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Kinetic resolution of epoxy alcohols with the Sharpless Ti-isopropoxide/tartaric ester complex

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ABSTRACT

When investigating the Sharpless epoxidation of enol-protected 4-hydroxy-1,2-cyclopentanediones, the ability of the asymmetric Ti(OiPr)₄/tartaric ester complex to discriminate between enantiomeric epoxides formed in situ was discovered, leading to the epoxide opening reaction of only one enantiomer. This observation was used in the kinetic resolution of racemic substituted 2,3-epoxy-4-hydroxy-cyclopentanol, to afford enantiomerically enriched epoxyalcohols in good yields and with *ees* up to 96%.

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1. Introduction

The kinetic resolution of allylic alcohols via Sharpless asymmetric epoxidation is a widely used reaction in the synthesis of various enantiomerically pure compounds¹ and in the total synthesis of several natural products.^{2,3}

It has previously been found that cyclic secondary allylic alcohols are poor substrates for Sharpless kinetic resolutions.⁴ In this respect, cyclohexenol has been found to be the worst compound, while substituted cyclohexenols⁵ and cyclopentenols⁶ afford slightly better results in the oxidations. Because of this knowledge, Sharpless asymmetric epoxidation is not usually used for the synthesis of enantiomerically pure cyclic secondary epoxy alcohols. However, there is a need for these compounds because they are important intermediates in the various regio- and stereoselective ring-opening reactions^{2,7} that afford chiral building blocks and intermediates.⁸

Usually, the in situ ring opening of the epoxy alcohols formed during Sharpless kinetic resolutions is the reaction that has to be avoided,⁹ thus making the synthesis of certain epoxy alcohols difficult using standard asymmetric epoxidation processes. 2-Alkylallylic alcohols often suffer from this limitation.¹⁰

Although the kinetic resolution of substituted 2,3-epoxy alcohols has been extensively studied, only a few efficient cases have been found: the resolution of *meso*-epoxy alcohols¹¹ (the opening of *meso*-epoxy alcohols with amines leads to chiral beta-amino alcohol units¹²) and terminal epoxy alcohols.¹³

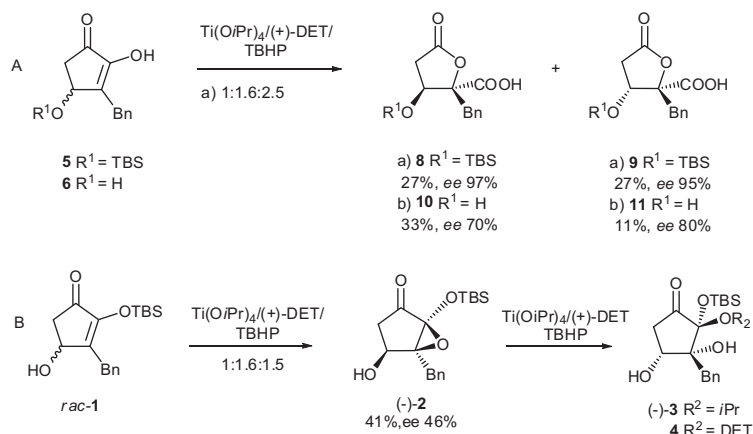
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We have previously found that the asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones with the Sharpless complex results in lactone carboxylic acids in good yield and with high *ee* values (Scheme 1, A, example a).¹⁴ We have also reported that a hydroxyl group in the allylic or homoallylic^{15,16} position plays an important role in determining the selectivity of the reaction. Thus, 3-benzyl-1,2-cyclopentanedione **5** with 4-silylprotected OH group gave lactone carboxylic acids as a mixture of two diastereomers in a 1:1 ratio with excellent enantioselectivities for both diastereomers **8** and **9** (*ee* values 97% and 95%), while the corresponding unprotected 4-hydroxy-3-benzyl-1,2-cyclopentanedione **6** afforded reduced enantiopurities of 70% *ee* and 80% *ee* for lactone acids **10** and **11**, but improved diastereoselectivity 3:1 (Scheme 1, A, example b). In the first case, only the highly stereoselective cascade oxidation¹⁷ may occur, while in the second case the highly stereoselectivity cascade oxidation and low stereoselectivity allylic oxidation of cyclic allylic alcohol compete, reducing the enantiopurity of the resulting product.

When the enol OH in 4-hydroxy-1,2-cyclopentanedione substrate is protected, only the epoxidation of the allyl alcohol moiety may occur. The Baeyer-Villiger-type oxidation does not proceed; instead, the ring opening reaction of the resulting epoxide may occur (Scheme 1, B).¹⁸

Herein, the oxidation of allylic systems with the subsequent epoxide opening is investigated. First, the obtained data on the oxidation of 4-hydroxy-1,2-cyclopentanedione enol ether **1** led us to the understanding that the enantiomers of the formed epoxide behave differently in the presence of the Sharpless complex: the epoxide openings proceed at different rates. This opens up the possibility of the kinetic resolution of these epoxides. Thus,



Scheme 1. Reactions of 4-hydroxy-1,2-cyclopentanediones.

