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# Multiselective enzymatic reactions for the synthesis of protected homochiral *cis*- and *trans*-1,3,5-cyclohexanetriols†

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**Abstract**

For the synthesis of the potentially antipsoriatic vitamin D derivative **3** (Ro 65-2299) an efficient and multiselective enzymatic step had been developed in which the easily accessible *trans*-1,3,5-triacetoxy-cyclohexane **5** was selectively monohydrolyzed in the presence of the *cis*-isomer **8** to give (1*R*,3*R*)-1,3-diacetoxy-5-hydroxy-cyclohexane **6** in high enantiomeric excess (>99%) and yield (84%). Furthermore, for the synthesis of the enantiomer of **3**, a simple and efficient enzymatic procedure for the asymmetric acetylation of *cis*-1,5-dihydroxy-3-(*tert*-butyldimethylsilanoxy)-cyclohexane **10** in an anhydrous organic solvent providing (1*R*,3*S*,5*S*)-1-acetoxy-3-hydroxy-5-(*tert*-butyldimethylsilanoxy)-cyclohexane **11** in >99% ee and quantitative yield is described. 

## 1. Introduction

For the treatment of psoriasis, one of the most common genetically determined skin diseases, novel orally active vitamin D analogues[1] have attracted much attention in recent years. Retiferol **3** (Ro 65-2299), a compound that lacks the C,D-ring,[2] was selected as a clinical candidate. In order to facilitate material supply a novel and very efficient synthesis suitable for the multi-kg scale was developed by Hilpert et al.[3] This new route features an efficient Julia coupling of the key precursors ketone **1** and sulfone **2** (Scheme 1).

The synthetic concept starting from the *trans*-cyclohexanetriol **4** (Scheme 2) represents a highly attractive and short route to ketone **1** but depends on a very demanding multiselective enzymatic hydrolysis of the triacetate **5**. To our knowledge no stereoselective hydrolysis of a *cis*- or *trans*-triacyloxycyclohexane has been described in the literature to date, though several such examples for the hydrolysis of 1,2-, 1,3- or 1,4-diacyloxycyclohexanes exist. The presence of a third identical acetyl group in the substrate demands additional discrimination, namely regioselectivity as well as enantioselectivity and limitation to monohydrolysis.

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† Dedicated to Dr. Hans Georg Leuenberger on the occasion of his 60th birthday.

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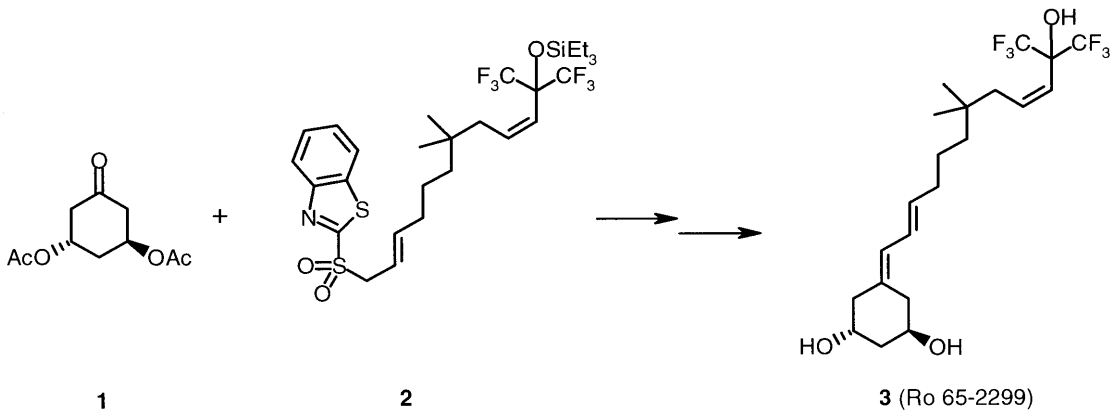
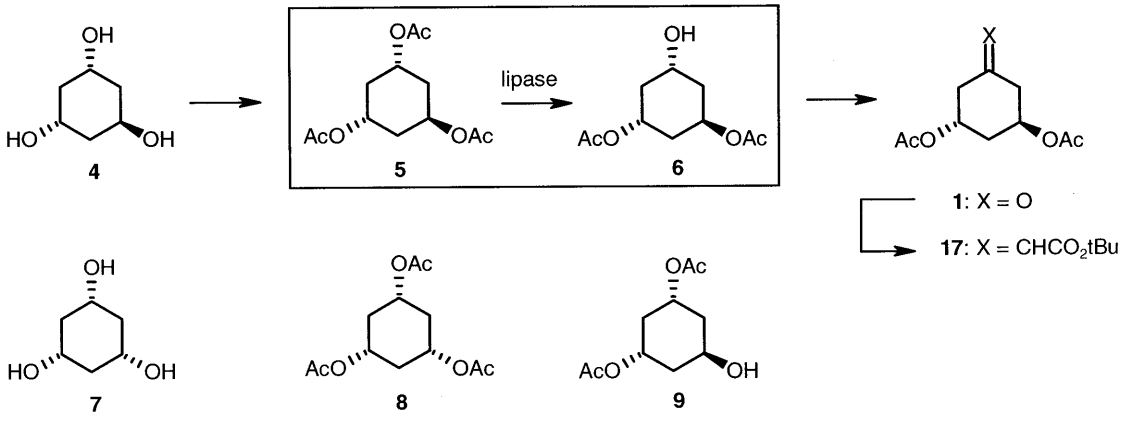


