 1. Sharpless' asymmetric epoxidation (SAE) of chiral secondary allyl alcohols ("vinylcarbinols").[1] DET = diethyl tartrate, D*i*PT = diisopropyl tartrate.

The opposite dependence of selectivity from time characterizes the SAEs shown in Scheme 2. They were pioneered by the groups of Takano[4] and Jäger[5] studying SAEs of penta-1,4-dien-3-ol (**3**, $R^1=R^2=H$). SAEs of symmetrically substituted penta-1,4-dien-3-ols **3** (R^1 and/or $R^2\neq H$, "divinyl carbinols") proceed similarly.[6–10] The essence of these reactions is threefold: They provide monoepoxy alcohols **4** in preference to bisepoxides **5**; they proceed with unusually high diastereoselectivities; they exhibit extraordinary enantiopurities (up to 99% *ee*). Scheme 2 reveals these features only implicitly. Explicitly, it explains how they arise. It does so by drawing from analogy to the reactions depicted in Scheme 1. Thereby the outcome of the SAEs of Scheme 2 can be understood as follows. Step 1 of the epoxidation of divinylcarbinols **3** reflects the reactivity pattern of the epoxidation of the racemic carbinol **1**/*ent*-**1** of Scheme 1. This is because structurally the reactive (*left*) moiety of **3** resembles the reactive (*left*) enantiomer **1**; likewise, the unreactive (*right*) moiety of **3** resembles the unreactive (*right*) enantiomer *ent*-**1**. Thus, it is plausible to assume that the major monoepoxide formed from **3** must possess stereostructure *anti*-**4** and that the minor monoepoxides should be *ent-anti*-**4** and *ent-syn*-**4**. Since monoepoxide *anti*-**4** is devoid of the reactive substructure **1**, it undergoes overepoxidation only slowly. In contrast, the minor monoepoxides *ent-anti*-**4** and *ent-syn*-**4** still contain substructure **1**. Therefore, monoepoxide *ent-anti*-**4** should be overepoxidized relatively fast, delivering bisepoxide *S*,*S*,*S*,*S*-**5**, and monoepoxide *ent-syn*-**4** should proceed to bisepoxide *meso*-**5** about as readily. The ensemble of the rate constants of these overepoxidation steps causes the initially obtained monoepoxide mixture to change composition upon continued reaction with the oxidant: In essence, monoepoxide *anti*-**4** enjoys longevity whereas monoepoxides *ent-anti*-**4** and *ent-syn*-**4** are annihilated. Differently expressed, the more the SAEs of Scheme 2 progress, the higher enantio- and diastereoselectivity of monoepoxide formation. The mathematical analysis of these relationships[6a,b,11] let Schreiber et al. point out that "the ratio of enantiomers can become *arbitrarily large* as the reaction goes to completion".[6a]

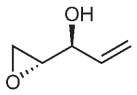


Scheme 2. SAE of achiral secondary allyl alcohols ("divinylcarbinols").[4–10] DET = diethyl tartrate, D*i*PT = diisopropyl tartrate.

Scheme 3 (upper part) compiles all divinylcarbinol monoepoxides or their enantiomers, which, to the best of our knowledge, have ermerged from SAEs to date. Penta-1,4-dien-3-ol was epoxidized asymmetrically by the groups of Takano,[4] Jäger,[5] and Schreiber,[6] yielding monoepoxide *anti*-**6**. The *ee* of *anti*-**6** increased dramatically with time [84% *ee* (after 3 h) to >97% *ee* (after 140 h)].[6a] 2,4-Dimethylpenta-1,4-dien-3-ol led to monoepoxide *anti*-**7** with an *ee*, which again improved considerably with increasing conversion [88% *ee* (after 0.5 h)→≥99.3% *ee* (after 1.5 h)].[6a,b] *E*,*E*-3,5-Dimethylhepta-2,5-dien-4-ol delivered monoepoxide *anti*-**8** (>95% *ee*).[10] In addition, we are aware of three *trans*,*trans*-disubstituted divinylcarbinols which were subjected to desymmetrizing SAEs (→*anti*-**9**,[7] *anti*-**10**,[8] *anti*-**11**[6a,b,9]). For monoepoxide *anti*-**11** once more, an inverse proportionality between *ee* and time was published [93% *ee* (after 1 h)→≥97% *ee* (after 44 h)].[6a]

The bottom half of Scheme 3 shows the monoepoxy alcohols (*anti*- and *syn*-**12**-*anti*- and *syn*-**14**) obtained from divinylcarbinols by the desymmetrizations investigated here.[12] Employing *t*-BuOOH/dialkyl D- or L-tartrate/Ti(O-*i*-Pr)$_4$ mixtures as the oxidant, non-racemic monoepoxy alcohols *anti*-**12–14** were obtained. Bis(*cis*-configured) divinylcarbinols (→*anti*-**12** and *anti*-**13**) had not been involved in this transformation before. Using *t*-BuOOH and a dialkyl D- or L-tartrate as before but now adding Zr(O-*i*-Pr)$_4$ instead of Ti(O-*i*-Pr)$_4$, the divinylcarbinols of the present study were desymmetrized by conversion into the non-racemic

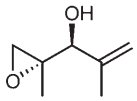
Literature:



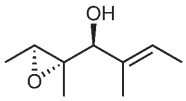
anti-**6** [4-6]

t [h]	*ds* of SAE	*anti*-Diastereomer Yield [%]	*ee* [%]	Ref.
3	84:16	_[a]	84	[6a]
24	99:1	_[a]	93	[6a]
140	>99:<1	_[a]	>97	[6a]

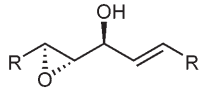
[a] Not published.



anti-**7** [6a,b]



anti-**8** [10]



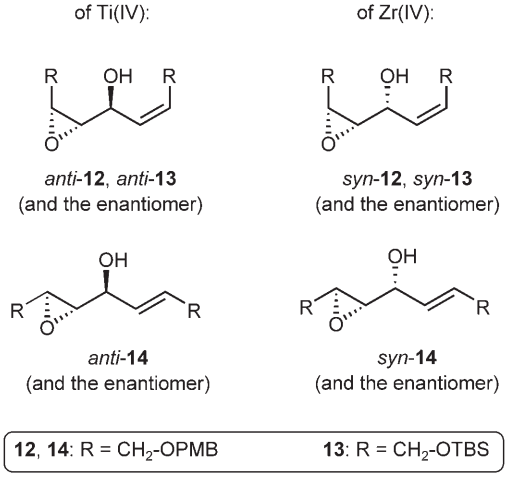
		t [h]	*ds* of SAE	*anti*-Diastereomer Yield [%]	*ee* [%]
anti-**9**:[7]	R = Ph[a]	42	88:12	63	99
anti-**10**:[8]	R = CH_2OTBS	_[b]	≥94:≤6	70-80	97
anti-**11**:[6a]	R = CH_2OBn	44	≥94:≤6	_[b]	>97
anti-**11**:[9]	R = CH_2OBn[c]	_[b]	_[b]	82	_[b]

[a] Only the synthesis of the enantiomer (*ent-anti*-**9**) was described, using D-D*i*PT as the chiral auxiliary.

[b] Not published.

[c] Only the synthesis of the enantiomer (*ent-anti*-**11**) was described by epoxidation, using D-DiPT as the chiral auxiliary.

This work: Major diastereomer obtained by epoxidation in the presence



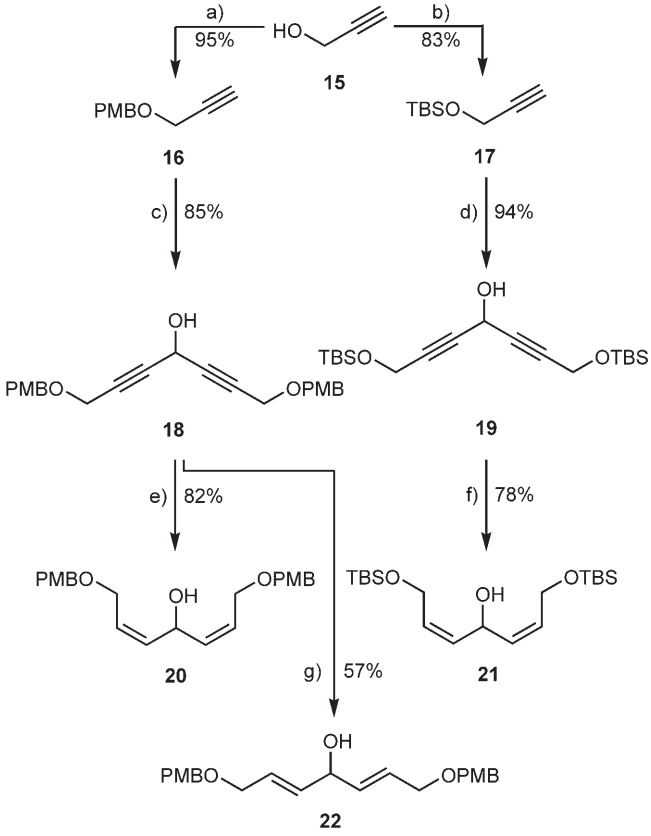
Scheme 3. Non-racemic epoxy alcohols from desymmetrizing epoxidations of divinylcarbinols reported earlier[4–10] or studied here.[12] TBS = *t*-BuMe_2Si, Bn = CH_2Ph, PMB = *para*-methoxybenzyl.

diastereomeric monoepoxy alcohols *syn*-**12**–*syn*-**14**. Accordingly, changing the metal counterpart of the isopropoxide additive made it feasible to realize asymmetric epoxidations with *complementary* favorite diastereoselectivities. In this regard, our Zr(IV)-mediated desymmetrizations represent a valuable extension of Sharpless' methodology.

Results and Discussion

Preparation of Disubstituted C_s-Symmetrical Divinylcarbinols

The required divinylcarbinols **20**–**22** were obtained in three steps and isomerically pure from propargyl alcohol (Scheme 4). Step 1 comprised etherifications of propargyl alcohol giving (*para*-methoxybenzyl) propargyl ether **16** (95%) and (*tert*-butyldimethylsilyl) propargyl ether **17** (83%), respectively. Conversion into the corresponding lithium acetylides and reaction



Scheme 4. Synthesis of bis(*cis*-configured) divinylcarbinols **20** and **21** and bis(*trans*-configured) divinylcarbinol **22**. *Reagents and conditions:* a) NaH (1.2 equiv.), DMF, 0 °C; addition of PMB-Cl (1.1 equiv.), 0 °C, 30 min, →room temperature, 14 h; 93%. b) TBS-Cl (1.03 equiv.), imidazole (2.8 equiv.), DMF, 0 °C, 14 h; 83%. c) **16** (2.3 equiv.), *n*-BuLi (2.1 equiv.), THF, −78 °C, 70 min, addition of HCO_2Et; → −35 °C, 20 h; 85%. d) **17** (2.03 equiv.), *n*-BuLi (2.03 equiv.), THF, −78 °C, 40 min, addition of HCO_2Et, →−30 °C, 15 h; 94%. e) Zn (20 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.0 equiv.), H_2O, room temperature, 10 min, addition of $AgNO_3$ (1.0 equiv.), 1 h, filtration, transfer of reductant into MeOH, addition of **18**, 40 °C, 14 h; 82%. f) Zn (15 equiv.), $Cu(OAc)_2 \cdot H_2O$ (0.75 equiv.), H_2O, room temperature, 10 min, addition of $AgNO_3$ (0.75 equiv.), 1 h; filtration, transfer of reductant into MeOH/H_2O (1:1), addition of **19**, room temperature, 14 h; 78%. g) Red-Al® (10 equiv.), THF, −40 °C, 29 h; 57%. TBS = *t*-BuMe_2Si, PMB = *para*-methoxybenzyl.

of two equivalents thereof with ethyl formate furnished dialkynylcarbinols **18** (85%) and **19** (94%), respectively, in step 2.

Initially, we reduced the C≡C bonds of dialkynylcarbinols **18** and **19** *cis*-selectively with Rieke zinc[13] – prepared from $ZnCl_2$ and molten potassium in refluxing THF[14] – in methanol. This furnished divinylcarbinols **20** and **21** in 75% and 72% yield, respectively.[12a] For larger scale work, we modified the reductant because of safety concerns, using zinc dust (15–20 equiv.) activated by $Cu(OAc)_2 \cdot H_2O$ (0.75–1.0 equiv.) and $AgNO_3$ (0.75–1.0 equiv),[15] again in methanol.[16] This was also a beneficial change for the yields, which were augmented to 82% **20** and 78% **21**, respectively. The *cis*-configuration of these compounds followed from the modest size of their olefinic H,H coupling constants (11.1 Hz both in **20** and **21**). The *trans*-reduction of the C≡C bonds of dialkynylcarbinol **18** was achieved at −40 °C with Red-Al® in THF.[17] It afforded divinylcarbinol **22** in 57% yield as a pure stereoisomer.[18] The *trans*-configuration of its C=C bonds was established by the magnitude of the olefinic H,H coupling constant (15.6 Hz), too.

Asymmetric Epoxidations of the Bis(*cis*-configured) Divinylcarbinol 20

Usually, SAEs of primary allyl alcohols are less enantioselective when the C=C bond is *cis*- rather than *trans*-configured.[2a,d] SAEs of monoethers of *cis*-2-butene-1,4-diol are no exception: Its PMB monoether is epoxidized with 85–88% *ee*[19] and the corresponding TBS monoether with 84–85% *ee*.[20] These compounds are partial structures of our divinylcarbinols **20** and **21**, respectively. Therefore, enantiocontrol of the monoepoxidation step of substrates **20** and **21** was expected to be less efficient, and a selective overepoxidation of the minor enantiomer seemed crucial for improving the initial *ee* value.