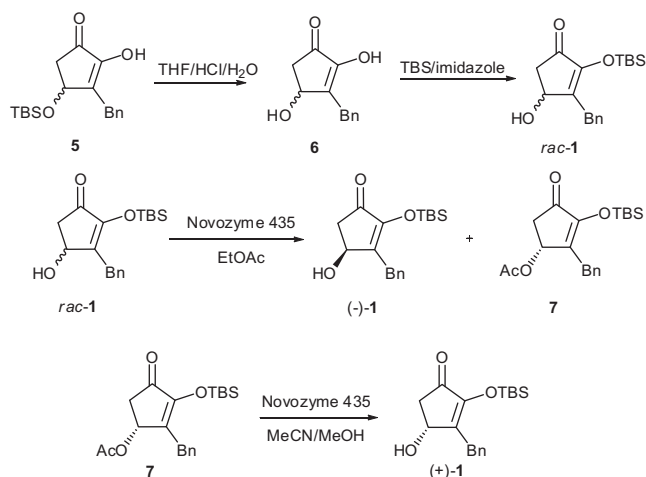
the epoxide opening of *rac-2*, cyclohexane epoxyalcohol *rac-15* and aliphatic epoxyalcohol *rac-13* were investigated.

Herein we have demonstrate the possibility of the kinetic resolution of racemic epoxides from 4-hydroxy-1,2-cyclopentanedione by using the Sharpless titanium isopropoxide/tartaric ester complex. We also found that with other common epoxy alcohols, the resolution is not efficient enough for preparative purposes.

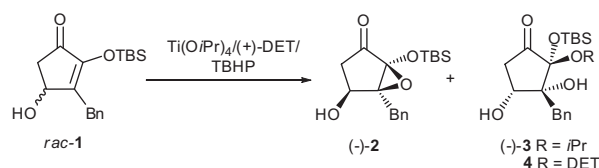
2. Results and discussion

2.1. Synthesis of substrates

The 4-silyloxy substituted 3-benzyl-1,2-cyclopentanedione **5** was prepared according to a procedure recently described by us.¹⁴ The protecting silyl group was removed with 3 M HCl in THF to afford **6** in 70% yield. The enol hydroxyl group of **6** was selectively protected to afford *rac-1* (yield 66%). For the synthesis of enantiomeric alcohols, the allylic alcohol was subjected to enzymatic acylation to afford (-)-**1** (yield 60%, *ee* 88%) and enriched acetate **7** in 30% yield. The other enantiomer was obtained by enzymatic deacetalization of enriched acetate **7** with Novozyme 435, resulting in (+)-**1** (yield 79%, *ee* 99%) (see Scheme 2).



Scheme 2. Synthesis of substrates.

Scheme 3. Sharpless kinetic resolution of substrate *rac-1*.

2.2. Allylic oxidation of cyclopentenols

The preliminary results of the oxidation of *rac-1* with (+)-DET (Scheme 3) showed that the substrate with an enol-protecting silyl group reacts, as expected, as an allylic alcohol to give epoxide (-)-**2** as a single diastereomer, with modest *ee* values. Additionally, the ring opening of the resulting epoxide also occurs to a certain extent, to give isopropyl acetal **3** and tartaric ester acetal **4** (as single diastereomers) (Fig. 1). This result suggests stereodifferentiation in the epoxide opening (Table 1, No. 1).

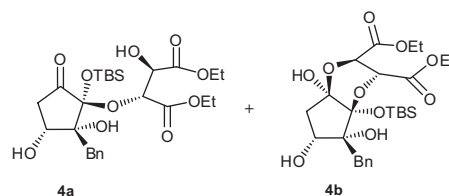


Figure 1. Tartaric ester acetals.

The epoxidation of highly enantioenriched (-)-**1** (*ee* = 96%) with $\text{Ti(OiPr)}_4/(-)\text{-DET/TBHP}$ complex gave epoxide (-)-**2** in 18% yield (*ee* 90%), isopropyl acetal (-)-**3** in 2% isolated yield (*ee* 98%) and DET acetal **4** in 24% isolated yield. There was 17% of unreacted substrate left, with *ee* 96%.

At the same time, the epoxidation of (-)-**1** (88% *ee*) with the $\text{Ti(OiPr)}_4/(+)\text{-DET/TBHP}$ complex gave epoxide (-)-**2** in 31% isolated yield and with 88% *ee*, as expected. The unreacted (-)-**1** retained its initial stereoisomeric state (88% *ee*). It is notable that in this case, no isolatable amounts of acetals **3** and/or **4** were formed.

We looked at this interesting phenomenon in more detail. When oxidizing substrates **1** with different enantiopurities with (+)-DET/TBHP complex, we observed that the product profile (ratio of acetals **3** + **4**/epoxide **2**) depended on the enantiomeric purity of the initial substrate (Fig. 2). The lower the excess of one enantiomer of the substrate, the higher the amount of formed acetals (Fig. 2).

