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Homo-Roche Ester Derivatives by Asymmetric Hydrogenation and Organocatalysis

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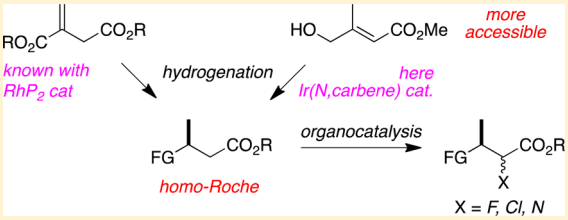
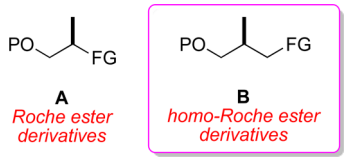
Supporting Information

ABSTRACT: Asymmetric hydrogenation routes to homologues of The Roche ester tend to be restricted to hydrogenations of itaconic acid derivatives, that is, substrates that contain a relatively unhindered, 1,1-disubstituted alkene. This is because in hydrogenations mediated by RhP_2 complexes, the typical catalysts, it is difficult to obtain high conversions using the alternative substrate for the same product, the isomeric trisubstituted alkenes (**D** in the text). However, chemoselective modification of the identical functional groups in itaconic acid derivatives are difficult; hence, it would be favorable to use the trisubstituted alkene. Trisubstituted alkene substrates can be hydrogenated with high conversions using chiral analogs of Crabtree's catalyst of the type IrN(carbene). This paper demonstrates that such reactions are scalable (tens of grams) and can be manipulated to give optically pure homo-Roche ester chirons. Organocatalytic fluorination, chlorination, and amination of the homo-Roche building blocks was performed to demonstrate that they could easily be transformed into functionalized materials with two chiral centers and α,ω-groups that provide extensive scope for modifications. A synthesis of (*S,S*)- and (*R,S*)-γ-hydroxyvaline was performed to illustrate one application of the amination product.

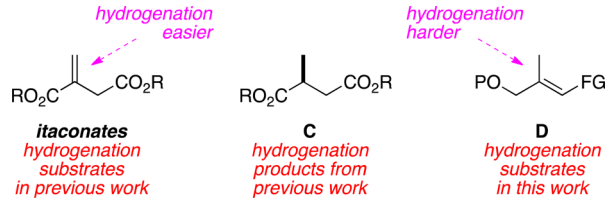


INTRODUCTION

Roche ester derivatives **A** are some of the most widely appreciated chirons in organic syntheses.[1−4] This is because such compounds have functional groups at both termini enabling bidirectional modifications and a tremendous scope for incorporating methyl-substituted chiral centers. It seems logical that the homologous chiron **B** would be similarly useful if it were more readily available. For the purposes of this study, we refer to the generic class of fragments **B** as homo-Roche ester derivatives.



Scalable syntheses of chirons **B** have not attracted much attention in the literature. Homologation of the parent chiron[5] is probably not the best route to obtain compounds **B**, even though they only contain one more skeletal carbon than **A** because The Roche ester is not a cheap starting material; small quantities tend to cost more than $1 per gram. Another approach is via asymmetric hydrogenations of itaconic acid or the corresponding diesters to give the C_5-building blocks **C**.[6,7] Bidirectional homologation of chirons **C** requires efficient chemoselective modification of one of the two esters; we are aware of only one method for doing this, and it features a relatively expensive lipase in a chemoenzymatic hydrolysis.[6] It is possible to instead begin with a monoester of itaconic acid and hydrogenate that, but in fact the enantioselectivities for this process tend to be less than the diacid or the diester.[6,8] Alternatively, it is possible to begin the syntheses with monoesters of itaconic acid, and indeed some of these are commercially available. However, these starting materials are expensive, so overall it is better to avoid this strategy. Any pathway that uses hydrogenation of itaconic acid, in fact, is vulnerable to the types of deactivation pathways that have been documented previously.[9,10] Another route to chirons **B** is via asymmetric additions of cuprates to α,β-unsaturated thioesters.[11]



Both the hydrogenation syntheses of chirons **B** described above feature bisphosphite complexes formed from Rh(COD)$_2^+$ *in situ*. