Lipase-Catalyzed Asymmetrization of Diacetate of *Meso*-2-(2-Propynyl)cyclohexane-1,2,3-triol toward the Total Synthesis of Aquayamycin

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Abstract: The diacetate of *meso*-2-(2-propynyl)cyclohexane-1,2,3-triol was efficiently asymmetrized by hydrolysis with *Candida antarctica* lipase to give the corresponding mono-acetate in enantiomerically pure form, which was used as the starting material for the total synthesis of aquayamycin. Application of the protocol to the related cyclohexanetriols is also described.

Key words: asymmetrization, hydrolysis, enzyme, meso compound, total synthesis

In our recent total synthesis of aquayamycin (**1**), the compound **2** was needed as the key AB ring intermediate that is with many oxygen functions including two tertiary alcohols.[1,2] As a possible access to **2**, it occurred to us to use the "meso trick" by exploiting enzymatic hydrolysis. Namely, the retrosynthesis involving reduction of the double bond and the ketone in **2** suggested the precursor **3**, and a further two-carbon disconnection at the side chain moiety led to the early synthetic intermediate **4** with a pseudo *Cs* symmetry.[3] Thus, our hope was the selective hydrolysis of one of the two enantiotopic acetates in the meso compound **5** (Figure 1).[4]

Although this asymmetrization seemed promising by the partial glyceride-like structure in **5**, there were two additional concerns, (1) further hydrolysis of the desired mono-acetate **4** that might increase or decrease its ee, but obviously reduce the chemical yield and more seriously, (2) the possible acyl migration in **4** as implied again by its glyceride-like structure.

Gratifyingly, however, the approach proved to offer a nice route to obtain **4** in enantiomerically pure form, which is described in this communication. Also described is the application of the protocol to the related compounds, providing stereo-defined cyclohexanetriol derivatives, **6** and **7** (Figure 1), that have potential utility in natural product synthesis.

As a substrate for the enzymatic hydrolysis, the diacetate **5** was prepared from the known enone **8**[5] derived from 2-cyclohexenone (Scheme 1). The enone **8** was converted to the acetonide **9** via the OsO_4-mediated dihydroxylation followed by the acetonide formation. Reduction of **9** with $LiAlH_4$ quantitatively gave the corresponding diastereomeric alcohols **10** and **10'** in 93:7 ratio, which were easily separated by silica-gel chromatography.[6] The major isomer **10** was subjected to acid hydrolysis followed by acetylation to give the diacetate **5**.[7]

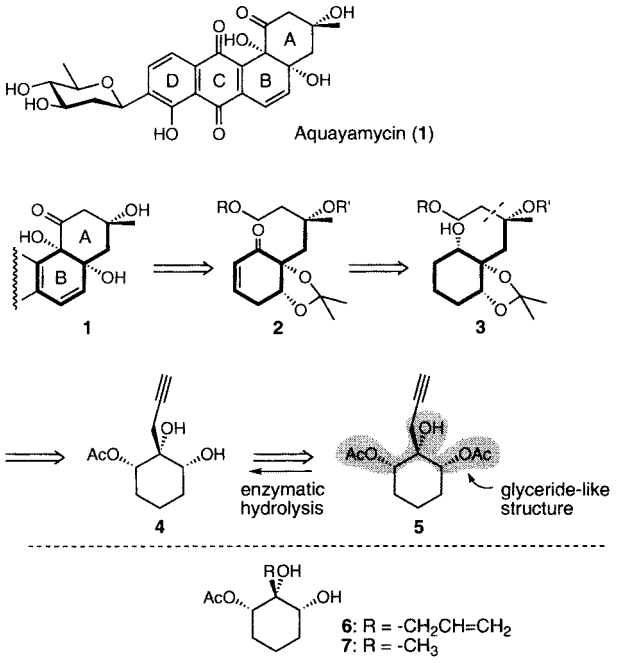

Figure 1

With the diacetate **5** in hand, we examined its hydrolysis by using several commercially available lipases with particular attention to the reactivity and the enantioselectivity. Thus, 50 mg of **5** was treated with the enzymes in pH 7 phosphate buffer (0.1 M) at 30 °C. As shown in Table, it turned out that three enzymes (PPL, PLE, or CAL) were effective for the asymmetric hydrolysis, thereby giving the diol (+)-**4**[7] in enantiomerically pure form. By contrast, the reaction was very slow with PFL to give a low enantioselectivity and PCL failed to catalyze the reaction.

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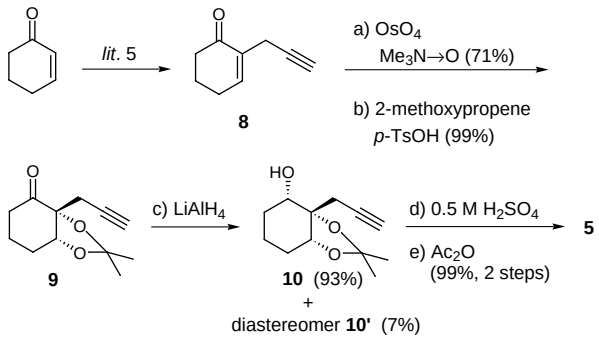
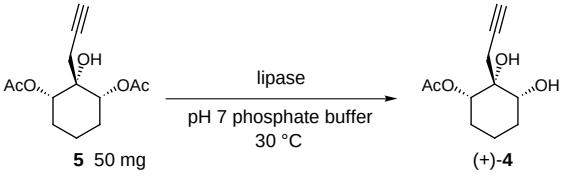


Scheme 1 Conditions: a) acetone, H_2O, 2 days; b) benzene, 10 min; c) THF, –78 °C, 30 min; d) 1,4-dioxane, 3 h; e) DMAP, pyridine, 30 min.

Table Lipase-Catalyzed Hydrolysis of **5**

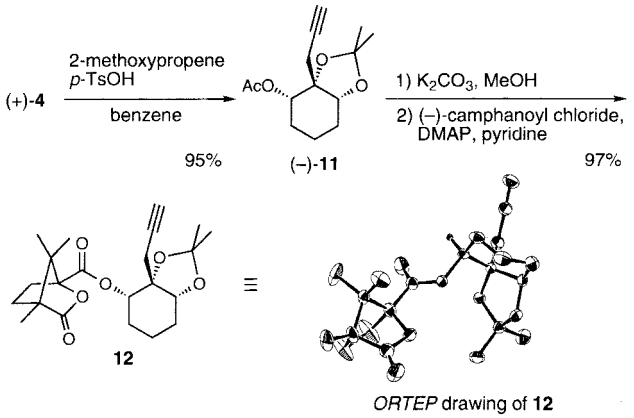


Lipase	Reaction period/ days	Yield of **4**/%	ee/%
PPL[a] (200 mg)	4	68[f]	>99
PLE[b] (10 mg)	0.4	89	>99
CAL[c] (20 mg)	1	80	>99
PFL[d] (100 mg)	5	15	60
PCL[e] (100 mg)	2	0	—

[a] Porcine pancreas lipase, Sigma, Type II.
[b] Pig liver esterase, Sigma.
[c] *Candida antarctica* lipase, Roche Diagnostics, Chirazyme L-2.
[d] *Pseudomonas fluorescence* lipase, Amano, Lipase AK.
[e] *Pseudomonas cepacia* lipase, Amano, Lipase PS.
[f] 32% of **5** was recovered.