Table 1
Sharpless epoxidation of 3-benzyl-1,2-cyclopentanediol **1***

No.	DET stereoisomer	Substrate 1	Epoxide 2	<i>i</i> PrOH acetal 3	DET acetals 4 (%)	Unreacted substrate 1
1	(+)-DET	<i>rac</i>	(-)- 2 , 29%, <i>ee</i> = 46%	(-)- 3 , 7%, <i>ee</i> = 14%	21	(-)- 1 , 12%, <i>ee</i> = 16%
2	(-)-DET	(-)- 1 , <i>ee</i> = 96%	(-)- 2 , 18%, <i>ee</i> = 90%	(-)- 3 , 2%, <i>ee</i> = 98%	24	(-)- 1 , 17%, <i>ee</i> = 96%
3	(+)-DET	(-)- 1 , <i>ee</i> = 88%	(-)- 2 , 31%, <i>ee</i> = 88%	—	—	(-)- 1 , 59%, <i>ee</i> = 88%

* Conditions: -20 °C; solvent CH₂Cl₂; overnight.

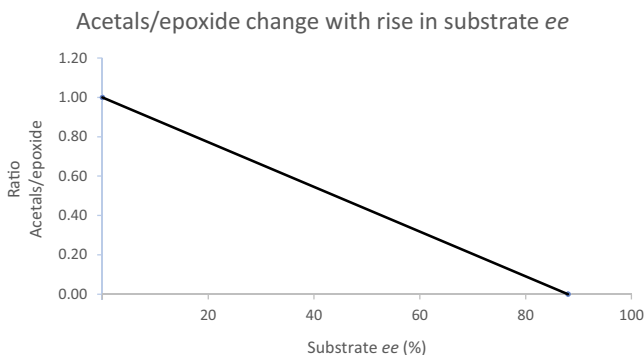
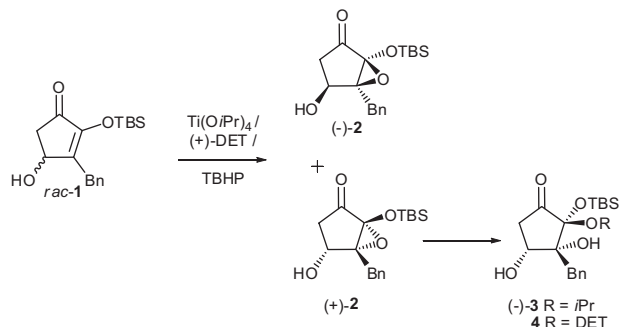


Figure 2. Illustration of the decrease in the ratio of acetals **3** + **4**/epoxide **2** with rise in substrate **1** *ee* value for reactions with (+)-DET (Table 1).

Figure 1 demonstrates that when the *ee* value of substrate **1** was higher, the yields of the acetals decreased. Also, in the experiment with enantiomerically enriched substrates, the combination of (-)-**1** with (-)-DET complex (Table 1, No. 2) produced more acetals than (-)-**1** with (+)-DET (Table 1, No. 3). All of the results presented above suggest a possible different behaviour of the enantiomers of the substrate and the formed epoxides with the chiral reagent. We propose that the obtained data may be rationalized as follows: in the two different reactions, epoxidation and epoxide opening, match and mismatch pairs of the substrate/reagent form, reacting at different rates and selectivities. First, the kinetic resolution in the course of the epoxidation of allylic cyclopentenol occurs with low selectivity; then, the second kinetic resolution occurs in the epoxide opening reaction (acetal formation). This reaction proceeds with high enantioselectivity and in this case the matched and mismatched pairs clearly cause different reaction rates. The (-)-**2** and (-)-DET combination results in the matched pair for epoxide opening (Table 1, No. 2). This conclusion is illustrated in Scheme 4.



Scheme 4. Sharpless kinetic resolution of *rac*-**1** and the following epoxide opening.

Table 2
Experiments with racemic epoxyalcohol **2**

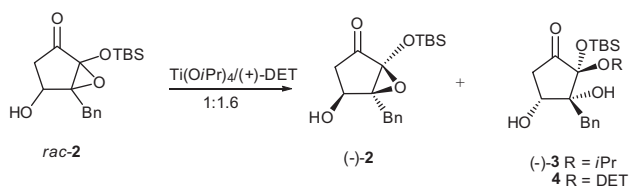
No.	Time (days)	DET stereoisomer	<i>i</i> PrOH acetal 3	DET acetals 4 (%)	Unreacted substrate
1	1	(+)-DET	(-)- 3 , 4%, <i>ee</i> 50%	29	(-)- 2 , 66%, <i>ee</i> 60%
2	3	(+)-DET	(-)- 3 , 10%, <i>ee</i> 12%	37	(-)- 2 , 53%, <i>ee</i> 96%
3	4	(-)-DET	(+)- 3 , 12%, <i>ee</i> 10%	33	(+)- 2 , 55%, <i>ee</i> 93%

* Yields from RP-HPLC.

If this conclusion is correct, there must be the possibility of separating the racemic 1,2-diketone epoxyalcohols by using Sharpless Ti/tartaric ester complexes.