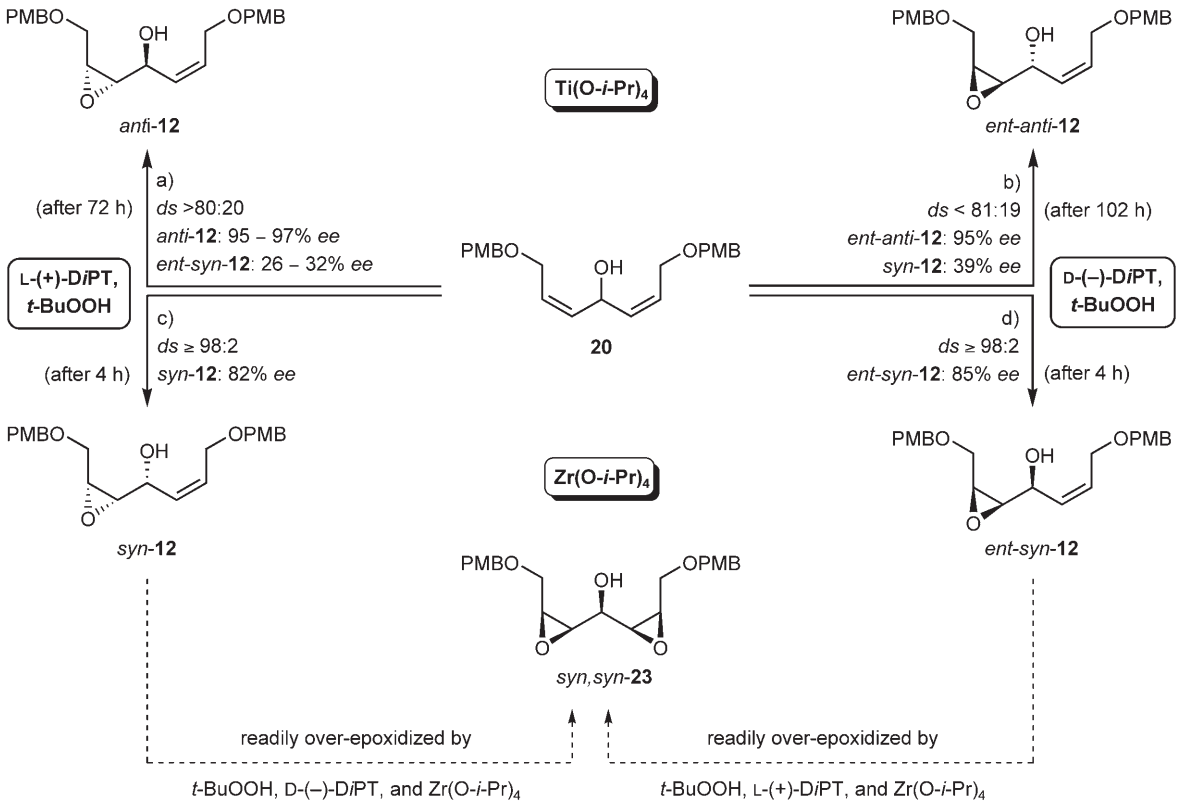
First, we subjected the PMB-containing divinylcarbinol **20** to standard SAEs (Scheme 5, top). We worked at −20 °C to −25 °Cin order to foster stereoselectivity – and we added 4 Å molecular sieves to the reaction mixtures and stoichiometric amounts of $Ti(O\text{-}i\text{-}Pr)_4$ and diisopropyl tartrate ("D*i*PT") in order to increase the turnover. Employing L-(+)- and D-(−)-D*i*PT as an additive, epoxy alcohols *anti*-**12** and *ent-anti*-**12**, respectively, resulted with moderate *anti*-selectivities ($ds \approx 75{:}25$[21] for the crude product and $\approx 80{:}20$[21] after flash-chromatography on silica gel[22]). Their enantiomeric excesses were 95–97%.[23] It was thereby shown for the first time that a bis(*cis*-configured) divinylcarbinol can be desymmetrized efficiently under SAE conditions. Unfortunately, separating the respective major from the respective minor diastereomer, i.e., *anti*-**12** from *ent-syn*-**12** and *ent-anti*-**12** from *syn*-**12** was difficult. Repeated passages through a flash chromatography column filled with silica gel[22] were required before we obtained pure *anti*-**12** (27%) and pure *ent-anti*-**12** (22%), respectively.

Next, we subjected the PMB-containing divinylcarbinol **20** to an otherwise identical epoxidation protocol in which we replaced $Ti(O\text{-}i\text{-}Pr)_4$ by $Zr(O\text{-}i\text{-}Pr)_4 \cdot i\text{-}PrOH$ (Scheme 5, bottom). The pertinent – albeit sole – literature precedent[24] for desymmetrizing epoxidations under these conditions suggested that the same product(s) as before would be obtained, yet possibly with a higher *ee* than in the presence of $Ti(O\text{-}i\text{-}Pr)_4$.[25] Actually we observed a significant acceleration (3 d→ 4 h) compared to the $Ti(O\text{-}i\text{-}Pr)_4$-mediated process *and a complete reversal of the diastereocontrol*: i.e., when we epoxidized divinylcarbinol **20** in the presence of $Zr(O\text{-}i\text{-}Pr)_4 \cdot i\text{-}PrOH$ and L-(+)-D*i*PT, we isolated epoxy alcohol *syn*-**12** exclusively ($ds \geq 98{:}2$;[21] 74% yield). Likewise, epoxidation in the presence of $Zr(O\text{-}i\text{-}Pr)_4 \cdot i\text{-}PrOH$ and D-(−)-D*i*PT afforded the enantiomeric epoxy alcohol *ent-syn*-**12** as a single diastereomer ($ds \geq 98{:}2$;[21] 64% yield).

Additionally, the last-mentioned epoxidations provided a bisepoxide in yields of 25% and 32%, respectively. It was sterically homogeneous and turned out to be the *meso*-compound *syn,syn*-**23**. The formation of this stereoisomer from divinylcarbinol **20** at the expense of the two conceivable diastereomers means that each C=C bond is epoxidized with high *syn*-diastereoselectivity. As implied (*vide infra*) by the investigation of Figure 1 the $Zr(O\text{-}i\text{-}Pr)_4$-mediated formation of bisepoxide *syn,syn*-**23** proceeds mostly *via* epoxy alcohol enantiomer *ent-syn*-**12** if L-(+)-D*i*PT is present. Hence, it must stem mostly from *syn*-**12** in the presence of D-(−)-D*i*PT.

Due to the much faster Zr(IV)- than Ti(IV)-mediated epoxidation of divinylcarbinol **20** we found it worthwhile testing whether catalytic rather than stoichiometric amounts of $Zr(O\text{-}i\text{-}Pr)_4 \cdot i\text{-}PrOH$ and L-(+)-D*i*PT suffice to effect the reaction (Table 1). However, reducing the amount of $Zr(O\text{-}i\text{-}Pr) \cdot i\text{-}PrOH$ from 1.0 to 0.1 equiv. did not result in any conversion even after 24 h (entry 1). Inertness persisted when the amount of $Zr(O\text{-}i\text{-}Pr) \cdot i\text{-}PrOH$ was doubled to 0.2 equiv. (entry 2). Increasing additionally the concentration of the substrate from 0.033 M to 0.1 M was no remedy either (entry 3). The only successful experiment of Table 1 was run at 0 °C instead of −20 °C (entry 4): After 20 h one half of the divinylcarbinol **20** had reacted.[26] Separation by flash chromatograph[22] furnished 37% of a 95:5 mixture[21] of monoepoxy alcohol *syn*-**12** ($ee = 32\%$[27]) and its *anti*-isomer. This result could not compete with the stoichiometric process.

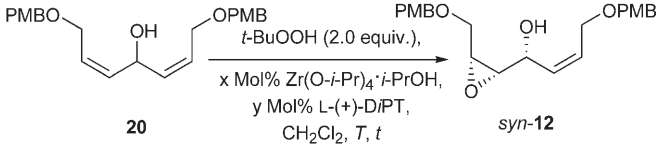
The weakness of the $Zr(O\text{-}i\text{-}Pr)_4$-mediated epoxidations of divinylcarbinol **20** *when allowed to proceed for only 4 h as displayed in* Scheme 5 was a lack of



Scheme 5. Desymmetrizations of divinylcarbinol **20** by classical SAE (top) and by its Zr-analogue (bottom). *Reagents and conditions:* a) Ti(O-*i*-Pr)$_4$ (1.05 equiv), L-(+)-D*i*PT (1.1 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C, 30 min, addition of *t*-BuOOH (2.0 equiv.), 1 h, addition of **20**, −20 °C, 72 h; 69–72% mixture of diastereomers, *ds* > 80:20, *anti*-**12**: 95–97% *ee*, *ent-syn*-**12**: 26–32% *ee*. b) Ti(O-*i*-Pr)$_4$ (1.0 equiv.), D-(−)-D*i*PT (1.1 equiv.), 4 Å molecular sieves, CH_2Cl_2, −25 °C, 1 h, addition of **20**, 1 h, addition of *t*-BuOOH (1.4 equiv.), −25 °C, 55 h, addition of *t*-BuOOH (0.7 equiv.), 47 h; 69% mixture of diastereomers, *ds* < 81:19, a*nti*-**12**: 95% *ee*, *syn*-**12**: 39% *ee*. c) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C; addition of L-(+)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 30 min, addition of **20**, −20 °C, 4 h; 74% *syn*-**12** (*ds* ≥ 98:2, 82% *ee*), 25% *syn*,*syn*-**23**. d) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C, addition of D-(−)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 30 min, addition of **20**, −20 °C, 4 h; 64% *ent-syn*-**12** (*ds* ≥ 98:2, 85% *ee*), 32% *syn*,*syn*-**23**. D*i*PT = diisopropyl tartrate; PMB = *para*-methoxybenzyl.

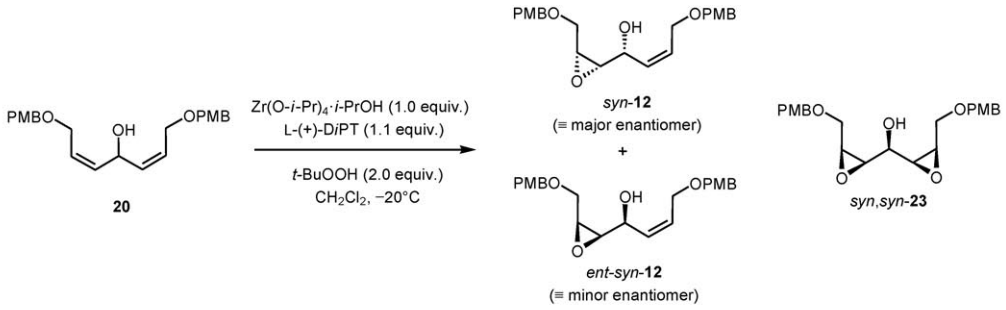
enantiocontrol. After the mentioned time, *syn*-**12** possessed 82% *ee*[27] and *ent-syn*-**12** 85% *ee*.[27] As discussed in the context of Scheme 2, an extended reaction time should increase the enantioselectivity. This effect was put to evidence and the underlying mechanism corroborated by monitoring the progress of the epoxidation **20**→*syn*-**12** from the start until 32 h later (Figure 1). To this end, we dissolved the substrate (1.56 mmol), L-(+)-D*i*PT (1.1 equiv.), and Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.) in CH_2Cl_2 (48 mL), added molecular sieves, cooled to −20 °C, and started the epoxidation at $t = t_0$ by the addition of excess *t*-BuOOH (2.0 equiv.). At appropriately spaced intervals (namely at $t_{sampling} = 1$, 2, 4, 8, 16, and 32 h), 8 mL aliquots were removed from the reaction mixture and worked up extractively as described in the Experimental Section. In the resulting crude product we ascertained the relative amounts of substrate (**20**), monoepoxide (*syn*-**12**), and bisepoxide (*syn*,*syn*-**23**) by 300 MHz ^{1}H NMR spectroscopy.[26] Subsequently, we

Table 1. Attempts to perform catalytic desymmetrizations of divinylcarbinol **20** in the presence of Zr(O-*i*-Pr)$_4$·*i*-PrOH.



Entry	x	y	T [°C]	t [h]	*syn*-**12** Yield [%]	*syn*:*anti*	*ee* [%]
1	10	11	−20	24	[a]	—	—
2	20	22	−20	24	[a]	—	—
3[b]	20	22	−20	24	[a]	—	—
4	20	22	0	20	37	95:5[18]	32[27]

[a] No conversion of **20** occurred according to TLC analysis.
[b] The concentration of **20** was three times higher than in entries 1, 2, and 4.



t [h]	1	2	4	8	16	32
molar ratio from ^{1}H-NMR spectroscopy:[26]						
20 : (*syn*-**12** + *ent-syn*-**12**) : *syn*,*syn*-**23**	4 : 80 : 16	2 : 74 : 24	0 : 66 : 34	0 : 55 : 45	0 : 44 : 56	0 : 36 : 64
molar ratio from HPLC analysis:[27]						
syn-**12** : *ent-syn*-**12**	87.5 : 12.5	90.5 : 9.5	95.5 : 4.5	97.5 : 2.5	99:1	99.5 : 0.5
molar ratios combined:						
20 : *syn*-**12** : *ent-syn*-**12** : *syn*,*syn*-**23**	4 : 70 : 10 : 16	2 : 67 : 7 : 24	0 : 63 : 3 : 34	0 : 53.6 : 1.4 : 45	0 : 43.6 : 0.4 : 56	0 : 35.8 : 0.2 : 64
ee [%] of *syn*-**12**/*ent-syn*-**12** mixtures:	75	81	91	95	98	99