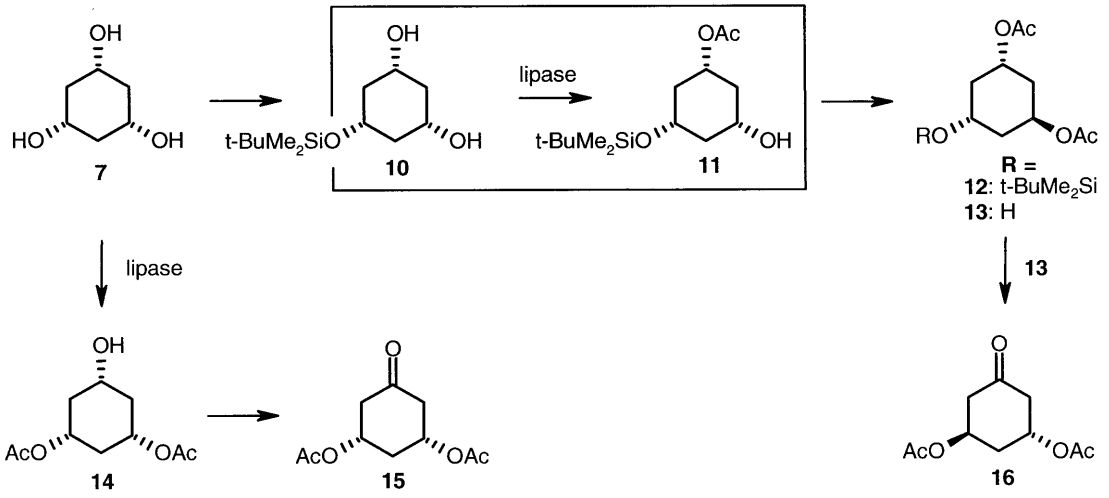

Scheme 1. Julia coupling of ketone **1** and sulfone **2** to retiferol Ro 65-2299




Scheme 2. Chemoenzymatic route to the *trans*-ketone **1**

The starting material *trans*-triol **4** is commercially available from Tokyo Kasei as a 1:1 mixture of **4** and the *cis*-isomer **7** which is converted to the corresponding 1:1 mixture of *trans*- and *cis*-triacetates **5** and **8**, respectively, by conventional means. For reasons of technical relevance we tried to avoid the necessity of completely removing the *cis*-isomer even though the presence of the *cis*-triacetate **8** increased the already demanding selectivity requirements for this enzymatic step considerably. Following the enzymatic step, alcohol **6** is converted to the diacetoxy ketone **1** by a bleach oxidation.[3] An even more direct alternative access to **6**, the selective enzymatic diacylation of *trans*-triol **4** in the presence of its *cis*-isomer **7** in anhydrous organic solvents, failed.

To enable clinical evaluation of the retiferol **3**, an analytical method was required to quantify various isomers. Therefore, we also developed a route to the enantiomeric ketone **16** and the *cis*-ketone **15** (Scheme 3); both intermediates can then be converted to the target isomers according to Scheme 1. *Meso*-diol **10** as substrate for the enzymatic acetylation reaction was obtained by a highly selective monosilylation of commercially available *cis*-cyclohexanetriol **7**.[3] The corresponding enzymatic step, the desymmetrization of diol **10**, was considered to be less demanding with respect to the required selectivity as the desymmetrization of numerous prochiral diols by asymmetric acylation has already been described in the literature. In the




Scheme 3. Chemoenzymatic routes to the *trans*-ketone **16** and *cis*-ketone **15**

context of the synthesis of vitamin D analogues we should mention Huang et al.,[4] who started an approach from *cis*-cyclohexane-1,3,5-triol which was diacetylated in vinyl acetate with lipase SAM (78% yield). The residual hydroxy group was tosylated followed by methanolysis of the acetyl groups. The resulting prochiral diol was then asymmetrically monoacylated with lipase SAM to the (1*R*,3*S*,5*S*)-1-acetoxy-3-hydroxy-5-tosyloxy-cyclohexane in >95% ee and 92% yield. In a reverse hydrolytic approach Suemune et al.[5] prepared the closely related (1*S*,3*R*,5*S*)-1-acetoxy-3-benzyloxy-5-hydroxy-cyclohexane from the corresponding diacetate by means of pig liver esterase (87% ee; 62% yield) or various lipases (1*R*,3*S*,5*R* in up to 84% ee; 16% yield). For the same reaction Carda et al.[6] reported 85% ee in 70% yield with pig liver esterase.

## 2. Results and discussion

### 2.1. Enzymatic preparation of (1R,3R)-1,3-diacetoxy-5-hydroxy-cyclohexane 6

The screening for the regio- and enantioselective monohydrolysis of *trans*-triacetate **5** with numerous lipases (EC 3.1.1.3) and esterases (EC 3.1.1.1) provided four commercially available lipases from *Candida rugosa* (formerly classified as *C. cylindracea*) which met all discrimination requirements and enabled a highly efficient solution of this problem. In addition, all four enzymes, namely lipases AY, MY, OF and Chirazyme L-3, exhibited a rather good *trans*/*cis*-selectivity so that a 1:1-mixture of the *trans*/*cis*-isomers **5** and **8** could be used as an easily accessible starting material. The four enzymes showed comparable selectivities with respect to the enantiomeric excess of **6**, the formation of the undesired *trans-meso*-diacetate **9** and over-hydrolysis: after ~95% conversion, product **6** was generated in roughly 36% (GLC area %) and >99% ee, besides ~0.5% *meso*-diacetate **9**, ~5% *cis*-diacetate **14**, <10% monoacetates/triols and the remaining substrates **8** (~50%) and **5** (~6%). Lipase MY exhibited the best overall-performance but Lipase OF was preferred because it showed an approximately six times faster reaction rate than the three other enzymes (on a weight basis). Optimization of lipase OF revealed that the use of a nonpolar biphasic cosolvent (cyclohexane), low temperature (6°C, freezing point of cyclohexane) and pH 7.0 enhanced the overall performance.

The mono- and triacetate isomers still present in the crude diacetate product **6** could be readily removed by a chromatographic filtration step (crude product/silica gel 1:10); however, neither the *trans-meso*-diacetate **9** nor the *cis*-diacetate **14** were depleted under these conditions. In order to reduce the latter and further improve the efficiency of the chromatographic filtration step the enzyme reaction was carried out with an enriched *trans*-isomer which could be obtained by a crystallization step.[3] Under optimized conditions and using a *trans*-enriched substrate (**5**/**8**=81:19) crude product **6** was generated, after conversion of 1.07 ester equivalents and before the chromatographic filtration step, in 71.1% purity (GLC area %) containing 1.9% *cis*-diacetate **14**, 0.5% *meso*-diacetate **9**, 0.5% monoacetate(s) and the remaining substrates **8** (18.5%) and **5** (2.2%). After chromatographic filtration diacetate **6** was obtained in 95.7% purity (99.5% ee) and 84% yield containing 2.6% **14** and 0.6% **9** (see Section 4.4).

Hydrolysis experiments with the corresponding tributyrate with lipase OF were unselective (formation of monobutyrate), as were butanolysis tests with the mentioned *Candida rugosa* enzymes in *tert*-butyl methyl ether/butanol 9:1. Also the experiments for an even shorter approach, the selective acylation of **4**/**7** mixtures with various acyl donors, were unsuccessful (essentially due to over-acylation or insufficient *cis*/*trans* selectivity).

### 2.2. Enzymatic preparation of (1R,3S,5S)-1-acetoxy-3-hydroxy-5-(tert-butyldimethylsilanoxy)-cyclohexane **11**

A broad panel of commercially available lipases was tested for the asymmetric acetylation of *meso*-diol **10** in vinyl acetate. It turned out that an amazingly high number of enzymes exhibited excellent selectivity with respect to both enantiomeric excess and diacetate formation (Table 1).

Table 1
Asymmetric acetylation of diol **10** with various lipases

| Lipase[a] | Conversion (GLC area %) | | % ee | Lipase[a] | Conversion (GLC area %) | | % ee |
|---|---|---|---|---|---|---|---|
| | **11** | **12** | **11** | | **11** | **12** | **11** |
| QL | 100 | 1.1 | >99 | SAM-2 | 80 | 0.2 | >99 |
| PL | 99 | 0.7 | >99 | B1 | 77 | 0.4 | >99 |
| Chirazyme L-1 | 99 | 1.2 | >99 | Chirazyme L-2 | 76 | 14 | 97 |
| Chirazyme L-6 | 99 | 0.7 | >99 | M-AP | 76 | 0.2 | 99 |
| Chirazyme L-3 | 97 | 0.5 | >99 | G | 74 | 0.6 | >99 |
| Chirazyme L-4 | 96 | 2.7 | >99 | *C. utilis* | 74 | 0.2 | >99 |
| AK | 95 | 0.4 | >99 | B | 73 | 0.1 | >99 |
| PS | 92 | 0.3 | >99 | AP | 69 | 0.1 | >99 |
| Chirazyme L-5 | 91 | 0.3 | >99 | IM-20 | 68 | 0.4 | 99 |
| MY | 88 | 0.2 | >99 | F13 | 67 | 0.1 | >99 |
| *C. cylindracea* | 87 | 0.3 | >99 | AY | 63 | – | 96 |
| OF | 86 | 0.5 | >99 | D | 60 | 0.1 | >99 |
| LIP | 86 | – | >99 | Chirazyme L-7 | 58 | 0.2 | 99 |
| F5 | 84 | 0.5 | >99 | | | | |

[a] Conditions: 4 mg of **10** dissolved in 1 ml of vinyl acetate was slightly agitated at rt in the presence of 0.5–3 mg of suspended enzyme.

The fastest enzyme, lipase QL from Meito Sangyo, was employed in a preparative experiment ($s/e=10$) using vinyl acetate/ethyl acetate 1:9 as both solvent and acylating agent. After termination of the reaction the enzyme was filtered off (for further reuse), and the product was obtained in high yield (99%) and purity (98%). Further optimization of the reaction towards higher substrate concentration was not carried out but is considered to be feasible.

### 2.3. Enzymatic preparation of cis-1,3-diacetoxy-5-hydroxy-cyclohexane **14**

In contrast to Huang et al.,[4] who used the relatively expensive lipase SAM for the preparation of *cis*-diacetate **14**, we employed lipase QL which recommended itself by virtue of its performance in the enzyme screening directed to the selective acylation of **4**/**7** mixtures for the preparation of **6**. In this screening, carried out in *tert*-butanol/vinyl acetate 10:1, only a few enzymes were found to be capable of diacetylating *cis*-triol **7** with reasonable activity. Among them lipase QL again afforded the best results. In a 50 g experiment the mono-, di- and triacetates were formed in a ratio of 1:13:1 (GLC area %). Removal of the side components by chromatographic filtration on silica gel yielded pure product **14** in 70% yield.

### 2.4. Determination of the absolute configuration of the alcohols **6** and **11**

The absolute configuration of the alcohols **6** and **11** was established as follows. The configuration of the remaining hydroxy group in alcohol **11** was inverted under Mitsunobu conditions to give compound **12**. Deprotection of the silyl-group afforded alcohol **13**. Compounds **6** and **13** showed identical $^1$H NMR, IR and MS spectra, $[\alpha]_D$ values with opposite signs, and they could be base-line separated on a chiral GC-column (BGB-174), thus corroborating the enantiomeric relationship of the two compounds. The absolute configuration of the alcohol **6** (and thus also of **11**) was unambiguously established by an X-ray analysis of the *tert*-butyl ester **17**, which was prepared from ketone **1** by Peterson olefination.

## 3. Conclusion

The two versatile protected homochiral 1,3,5-cyclohexanetriol building blocks **6** and **11** could be efficiently prepared by two highly selective enzymatic desymmetrizations of *meso*-compounds: the *trans*-isomer **6** by asymmetric monohydrolysis of the corresponding triacetate **5** in the presence of the *cis*-isomer **8**, and the *cis*-isomer **11** by asymmetric acylation of the monosilylated *cis*-triol **10** in an anhydrous organic solvent. Especially the first reaction represents an extremely attractive biotransformation with unusually high multiple selectivity.

The homochiral building blocks open, for example, an efficient way to the A-ring moiety of vitamin D derivatives, which become accessible in both enantiomeric forms.

## 4. Experimental

### 4.1. General

NMR spectra were recorded on a Bruker AC (250 MHz) or a Bruker AM (400 MHz), and IR spectra on a Nicolet-FTIR 20 SXB. MS-EI were measured on an SSQ 7000 Finnigan MAT.

Optical rotations were determined on a Perkin–Elmer Polarimeter 241, and melting points (uncorrected) on a Tottoli apparatus. GC determinations were carried out on a Perkin–Elmer AutoSystem and an HP5890-II. BGB-capillary columns were purchased from BGB-Analytik AG, Anwil, Switzerland.

### 4.2. Enzymes

Lipases MY, OF, PL and QL were a kind gift from Meito Sangyo Co. (Tokyo), lipases AP, AK, AY, CE, D, F-AP, G, M-AP, PS from Amano Pharmaceutical Co. (Nagoya, Japan) and lipase IM-20 from Novo Nordisk (Bagsvaerd, Denmark). Lipases B1, F5 and F13 were purchased from Enzymatix (Cambridge, UK), lipase B from Wako Pure Chemical Industries (Osaka), lipase LIP from Asahi Chemical Industry Co. (Tokyo), lipase from *C. cylindracea* from Sigma and lipase SAM-2 and lipase from *C. utilis* from Fluka. Chirazymes were from Roche Diagnostics (Mannheim).

### 4.3. Preparation of enriched trans-*1,3,5*-triacetoxy-cyclohexane **5**

A suspension of 44.00 g (333.0 mmol) cyclohexanetriol (enriched to a 76:18 mixture of *trans*/*cis* as described by Hilpert et al.[3]) in 110 ml pyridine was treated at 22°C with 157 ml acetic anhydride (1665 mmol) over 45 min, after which time the temperature rose to 45°C. The yellow solution was stirred at 45°C until completion of the reaction (4 h). The mixture was evaporated to dryness at 52°C/10 mbar, the residue was dissolved in 300 ml dichloromethane and the organic layer washed with 300 ml 0.2N HCl and 200 ml deionized water. The aqueous layers were extracted with 200 ml dichloromethane, the combined organic layers were dried over magnesium sulfate and evaporated to dryness to give 85.73 g (331.9 mmol) of crude **5** as a pale yellow oil: GLC (area %): 77.0% *trans*-triacetate **5**, 17.7% *cis*-triacetate **8**. IR (neat): 2961 m, 1736 s br (C=O), 1438 m, 1370 s, 1229s br, 1131 s, 1029 s, 980 s. $^1$H NMR (400 MHz, $CDCl_3$): 1.35–1.65 and 2.07–2.35 (m each, 6H, 3×$CH_2$), 2.04 and 2.07 (ratio 2.8:1, s each, 9H, 3×$CH_3$), 4.78 (m, 0.8 H, 3×H–CO of *cis*-isomer), 5.09 and 5.39 (ratio 2:1, m each, 3H, 3×H–CO of *trans* isomer). MS (EI): 199/7 ($M^+$–OAc), 138/20, 96/90, 78/35, 43/100. $C_{12}H_{18}O_6$ requires: C, 55.81; H, 7.03%; found: C, 55.94; H, 7.10.

### 4.4. Enzymatic preparation of (*1*R,*3*R)-*1,3*-diacetoxy-*5*-hydroxy-cyclohexane **6**

Crude **5** (81.74 g, 316.5 mmol; 77.0% GLC) obtained above was taken up in 200 ml cyclohexane and to the suspension added 1.3 l 0.1 M sodium chloride solution and 50 ml 0.1 M sodium phosphate buffer pH 7.0 under vigorous stirring. The resulting suspension/solution was cooled to 5–6°C and the pH readjusted to 7.0 with a few drops of 1N sodium hydroxide solution. The reaction was started by adding 1.60 g lipase OF dissolved in 15 ml 0.1 M sodium chloride solution and the pH kept constant at 7.0 by the controlled addition (pH stat) of 1.0N sodium hydroxide solution under vigorous stirring at 5–6°C. After 21.5 h, after the consumption of 260 ml (1.07 equiv.), the reaction mixture (having become homogeneous) was extracted with 1.5 l of dichloromethane. The organic phase was very turbid and was clarified by filtration through Dicalite Speedex (100 g, prewashed with water). The aqueous phase additionally obtained by this step was combined with the first and extracted once more with 1.5 l

dichloromethane (passed through the same filter bed). The combined organic phases were dried over sodium sulfate, concentrated and dried on HV. The residue (66.1 g; 71% GLC) was chromatographed on 700 g of silica (40–63 μm) with hexane/ethyl acetate 3:2 to give 46.3 g (214.1 mmol; 95.7% GLC; 84%) *trans*-diacetate **6** as a colourless oil: GLC (area %): 95.7% *trans*-diacetate **6**, 2.6% *cis*-diacetate **14**, 0.6% *trans*-meso-diacetate **9**. 99.5% ee. $[\alpha]_D = -14.4$ ($CHCl_3$, 1%). IR (neat): 3452m br (OH), 2957m, 1735 s br (C=O), 1464m, 1438m, 1371m, 1236m br, 1122m, 1073m, 1026m, 977m. $^1$H NMR (400 MHz, $CDCl_3$): 1.43–1.65, 2.05–2.31 (m each, 4H and 3H, 3×$CH_2$ and OH), 2.04 and 2.05 (s each, 3H each, 2×$CH_3$), 4.04 (m, 1H, H–C(5)), 5.05 and 5.29 (m each, 1H each, H–C(1) and H–C(3)). MS (EI): 156/2 ($M^+$–OAc), 96/75, 43/100. $C_{10}H_{16}O_5$ requires: C, 55.55; H, 7.46%; found: C, 55.76; H, 7.37.

### 4.5. Preparation of *all*-cis-*5-(*tert-*butyldimethyl-silanyloxy)-cyclohexane-1,3-diol* ***10***

To a suspension of 74.01 g (560.0 mmol) of dry *cis*-triol **7** in 1480 ml of THF was added subsequently at 22°C 95.72 g of *tert*-butyldimethylsilyl chloride and 62.33 g of triethylamine, and the suspension was treated in one portion with 24.44 g of NaH (60% in oil) whereby the temperature rose slowly to 45°C within 30 min. After 2 h at 40°C the suspension was cooled to 10°C and filtered. The filtrate was evaporated and the residue triturated at 22°C with 750 ml of hexane. Filtration of the suspension and drying of the residue afforded 128.0 g (519.4 mmol; 93%) of pure (GLC) diol **10** as a white solid, mp 121–122°C. IR (nujol): 3418m, 3337m and 3256m (OH), 2929s, 2856s, 1466m, 1461m, 1360m, 1257m 1012s. $^1$H NMR (250 MHz, $CDCl_3$): 0.08 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 1.55 and 1.93–2.28 (m each, 3H and 5H, 3×$CH_2$ and 2×OH), 3.78 (m, 3H, 3×H–CO). MS (EI): 189/2 ($M^+$–$C(CH_3)_3$), 171/45, 129/30, 119/28, 75/100. $C_{12}H_{26}O_3Si$ requires: C, 58.49; H, 10.64%; found: C, 58.53; H, 10.51.

### 4.6. Enzymatic preparation of *(1*R,*3*S,*5*S*)-1-acetoxy-3-hydroxy-5-(*tert-*butyldimethylsilanoxy)-cyclohexane* ***11***

Diol **10 (**8.95 g, 36.3 mmol) was dissolved in 90 ml vinyl acetate and 810 ml ethyl acetate. Lipase QL (895 mg) was added and the reaction mixture stirred at rt. After termination of the reaction (46 h) the enzyme was filtered off, the filtrate concentrated and the residue dried overnight on HV to give 10.55 g (36.5 mmol; 100%) of **11** as a yellowish oil: GLC (area %): 98.5%, >99% ee; $[\alpha]_D = +5.0$ ($CHCl_3$, 1%); $[\alpha]_{365} = +18.7$ ($CHCl_3$, 1%). IR (neat): 3431m (OH), 2953s, 2858s, 1738s (C=O), 1472m, 1365m, 1249s, 1110s, 1052s, 1028s, 873m, 838s, 777m. $^1$H NMR (250 MHz, $CDCl_3$): 0.06 and 0.07 (s each, 3H each, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3C$), 1.37–1.54 (m, 3H, H–C(2,4,6)), 2.03–2.22 (m and s br, 4H, H–C(2,4,6) and OH), 2.04 (s, 3H, $COCH_3$), 3.73 (m, 2H, H–C(3,5)), 4.76 (m, 1H, H–C(1)). MS (EI): 289/1 ($M+H^+$), 171/100, 129/33, 117/55, 79/45, 75/60, 43/47. $C_{14}H_{28}O_4Si$ requires: C, 58.29; H, 9.78%; found: C, 57.93; H, 9.48.

### 4.7. Enzymatic preparation of cis-*1,3-diacetoxy-5-hydroxy-cyclohexane* ***14***

*cis*-Triol **7** (51.6 g, 390.4 mmol) was suspended in 1.0 l *tert*-butanol and 0.1 l vinyl acetate. After addition of 2.58 g of lipase QL the reaction mixture was stirred at rt (in the course of the reaction the substrate dissolved). After termination of the reaction (93 h) the enzyme was filtered off and the filtrate concentrated to dryness to give crude **14** (81.4% GLC, 6.5% *cis*-monoacetate,

6.2% **8**). This material (88.0 g) was chromatographed on 1.5 kg of silica (40–63 μm) with hexane/ethyl acetate 3:2 to give 59.1 g (273.4 mmol; 70%) of the *cis*-diacetate **14** as a white solid, mp 71.6–72.4°C. GLC (area %): 98.6%. IR (nujol): 3494m (OH), 2949s, 2864s, 1736s br (C=O), 1466s, 1450m, 1420m, 1376s, 1246s br, 1134s, 1024s, 977s. $^1$H NMR (400 MHz, $CDCl_3$): 1.43 and 2.28 (m each, 3H each, 3×$CH_2$), 1.88 (s br, 1H, OH), 2.04 (s, 6H, 2×$CH_3$), 3.78 (m, 1H, H–C(5)), 4.78 (m, 2H, H–C(1) and H–C(3)). MS (EI): 217/10 ($M+H^+$), 96/45, 43/100. $C_{10}H_{16}O_5$ requires: C, 55.55; H, 7.46%; found: C, 55.47; H 7.29.

### *4.8. GLC analysis*

GLC purity of **6**: GLC: OV-1-OH (25 m×0.32 mm; $H_2$; 100 kPa), 100–250°C with 10°C/min; Inj.: 240°C. Det.: 320°C. Retention times (min): 6.32 *cis*- and *trans*-monoacetate, 7.50 *trans*-diacetate **6**, 7.85 *cis*-diacetate **14**, 8.04 *trans-meso*-diacetate **9**, 8.74 *trans*-triacetate **5** and 9.33 *cis*-triacetate **8**. Enantiomeric excess of **6**: BGB-174 (15 m×0.25 mm; He; 80 kPa), 100–200°C with 2°C/min; Inj.: 210°C. Det.: 210°C. Retention times (min): 29.8 ent-**6**, 30.6 **6**.

GLC purity of **11**: GLC: OV-1-OH (25 m×0.32 mm; $H_2$; 100 kPa), 100–250°C with 10°C/min; Inj.: 240°C. Det.: 320°C. Retention times (min): 9.1 diol **10**, 10.4 monoacetate **11**, 11.4 diacetate **12**. Enantiomeric excess of **11**: BGB-172 (15 m×0.25 mm; $H_2$; 80 kPa), 120–160°C with 1°C/min; Inj.: 180°C. Det.: 200°C. Retention times (min): 32.0 **11**, 33.2 ent-**11**.

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