2.3. Kinetic resolution of allylic epoxides with the Sharpless complex

Our assumption was tested by reacting racemic epoxyalcohol *rac*-**2** with the (+)-DET Sharpless complex. The selective epoxide opening should eliminate (+)-**2**. Indeed, after a 1-day reaction there was 66% of epoxide (-)-**2** left with 60% *ee* (see Scheme 5).



Scheme 5. Kinetic resolution of racemic epoxy alcohol *rac*-**2**.

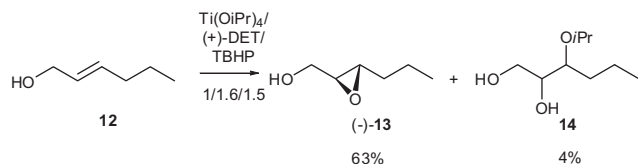
The obtained DET-acetal **4** was formed in 29% and *i*PrOH-acetal **3** was formed in 4% yield (*ee* 50%). To obtain better conversion, the reaction time was prolonged to 3 days, after which 54% of highly enantioenriched unreacted epoxide (-)-**2** was left (*ee* 96%). DET-acetal **4** was formed in 36% yield and acetal **3** as a single diastereomer in 12% yield (*ee* 10%) (Table 2).

These experiments demonstrate that the kinetic resolution of epoxide *rac*-**2** in the ring opening proceeded with high selectivity. Of the formed acetals, isopropyl acetal **3** had lower enantiopurity, while tartaric ester acetal **4** gave high enantioselectivity in the epoxide opening reaction.

2.4. Kinetic resolution of other epoxy alcohols

Sharpless had previously noted that after 100% conversion in the kinetic resolution of allylic alcohols, the *erythro*/*threo* ratio of the obtained epoxy alcohols increases due to an enantioselective opening process.⁴ Because of this knowledge, we were further encouraged to try our conditions with other epoxyalcohols. To elucidate the scope of the reaction, attempts at the kinetic resolution of an aliphatic epoxyalcohol **13** from hex-2-en-1-ol and cyclic epoxy alcohol **15** were made. In the first case, the Sharpless oxidation led to epoxy alcohol (-)-**13** in 63% yield and with 92% *ee*. The

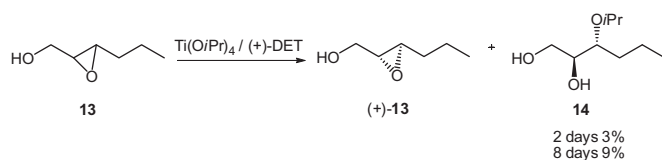
formation of a small amount of isopropyl ether **14** (4%) was also observed, which indicated that the kinetic resolution of *rac*-**12** should be possible (Scheme 6).



Scheme 6. Sharpless kinetic resolution of allylic alcohol **12**.

Compound *rac*-**13** was prepared by using an *m*CPBA oxidation of allylic alcohol **12**, resulting in 88% of the target product.

When *rac*-**13** was subjected to a reaction with the (+)-DET Sharpless complex with a substrate/reagent ratio of 1:1.6, after two days 56% of unreacted substrate (+)-**13** was left with *ee* 14% (Scheme 7). After 8 days of reaction, the enantiomeric purity of (+)-**13** increased to 42%. At the same time, several by-products formed, and we were able to isolate 9% of *i*PrOH-ether **14** (Table 3, Nos. 1–2).

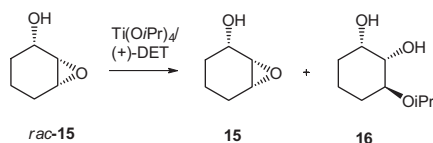


Scheme 7. Kinetic resolution of epoxy alcohol **13** with the Sharpless complex.

Table 3
Kinetic resolution of epoxy alcohols **13** and **15** with the Sharpless complex

No.	Substrate	Time (days)	Unreacted substrate	<i>i</i> PrOH-ether
1	<i>rac</i> - 13	2	13 ; 56%, <i>ee</i> 14%	14 ; 3%
2	<i>rac</i> - 13	8	13 ; 30%, <i>ee</i> 42%	14 ; 9%
3	<i>rac</i> - 15	3	15 ; 44%, <i>ee</i> 6%	16 ; 1%
4	<i>rac</i> - 15	7	15 ; 56%, <i>ee</i> 10%	16 ; 2%

We also prepared epoxyalcohol **15** from cyclohex-2-ene-1-ol with *m*CPBA in 73% yield. The kinetic resolution of the product with Ti(OiPr)₄/(+)-DET led to a small enantioenrichment of the starting epoxide, less than in the case of the aliphatic compound **13** (Scheme 8). Prolonging the reaction time led to small improvements: after three days, **15** was isolated with 6% *ee*, and after 7 days, with 10% *ee*. We were able to isolate small amounts of *i*PrOH-ether **16** from a mixture of several by-products (Table 3, Nos. 3–4).



Scheme 8. Kinetic resolution of epoxy alcohol **15** with the Sharpless complex.