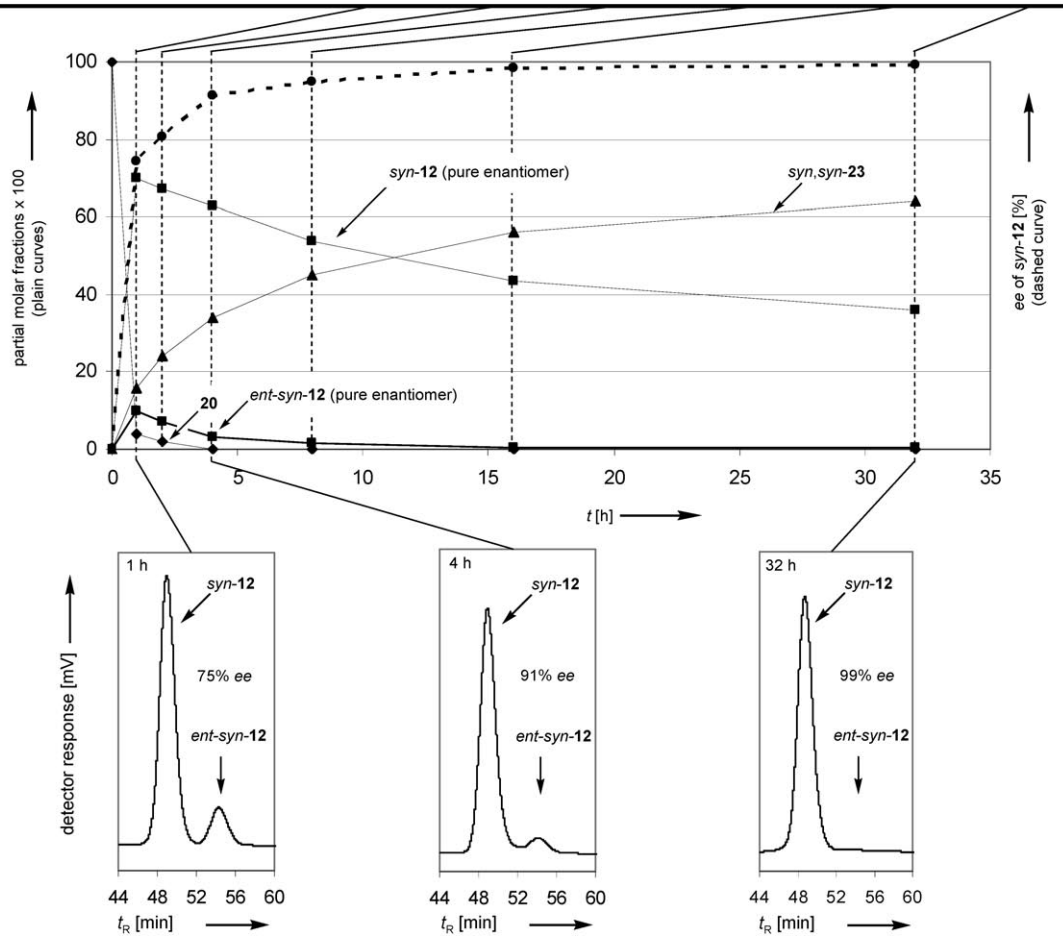


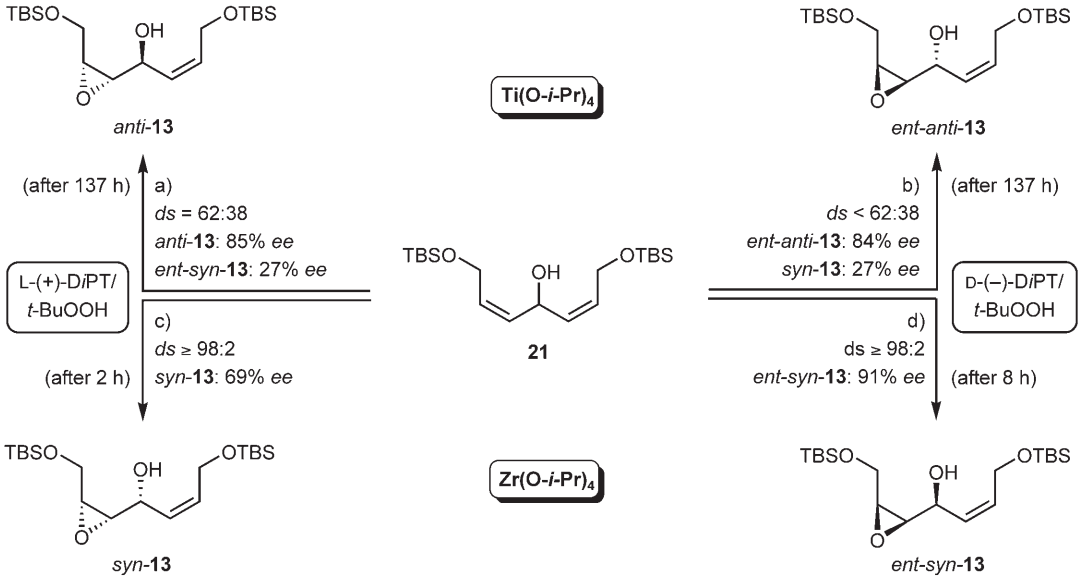
Figure 1. Time-resolved analysis of the desymmetrization of divinylcarbinol **20** by a Zr(O-*i*-Pr)$_4$-mediated epoxidation (→ *syn*-**12**+*ent-syn*-**12**) and overepoxidation (→*syn*,*syn*-**23**) in the presence of L-(+)-D*i*PT. Elucidating the composition of **20**/(*syn*-**12**+*ent-syn*-**12**)/*syn*,*syn*-**23** mixtures[26] sampled at progressive points of the experiment and determining – after separation from the other components – the enantiopurity of the *syn*-**12**/*ent-syn*-**12** mixture established the relative amounts of all mentioned species as a function of the reaction time. These values – expressed as partial molar fractions × 100 – are listed in the table and plotted in the diagram (full lines). The diagram also traces the evolution of the *ee* value with the reaction time (dashed line). Sections from representative HPLC chromatograms,[27] from which the *syn*-**12**/*ent-syn*-**12** ratios and *ee* values were obtained are inserted.

isolated the monoepoxy alcohol *syn*-**12** by flash chromatography on silica gel.[22] Finally, we determined the enantiopurity of *syn*-**12** by HPLC.[27]

In the preceding paragraph, "*syn*-**12**" is a shorthand designation for a "mixture composed mainly of the pure enantiomer *syn*-**12** and to a lesser extent of the pure enantiomer *ent-syn*-**12**". Bearing this in mind, our study revealed at each cumulative reaction time $t_{sampling}$ the relative amounts of **20**, *syn*-**12**+*ent-syn*-**12** combined, and *syn*,*syn*-**23** in the reaction mixture (from ^{1}H NMR analysis) *and* the proportion of the pure enantiomers *syn*-**12** and *ent-syn*-**12** (from the *ee* value of "*syn*-**12**"). This allowed plotting the relative amounts of the starting material **20** and its three oxidation products *syn*-**12**, *ent-syn*-**12**, and *syn*,*syn*-**23** as a function of the reaction time (Figure 1, plain curves). When the reaction of Figure 1 had proceeded for 1 h, only 4% of the divinylcarbinol **20** were left and after 2 h just 2% **20**, while after 4 h **20** had been completely consumed. As a consequence, at $t_{sampling}$ = 1 h already we detected the largest proportion of monoepoxy alcohols (80%; 70% *syn*-**12**+10% *ent-syn*-**12**) of the whole experiment; concomitantly, we found a smaller proportion of the bisepoxide (16%) than ever again. By the subsequent analyses (at $t_{sampling}$ = 2, 4, 8, 16, and 32 h) we detected decreasing amounts of the monoepoxy alcohols (74, 66, 55, 44, and 36%) and increasing amounts of the bisepoxy alcohol (24, 34, 45, 56, and 64%), which both was due to the interference of overepoxidation. According to the data tabulated in Figure 1 overepoxidation affected the minor monepoxy alcohol enantiomer *ent-syn*-**12** *disproportionately* more than the major monepoxy alcohol enantiomer *syn*-**12**. Therefore, the yield ratio *ent-syn*-**12**/*syn*-**12** shrank the more the overepoxidation interfered: from its largest value 0.014 (=10%/70%) at $t_{sampling}$ = 1 h *via* distinctly smaller values like 0.026 (=1.38%/53.6%) at $t_{sampling}$ = 8 h to a minimum value of only 0.0050 (=0.18%/35.8%) at $t_{sampling}$ = 32 h. Correspondingly, the *ee* value of *syn*-**12** went up (Figure 1, dashed curve): from 75% *ee* after 1 h *via* 95% *ee* after 8 h to 99% *ee* after 32 h. At the latter point in time we stopped the epoxidation experiment of Figure 1 for good because the enantiopurity, which we had reached, was superb. Admittedly, this *ee* improvement cost its (intrinsic) price: the loss of a little more than half of the initially detected monoepoxy alcohol between $t_{sampling}$ = 1 h and 32 h.

Asymmetric Epoxidations of the Bis(*cis*-configured) Divinylcarbinol 21

Scheme 6 shows the outcome of asymmetric epoxidations of the TBS-containing bis(*cis*-configured) divinylcarbinol **21** under similar conditions as previous-



Scheme 6. Desymmetrizations of divinylcarbinol **21** by classical SAE (top) and by its Zr-analogue (bottom). *Reagents and conditions:* a) Ti(O-*i*-Pr)$_4$ (1.0 equiv.), L-(+)-D*i*PT (1.1 equiv.), 4 Å molecular sieves, CH_2Cl_2, −25 °C, 50 min, addition of **21**, 1 h, addition of *t*-BuOOH (1.4 equiv.), 5 d, addition of *t*-BuOOH (0.65 equiv.), −25 °C, 17 h; 77% mixture of diastereomers, *ds* = 62:38, *anti*-**13**: 85% *ee*, *ent-syn*-**13**: 27% *ee*, 17% reisolated **21**. b) Ti(O-*i*-Pr)$_4$ (1.0 equiv.), D-(−)-D*i*PT (1.1 equiv.), 4 Å molecular sieves, CH_2Cl_2, −25 °C, 50 min, addition of **21**, 1 h, addition of *t*-BuOOH (1.4 equiv.), 5 d, addition of *t*-BuOOH (0.65 equiv.), −25 °C, 17 h; 74% mixture of diastereomers, *ds* = 62:38, *ent-anti*-**13**: 84% *ee*, *syn*-**13**: 27% *ee*, 14% reisolated **21**. c) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C; addition of L-(+)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 30 min, addition of **21**, −20 °C, 2 h; 66% *syn*-**13** (*ds* ≥ 98:2, 69% *ee*). d) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C; addition of D-(−)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 30 min, addition of **21**, −20 °C, 8 h; 49% *ent-syn*-**13** (*ds* ≥ 98:2, 91% *ee*). D*i*PT = diisopropyl tartrate; TBS = *t*-BuMe_2Si.

ly applied to the (*para*-methoxybenzyl)-containing divinylcarbinol **20** (Scheme 5, Figure 1). A remarkable difference between substrates **21** and **20** was the lower reactivity of the former. The SAEs of compound **21** in the presence of stoichiometric amounts of Ti(O-*i*-Pr)$_4$ and L-(+)-D*i*PT (→*anti*-**13**) or D-(−)-D*i*PT (→*ent-anti*-**13**) proceeded particularly sluggishly (Scheme 6, upper part). Even after 6 d unreacted **21** was recovered in yields of 17% and 14%, respectively. A more disturbing shortcoming of the two reactions were their low levels of diastereocontrol (→*anti*-**13**:*ent-syn*-**13** = 62:38 and *ent-anti*-**13**:*syn*-**13** = 62:38, respectively[28]) and enantiocontrol ($ee_{anti\text{-isomer}} = 85$ and 84%, respectively;[29] $ee_{syn\text{-isomer}} = 27\%$ in both cases[30]). Work-up and purification by "routine" flash chromatography on silica gel[22] provided the monoepoxy alcohols *anti*-**13**/*ent-syn*-**13** (77% yield) and *ent-anti*-**13**/*syn*-**13** (74% yield), respectively. Careful renewed purification by flash chromatography provided access to 39% pure diastereomer *anti*-**13** in one optical series and to pure diastereomer 19% *ent-anti*-**13** in the other; no pure *syn*-isomers could be obtained, though.

The Zr-mediated epoxidations of divinylcarbinol **21** with L-(+)-D*i*PT proceeded much faster than the corresponding Ti(IV)-based SAE (Scheme 6, lower left). After 2 h **21** was already completely consumed (according to TLC analysis). Monoepoxy alcohol *syn*-**13** resulted in 66% yield with almost perfect diastereoselectivity ($ds \geq 98{:}2$[28]). It exhibited 69% *ee*,[30] which is somewhat inferior to the enantiocontrol of the Zr-mediated epoxidation of divinylcarbinol **20**: 74% *ee* after 1 h (Figure 1).

The Zr-mediated epoxidation of divinylcarbinol **21** in the presence of D-(−)-D*i*PT furnished the enantiomeric monoepoxy alcohol *ent-syn*-**13** (Scheme 6, lower right). In this experiment we prolonged the reaction time from 2 to 8 h, hoping for an increased level of enantioselectivity due to the greater susceptibility of one monoepoxy alcohol enantiomer than to overepoxidation. Indeed these conditions furnished a diastereomerically pure[28] specimen of *ent-syn*-**13** with an improved *ee* of 91%[30] in a somewhat reduced yield (49%). The expected bisepoxy alcohol(s) evaded our attention, though.

