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A Chemo-enzymatic Elaboration of a Quarternary Chiral Center: an Alternative Approach to the Side Chain of Furaquinocin D

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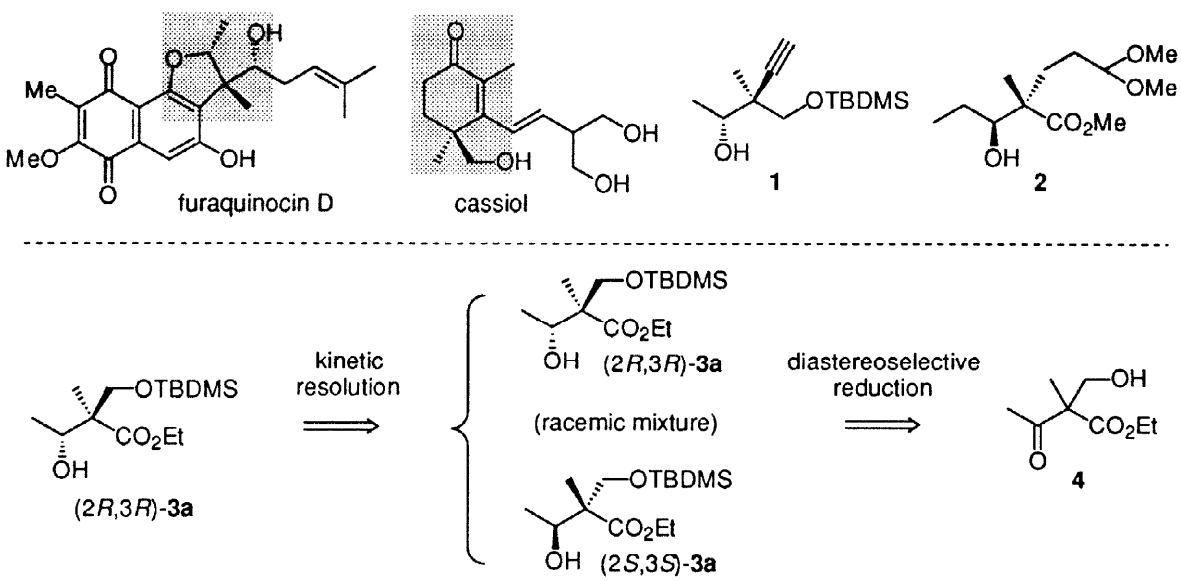
Abstract: A new approach to ethyl (2*R*, 3*R*)-2-*t*-butyldimethylsilyloxymethyl-3-hydroxy-2-methylbutanoate, a compound which is related to a synthetic intermediate of the side chain of furaquinocin D, is described. The characteristic feature of this compound is a quarternary chiral center and an adjacent secondary alcohol, both of which are in a stereochemically defined state, and the set-up of these functionalities was achieved by a combination of stereoselective chemical and enzymatic reactions. The reduction of ethyl 2-hydroxymethyl-2-methyl-3-oxobutanoate with excess $NaBH_4$ afforded (2*R**,3*R**)-(±)-hydroxy ester with a high diastereomeric excess. After protecting the primary hydroxy group as TBDMS ether, the optical resolution was achieved by lipase-catalyzed hydrolysis of the corresponding chloroacetate in a highly enantioselective manner.

Introduction

The elaboration of quarternary chiral centers in a stereochemically controlled manner has recently been gaining the wide interests of synthetic organic chemists.[1] Representative examples of naturally occurring products containing a quarternary chiral center, furaquinocin D[2,3] and cassiol[4,5] are shown in Scheme 1. In synthetic studies of both compounds, the intermediates containing contiguous chiral centers, which consist of a quarternary chiral center and an adjacent secondary alcohol (**1** and **2**), played important roles.[3,5] Indeed, an alkynyl alcohol **1** was emphasized in the construction of the desired chiral centers of the terpenoidal side chain, in the synthesis of an enantiomerically enriched form of furaquinocin D presented by Suzuki and co-workers.[3]