3. Conclusion

The kinetic resolution of secondary allylic cyclopentenol *rac*-**1** gives epoxides and acetals with excellent diastereoselectivity, but

modest stereoselectivity. Two subsequent processes occur: allylic epoxidation, which proceeds with low stereoselectivity, and the epoxide opening, which is a highly stereoselective process. We found that the Sharpless complex is able to discriminate between enantiomeric in epoxides **2**, thus catalysing their epoxide opening at different rates. As a result, a kinetic resolution occurs, leading to acetals from predominantly one enantiomer only. The unreacted epoxide **2** can thus be obtained with high enantiomeric purity. This method is also applicable to simple racemic epoxy alcohols, such as **13** and **15**, but with less impressive results. We have demonstrated that the Sharpless complex can be used not only for epoxidation but also, as in the present case, for the kinetic resolution of racemic epoxides.

4. Experimental

The full assignment of the ¹H and ¹³C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz or Bruker Avance III 800 MHz instrument. High resolution mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Elemental analyses were done by using Elementar vario Micro. IR spectra were recorded on a Bruker Tensor 27 FT infrared spectrophotometer. MS spectra were measured on a Shimadzu GSMS-QP2010 spectrometer on a 70 eV EI. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. Chiral GC was performed using Shimadzu GC-2010 Supelco β-DEX™ 225 column (30 m × 0.25 mm). Chiral HPLC was performed using Chiralpak AD-H (250 × 4.6 mm), Chiralcel OJ-H (250 × 4.6 mm), Chiralcel OD-H (250 × 4.6 mm), Chiralpak AS-H (250 × 4.6 mm) or Lux 3u Amylose-2 (250 × 4.6 mm) columns. Precoated silica gel 60 F₂₅₄ plates from Merck were used for TLC, whereas for column chromatography silica gel Kieselgel 40–63 μm was used. Purchased chemicals and solvents were used as received. DCM was distilled over phosphorous pentoxide. Petroleum ether has a boiling point 40–60 °C. The reactions were performed under air atmosphere without additional moisture elimination unless stated otherwise.

4.1. Synthesis of 3-benzyl-2,4-dihydroxycyclopent-2-enone **6**

To a solution of diketone **5** (1.017 g, 3.2 mmol) in THF (20 mL), a 3 M HCl solution (7.7 mL) was added, and the reaction mixture was stirred for 3 h at room temperature. Next, H₂O (40 mL) was added and the mixture was extracted 3 times with EtOAc. The extracts were dried over MgSO₄, and the crude product was purified by column chromatography (heptane:acetone 10:3). 394 mg (60%) of diketone **6** were obtained as a colourless oil. **6**: ¹H NMR (400 MHz, MeOD) δ 7.37–7.07 (m, 5H, Ph), 4.53 (d, *J* = 6.1 Hz, 1H, H-4), 3.94 and 3.54 (2d, *J* = 14.2 Hz, 2H, Ph-CH₂), 2.74–2.62 (m, 1H, H-5), 2.21–2.10 (m, 1H, H-5). ¹³C NMR (101 MHz, MeOD) δ 201.10 (C-1), 149.88 (C-2), 145.42 (C-3), 137.87 (*s*-Ph), 129.10 (Ph), 128.66 (Ph), 126.54 (*p*-Ph), 65.96 (C-4), 42.68 (C-5), 31.16 (Ph-CH₂). IR (film, cm⁻¹): 3265, 1702, 1658, 1385, 1049, 980, 762, 637. MS (*m/z* %): 186, 158, 129 (main peak), 115, 105, 91, 77, 65, 51. Elemental analysis calcd for C₁₂H₁₂O₃ C, 70.57; H, 5.92; found C, 69.76; H, 6.19.

4.2. Synthesis of 3-benzyl-2[*tert*-butyldimethylsilyl]oxy-4-hydroxycyclopent-2-enone *rac*-**1**

Diketone **6** (110 mg, 0.54 mmol) was dissolved in CH₂Cl₂ (5 mL), after which imidazole (52 mg, 0.77 mmol) and TBSCl (89 mg, 0.59 mmol) were added. The mixture was stirred at room temperature for 1.5 h, after which H₂O (10 mL) was added. The mixture

was extracted 3 times with CH_2Cl_2 , and the extracts were dried over MgSO_4 . The obtained crude product was purified by column chromatography (heptane:EtOAc 20:1–20:3). 269 mg (66%) of diketone **rac-1** was obtained as a colourless oil. **rac-1**: ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.19 (m, 5H, Ph), 4.60 (d, J = 5.5 Hz, 1H, H-4), 3.94 and 3.61 (2d, J = 14.4 Hz, 2H, Ph- CH_2), 2.73–2.63 (m, 1H, H-5), 2.26–2.18 (m, 1H, H-5), 1.92 (br s, 1H, OH), 0.98 (s, 9H, *t*-Bu), 0.26 and 0.25 (s, 6H, CH_3 -Si- CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 199.95 (C=O), 150.83 (C-2), 150.28 (C-3), 137.77 (*s*-Ph), 129.09 (Ph), 128.94 (Ph), 126.84 (*p*-Ph), 66.25 (C-4), 42.89 (C-5), 31.65 (Ph- CH_2), 25.86 (*t*-Bu CH_3), 18.52 (*t*-Bu C), –3.71 (Si- CH_3), –3.90 (Si- CH_3). IR (film, cm^{-1}): 3252, 2856, 1748, 1496, 1389, 1258, 1064, 837, 779, 701. Elemental analysis calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3\text{Si}$ C, 67.88; H, 8.23; found C, 67.38; H, 8.36.