Asymmetric Epoxidations of the Bis(*trans*-configured) Divinylcarbinol 22

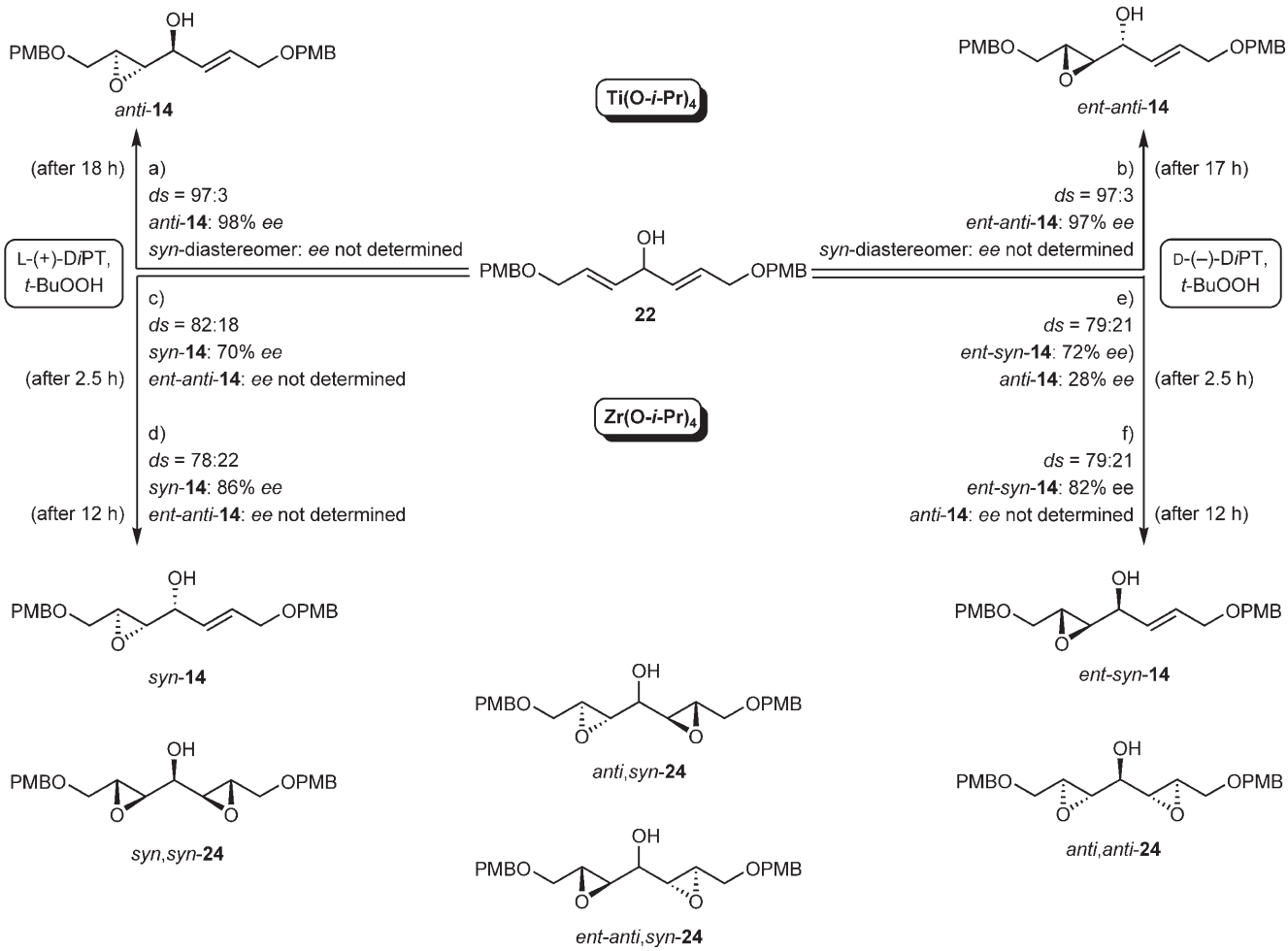
So far, the bis(*cis*-configured) divinylcarbinols **20** and **21** had been desymmetrized by asymmetric epoxidations such that the Ti(O-*i*-Pr)$_4$- and the Zr(O-*i*-Pr)$_4$-mediated processes exhibited complementary diastereoselectivities: The former epoxidation was *anti*- and the latter *syn*-selective. The same bias was displayed by analogous desymmetrizations of the bis(*trans*-configured) divinylcarbinol **22** (Scheme 7).

While the SAEs of the bis(*cis*-configured) substrates **20** (Scheme 5) and **21** (Scheme 6) required stoichiometric amounts of both the isopropoxide and the tartrate, the presence of 7 mol% of Ti(O-*i*-Pr)$_4$ and 9 mol% either of L-(+)- or D-(−)-D*i*PT sufficed to let the bis(*trans*-configured) substrate **22** react to completion within 17–18 h (Scheme 7, top). This furnished 82% of the monoepoxy alcohol *anti*-**14** highly diastereoselectively ($ds = 97{:}3$[31]) and highly enantioselectively (98% *ee*[32]) and its enantiomer *ent-anti*-**14**, respectively, with comparably good values (78% yield, $ds = 97{:}3$,[31] 97% *ee*[32]). This is in full agreement with the quality of the Hatakeyama and Schreiber syntheses, by the same desymmetrization technique (Scheme 1), of the analogous bisbenzyl-containing monoepoxy alcohol *anti*-**11** (70–80% yield, $ds \geq 94 \leq 6$, 97% *ee*).[6a,8]

The Zr(O-*i*-Pr)$_4$-mediated monoepoxidations of the bis(*trans*-configured) substrate **22** were less *syn*-selective ($ds \approx 80{:}20$[31]; Scheme 7, bottom) than their predecessors in the *cis* series ($ds \geq 98{:}2$, Scheme 5, Scheme 6). Epoxidizing for 2.5 h in the presence of L-(+)-D*i*PT, we isolated 19% unchanged divinylcarbinol **22**, 40% of a 81:18 mixture[31] of monoepoxy alcohol *syn*-**14** and the isomer *ent-anti*-**14**, and 17% of a mixture of the three conceivable diastereomeric bisepoxides **24**.[33] Monoepoxy alcohol diastereomer *syn*-**14** was enriched as a 97:3 mixture[31] with the mentioned *anti*-isomer by repeated flash chromatography on silica gel.[22] Its *ee* was 70%.[34] As expected, the Zr-mediated epoxidation of substrate **22** under the influence of the enantiomeric auxiliary D-(−)-D*i*PT delivered a closely related result [25% recovered **22**, 38% of a 79:21 mixture[31] of monoepoxy alcohol *ent-syn*-**14** (72% *ee*[34]) and isomer *anti*-**14** (28% *ee*[32]), 19% of the mixture of three diastereomeric bisepoxides **24**].[33] Allowing the reactions to proceed for 12 rather than 2.5 h, we isolated the monoepoxy alcohols *syn*-**14** ($ds = 78{:}22$[31]) and *ent-syn*-**14** ($ds = 79{:}21$[31]) in yields of 31% and 34% yield, respectively. Their enantiopurities had increased to 86% and 82% *ee*,[34] respectively. However, in both reactions the major oxidation product was a ternary mixture of bisepoxides (57% and 55% yield, respectively).

Stereochemical Assignment of Monoepoxy Alcohols 12–14

The relative configurations of the epoxy alcohols *anti*- and *syn*-**13** containing the *tert*-butyldimethylsilyl groups were assigned such that the chemical shift differences of their ^{1}H NMR signals resemble the corresponding ^{1}H NMR shift differences of the *para*-methoxybenzyl-containing epoxy alcohols *anti*- and *syn*-**12**. The respective chemical shift values of Table 2 render credence to the correctness of this attribution.

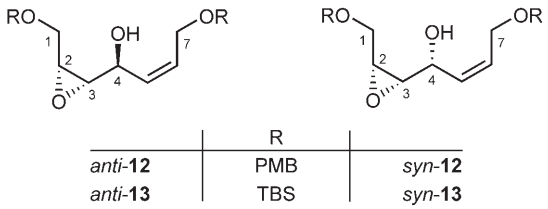


Scheme 7. Desymmetrizations of divinylcarbinol **22** by classical SAE (top) and by its Zr-analogue (bottom). *Reagents and conditions:* a) Ti(O-*i*-Pr)$_4$ (7 mol%), L-(+)-D*i*PT (9 mol%), 4 Å molecular sieves, CH_2Cl_2, −25 °C, 30 min, addition of *t*-BuOOH (2.0 equiv.), 45 min, addition of **22**, −25 °C, 18 h; 82% *anti*-**14** (*ds* = 97:3, 98% *ee*). b) Ti(O-*i*-Pr)$_4$ (7 mol%), D-(−)-D*i*PT (9 mol%), 4 Å molecular sieves, CH_2Cl_2, −25 °C, 30 min, addition of *t*-BuOOH (2.0 equiv.), 45 min, addition of **22**, −25 °C, 17 h; 78% *ent-anti*-**14** (*ds* = 97:3, 97% *ee*). c) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C; addition of L-(+)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 1 h, addition of **22**, −20 °C, 2.5 h; 40% 82:18 mixture *syn*-**14**:*ent-anti*-**14**, *syn*-**14**: 70% *ee*, 17% mixture of 3 diastereomeric bisepoxy alcohols;[33] second flash chromatography 25% *syn*-**14** (*ds* = 97:3, 70% *ee*). d) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C, addition of L-(+)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 1 h, addition of **22**, −20 °C, 12 h; 31% 78:22 mixture *syn*-**14**:*ent-anti*-**14**, *syn*-**14**: 86% *ee*, 57% 67:27:7 mixture *syn*,*syn*-**24**:*anti*,*syn*-**24**/*ent-anti*,*syn*-**24**:*anti*,*anti*-**24** (the section of the ^{1}H NMR spectrum, which corroborates this assignment, is shown in Figure 2). e) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C, addition of D-(−)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 1 h, addition of **22**, −20 °C, 2.5 h; 38% 79:21 mixture *ent-syn*-**14**:*anti*-**14**, *ent-syn*-**14**: 72% *ee*, *anti*-**14**: 28% *ee*, 19% mixture of 3 diastereomeric bisepoxy alcohols.[33] f) Zr(O-*i*-Pr)$_4$·*i*-PrOH (1.0 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C, addition of D-(−)-D*i*PT (1.1 equiv.), *t*-BuOOH (2.0 equiv.), 1 h, addition of **22**, −20 °C, 12 h; 34% 79:21 mixture *ent-syn*-**14**:*anti*-**14**, *ent-syn*-**14**: 82% *ee*, 55% mixture of 3 diastereomeric bisepoxy alcohols.[33] D*i*PT = diisopropyl tartrate; PMB = *para*-methoxybenzyl.

The relative configuration of the stereocenters in the epoxy alcohol *anti*-**12** follows from the distinctness of its ^{1}H and ^{13}C NMR spectra from the corresponding spectra of epoxy alcohol *syn*-**12**. This deduction implies, of course, that the epoxidation, which gave rise to *anti*- and *syn*-**12**, rendered *cis*-substituted oxiranes. Since this kind of stereoselectivity has not been violated in SAE chemistry,[1–3] our access to diastereomer *anti*-**12** *via* this reaction could not possibly be an exception.[35]

The *syn*-configuration within epoxy alcohol *syn*-**12** was established by a chemical correlation beginning with a tandem reduction by Red-Al® (Scheme 8, top right). At −30 °C, a nucleophilic opening of the epoxide ring occurred with some considerable regioselectivity. Heating to +60 °C accomplished another reduc-

Table 2. Selected ^{1}H NMR data (500 MHz, $CDCl_3$, Me_4Si as internal standard) of the *anti*- and *syn*-diastereomers of the bis(*cis*-configured) epoxy alcohols **12** and **13**. PMB = *para*-methoxybenzyl, TBS = *t*-BuMe_2Si.



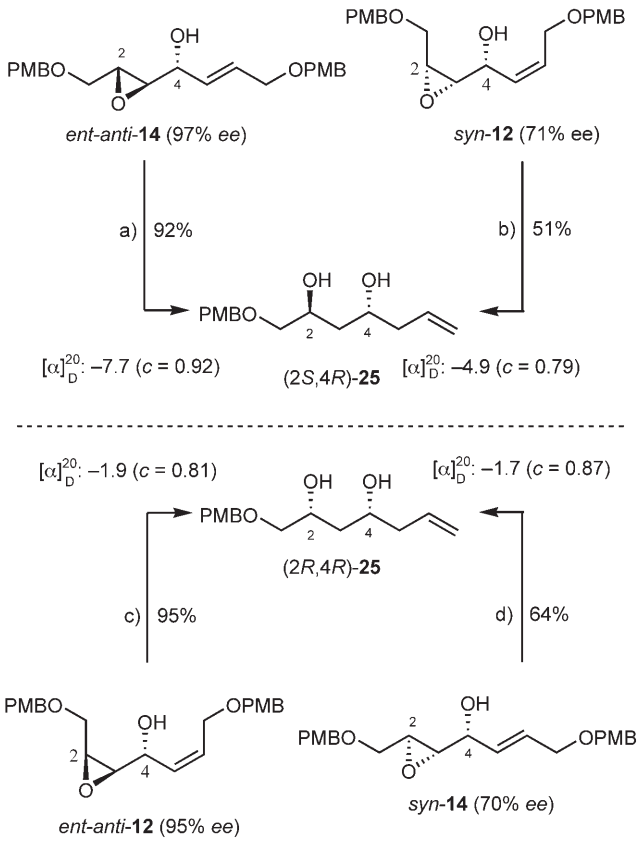
Proton	*anti*-**12**	*syn*-**12**	*anti*-**13**	*syn*-**13**
	δ(^{1}H) [ppm] (multiplicity)			
1-H^A	3.63 ([a])	3.50 ([a])	3.83 ([a])	3.75 ([a])
1-H^B	3.79 ([b])	3.65 ([b])	4.02 ([b])	3.82 ([b])
2-H	3.25 (m_C)	3.25 (ddd)	3.19 (m_C)	3.17 (ddd)
3-H	3.00 (dd)	3.07 (dd)	3.02 (dd)	3.07 (dd)
4-H	4.25 (br. dd)	4.27 (dd)	4.31–4.37 (m)[c]	4.29–4.32 (m)[d]

[a] A-part of ABM signal.
[b] B-part of ABM signal.
[c] Not interpretable due to overlap with the AB signal caused by 7-H_2.
[d] Not interpretable due to overlap with the AB signal caused by 7-H_2

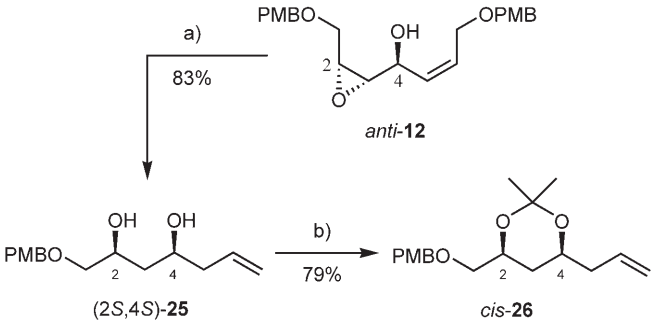
tion, which consisted of an S_N' displacement of the allylic *para*-methoxybenzyloxy group by the reductant.[36] An inseparable 65:35 mixture of the 1,3-diol (2*S*,4*R*)-**25** and an isomeric 1,2-diol resulted.[37] Sodium periodate cleaved the 1,2-diol portion in this mixture but let the 1,3-diol intact. This made the latter readily isolable (51% yield). In order to clarify whether diol (2*S*,4*R*)-**25** is *anti*- or *syn*-configured we prepared a diastereomer thereof by subjecting epoxy alcohol *anti*-**12** to the same two-step reduction by Red-Al® (Scheme 9), which provided 1,3-diol (2*S*,4*S*)-**25**. The latter was converted into acetonide *cis*-**26** and the *cis*-configuration of this compound established by NMR spectroscopy.[12a] This proves that the underlying diol (2*S*,4*S*)-**25** is *syn*-configured, which in turn implies that the diol (2*S*,4*R*)-**25** discussed above is *anti*-configured.[38,39]

The epoxy alcohols resulting from the bis(*trans*-configured) divinylcarbinol **22** by the Ti(O-*i*-Pr)$_4$-mediated (→*anti*-**14** and *ent*-*anti*-**14**, respectively) *vs.* Zr(O-*i*-Pr)$_4$-mediated epoxidations of Scheme 7 (→ *syn*-**14** and *ent*-*syn*-**14**, respectively) were diastereomers since their ^{1}H NMR spectra differed from one another (*cf.* Table 3).