Scheme 1

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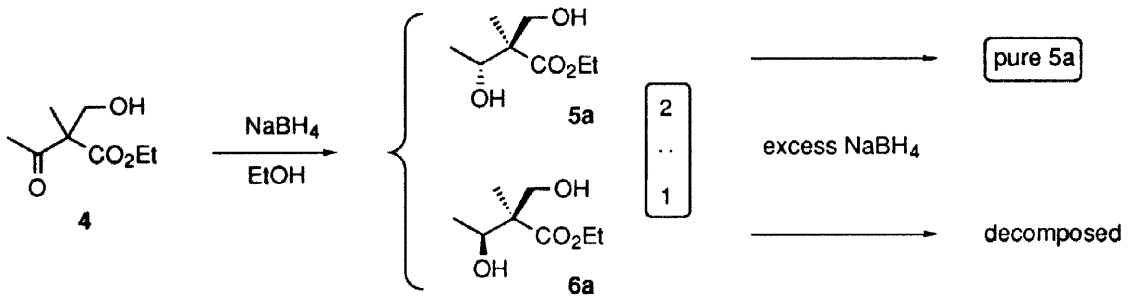
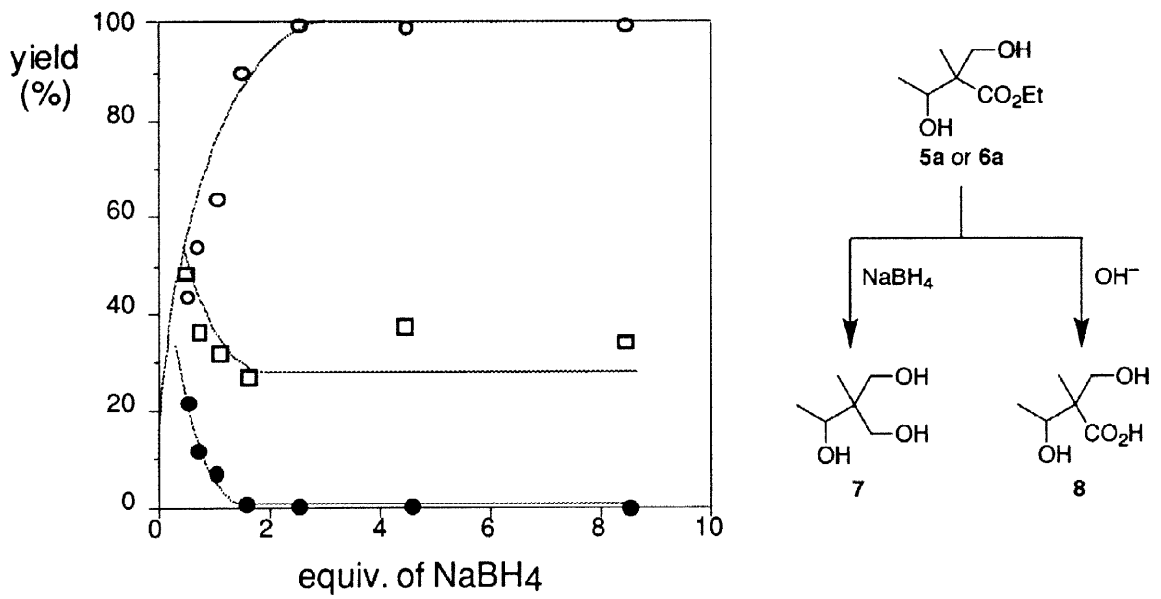
Although the synthesis of **1** was accomplished in an elegant manner utilizing migration of an alkyne-Cobalt complex,[6] it involved multi-step transformation of the starting material, tiglaldehyde. In this paper, we report a chemo-enzymatic short-step approach to (*2R,3R*)-**3a**, another synthetic equivalent of **1**. Our chemo-enzymatic approach for the desired carbon skeleton, as shown in Scheme 1, is based on preparation of a diastereomerically defined racemic alcohol and subsequent lipase-catalyzed kinetic resolution.

Attempts for Diastereoselective Reduction

The most convenient procedure for the reduction was the treatment of **4**[7] with $NaBH_4$ (0.8 eq), a mixture of **5a** and **6a** (total 67% yield, 2 : 1) was obtained. Although the ratio of the diastereomeric products could be estimated on the basis of the ^1H NMR spectra, the isolation of each diastereomer in a pure state by chromatography was not possible. This situation prompted us to secure reagents for a diastereoselective reduction. The initial attempts, however, turned out to be fruitless. The use of reducing agent such as $NaBH_4$, $NaBH_3CN$, or $LiAlH(O\text{-}t\text{Bu})_3$, at various temperature and in various solvent, resulted only in a moderate ratio (2 : 1 to 4 : 1) of **5a** and **6a**.



Scheme 2



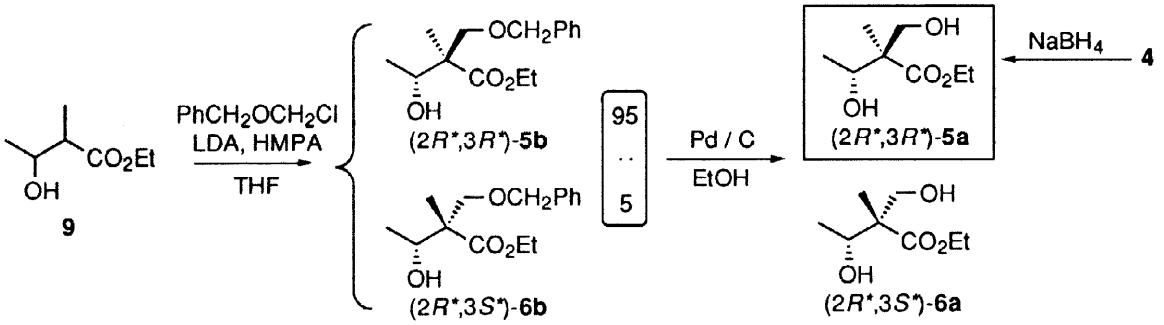
□ : (*2R*,3R**)-**5a**; ● : (*2R*,3S**)-**6a**; ○ : *d.e.*

Figure 1

A clue for overcoming the problem of low diastereoselectivity was obtained from two unexpected results shown below. When a mixture containing **5a** and **6a** in a ratio of 2 : 1 and a small amount of ketone **4** as contaminant was treated again with $NaBH_4$, the ratio of **5a** and **6a** surprisingly changed to 10 : 1. In the other experiment when the substrate **4** was treated with an excess amount of $NaBH_4$ (8 eq.), the ratio of **5a** and **6a** similarly changed to 10 : 1, although the combined yield of the two diastereomers was as low as 20%. These results suggested to us that the reduction itself did not proceed in a completely diastereoselective manner, but the preferential degradation of the one diastereomer **6a** by an action of excess $NaBH_4$ occurred in the reaction process.

In this context, an experiment starting from a mixture of **5a** and **6a** (2 : 1) was performed, by treating with $NaBH_4$ in varying equivalents. The results shown in Figure 1 clearly show a preferential degradation of one diastereomer and the kinetic ratio between the diastereomers was estimated as *ca.* 3.6 : 1. In the case of another degradation experiment under a forced condition using 15 equivalents of $NaBH_4$, the isolable products were very hydrophilic components, a triol **7** (as its acetates after acetylation, *ca.* 60%), and carboxylic acid **8** (as its methyl ester after methylation, *ca.* 35%).

This result indicated that both an overreduction and a hydrolysis of ester group occurred under the reaction condition, however, the mechanism that one diastereomer **6a** preferentially reacted in this manner was not clear. Anyway, based on these observations, the reduction condition of **4** was established; the treatment with 8 equivalents of $NaBH_4$ at 0°C for 10 min afforded an almost diastereomerically pure product, (2*R**,3*R**)-**5a** (18% yield, >99%*d.e.*).



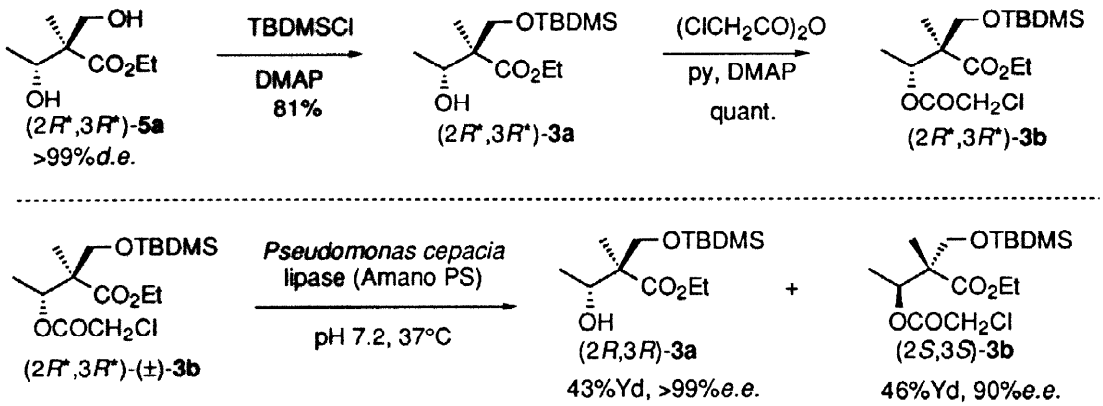
Scheme 3

The relative configuration of **5a** and **6a** was determined on the basis of the stereochemistry in Fráter's alkylation as above (Scheme 3). A hydroxy ester **9** was alkylated[*cf.*5,8,9] with benzyloxymethyl chloride to a benzyloxymethyl (BOM) ether (2*R**,3*R**)-**5b** (major product, *anti*-isomer) and **6b** (minor product, *syn*-isomer). This mixture was hydrogenolyzed to give (2*R**,3*R**)-**5a** and (2*R**,3*S**)-**6a** (95 : 5, 90%*d.e.*, 19% yield for 2 steps from **9**). By comparing the ^1H NMR spectrum of this sample with that of the product given by the reduction of **4** with $NaBH_4$, the relative configuration of major product **5a** in the $NaBH_4$-mediated reduction was clarified to be (2*R**,3*R**).

Lipase-catalyzed Kinetic Resolution

Selective protection of primary alcohol of **5a** worked well by treatment with TBDMSCl (1 eq.) and DMAP (2 eq.) in CH_2Cl_2 to give **3a** in 81% yield. Combined screening of the substrate and enzymes gave successful results; the enantioselective hydrolysis of the corresponding chloroacetate **3b** by lipases[10] from *Pseudomonas cepacia* (Amano PS) and *Candida antarctica* (Novo SP525) equally worked well [E(p)[11] >

100]. For example, the use of *Pseudomonas* lipase yielded (2*R*,3*R*)-**3a** (43% yield, enantiomerically pure) and (2*S*,3*S*)-**3b** (46% yield, 90%*e.e.*).



Scheme 4

Conclusion

Starting from a commercially available ketoester, the preferential degradation of one diastereomer by the action of excess $NaBH_4$ and the subsequent kinetic resolution by lipase from *Pseudomonas cepacia* yielded (2*R*,3*R*)-**3a** (>99%*d.e.*, >99%*e.e.*) and (2*S*,3*S*)-**3b** (>99%*d.e.*, 90%*e.e.*) in a preparative scale.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-202 spectrometer. ^1H NMR spectra were measured in $CDCl_3$ with TMS as the internal standard at 270 MHz on a JEOL JNM EX-270 spectrometer unless otherwise stated. Mass spectra were recorded on Hitachi M-80B spectrometer at 70 eV. Optical rotations were recorded on a Jasco DIP 360 polarimeter. Wako Gel B-5F and silica gel 60 K070-WH (70-230 mesh) of Katayama Chemical Co. were used for preparative TLC and column chromatography, respectively.