4.3. Synthesis of (4S)-3-benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-hydroxycyclopent-2-enone (–)-1

Novozym SP 435 (195 mg) was added to a solution of diketone **1** (195 mg, 0.61 mmol) in EtOAc (4 mL). The reaction mixture was then stirred overnight after which it was filtered and concentrated. The products were separated by column chromatography (Heptane:EtOAc 10:1). Product (–)-**1** (151 mg, 77%) was obtained as a colourless oil and acylated diketone **7** (39 mg, 18%) was obtained as a colourless oil. (–)-**1**: $[\alpha]_D^{25}$ = –89.6 (c 1.27, CHCl_3); IR (film, cm^{-1}): 3421, 3064, 1720, 1642, 1365, 1253, 1117, 1053, 840, 699; HPLC: AD-H Hex-*i*PrOH 97:3, 1 ml/min, 210 nm, ee = 88%, major 9.1 min, minor 11.9 min.

4.4. Synthesis of (4R)-3-benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-4-dihydroxycyclopent-2-enone (+)-1

Novozym SP 435 enzyme (225 mg) was added to a solution of acylated diketone **7** (150 mg, 0.42 mmol) in MeCN/MeOH (7.5 mL, 0.3 mL of MeOH and 7.2 mL of MeCN). After 4 days the reaction mixture was filtered and concentrated. The crude product was purified by column chromatography (Heptane:EtOAc 10:1). Diketone (+)-**1** (104 mg, 79%) was obtained as a colourless oil. (+)-**1**: $[\alpha]_D^{25}$ = +122.8 (c 0.36, CHCl_3); HPLC: AD-H Hex-*i*PrOH 97:3, 1 ml/min, 210 nm, ee = 99%, major 11.9 min, minor 8.9 min.

4.5. Synthesis of 1-benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-6-oxabicyclo[3.1.0]hexane-4-one (+)-2

At first, (–)-DET (0.14 mL, 0.78 mmol) was added at –20 °C under an argon atmosphere to a solution of $\text{Ti}(\text{O}-i\text{-Pr})_4$ (0.15 mL, 0.49 mmol) and molecular sieves (49 mg) in CH_2Cl_2 (3 mL). After 15 min of stirring, compound **1** (156 mg, 0.49 mmol) was added as a solution in CH_2Cl_2 (1 mL). After stirring for 30 min, TBHP (0.13 mL, 0.78 mmol) was added. After an overnight reaction, diethyl ether (10 mL) and a saturated Na_2SO_4 solution (0.49 mL) were added at –20 °C and the mixture was stirred for 2 h at room temperature. The mixture was filtered through Celite and concentrated. The crude mixture was purified by column chromatography (Heptane:EtOAc 15:1–10:3) to afford 60 mg (37%) of epoxide (+)-**2** as an amorphous solid, 19 mg (10%) of acetal (+)-**3** as a colourless oil and 49 mg (18%) of acetals **4** as a colourless oil. (+)-**2**: $[\alpha]_D^{25}$ = +72.7 (c 1.7, CHCl_3), ^1H NMR (400 MHz, chloroform-*d*) δ 7.43–7.11 (m, 5H, Ph), 4.10 (d, J = 6.0 Hz, 1H, H-2), 3.44 and 3.04 (2d, J = 14.2 Hz, 2H, Ph- CH_2), 2.55–2.04 (m, 2H, H-3), 0.99 (s, 9H, *t*-Bu), 0.34 (s, 3H, Si- CH_3), 0.24 (s, 3H, Si- CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 203.67 (C=O), 135.55 (*s*-Ph), 129.62 (Ph), 129.09 (Ph), 127.35 (*p*-Ph), 88.27 (C-5), 73.81 (C-1), 65.43 (C-2), 41.33 (C-3), 33.23 (Ph- CH_2), 25.71 (*t*-Bu CH_3), 18.14 (*t*-Bu C), –3.84 (Si- CH_3), –4.03 (Si- CH_3). IR (KBr, cm^{-1}): 3000, 1764, 1608, 1496, 1254, 1065, 858, 702. HPLC: AS-H Hex-*i*PrOH 97.5:2.5,

1 ml/min, 210.8 nm, ee = 58%, major 9.7 min, minor 8.4 min. HRMS (ES) m/z calcd for $[\text{M}-\text{H}]^-$ 333.1528; found 333.1524.