The *anti*-configuration of the stereocenters in epoxy alcohol *ent*-*anti*-**14** was proved by reduction with Red-Al® (Scheme 8, top left). It provided the 1,3-diol (2*S*,4*R*)-**25** in 92% yield as a pure regioisomer. We had established the *anti*-configuration of this compound already at the occasion of its preparation from epoxy alcohol *syn*-**12** (*vide supra*). The signs of the specific rotation of the two samples of the diol



Scheme 8. Elucidation of the relative and absolute configurations in selected epoxy alcohol isomers. *Reagents and conditions:* a) Red-Al® (10 equiv.), toluene, −30 °C→60 °C, 2.5 h; 92%. b) Red-Al® (10 equiv.), toluene, −30 °C→60 °C, 4.5 h; $NaIO_4$ (1.0 equiv.), THF/H_2O (1:1), room temperature, 2 h; 51%. c) Red-Al® (4.0 equiv.), THF, −15 °C→60 °C, 2 h; 95%. d) Red-Al® (10 equiv.), toluene, −30 °C→60 °C, 4.5 h; 64%. PMB = *para*-methoxybenzyl.



Scheme 9. Determination of the relative configuration of stereocenters C-2 and C-4 in epoxy alcohol *anti*-**12**. *Reagents and conditions:* a) Red-Al® (4 equiv.), toluene, 60 °C, 2 h. b) 2,2-Dimethoxypropane (6 equiv.), pyridinium *para*-toluenesulfonate (4 mol%), acetone, 10 °C, 16 h. PMB = *para*-methoxybenzyl.

(2*S*,4*R*)-**25**, which we had prepared, were identical and the absolute values of their specific rotations were almost the same (taking into account the different enantiopurities of their precursors *syn*-**12** and *ent-anti*-**14**, namely 71% *ee*[40] and 97% *ee*, respectively). This means that the stereocenters C-2 and C-4 of epoxy alcohols *syn*-**12** and *ent-anti*-**14** have the same, albeit not yet known absolute configurations.

The *syn*-configured 1,3-diol (2*R*,4*R*)-**25**, first prepared from epoxy alcohol *ent-anti*-**12** and Red-Al® (Scheme 8, bottom left), was also accessible by the Red-Al® reduction of epoxy alcohol *syn*-**14** (Scheme 8, bottom right). It provided 64% of the mentioned 1,3-diol and 18% of a mixture with the regioisomeric 1,2-diol[41]. The identity of the 1,3-diols was established by NMR spectroscopy and the close match of their specific rotational values. The same kind of reasoning as above revealed the relative configuration of the stereocenters in epoxy alcohol *syn*-**14**. By the same token the stereocenters C-2 and C-4 of epoxy alcohols *syn*-**14** and *ent-anti*-**12** possess identical but still unknown absolute configurations.

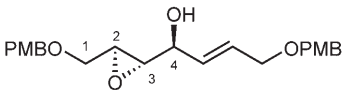
The last reduction of an epoxy alcohol with Red-Al® shown in Scheme 8 (bottom left) affected epoxy alcohol *ent-anti*-**12**. It afforded the same *syn*-1,3-diol (2*R*,4*R*)-**25** (95% yield), which was previously obtained from the Red-Al® reduction of epoxy alcohol *syn*-**14**. The near identity of the specific rotations of the two samples implies that their epoxy alcohol precursors *ent-anti*-**12** and *syn*-**14** are identically configured in the absolute sense at the stereocenters labelled 2 and 4.[39]

The ultimate step of the stereochemical assignments of our epoxy alcohols concerned their absolute configurations. We felt safe about attributing the absolute configuration to the stereocenters of epoxy alcohol *anti*-**14**, which we prepared by a SAE in the presence of L-(+)-D*i*PT (Scheme 7, top left). This was because the same epoxidation conditions had provided the closely related epoxy alcohol *anti*-**11** (*cf.* Scheme 3).[6a,b,9b–e] The 3D-structure of the latter was proved unambiguously by conversions into the natural products 3-deoxy-D-manno-2-octulosonic acid [(+)-KDO],[6b] (11*R*,12*S*,13*S*,9*Z*,15*Z*)-9,12,13-trihydroxyoctadeca-9,15-dienoic acid,[9b] prelactone C,[9c] (+)-aspilicin,[9d] and dysiherbaine.[9e] Knowing the absolute configuration of the enantiomeric epoxy alcohol *ent-anti*-**14** then, too, the stereochemical correlation depicted in the upper moiety of Scheme 8 clarified the absolute configuration of epoxy alcohol *syn*-**12**.

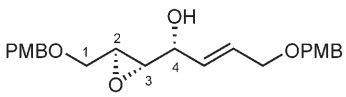
The absolute configuration of the stereocenters in epoxy alcohol *anti*-**12** could not be elucidated earlier than after a multistep transformation – undertaken for a synthetic objective – which led to the *para*-bromobenzoate **27**. Its stereostructure was determined by anomalous X-ray diffraction.[42] The mirror-inverted configuration was assigned to the enantiomeric epoxy alcohol *ent-anti*-**12** (Scheme 10). Thereupon, the stereochemical correlation depicted in the bottom section of Scheme 8 revealed the absolute configuration of epoxy alcohol *syn*-**14**.

Finally, it may be assumed that the absolute configurations of the TBS-containing epoxy alcohols *syn*- and *ent-syn*-**13** are the same as in the analogous PMB-containing epoxy alcohols *syn*- and *ent-syn*-**12**, respectively.

Table 3. Selected ^{1}H NMR shifts (500 MHz, $CDCl_3$, Me_4Si as internal standard) of epoxy alcohols *anti*- and *syn*-**14**. PMB = *para*-methoxybenzyl.



anti-**14**

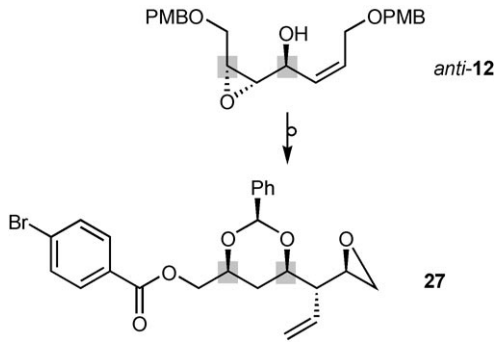


syn-**14**

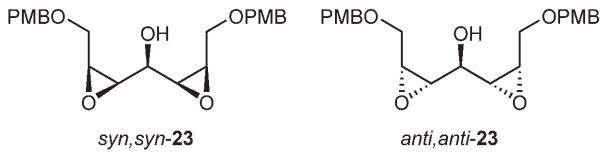
Proton	δ(^{1}H) [ppm] *anti*-**14**	*syn*-**14**
1-H^A	3.45	3.46
1-H^B	3.74	3.72
2-H	3.24 (m_C)	3.19 (ddd)
3-H	3.02 (dd)	2.99 (dd)
4-H	4.35 (m)	4.09 (m)

Stereochemical Assignment of Bisepoxy Alcohols 23 and 24

Overepoxidation of the non-racemic monoepoxy alcohol *syn*-**12** in the presence of $Zr(O\text{-}i\text{-}Pr)_4$ and L-(+)-D*i*PT had led to the formation of an isomerically pure bisepoxy alcohol **23** (Scheme 6, Figure 1). The following set of data is in accordance with a *meso*-



Scheme 10. Proof of the absolute configuration of epoxy alcohol *anti*-**12** by anomalous X-ray diffraction of the derived *para*-bromobenzoate **27**.[42] PMB = *para*-methoxybenzyl.



structure, i.e., with stereoformulas *syn,syn*-**23** or *anti,anti*-**23**. (1) The specific rotation of **23** was ± 0. (2) The 500 MHz ^{1}H NMR spectrum of **23** displayed a single set of resonances for the two halves of the molecule. (3) The 126 MHz ^{13}C NMR spectrum of **23** exhibited identical subspectra for both moieties of the molecule. However, none of these data gives a clue as to whether stereostructure *syn,syn*-**23** or stereostructure *anti,anti*-**23** is correct. The time-dependent investigation of Figure 1 allows us to make this distinction, though, because it demonstated unequivocally from which precursor(s) the bisepoxide **23** forms: from both enantiomers of the initially obtained monoepoxy alcohol. Since the latter arose as a pure *syn*-diastereomer, the overepoxidation product needed to retain a *syn*-configured epoxy alcohol substructure. This requirement is only met when the overepoxidation product possesses stereostructure *syn,syn*-**23**.

The inseparable mixture of bisepoxides **24** obtained by overepoxidation of the bis(*trans*-configured) divinylcarbinol **22** consisted of all three conceivable bisepoxide diastereomers according to the the 400 MHz ^{1}H NMR spectrum. That indeed each of the compounds compounds *syn,syn*-**24**, *anti,syn*-**24** (or *ent-anti,syn*-**24**), and *anti,anti*-**24** was present was concluded from how many doublets of doublets protons the protons 3-H and 5-H caused to arise (*cf.* Figure 2). The best-resolved spectrum[33] displayed these protons as four doublets of doublets. Two of them were superimposed and two were completely separated. The major constituent (67%) and the minor constituent (6%) gave rise to a single doublet of doublet, each [$\delta_{3\text{-H and }5\text{-H}} = 3.07$ (dd) and 3.029 Hz (dd), respectively], while the 27% component of the mixtures caused two such signals [$\delta_{3\text{-H and }5\text{-H}} = 3.031$ (dd) and 3.10 Hz (dd)]. Accordingly, the latter component is chiral – whether it equals enantiomer *anti,syn*-**24** or its antipode *ent-anti,syn*-**24** is unknown – and the former components are *meso*-compounds. Because of the *ca.* 80:20 bias for *syn- vs. anti*-selectivity in the Zr(O-*i*-Pr)$_4$-mediated monoepoxidation step of Scheme 7, it is likely (but not proved) that the major *meso*-bisepoxide possesses stereoformula *syn,syn*-**24** and the minor *meso*-bisepoxide stereoformula *anti,anti*-**24**.

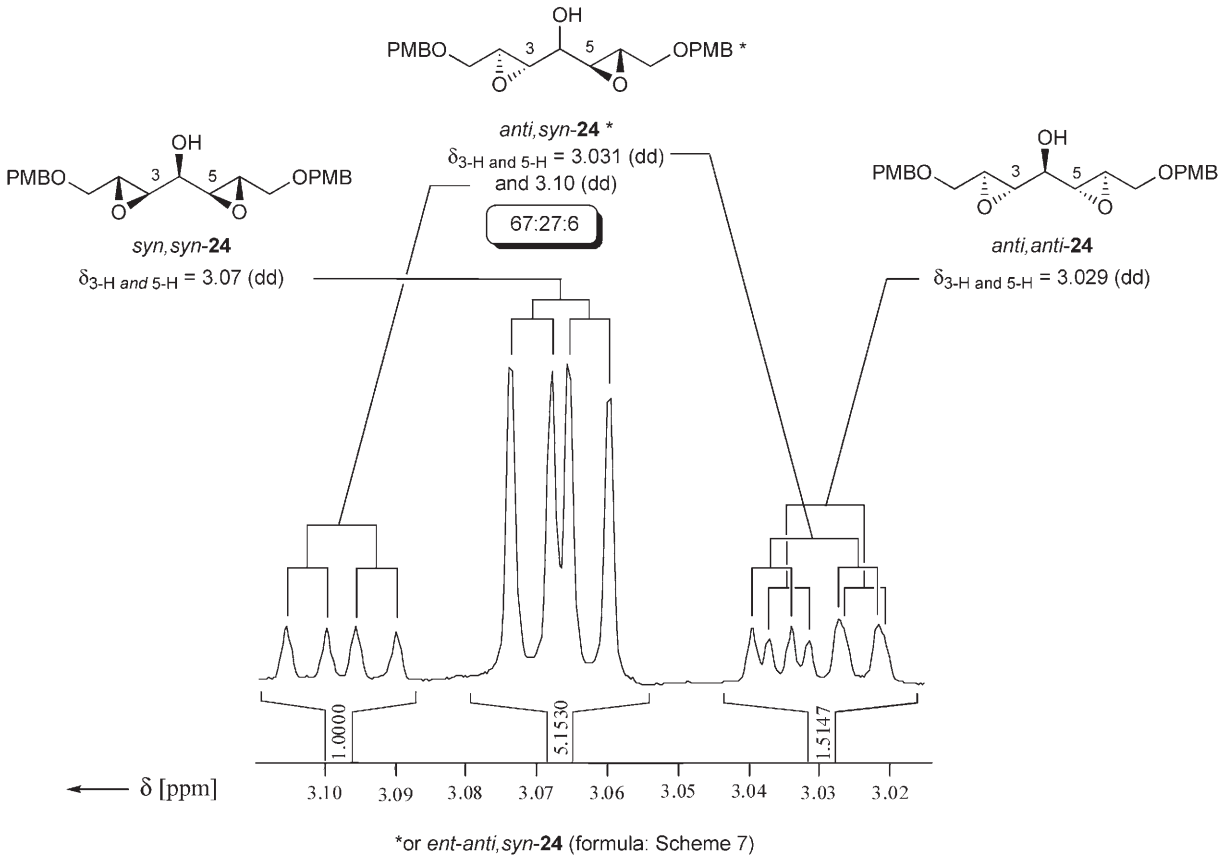


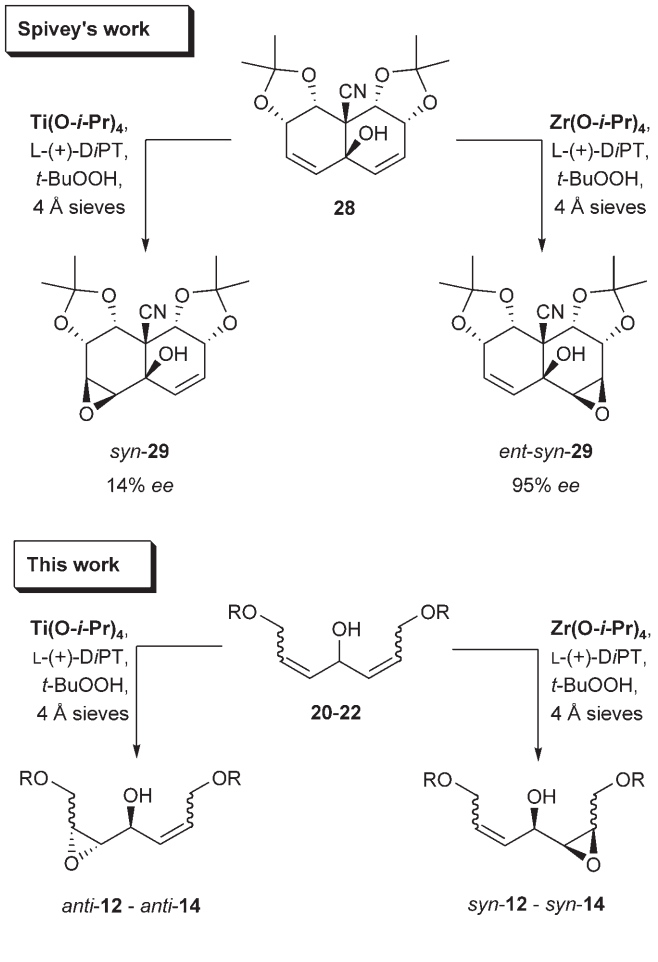
Figure 2. Section from the ^{1}H NMR spectrum (400 MHz, $CDCl_3$, Me_4Si as internal standard) of the ternary mixture of bisepoxy alcohols *syn,syn*-**24**, *anti,syn*- or *ent-anti,syn*-**24**, and *anti,anti*-**24**. PMB = *para*-methoxybenzyl.