Preparation of Ethyl 2-Hydroxymethyl-2-methyl-3-oxobutanoate (4). *cf.*[12] To a mixture of ethyl 2-methyl-3-oxobutanoate (5.0 g, 34.7 mmol) and aqueous formaldehyde solution (35%, 18.0 mL, 210 mmol) in EtOH (250 mL), KOH (5.79 g, 103.2 mmol) was added portionwise at -20°C with stirring. After 15 min, the reaction mixture was poured into phosphate buffer (1M, pH 6.0) below 0°C. The conventional workup and chromatographic purification afforded **4** (5.99 g, 99%). ^1H NMR ($CDCl_3$) δ 4.24 (q, 2H, *J* = 7.1 Hz), 3.88 (dd, 1H, *J* = 11.5, 6.6 Hz), 3.80 (dd, 1H, *J* = 11.5, 7.3 Hz), 2.73 (dd, 1H, *J* = 7.3, 6.6 Hz), 2.23 (s, 3H), 1.39 (s, 3H), 1.29 (t, 3H, *J* = 7.1 Hz); IR (NaCl) 3500, 2990, 2950, 1710, 1450, 1425, 1365, 1290, 1250, 1210, 1110, 1050, 1025, 980, 860 cm^{-1}.

Preparation of Ethyl (2*R,3*R**)-3-Hydroxy-2-hydroxymethyl-2-methylbutanoate (5a).** To a solution of **4** (1.0 g, 5.74 mmol) in EtOH (35 mL) was added $NaBH_4$ (1.70 g, 45.0 mmol) in one portion at 0°C with stirring. After 10 min, the reaction mixture was poured into sat. NH_4Cl aq. The conventional workup and chromatographic purification (silica gel, hexane / EtOAc = 1 / 1) afforded **5a** (220 mg, 22%). ^1H NMR ($CDCl_3$) δ 4.25 (q, 2H, *J* = 7.1 Hz), 3.96 (dq, 1H, *J* = 6.8, 6.6 Hz), 3.85 (dd, 1H, *J* = 11.2, 6.1 Hz), 3.70 (dd,

1H, J = 11.2, 6.1 Hz), 3.21 (d, 1H, J = 6.8 Hz), 2.95 (dd, 1H, J = 6.1, 6.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 1.26 (d, 3H, J = 6.6 Hz), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.7, 72.9, 69.3, 61.0, 51.4, 18.6, 16.5, 14.2; IR (NaCl) 3400, 2950, 2910, 1710, 1450, 1370, 1290, 1220, 1120, 1090, 1030, 900, 855 cm^{-1}. HRMS m/z Found 177.1111 (M^++1). $C_8H_{17}O_4$ requires 177.1125.
The diastereomer **6a** showed the following signals: δ 3.13 (d, 1H, J = 6.8 Hz), 3.10 (dd, 1H, J = 6.1, 6.1 Hz), 1.25 (d, 3H, J = 6.6 Hz), 1.02 (s, 3H) and the diastereomeric ratio was determined by the comparison of the area of signals as above.

Exhaustive Degradation of a Mixture of 5a and 6a with Far Excess of $NaBH_4$. In the case using 15 equivalents of $NaBH_4$ for the reduction, acetates of triol **7** were obtained as the neutral fraction of byproducts after quenching the reduction and the subsequent acetylation. Due to congested properties of the hydroxy groups in **7**, the product was obtained as a mixture of triacetate and diacetates, even after a prolonged reaction. Triacetate (7%); Rf = 0.78 (hexane / EtOAc = 1 / 6), ^{1}H NMR ($CDCl_3$) δ 5.01 (q, 1H, J = 6.5 Hz), 4.08 (d, 1H, J = 11.2 Hz), 4.06 (d, 1H, J = 11.2 Hz), 3.97 (d, 1H, J = 11.2 Hz), 3.92 (d, 1H, J = 11.2 Hz), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.19 (d, 3H, J = 6.5 Hz), 0.98 (s, 3H). A diacetate (27%, with two primary acetates); Rf = 0.63 (hexane / EtOAc = 1 / 6), ^{1}H NMR ($CDCl_3$) δ 4.21 (d, 1H, J = 11.4 Hz), 4.09 (d, 1H, J = 11.4 Hz), 4.03 (d, 1H, J = 11.4 Hz), 3.94 (d, 1H, J = 11.4 Hz), 3.75 (q, 1H, J = 6.5 Hz), 2.08 (s, 6H), 1.18 (d, 3H, J = 6.5 Hz), 0.91 (s, 3H). Diacetates (27%, with one primary acetate and one secondary acetate, and its diastereomer); Rf = 0.63 (hexane / EtOAc = 1 / 6), ^{1}H NMR ($CDCl_3$) δ 5.06 (q, 1H, J = 6.5 Hz), 4.13 (d, 1H, J = 11.4 Hz), 3.99 (d, 1H, J = 11.4 Hz), 3.45 (d, 1H, J = 11.4 Hz), 3.40 (d, 1H, J = 11.4 Hz), 2.09 (s, 3H), 2.07 (s, 3H), 1.23 (d, 3H, J = 6.5 Hz), 0.94 (s, 3H). Its diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.04 (q, 1H, J = 6.5 Hz), 4.12 (d, 1H, J = 11.4 Hz), 3.97 (d, 1H, J = 11.4 Hz), 2.08 (s, 3H), 2.05 (s, 3H), 1.22 (d, 3H, J = 6.5 Hz), 0.89 (s, 3H). On the other hand, a diastereomeric mixture of carboxylic acids **8** was obtained as the acid fraction of byproduct (35 %) as methyl esters after quenching the reduction and the subsequent esterification with diazomethane; ^{1}H NMR ($CDCl_3$) δ 4.14 (q, 1H, J = 6.5 Hz), 3.94 (d, 1H, J = 11.0 Hz), 3.69 (d, 1H, J = 11.0 Hz), 3.30 (s, 3H), 1.17 (d, 3H, J = 6.5 Hz), 0.88 (s, 3H). Its diastereomer: ^{1}H NMR ($CDCl_3$) δ 3.97 (d, 1H, J = 11.0 Hz), 3.96 (q, 1H, J = 6.5 Hz), 3.56 (d, 1H, J = 11.0 Hz), 3.33 (s, 3H), 1.19 (d, 3H, J = 6.5 Hz), 0.92 (s, 3H).

Preparation of Authentic Samples of 5a and 6a: Preparation of Ethyl (2*R,3*R**)-2-Benzyloxymethyl-3-hydroxy-2-methylbutanoate (5b).** *cf.*[5,8,9] A solution of LDA was prepared by the dropwise addition of *n*-BuLi solution (1.68 N in *n*-hexane, 2.4 mL, 4.0 mmol) to a stirred and cooled solution of (i-Pr)$_2$NH (0.56 mL, 4.0 mmol) in dry THF (1 mL) at –70 to –60°C under Ar. The mixture was stirred for 30 min at –10 to –5°C. To the stirred and cooled (–65°C) solution of LDA was added dropwise a solution of **9** (120.1 mg, 0.82 mmol) in dry THF (0.2 mL). The mixture was stirred for 1 h at –30 to –20°C. After the addition of HMPA (0.71 mL, 4.3 mmol), the mixture was cooled to –65°C. To this mixture was added a solution of benzyloxymethyl chloride (321.3 mg, 2.1 mmol) in dry THF (3 mL) at –70 to –60°C. The mixture was stirred for 6 h at –20°C and for 2 h at 0°C. The reaction was quenched with sat. NH_4Cl solution at –20°C. The conventional workup and chromatographic purification (silica gel, hexane / EtOAc = 3 / 1) gave an analytical sample of (2*R**,3*R**)-**5b** (214.3 mg): ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.50 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 4.09 (m, 1H), 3.70 (d, 1H, J = 9.1 Hz), 3.11 (d, 2H, J = 6.8 Hz), 1.26 (t, 3H, J = 7.2 Hz), 1.20 (s, 3H), 1.14 (d, 3H, J = 6.5 Hz). The spectrum also showed the signal of its diastereomer (2*R**,3*S**)-**6b**: δ 3.77 (d, 1H, J = 6.5 Hz), 3.22 (d, 2H, J = 6.8 Hz). This was employed for the next step without further purification.

Preparation of (2*R,3*R**)-5a.** To a solution of a mixture (214.3 mg) containing (2*R**,3*R**)-**5b** as above in EtOH (5 mL) was added 10% palladium on activated carbon (100 mg) and the mixture hydrogenated for 1 day at room temp. The mixture was filtered and evaporated. Chromatographic purification (silica gel, hexane / AcOEt = 1 / 2) gave (2*R**,3*R**)-**5a** (25.9 mg, 19% for 2 steps, 90%*d.e.*). Its NMR and IR spectra was identical with **5a**. The diastereomeric ratio was determined by the comparison of the area of the following signals: ^{1}H NMR ($CDCl_3$) δ 1.08 (95%), 1.02 (5%).

Preparation of Ethyl (2*R,3*R**)-2-*t*-Butyldimethylsilyloxymethyl-3-hydroxy-2-methylbutanoate (3a).** To a mixture of **5a** (268.3 mg, 1.52 mmol) and DMAP (375.6 mg, 3.07 mmol) in CH_2Cl_2 (4.5 mL) was added TBDMSCl (230.1 mg, 1.53 mmol) and the mixture was stirred and refluxed for 12 h. The conventional workup and chromatographic purification (silica gel, hexane / EtOAc = 10 / 1) afforded **3a** (359 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 4.17 (q, 2H, *J* = 7.2 Hz), 4.05 (dq, 1H, *J* = 6.9, 6.8 Hz), 3.85 (d, 1H, *J* = 9.7 Hz), 3.71 (d, 1H, *J* = 9.7 Hz), 3.17 (d, 1H, *J* = 6.9 Hz), 1.27 (t, 3H, *J* = 7.2 Hz), 1.17 (d, 3H, *J* = 6.8 Hz), 1.16 (s, 3H), 0.87 (s, 9H), 0.04 (s, 2 x 3H); IR (NaCl) 3500, 2950, 2875, 1730, 1465, 1390, 1365, 1300, 1255, 1100, 1030, 945, 915, 845, 780, 670 cm^{-1}. Based on its ^{1}H NMR spectrum, the homogeneity of **3a** was again confirmed; diastereomer of **3a**: δ 4.15 (q, 2H, *J* = 7.2 Hz), 3.95 (d, 1H, *J* = 9.7 Hz), 3.72 (d, 1H, *J* = 9.7 Hz), 3.27 (d, 1H, *J* = 5.9 Hz), 1.26 (t, 3H, *J* = 7.2 Hz), 1.14 (s, 3H), 0.87 (s, 9H), 0.04 (s, 2 x 3H).

Preparation of Ethyl (2*R,3*R**)-2-*t*-Butyldimethylsilyloxymethyl-3-chloroacetoxy-2-methylbutanoate (3b).** *cf.*[13] Starting from 49.9 mg of **3a**, the conventional workup and chromatographic purification (silica gel, hexane / EtOAc = 10 / 1) gave **3b** (63.3 mg, quant). ^{1}H NMR ($CDCl_3$) δ 5.43 (q, 1H, *J* = 6.5 Hz), 4.05-4.22 (m, 2H), 3.99 (s, 2H), 3.66 and 3.62 (ABq, 2H, *J* = 9.7 Hz), 1.25 (d, 3H, *J* = 6.5 Hz), 1.24 (t, 3H, *J* = 7.2 Hz), 1.19 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); IR (NaCl) 2975, 2850, 1754, 1470, 1420, 1395,1370, 1350, 1300, 1260, 1200, 1155, 1105, 1070, 1040, 965, 950, 850, 830, 790, 760, 710, 670 cm^{-1}; HRMS m/z Found 321.1204 [M^+–(OCH_2CH_3)]. $C_{16}H_{31}O_5ClSi$ requires 321.1197. Based on its ^{1}H NMR spectrum, the homogeneity of **3b** was again confirmed; diastereomer of **3b**: δ 5.38 (q, 1H, *J* = 6.5 Hz), 4.02 (s, 1H), 4.02 (s, 1H), 3.75 (d, 1H, *J* = 9.5 Hz), 3.60 (d, 1H, *J* = 9.5 Hz), 1.26 (d, 3H, *J* = 6.5 Hz), 1.19 (s, 3H), 0.85 (s, 9H), 0.00 (s, 2 x 3H).

Lipase-catalyzed Hydrolysis of 3b. To a mixture of **3b** (3.00 g, 8.18 mmol) and 0.1M phosphate buffer (150 mL, pH 7.2) was added *Pseudomonas cepacia* lipase (Amano PS, 3.00 g) and the mixture was stirred at 37°C for 3 d. The conventional workup and chromatographic purification (silica gel, hexane / EtOAc = 10 / 1) afforded the recovered starting material **3b** (1.38 g, 46%), $[\alpha]_D^{24}$ +1.37 (*c* 1.06, $CHCl_3$); Its NMR and IR spectra were identical with the racemic starting material. This was hydrolyzed with aqueous ethanolic potassium carbonate solution for 1 day at room temp to give (+)-**3a**, $[\alpha]_D^{22}$ +7.17 (*c* 1.01, $CHCl_3$); Its *e.e.* was estimated to be 90 % after conversion to the corresponding (*R*)-MTPA ester **3c**: ^{1}H NMR ($CDCl_3$) δ 3.53 (s, OMe, 95%), 3.50 (s, OMe, 5%).

Further elution of the chromatography yielded **3a** (1.01 g, 43%). $[\alpha]_D^{25}$ –8.17 (*c* 1.04, $CHCl_3$); Its NMR and IR spectra were identical with the racemic **3a**. Its *e.e.* was estimated to be >99% after the conversion to (*R*)-MTPA ester **3d**.

The (3*R*) configuration of (–)-**3a** was concluded by the comparison of the NMR spectrum of the corresponding (*R*)-MTPA ester, based on the modified Mosher method.[14] ^{1}H NMR ($CDCl_3$) **3d** from (–)-**3a** δ 5.601 (q, 1H, *J* = 6.4 Hz, H-3), 4.050 (dq, 1H, *J* = 10.7, 7.1 Hz, –C*H*HCH_3), 3.975 (dq, 1H, *J* = 10.7, 7.1

Hz, –CH*H*CH$_3$), 3.639 (d, 1H, *J* = 9.6 Hz, –C*H*HOSi), 3.587 (d, 1H, *J* = 9.6 Hz, –CH*H*OSi), 1.138 (d, 3H, *J* = 6.4 Hz, H-4), 1.179 (dd, 3H, *J* = 7.1, 7.1 Hz, –CH$_2$C*H*$_3$), 1.153 (s, 3H, 2–C*H*$_3$); **3c** from (+)-**3a** δ 5.649 (q, 1H, *J* = 6.4 Hz, H-3), 4.104 (dq, 1H, *J* = 10.7, 7.1 Hz, –C*H*HCH$_3$), 4.035 (dq, 1H, *J* = 10.7, 7.1 Hz, –CH*H*CH$_3$), 3.651 (d, 1H, *J* = 9.6 Hz, –C*H*HOSi), 3.617 (d, 1H, *J* = 9.6 Hz, –CH*H*OSi), 1.255 (d, 3H, *J* = 6.4 Hz, H-4), 1.188 (dd, 3H, *J* = 7.1, 7.1 Hz, –CH$_2$C*H*$_3$), 1.150 (s, 3H, 2–C*H*$_3$).

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