4.5.1. 3-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-3,4-dihydroxy-2-isopropoxycyclopentanone (+)-3

$[\alpha]_D^{25}$ = +127 (c 0.07, CHCl_3) ^1H NMR (400 MHz, chloroform-*d*) δ 7.32–7.17 (m, 5H, Ph), 4.44–4.34 (m, 1H, H-4), 4.03 (hept, J = 6.2 Hz, 1H, *i*Pr CH), 3.06 and 2.97 (2d, J = 13.8 Hz, 2H, Ph- CH_2), 2.69 (dd, J = 19.4, 8.7 Hz, 1H, H-5), 2.48 (s, 1H, 3-OH), 1.98 (dd, J = 19.4, 7.4 Hz, 1H, H-5), 1.21 (s, 1H, 4-OH) 1.16 and 0.92 (2d, J = 6.2 Hz, 6H, *i*Pr 2 $\times$ CH_3), 0.79 (s, 9H, *t*-Bu), 0.20 (s, 3H, Si- CH_3), –0.00 (s, 3H, Si- CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 208.24 (C=O), 137.32 (*s*-Ph), 130.39 (Ph), 129.06 (Ph), 127.07 (*p*-Ph), 101.88 (C-2), 78.97 (C-3), 69.95 (C-4), 65.61 (*i*Pr CH), 40.45 (C-5), 37.15 (Ph- CH_2), 26.03 (*t*-Bu CH_3), 24.89 (*i*Pr CH_3), 23.16 (*i*Pr CH_3), 18.81 (*t*-Bu C), –2.94 (Si- CH_3), –3.32 (Si- CH_3). HPLC: AD-H Hex-*i*PrOH 97:3, 1 ml/min, 210 nm, ee = 74%, major 4.9 min, minor 5.9 min. HRMS (ES) m/z calcd for $[\text{M}-\text{H}]^-$ 393.2103; found 393.2116.

4.5.2. 3-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-2,3,4-trihydroxycyclopentane-1-one diethyl tartrate acetal **4a**

^1H NMR (800 MHz, chloroform-*d*) δ 7.33–7.28 (m, 5H, Ph), 4.75 (d, J = 3.6 Hz, 1H, DET CHO), 4.45 (br dd, J = 8.0, 3.6 Hz, 1H, DET CHO), 4.34–4.22 (m, 4H, DET OCH_2), 4.23 (br s, 1H, 4-OH), 4.18–4.15 (br m, 1H, H-4), 3.76 (s, 1H, 3-OH), 3.35 (d, J = 8.9 Hz, 1H, DET OH), 3.17 (d, J = 14.2 Hz, 1H, Ph- CH_2), 2.67 (dd, J = 20.0, 7.9 Hz, 1H, H-5), 2.52 (d, J = 14.2 Hz, 1H, Ph- CH_2), 2.36 (dd, J = 20.0, 4.2 Hz, 1H, H-5), 1.34 and 1.32 (2t, J = 7.2 Hz, 6H, DET CH_3), 0.93 (s, 9H, *t*-Bu), 0.41 (s, 3H, Si- CH_3), 0.09 (s, 3H, Si- CH_3). ^{13}C NMR (201 MHz, chloroform-*d*) δ 208.44 (C=O), 171.28 (DET C=O), 169.65 (DET C=O), 136.22 (*s*-Ph), 130.68 (*o*-Ph), 128.62 (*m*-Ph), 127.08 (*p*-Ph), 102.26 (C-2), 79.24 (C-3), 74.17 (DET CHO), 72.44 (DET CHO), 68.50 (C-4), 62.36 (DET OCH_2), 62.02 (DET OCH_2), 41.34 (C-5), 38.07 (Ph- CH_2), 25.89 (*t*-Bu CH_3), 18.70 (*t*-Bu C), 14.22 (DET CH_3), 14.11 (DET CH_3), –2.60 (Si- CH_3), –4.13 (Si- CH_3). HRMS (ES) m/z calcd for $[\text{M}+\text{Na}]^+$ 563.2283; found 563.2298.

4.5.3. 3-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-2,3,4-trihydroxycyclopentane-1-one diethyl tartrate diacetal **4b**

^1H NMR (800 MHz, chloroform-*d*) δ 7.29–7.24 (m, 5H, Ph), 4.55 (d, J = 9.3 Hz, 1H, DET CHO), 4.47 (d, J = 9.3 Hz, 1H, DET CHO), 4.27–4.22 (m, 2H, DET OCH_2), 4.12 and 4.11 (2q, J = 7.2 Hz, 2H, DET OCH_2), 3.77 (s, 1H, 3-OH), 3.74 (br m, 1H, H-4), 3.15 (br s, 1H, 1-OH), 3.06 (d, J = 14.7 Hz, 1H, Ph- CH_2), 2.90 (dm, J = 14.7 Hz, 1H, Ph- CH_2), 2.85 (br d, J = 10.4 Hz, 1H, 4-OH), 2.55 (dd, J = 16.5, 7.9 Hz, 1H, H-5), 2.26 (dm, J = 16.5 Hz, 1H, H-5), 1.30 and 1.29 (2t, J = 7.2 Hz, 6H, DET CH_3), 1.00 (s, 9H, *t*-Bu), 0.47 (s, 3H, Si- CH_3), 0.29 (s, 3H, Si- CH_3). ^{13}C NMR (201 MHz, chloroform-*d*) δ 167.67 (DET C=O), 167.15 (DET C=O), 136.49 (*s*-Ph), 131.12 (*o*-Ph), 128.17 (*m*-Ph), 126.73 (*p*-Ph), 100.24 (C-2), 99.34 (C-1), 80.49 (C-3), 72.57 (DET CHO), 69.41 (C-4), 69.11 (DET CHO), 62.38 (DET OCH_2), 62.23 (DET OCH_2), 40.46 (C-5), 37.93 (Ph- CH_2), 26.24 (*t*-Bu CH_3), 18.75 (*t*-Bu C), 14.08 (DET CH_3), 14.02 (DET CH_3), –1.56 (Si- CH_3), –3.11 (Si- CH_3).

4.6. General procedure for the synthesis of racemic epoxy alcohols

To a solution of allylic alcohol (1 mmol) in CH_2Cl_2 (3.5 mL), *m*-CPBA (1.2 equiv) was added at 0 °C. The mixture was allowed to gradually warm up to room temperature. After 30 min, 1.5 mL of saturated NaHCO_3 and 1.5 mL of 10% $\text{Na}_2\text{S}_2\text{O}_3$ were added and the mixture was stirred for 30 min. The organic layer was separated and the mixture was extracted with CH_2Cl_2 , then washed with saturated NaHCO_3 and brine, and dried with Na_2SO_4 . The

filtered and concentrated crude product was purified by column chromatography (Petroleum ether:Acetone 10:2).

4.7. Procedure for the kinetic resolution of *rac*-2, *rac*-13 and *rac*-15

At first, (–)-DET (0.16 mL, 0.82 mmol) solution in CH₂Cl₂ (0.5 mL) was added at –20 °C under an argon atmosphere to a solution of Ti(OiPr)₄ (0.16 mL, 0.51 mmol) and molecular sieves (51 mg) in CH₂Cl₂ (2.5 mL). After 15 min of stirring, the epoxyalcohol substrate (0.55 mmol) was added as a solution in CH₂Cl₂ (2 mL). After an overnight reaction, diethyl ether (11 mL) and saturated Na₂SO₄ solution (0.51 mL) were added at –20 °C and the mixture was stirred for 2 h at room temperature. The mixture was then filtered through Celite and concentrated. The crude mixture was purified by column chromatography with Hept:EtOAc 15:1–10:3 mixture to yield 89 mg (53%) of epoxide (–)-2, 6 mg (4%) of acetal 3 and 43 mg (16%) of acetals 4.

4.8. Kinetic resolution of 2,3-epoxyhexanol 13

From the epoxyalcohol substrate 13 (87 mg, 0.75 mmol) with (–)-DET (0.23 mL, 1.2 mmol), Ti(OiPr)₄ (0.23 mL, 0.75 mmol) in CH₂Cl₂ (7 mL), 49 mg (56%) of epoxyalcohol (+)-13 and 4 mg (3%) of isopropyl ether 14 were obtained. The data for the compounds were in accordance with the literature.¹⁹ 13 [α]_D²⁵ = +1.7 (c 0.49, CHCl₃), ¹H NMR (400 MHz, CDCl₃) δ 3.94–3.86 (m, 1H), 3.66–3.57 (m, 1H), 2.98–2.89 (m, 2H), 2.02–1.87 (m, 1H), 1.59–1.40 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H). Chiral GC β -DEXTM 225 column: *ee* = 14% major 11.0 min, minor 10.8 min. 3-Isopropoxyhexane-1,2-diol 14: ¹H NMR (400 MHz, CDCl₃) δ 3.83–3.75 (m, 1H), 3.75–3.68 (m, 1H), 3.65–3.58 (m, 2H), 3.51 (dt, *J* = 7.0, 3.9 Hz, 1H), 2.71 (br, 2H), 1.60–1.26 (m, 4H), 1.15 and 1.14 (2d, *J* = 6.1 Hz, 2 $\times$ 3H), 0.93 (t, *J* = 7.0 Hz, 3H).

4.9. Kinetic resolution of 2,3-epoxycyclohexanol 15

From the epoxyalcohol substrate 15 (69 mg, 0.7 mmol), (–)-DET (0.21 mL, 1.12 mmol), Ti(OiPr)₄ (0.2 mL, 0.7 mmol) in CH₂Cl₂ (6.5 mL), 35 mg (44%) of epoxyalcohol 15 were obtained. The data for the epoxyalcohol were in accordance with the literature.²⁰

HPLC analysis was performed after benzylation of the product. 15: ¹H NMR (400 MHz, CDCl₃) δ 4.04–3.95 (m, 1H), 3.36–3.28 (m, 2H), 2.20–2.11 (m, 1H), 1.91–1.68 (m, 2H), 1.61–1.49 (m, 2H), 1.50–1.37 (m, 1H), 1.32–1.18 (m, 1H). HPLC AD-H 95:5, 1 ml/min, 230 nm, major 7.9 min, minor 9.1 min, *ee* = 10%.

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