The ee of (+)-**4** was determined by chiral GC analysis of the corresponding acetonide (–)-**11**.[8] The absolute configuration was determined by X-ray analysis after derivation to the camphanic acid ester **12** (Scheme 2).[9] Thus, the sense of the stereoselection proved to be in accordance with the well-known empirical rule for predicting the favored enantiomer in the lipase-catalyzed hydrolysis of the esters of chiral secondary alcohols (Figure 2).[10]

For further optimization, we focused on CAL[11] considering the disadvantages of other two enzymes, i.e. slow reaction rate (PPL) and high price (PLE). Thus, the reaction conditions with CAL were optimized with particular attention to the catalyst load in the larger-scale reaction by varying the catalyst/substrate ratio. As the result, it proved that even when the catalyst was reduced to 18% by weight, the reaction rate was acceptable without sacrificing the high yield and the complete enantioselectivity.



Scheme 2

Scheme 3 shows a 10-g scale reaction by employing 1.8 g of CAL, thereby giving, after 3 days, (+)-**4** in enantiomerically pure form in 94% yield and recovery of **5** (6%).

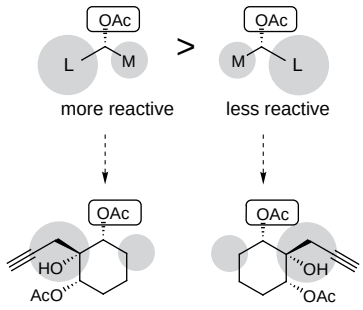
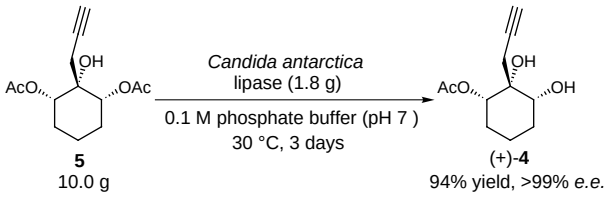


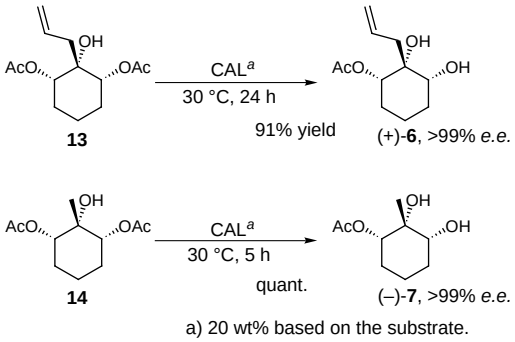
Figure 2

It is notable that the over-hydrolysis into the corresponding triol, which potentially causes the kinetic resolution of **4**, did not occur under these conditions. Therefore, the ee value of (+)-**4** just reflects the selectivity of the hydrolysis of the diacetate **5**. Furthermore, another concern at the outset, i.e. the acyl migration, did not occur.



Scheme 3

It is also significant to note that this protocol is applicable to the related diacetates, **13** and **14**,[12] thereby giving the enantiomerically pure diols, **6** and **7** (Scheme 4). Synthetic utility of these compounds seems promising, because polyhydroxy cyclohexanes containing the stereogenic tertiary alcohol center(s) are abundant as the structural motif in various natural products, while the availability of the chiral building block for such structures is limited.



Scheme 4

References and Notes

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(6) Although $LiEt_3BH$ or $Li(s\text{-}Bu)_3BH$ showed the complete stereoselectivity, we did not opt for these reagents for the synthetic purpose. With these reagents, the starting material **9** was not consumed even by using 3 equivalents and the separation of **9** from the product **10** was not easy.

Reduction of **9** with other reagents.

Reagent[a]	Conditions	Yield/% (recovery of **9**)	Selectivity[b]
$NaBH_4$	MeOH/r.t.	no reaction	--
$LiEt_3BH$	THF/-78 °C→r.t.	89 (7)	>99:1
$Li(s\text{-}Bu)_3BH$	THF/-78 °C→r.t.	80 (1)	>99:1
$(i\text{-}Bu)_2AlH$	THF/-78 °C →0 °C	93 (--)	92:8

[a] Used in three equivalents.
[b] **10**:**10'**.