Conclusions

We have realized the first asymmetric monoepoxidations of secondary divinylcarbinols – namely compounds **20** (*cis*-configured, PMBO-containing), **21** (*cis*-configured, TBSO-containing), and **22** (*trans*-configured, PMBO-containing) – by *t*-BuOOH in the presence of an enantiomerically pure diisopropyl tartrate (D*i*PT) and Zr(O-*i*-Pr)$_4$. In each case, the enantiopurity of the major monoepoxy alcohol product increased with epoxidation time. For substrate **20**, we established that this effect is due to a kinetic resolution of an initially less enantiomerically pure monoepoxy alcohol by the preferential overepoxidation of the minor enantiomer. Based on this enrichment process we obtained the monoepoxy alcohol *syn*-**12** with up to 99% *ee*.

The mentioned asymmetric monoepoxidations of the secondary divinylcarbinols **20**–**22** in the presence of Zr(O-*i*-Pr)$_4$ take a different steric course than their counterparts in the presence of Ti(O-*i*-Pr)$_4$, which we investigated as well. Interestingly, the two procedures exhibit opposite diastereoselectivities, i.e., they are stereocomplementary: Leaning on Ti(O-*i*-Pr)$_4$, epoxy alcohols *syn*-**12**–*syn*-**14** were obtained, and leaning on Zr(O-*i*-Pr)$_4$, epoxy alcohols *anti*-**12**–*anti*-**14** (Scheme 11, bottom part). The controllability of this bias turns the Zr(O-*i*-Pr)$_4$-mediated desymmetrizations into a valuable extension of the (now) classical Sharpless methodology.

It is constructive to compare the stereochemical outcomes of Zr(IV)- *vs.* Ti(IV)-mediated asymmetric epoxidations of the secondary divinylcarbinols **20**–**22** (cf. Scheme 11, bottom part). 1) In the presence of a given D*i*PT enantiomer the Zr(IV)- *vs.* Ti(IV)-mediated monoepoxidation provides mainly an epoxy alcohol, which exhibits *identically* configured stereocenters in the epoxide ring and a *differently* configured stereocenter in the alcohol moiety. Differently expressed, a given divinylcarbinol and a given D*i*PT auxiliary furnish epoxy alcohol *epimers* when monoepoxidized with *t*-BuOOH in the presence of a particular D*i*PT enantiomer and Zr(O-*i*-Pr)$_4$ or Ti(O-*i*-Pr)$_4$, respectively. 2) A *syn*-configured monoepoxy alcohol with the *R*-configuration in the alcohol moiety is obtained from the secondary divinylcarbinols **20**–**22** by treatment with *t*-BuOOH, L-(+)-D*i*PT, and Zr(O-*i*-Pr)$_4$, while the *anti*-configured monoepoxy alcohol with the *identical* *R*-configuration in the alcohol moiety is obtained from the same substrates and *t*-BuOOH, D-(−)-D*i*PT, and Ti(O-*i*-Pr)$_4$. Similarly, the *syn*-configured (*anti*-configured) monoepoxy alcohols with the *S*-configuration in the alcohol moiety are obtained from the secondary divinylcarbinols **20**–**22**, *t*-BuOOH, D-(−)-D*i*PT [L-(+)-D*i*PT], and Zr(O-*i*-Pr)$_4$ [Ti(O-*i*-Pr)$_4$].



RO—CH_2—		Diastereoselectivity of *anti*-epoxy alcohol formation *	Diastereoselectivity of *syn*-epoxy alcohol formation *
cis-PMBO—CH_2—	**20**, **12**	moderate	high
cis-TBSO—CH_2—	**21**, **13**	low	high
trans-PMBO—CH_2—	**22**, **14**	high	moderate

* Enantioselectivity of epoxy alcohol formation increases with overepoxidation.

Scheme 11. The Ti(IV)- or Zr(IV)-mediated desymmetrization of the tertiary divinylcarbinol **28** realized by Spivey et al.[24] *vs.* the Ti(IV)- or Zr(IV)-mediated desymmetrizations of the secondary divinylcarbinols **20**–**22** described here. D*i*PT = diisopropyl tartrate; PMB = *para*-methoxybenzyl; TBS = *t*-BuMe_2Si.

Finally, Scheme 11 juxtaposes the L-(+)-D*i*PT-mediateded desymmetrizations of the current study – affecting secondary divinylcarbinols – and those reported by Spivey et al. for the tertiary divinylcarbinol **28**.[24] With respect to the latter substrate turning from Ti(O-*i*-Pr)$_4$- to Zr(O-*i*-Pr)$_4$-assistance was tantamount to producing epoxy alcohol *ent-syn*-**29** rather than epoxy alcohol *syn*-**29**. Accordingly, switching the metal inverted the sense and the extent of enantio-

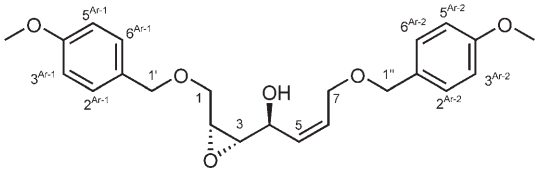
control of the latter epoxidations[43] while it maintained the sense and increased the extent of diastereocontrol. With respect to our substrates (**20**–**22**) the main effect of replacing Ti(IV) by Zr(IV) was turning the epoxidation from *anti*- to *syn*-diastereoselective.

Last but not least, it is pointed out that divinylcarbinol monoepoxides *anti*-**6**,[4,6b,c] **7**,[6a,b] *anti*-**10**[8], and *anti*-**11**[6b,9b–e,10] served as polyfunctional building blocks in variety of natural product syntheses. Hence, applications of divinylcarbinol monoepoxides **12**–**14** in asymmetric synthesis are conceivable, too.[42]

Experimental Section

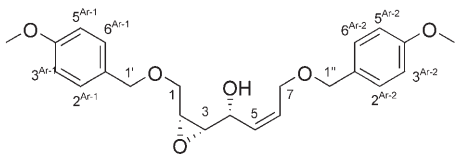
General remarks and a complete set of procedures and characterization data are found in the Supporting Informations.

cis-(2*R*,3*S*,4*S*)-2,3-Epoxy-1,7-bis[(4-methoxybenzyl)-oxy]hept-5-en-4-ol (*anti*-12)



At −20 °C L-(+)-D*i*PT (11.9 mL, 13.3 g, 56.8 mmol, 1.1 equiv.) was added to a suspension of Ti(O-*i*-Pr)$_4$ (14.7 mL, 15.4 g, 54.1 mmol, 1.05 equiv.) and powdered 4 Å molecular sieves (1.5 g) in CH_2Cl_2 (700 mL). After 30 min *t*-BuOOH (4.4 M in CH_2Cl_2, 23.2 mL, 102 mmol, 2.0 equiv.) was added and the mixture was stirred for 1 h. Then a solution of divinylcarbinol **20** (19.8 g, 51.6 mmol) in CH_2Cl_2 (70 mL) was added dropwise within 20 min. The reaction mixture was stirred for 3 d at −20 °C and the reaction was terminated by adding a solution of $FeSO_4$ (222 g) and citric acid (81 g) in H_2O (750 mL). With vigorous stirring the mixture was allowed to reach room temperature and the phases were separated. The aqueous phase was extracted with *t*-BuOMe (4×150 mL) and the combined organic phases were evaporated under vacuum to a volume of approximately 250 mL. The remaining solution was treated with a solution (20 mL) prepared from NaOH (30 g), NaCl (5 g) and H_2O (90 mL) and the resulting mixture was vigorously stirred at room temperature for 1 h. Thereafter the phases were separated and the organic phase was dried over Na_2SO_4. The solvents were evaporated under vacuum and the residue was submitted to flash chromatography (12 cm, cyclohexane/EtOAc, 2:1) to afford a 84:16 mixture[21]·* of *anti*-**12** and *ent-syn*-**12** (fractions 30–63, 14.9 g, 72%). [*During flash-chromatography only fractions which according to TLC control contained the major diastereomer *anti*-**12** were collected]. All following fractions which contained only the minor diastereomer *syn*-**12** or mixtures of diastereomeric bisepoxy alcohols were discarded. The ratio of *anti*-**12** and *ent-syn*-**12** before flash chromatography was determined as ≈75:25[21] by ^{1}H NMR spectroscopic analysis of the crude material. ^{1}H NMR (400.13 MHz, $CDCl_3$/TMS): δ=2.52 [br. d, 1H of this isomer, $J_{OH,4}$=3.9 Hz, 4-OH (*syn*-**12**)], 2.78 [br. d, 1H of this isomer, $J_{OH,4}$=2.8 Hz, 4-OH (*anti*-**12**)], 3.00 [dd, 1H of this isomer, $J_{3,4}$=7.7 Hz, $J_{3,2}$=4.3 Hz, 3-H (*anti*-**12**)], 3.07 [dd, 1H of this isomer, $J_{3,4}$=7.3 Hz, $J_{3,2}$=4.7 Hz, 3-H (*syn*-**12**)], 3.25 [ddd, 2H of both isomers, $J_{2,1\text{-H(A)}}$=$J_{2,1\text{-H(B)}}$=5.3 Hz, $J_{2,3}$=4.6 Hz, 2-H (*anti*- and *syn*-**12**)], AB signal [δ_A=3.51, δ_B=3.61–3.67*, 2H of this isomer, J_{AB}=11.6 Hz, in addition split by $J_{A,2}$=6.4 Hz, 1-H$_2$ (*syn*-**12**); [* low-field portion superimposed by highfield portion of the following AB signal], AB signal [δ_A=3.63, δ_B=3.79, 2H of this isomer, J_{AB}=11.1 Hz, in addition split by $J_{A,2}$=5.4 Hz, $J_{B,2}$=6.0 Hz, 1-H$_2$ (*anti*-**12**)], low-field portion superimposed by 3.79 [s, OMe, 3H of both isomers (*anti*- and *syn*-**12**)], 4.00–4.15 {m, 2H of both isomers, 7-H$_2$ (*anti*- and *syn*-**12**), therein interpretable: AB signal [δ_A=4.05, δ_B=4.12, J_{AB}=12.4 Hz, in addition split by $J_{A,6}$=5.5 Hz, $^4J_{B,5}$=1.3 Hz and $J_{B,6}$=7.1 Hz, $^4J_{B,5}$=1 Hz.4, 7-H$_2$ (*anti*-**12**)], the respective AB signal for the minor diastereomer *syn*-**12** is not interpretable}, 4.25 [br. ddd, 1H of this isomer, $J_{4,3}$=$J_{4,5}$=8.2 Hz, $J_{4,OH}$=3.0 Hz, 4-H (*anti*-**12**)] superimposed by 4.27 [br. dd, 1H of this isomer, $J_{4,5}$=$J_{4,3}$=7.8 Hz, 4-H (*syn*-**12**)], 4.40–4.56 {m, 4H of both isomers, 1′-H$_2$, 1″-H$_2$ (*anti*- and *syn*-**12**); interpretable: δ=4.43 [s, 1″-H$_2$* (*anti*-**12**)], AB signal [δ_A=4.54, δ_B=4.46, J_{AB}=11.4 Hz, 1′-H$_2$* (*anti*-**12**)]; {*assignment interchangeable}, 5.62–5.84 {m, 2H of both isomers, 5-H, 6-H (*anti*- and *syn*-**12**), interpretable: δ=5.70 [dddd, $J_{5,6}$=11.4 Hz, $J_{5,4}$=7.5 Hz, 5-H (*anti*-**12**)] and δ=5.82 [ddd, $J_{6,5}$=11.5 Hz, $J_{6,7\text{-H(A)}}$=$J_{6,7\text{-H(B)}}$=5.7 Hz, 6-H (*anti*-**12**)]}, 4 superimposed AA′BB′-signals at δ=6.85–6.91 and 7.22–7.29 [2×4H of both isomers, 2-H$^{Ar\text{-}1}$, 3-H$^{Ar\text{-}1}$, 5-H$^{Ar\text{-}1}$, 6-H$^{Ar\text{-}1}$, 2-H$^{Ar\text{-}2}$, 3-H$^{Ar\text{-}2}$, 5-H$^{Ar\text{-}2}$, 6-H$^{Ar\text{-}2}$ (*anti*- and *syn*-**12**)]; for analytical data of the pure major diastereomer *anti*-**12** see ref.[12a]; *ee* (*anti*-**12**)=96% (by HPLC)[23]; *ee* (*ent-syn*-**12**)=27% (by HPLC)[27].

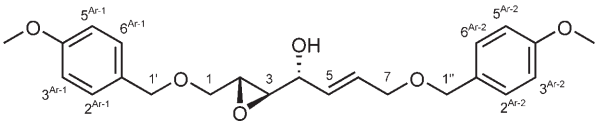
cis-(2*R*,3*S*,4*R*)-2,3-Epoxy-1,7-bis[(4-methoxybenzyl)-oxy]hept-5-en-4-ol (*syn*-12)



At −20 °C L-(+)-D*i*PT (51 μL, 57 mg, 0.24 mmol, 1.1 equiv.) and a solution of *t*-BuOOH (4.43 M in CH_2Cl_2, 100 μL, 0.44 mmol, 2.0 equiv.) were added to a suspension of Zr(O-*i*-Pr)$_4$·*i*-PrOH (84 mg, 0.22 mmol, 1.0 equiv.) and powdered 4 Å molecular sieves (140 mg) in CH_2Cl_2 (4.5 mL). The mixture was stirred for 1 h at −20 °C before a solution of divinylcarbinol **20** (85 mg, 0.22 mmol) in CH_2Cl_2 (2.0 mL) was slowly added. After stirring for 4 h at −20 °C, the reaction was terminated by adding a solution (1.0 mL) prepared from NaOH (30 g), NaCl (5 g) and H_2O (90 mL). The cooling bath was removed and the mixture was stirred for 2 h at room temperature. After addition of *t*-BuOMe (10 mL), H_2O was removed by addition of Na_2SO_4 and the resulting mixture was filtered through a pad of Celite. The filter cake was washed with *t*-BuOMe. Excess *t*-BuOOH was removed by azeotropic distillation with toluene (4×5 mL). The residue was purified by flash chromatography (2.0 cm, cyclohex-

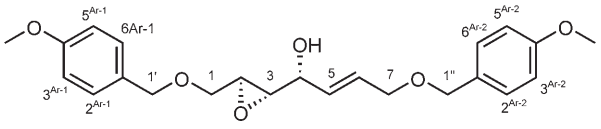
ane/EtOAc, 5:2) to afford monoepoxy alcohol *syn*-**12** (fractions 35–46, 56 mg, 63%) as pure diastereomer and a 68:32 mixture of bisepoxide *syn,syn*-**23** and monoepoxy alcohol *syn*-**12** (fractions 47–70, 33 mg; ratio pure *syn*-**12**: 12 mg, 11% and 23 mg bisepoxide *syn,syn*-**23**, 25%). Both samples were colorless liquids. The total yield of diastereomerically pure monoepoxy alcohol *syn*-**12** was 74% and its *ee* value was 82% (by HPLC)[27]; $[\alpha]_D^{20}$: −8.7 (*c* 0.8, $CHCl_3$); $[\alpha]_{365}^{20}$: −33.1 (*c* 0.8, $CHCl_3$) {this sample stems from the time-resolved experiment (Figure 1) after 16 h, 44% yield and 98% *ee* (by HPLC)[27]}; ^{1}H NMR (499.87 MHz, $CDCl_3$/TMS): δ = 2.67 (br s, 1H, OH), 3.07 (dd, 1H, $J_{3,4}$ = 7.4 Hz, $J_{3,2}$ = 4.5 Hz, 3-H), 3.25 (ddd, 1H, $J_{2,1\text{-H(A)}}$ = 6.5 Hz, $J_{2,3}$ = $J_{2,1\text{-H(B)}}$ = 4.2 Hz, 2-H), AB signal (δ_A = 3.50, δ_B = 3.65, 2H, J_{AB} = 11.4 Hz, in addition split by $J_{A,2}$ = 6.6 Hz, $J_{B,2}$ = 3.7 Hz, 1-H_2), 3.79 (s, 3H, 2×O-CH_3), AB signal (δ_A = 4.02, δ_B = 4.06, 2H, J_{AB} = 12.8 Hz, in addition split by $J_{A,6}$ = 5.9 Hz, $^4J_{A,5}$ = 1.2 Hz, $J_{B,6}$ = 6.2 Hz, $^4J_{B,5}$ = 1.5 Hz, 7-H_2), 4.27 (br. dd, 1H, $J_{4,5}$ = $J_{4,3}$ = 7.8 Hz, 4-H), 4.39–4.51 (m, 4H, 1′-H_2, 1″-H_2), AB signal (δ_A = 5.66, δ_B = 5.78, 2H, J_{AB} = 11.3 Hz, in addition split by $J_{A,4}$ = 8.2 Hz, $J_{B,7\text{-H(A)}}$ = $J_{B,7\text{-H(B)}}$ = 5.9 Hz, A: 5-H, B: 6-H), overlapping AA′BB′ signals centered at δ = 6.87 and δ = 7.24 [2×4H, 2×C_6H_4; contains solvent peak at δ = 7.26 ($CHCl_3$)]; ^{13}C NMR (125.69 MHz, $CDCl_3$/$CDCl_3$): δ = 55.33 (2×O-CH_3), 56.00 (C-2), 58.93 (C-3), 65.83 (C-7), 66.79 (C-4), 67.79 (C-1), 72.41 and 73.02 (2×C-1′, C-1″), 113.92 and 113.96 (C-$2^{Ar\text{-}1}$, C-$2^{Ar\text{-}2}$, C-$6^{Ar\text{-}1}$, C-$6^{Ar\text{-}2}$), 129.52 and 129.56 ($3^{Ar\text{-}1}$, C-$3^{Ar\text{-}2}$, C-$5^{Ar\text{-}1}$, C-$5^{Ar\text{-}2}$), 129.78 (C-$1^{Ar\text{-}1}$, C-$1^{Ar\text{-}2}$), 130.24 (C-5), 130.38 (C-6), 159.43 and 159.44 (C-$4^{Ar\text{-}1}$, C-$4^{Ar\text{-}2}$); IR ($CDCl_3$): ν = 3590, 3420, 3005, 2960, 2935, 2840, 1615, 1515, 1465, 1305, 1250, 1175, 1085, 1035, 905, 850, 825 cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{28}O_6$ (400.5): C 68.98, H 7.05; found: C 69.16, H 7.16. For analyctical data of a pure sample of bisepoxy alcohol *syn,syn*-**23** see ref.[12b].

trans-(2*R*,3*R*,4*R*)-2,3-Epoxy-1,7-bis[(4-methoxybenzyl)oxy]hept-5-en-4-ol (*ent-anti*-14)



ent-anti-**14** was prepared from divinylcarbinol **22** (200 mg, 0.52 mmol) by the same procedure as described for *anti*-**12** using D-(−)-D*i*PT (9.5 μL, 11 mg, 45 μmol, 9 mol%) as chiral additive (see above). The epoxidation was performed using Ti(O-*i*-Pr)$_4$ (10.5 μL, 10.0 mg, 35 μmol, 7 mol%), *t*-BuOOH (4.43 M in CH_2Cl_2, 226 μL, 1.0 mmol, 2.0 equiv.) and powdered 4 Å molecular sieves (310 mg) in CH_2Cl_2 (total volume: 7.5 mL) at −25 °C. After 17 h the reaction was terminated by addition of a cold solution (1.0 mL) prepared from NaOH (30 g), NaCl (5 g) and H_2O (90 mL). The residue of the work-up was purified by flash chromatography (2.0 cm, cyclohexane/EtOAc, 5:2) to afford the title compound together with 3 mol% of the diastereomeric monoepoxy alcohol *syn*-**14** (fractions 44–75, 164 mg, 82%, *ds* = 97:3[31]) as colorless oil; *ee* (*ent-anti*-**14**) = 97% (by HPLC)[32]; *ee* (*syn*-**14**) not determined; $[\alpha]_D$: −7.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR [499.87 MHz, $CDCl_3$/TMS; sample contains 3 mol% of the diastereomeric monoepoxy alcohol *syn*-**14** (signals not listed)]: δ = 2.09 (br. s, 1H, OH), 3.02 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{3,2}$ = 2.3 Hz, 3-H), 3.24 (ddd, 1H, $J_{2,1\text{-H(A)}}$ = 5.5 Hz, $J_{2,3}$ = $J_{2,1\text{-H(B)}}$ = 2.6 Hz, 2-H), AB signal (δ_A = 3.45, δ_B = 3.74, 2H, J_{AB} = 11.7 Hz, in addition split by $J_{A,2}$ = 5.7 Hz, $J_{B,2}$ = 2.8 Hz, 1-H_2), 3.790 and 3.794 (2 × s, 2×3H, 2×O-CH_3), 4.01 (dm$_C$, 2H, $J_{7,6} \approx$ 5.5 Hz, 7-H_2), 4.35 (m$_C$, 1H, 4-H), 4.45 (s, 2H, Ar-CH_2^1), AB signal (δ_A = 4.47, δ_B = 4.51, 2H, J_{AB} = 11.5 Hz, Ar-CH_2^2), AB signal (δ_A = 5.74, δ_B = 5.92, 2H, J_{AB} = 15.7 Hz, in addition split by $J_{A,4}$ = 6.5 Hz, $^4J_{A,7}$ = 1.5 Hz, $J_{B,7}$ = 5.8 Hz, $^4J_{B,4}$ = 1.2 Hz, A: 5-H, B: 6-H), overlapping AA′BB′ signals centered at δ = 6.866 or 6.869 and δ = 7.251 or 7.255 respectively [2×4H, 2×C_6H_4; contains solvent peak at δ = 7.26 ($CHCl_3$)]; ^{13}C NMR (125.68 MHz, $CDCl_3$/$CDCl_3$): δ = 53.72 (C-2), 55.33 (2×O-CH_3), 57.37 (C-3), 69.24 (C-4), 69.29 (C-1), 69.60 (C-7), 72.12 and 72.99 (C-1′, C-1″), 113.88 and 113.90 (C-$2^{Ar\text{-}1}$, C-$2^{Ar\text{-}2}$, C-$6^{Ar\text{-}1}$, C-$6^{Ar\text{-}2}$), 129.44 and 129.47 (C-$3^{Ar\text{-}1}$, C-$3^{Ar\text{-}2}$, C-$5^{Ar\text{-}1}$, C-$5^{Ar\text{-}2}$), 129.64 (C-5), 129.93 and 130.23 (C-$1^{Ar\text{-}1}$, C-$1^{Ar\text{-}2}$), 130.42 (C-6), 159.32 and 159.38 (C-$4^{Ar\text{-}1}$, C-$4^{Ar\text{-}2}$); IR ($CDCl_3$): ν = 3605, 3005, 2955, 2935, 2860, 1615, 1585, 1515, 1465, 1445, 1365, 1300, 1250, 1175, 1100, 1035, 975, 915, 895, 825 cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{28}O_6$ (400.5): C 68.98, H 7.05; found: C 68.89, H 7.22.

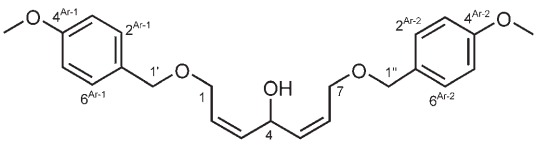
trans-(2*S*,3*S*,4*R*)-2,3-Epoxy-1,7-bis[(4-methoxybenzyl)oxy]hept-5-en-4-ol (*syn*-14)



At −20 °C L-(+)-D*i*PT (240 μL, 268 mg, 1.14 mmol, 1.1 equiv.) and a solution of *t*-BuOOH (4.43 M in CH_2Cl_2, 472 μL, 2.08 mmol, 2.0 equiv.) were added to a suspension of Zr(O-*i*-Pr)$_4$·*i*-PrOH (404 mg, 1.04 mmol, 1.0 equiv.) and powdered 4 Å molecular sieves (210 mg) in CH_2Cl_2 (26 mL). The mixture was stirred for 1 h at −20 °C before a solution of divinylcarbinol **22** (400 mg, 1.04 mmol) in CH_2Cl_2 (4.0 mL) was slowly added. After stirring for 2.5 h at −20 °C, the reaction was terminated by addition of a cold solution (1.0 mL) prepared from NaOH (30 g), NaCl (5 g) and H_2O (90 mL). The cooling bath was removed and the mixture was stirred for 2 h at room temperature. After addition of *t*-BuOMe (10 mL), H_2O was removed by addition of Na_2SO_4 and the resulting mixture was filtered through a pad of Celite. The filter cake was washed with *t*-BuOMe. Excess *t*-BuOOH was removed by azeotropic distillation with toluene (4×5 mL). The residue was purified by flash chromatography (3.0 cm, cyclohexane/EtOAc, 3:1 fraction 160, 2:1). Fractions 71–91 afforded divinylcarbinol **22** (76 mg, 19%). Fractions 95–151 furnished a 92:8[31] mixture of the monoepoxy alcohols *syn*-**14** and *anti*-**14** (72 mg, 18%) and the following fractions 122–161 afforded a 75:25[31] mixture of the monoepoxy alcohols *syn*-**14** and *anti*-**14** (93 mg, 22%). Finally in fractions 163–180 a mixture of 3 diastereomeric bisepoxy alcohols[33] (73 mg, 17%) was obtained. The total yield of both diastereomeric monoepoxy alcohols *syn*-**14** and *ent-syn*-**14** was 40% (49% based on recovered starting material) and the ratio of *syn*-**14** and *anti*-**14** was 82:18.[31] The 92:8 mixture of monoepoxy alcohols *syn* < β > -**14** < /β > and *anti*-

14 was submitted to a second flash chromatography (2.0 cm, cyclohexane/EtOAc, 3:1) delivering the title compound together with 3 mol% of the diastereomeric monoepoxy alcohol *syn*-**14** (fractions 70–92, 46 mg, *ds* = 97:3[31]) as colorless oil; *ee* (*anti*-**14**) = 70% (by HPLC)[32]; *ee* (*syn*-**14**) not determined; $[\alpha]_D^{20}$: −2.04 (*c* 1.08, $CHCl_3$); ^{1}H NMR [499.87 MHz, $CDCl_3$; sample contains 3 mol% of the diastereomeric monoepoxy alcohol *anti*-**14** (signals not listed)]: $\delta = 2.12$ (br. s, 1H, OH), 2.99 (dd, 1H, $J_{3,4} = 4.6$ Hz, $J_{3,2} = 2.3$ Hz, 3-H), 3.19 (ddd, 1H, $J_{2,1\text{-H(A)}} = 5.4$ Hz, $J_{2,3} = J_{2,1\text{-H(B)}} = 2.6$ Hz, 2-H), AB signal ($\delta_A = 3.46$, $\delta_B = 3.72$, 2H, $J_{AB} = 11.7$ Hz, in addition split by $J_{A,2} = 5.5$ Hz, $J_{B,2} = 3.0$ Hz, 1-H_2), 3.791 and 3.795 (2×s, 2×3H, 2×O-CH_3), 4.01 (ddd, 2H, $J_{7,6} = 5.4$ Hz, $^4J_{7,5} = {}^5J_{7,4} = 1.2$ Hz, 7-H_2), 4.09 (m_C, 1H, presumably interpretable as br. ddd, $J_{4,5} \approx J_{4,3} \approx J_{4,OH} \approx 4.6$ Hz, 4-H), 4.45 (s, 2H, Ar-CH_2^1), AB signal ($\delta_A = 4.47$, $\delta_B = 4.51$, 2H, $J_{AB} = 11.5$ Hz, Ar-CH_2^2), AB signal ($\delta_A = 5.82$, $\delta_B = 5.92$, 2H, $J_{AB} = 15.7$ Hz, in addition split by $J_{A,4} = 5.7$ Hz, $^4J_{A,7} = 1.4$ Hz, $J_{B,7} = 5.4$ Hz, $^4J_{B,4} = 1.2$ Hz, A: 5-H, B: 6-H), overlapping AA′BB′ signals centered at $\delta = 6.868$ or 6.870 and 7.250 or 7.254, respectively [2×4H, 2×C_6H_4; contains solvent peak at $\delta = 7.26$ ($CHCl_3$)]; ^{13}C NMR (125.69 MHz, $CDCl_3/CDCl_3$): $\delta = 54.94$ (C-2), 55.33 (2×O-CH_3), 58.11 (C-3), 69.20 (C-1), 69.61 (C-7), 71.03 (C-4), 72.14 and 73.03 (C-1′, C-1″), 113.88 and 113.90 (C-$2^{Ar\text{-}1}$, C-$2^{Ar\text{-}2}$, C-$6^{Ar\text{-}1}$, C-$6^{Ar\text{-}2}$), 129.44 and 129.47 (C-$3^{Ar\text{-}1}$, C-$3^{Ar\text{-}2}$, C-$5^{Ar\text{-}1}$, C-$5^{Ar\text{-}2}$), 129.49 (C-6), 129.92 and 130.24 (C-$1^{Ar\text{-}1}$, C-$1^{Ar\text{-}2}$), 130.52 (C-5; same intensity as peak at $\delta = 129.49$), 159.31 and 159.39 (C-$4^{Ar\text{-}1}$, C-$4^{Ar\text{-}2}$); IR ($CDCl_3$): $\nu = 3690$, 3605, 2980, 2935, 2900, 2860, 2840, 1615, 1585, 1515, 1465, 1385, 1365, 1300, 1250, 1175, 1100, 1035, 975, 940, 825 cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{28}O_6$ (400.5): C 68.98, H 7.05; found: C 68.96, H 7.10.

(*cis,cis*)-1,7-Bis[(4-methoxybenzyl)oxy]hepta-2,5-dien-4-ol (20)



At room temperature $Cu(OAc)_2 \cdot H_2O$ (12.5 g, 62.5 mmol, 1.0 equiv.) was added in one portion to a suspension of Zn dust (86,3 g, 1.25 mol, 20 equiv.) in H_2O (500 mL). After stirring at this temperature for 10 min $AgNO_3$ (10.6 g, 62.5 mmol, 1.0 equiv.) was added in small portions within 30 min (***Caution! exothermic reaction***) and stirred for 1 h. The suspension was filtered under an inert atmosphere maintained by placing over the apparatus an inverted funnel through which N_2 was continuously passed. The residue was successively washed with H_2O (200 mL), methanol (400 mL), acetone (400 mL) and *t*-BuOMe (400 mL). The metal powder was suspended in methanol (100 mL) and a solution of dialkynylcarbinol **18** (23.8 g, 62.5 mmol) in methanol (60 mL) was added at room temperature. The resulting mixture was vigorously stirred at 40 °C for 14 h. The reaction mixture was cooled to room temperature, filtered through a pad of celite, and the filter cake was washed with *t*-BuOMe. The filtrate and washings were washed with saturated aqueous $NaHCO_3$ (300 mL) and saturated aqueous NaCl (300 mL). After drying of the organic phase over Na_2SO_4 the solvent was evaporated under reduced pressure and the residue was submitted to flash chromatography (12 cm, cyclohexane/EtOAc, 3:2) to afford the title compound (fractions 14–46, 19.8 g, 82%) as a slightly yellow oil. ^{1}H NMR (499.87 MHz, $CDCl_3$/TMS): $\delta = 2.35$ (br. d, 1H, $J_{OH,4} = 3.1$ Hz, 4-OH), 3.79 (s, 6H, 2×O-CH_3), AB signal ($\delta_A = 4.01$, $\delta_B = 4.08$, 4H, $J_{AB} = 12.5$ Hz, in addition split by $J_{A,2}$ and $J_{A,6} = 5.2$ Hz respectively, $J_{B,2}$ and $J_{B,6} = 5.2$ Hz respectively, 1-H_2 and 7-H_2 respectively), 4.42 (s, 4H, 1′H_2, 1″-H_2), 5.15 (td, 1H, $J_{4,3} = J_{4,5} = 6.8$ Hz, $J_{4,OH} = 2.9$ Hz, 4-H), 5.62–5.70 {m, 4H, approximately interpretable as AB signal [$\delta_A = 5.64$, $\delta_B = 5.67$, $J_{AB} = 11.1$ Hz ($\equiv J_{cis}$), in addition split by $J_{A,4} = 6.6$ Hz, $J_{B,1}$ and $J_{B,7} = 5.5$ Hz, respectively; A: 3-H and 5-H respectively, B: 2-H and. 6-H respectively)}, AA'BB' signal centered at $\delta = 6.87$ and $\delta = 7.25$ [2×4H, 2×C_6H_4; contains solvent peak at $\delta = 7.26$ ($CHCl_3$)]; ^{13}C NMR (125.69 MHz, $CDCl_3/CDCl_3$): $\delta = 55.26$ (2×OCH_3), 64.48 (C-4), 65.61 (C-1, C-7), 72.15 (C-1′, C-1″), 113.85 (C-$2^{Ar\text{-}1}$, C-$2^{Ar\text{-}2}$, C-$6^{Ar\text{-}1}$, C-$6^{Ar\text{-}2}$), 128.04 (C-2, C-6), 129.46 (3$^{Ar\text{-}1}$, C-$3^{Ar\text{-}2}$, C-$5^{Ar\text{-}1}$, C-$5^{Ar\text{-}2}$), 129.97 (C-$1^{Ar\text{-}1}$, C-$1^{Ar\text{-}2}$), 134.22 (C-3, C-5), 159.32 (C-$4^{Ar\text{-}1}$, C-$4^{Ar\text{-}2}$); IR (film): $\nu = 3415$, 3010, 2995, 2910, 2855, 2840, 1615, 1585, 1515, 1460, 1385, 1300, 1250, 1175, 1080, 1035, 820, 760, 710 cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{28}O_5$ (384.5): C 71.85%, H 7.34%; found: 71.75%, 7.40%.

Acknowledgements

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[25] This precedent is compared with our results in the concluding section of this paper.
[26] The molar ratio of divinylcarbinol **20**, monoepoxy alcohol *syn*-**12** (including some enantiomer), and bisepoxy alcohol *syn*,*syn*-**23** in the reaction mixture was determined from the ratio of the integrals over the following ^{1}H NMR signals of the isolated crude product (300 MHz, $CDCl_3$, Me_4Si as internal standard): $\delta = 3.00$ [dd, $J_{3,4} = 7.7$ Hz, $J_{3,2} = 4.3$ Hz, 3-H (*syn*-**12**)] *vs.* $\delta = 3.13$ [dd, $J_{3,4} = J_{5,4} = 6.0$ Hz, $J_{3,2} = J_{5,6} = 4.5$ Hz, 3-H, 5-H (*syn*,*syn*-**23**)] *vs.* $\delta = 5.23$ [dm_c, $J_{4,OH} \approx 7.5$, 4-H (**20**)].
[27] The *ee* of monoepoxy alcohol *syn*-**12** and its enantiomer were determined by HPLC (Chiralpak AD column, *n*-heptane/*i*-PrOH 90:10, UV detector: 238 min, flow rate: 1.0 mL min^{-1}, 15 °C isothermal); $t_R = 48.8$ min for *syn*-**12**, $t_R = 54.0$ min for *ent-syn*-**12**.
[28] The diastereomeric compositions of monoepoxy alcohol **13** and its enantiomer were determined from the ratio of the integrals over the following ^{1}H NMR signals (300 MHz, $CDCl_3$, Me_4Si as internal standard): $\delta =$ 3.02 [dd, $J_{3,4} = 7.5$ Hz, $J_{3,2} = 4.1$ Hz, 3-H (*anti*-**13**)] *vs.* $\delta =$ 3.07 [dd, $J_{3,4} = 7.4$ Hz, $J_{3,2} = 4.5$ Hz, 3-H (*syn*-**13**)]. "*ds* ≥ 98:2" means that the mentioned ^{1}H NMR signal of the minor diastereomer could not be detected.
[29] The *ee* of monoepoxy alcohol *anti*-**13** and its enantiomer were determined by HPLC (Chiralpak OD-H column, *n*-heptane/*i*-PrOH, 99.5:0.5, UV detector: 210 min, flow rate: 1.0 mL min^{-1}, 20 °C isothermal); $t_R = 13.8$ min for *ent-anti*-**13**, $t_R = 15.1$ min for *anti*-**13**.
[30] The *ee* of monoepoxy alcohol *syn*-**13** and its enantiomer were determined by HPLC (Chiralpak OD-H column, *n*-heptane/*i*-PrOH, 200:1, UV detector: 210 min, flow rate: 1.0 mL min^{-1}, 20 °C isothermal); $t_R = 24.5$ min for *syn*-**13**, $t_R = 27.8$ min for *ent-syn*-**13**.
[31] The diastereomeric compositions of monoepoxy alcohol **14** and its enantiomer were determined from the ratio of the integrals over the following ^{1}H NMR sig-

nals (500 MHz, $CDCl_3$, Me_4Si as internal standard): $\delta =$ 2.99 [dd, $J_{3,4} = 4.6$ Hz, $J_{3,2} = 2.3$ Hz, 3-H (*syn*-**14**)] *vs.* $\delta =$ 3.02 [dd, $J_{3,4} = 3.2$ Hz, $J_{3,2} = 2.3$ Hz, 3-H (*anti*-**14**)].

[32] The *ee* of monoepoxy alcohol *anti*-**14** and its enantiomer were determined by HPLC (Chiralpak AD column, *n*-heptane/*i*-PrOH, 85:15, UV detector: 227 min, flow rate: 1.0 mL min^{-1}, 30 °C isothermal); $t_R = 52.7$ min for *anti*-**14**, $t_R = 58.1$ min for *ent-anti*-**14**.

[33] The molar ratio of bisepoxy alcohols *syn*,*syn*-**24**, *anti*,-*anti*-**24**, and *anti*,*syn*-**24**/*ent-anti*,*syn*-**24** could be extacted from a 400 MHz ^{1}H NMR spectrum ($CDCl_3$) as shown in Figure 2, but not from the routinely registered 300 MHz ^{1}H NMR spectra.

[34] The *ee* of monoepoxy alcohol *syn*-**14** and its enantiomer were determined by HPLC (Chiralpak AD-H column, *n*-heptane/*i*-PrOH, 80:20, UV detector: 227 min, flow rate: 1.0 mL min^{-1}, 30 °C isothermal); $t_R = 26.6$ min for *ent-syn*-**14**, $t_R = 28.8$ min for *syn*-**14**.

[35] Apart from this, the *cis*-configuration of the oxirane rings in the monoepoxy alcohols in question can be deduced from the absolute value of the H,H coupling between the ring protons: It was relatively large (4.2 Hz) in compounds *anti*-**12** and *syn*-**12** and smaller (2.3 Hz) in the isomeric epoxy alcohols *anti*- and *syn*-**14**, each of which contains a *trans*-configured oxirane ring. Both values agree well with the rule of thumb, according to which $^3J_{cis\text{-oxirane}}$ is typically 4.5 Hz and $^3J_{trans\text{-oxirane}}$ 3.0 Hz according to: E. Pretsch, H. Seibl, W. Simon, *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden*, 3rd edn., Springer Verlag, Berlin **1990**, H65.

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[39] The absolute configurations mentioned in this paragraph and drawn in Scheme 8 and Scheme 9 were not yet known at this point of our investigation.

[40] The reduction of monoepoxy alcohol *syn*-**12** was performed before we learnt to prepare this compound as enantioselectively as documented in Scheme 4 and Figure 1. The enantiomeric monoepoxy alcohol *ent-syn*-**12** (85% *ee*) was transformed into the enantiomeric 1,3-diol 2*R*,4*S*-**25** {$[\alpha]_D$: +5.1 (*c* 0.98, $CHCl_3$)} by same procedure (47% yield).

[41] The composition of this mixture could not be determined by ^{1}H NMR analysis (300 MHz, $CDCl_3$, Me_4Si as internal standard) due to insufficiently separated signals ($\Rightarrow$1,3-diol:1,2-diol $\geq$ 79:21).

[42] a) R. Kramer, *Dissertation*, Universität Freiburg, **2007**; b) R. Kramer, R. Brückner, manuscript in preparation.

[43] It was no surprise that **28** underwent SAE with as little as 14% *ee* because it is well-known that tertiary allyl alcohols bind poorly to the tartrate/titanium complex;[2] *cf.* also p. 721 in D. C. Dittmer, R. P. Discordia, Y. Zhang, C. K. Murphy, A. Kumar, A. S. Pepito, Y. Wang, *J. Org. Chem.* **1993**, *58*, 718–731.