(7) Data for selected compounds follow; **5**: Mp 177–178 °C (colorless needles; hexane–ether); ^{1}H NMR ($CDCl_3$) δ 4.92 (dd, 2 H, *J* = 4.6, 11.2 Hz), 2.52 (d, 2 H, *J* = 2.7 Hz), 2.12 (s, 6 H), 2.05 (t, 1 H, *J* = 2.7 Hz), 1.5-2.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 78.5, 74.2, 73.5, 71.6, 25.7, 25.2, 21.1, 19.2; IR (KBr) 3471, 2120, 1738, 1712 cm^{-1}; Anal. calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.63; H, 7.36. (+)-**4**: Mp 98.5–99.0 °C (colorless needles; hexane–ether); $[\alpha]^{28}_D$ +6.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.90 (dd, 1 H, *J* = 4.6, 11.6 Hz), 3.71 (ddd, 1 H, *J* = 4.9, 8.1, 11.2 Hz), 2.68 (dd, 1 H, *J* = 2.6, 16.8 Hz), 2.60 (dd, 1 H, *J* = 2.6, 16.8 Hz), 2.50 (s, 1 H), 2.38 (d, *J* = 8.1 Hz), 2.11 (s, 3 H), 2.06 (t, 1 H, *J* = 2.6 Hz), 1.5-1.9 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 79.6, 74.7, 74.0, 71.3, 71.0, 29.3, 25.7, 25.0, 21.1, 19.3; IR (KBr) 3466, 2114, 1734, 1706 cm^{-1}; Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.39; H, 7.71. (–)-**11**: Mp 92.5–93.0 °C (colorless needles; hexane); $[\alpha]^{27}_D$ –41 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.01 (dd, 1 H, *J* = 3.7, 9.0 Hz), 4.31 (t, 1 H, *J* = 2.9 Hz), 2.64 (dd, 1 H, *J* = 2.7, 16.8 Hz), 2.43 (dd, 1 H, *J* = 2.7, 16.8 Hz), 2.05 (s, 3 H), 1.99 (t, 1 H, *J* = 2.7 Hz), 1.5-1.9 (m, 6 H), 1.48 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 108.7, 79.5, 79.1, 78.5, 71.5, 71.3, 27.4, 26.8, 26.2, 24.1, 23.1, 21.4, 14.9; IR (KBr) 3265, 2118, 1740 cm^{-1}; Anal. calcd for $C_{14}H_{20}O_4$: C, 66.12; H, 7.93. Found: C, 66.24; H, 8.10.

(8) Column: CP-Chirasil Dex CB (GL Sci. Inc.), 0.32 mm × 30 m; Conditions: 130 °C for 5 min then +12.5 °C/min to 140 °C, He 180 kPa; Retention time: 6.2 min for (–)-**11** and 6.4 min for (+)-**11**.

(9) We express deep appreciation to Ms. Sachiyo Kubo, Tokyo Institute of Technology, for X-ray analysis.

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(11) (a) A review on the application of *Candida antarctica* lipase in organic synthesis:Anderson, E. M.; Larsson, K. M.; Kirk, O. *Biocatal. Biotransform.* **1998**, *16*, 181. (b) For an example of CAL-mediated asymmetrization of meso compounds, see ref. 4c.

(12) The diacetate **13** was synthesized from the alcohol **10** in 4 steps [(1) Ac_2O, pyridine; (2) H_2, Lindlar's catalyst, quinoline, hexane; (3) 0.5 M H_2SO_4 aq., 1,4-dioxane; (4) Ac_2O, pyridine (88% yield, overall)]. Attempted hydrogenations of **5** into **13** with Lindlar's catalyst were accompanied by the over-hydrogenation. The diacetate **14** was synthesized from 2-methyl-2-cyclohexen-1-one in a similar manner as Scheme 1.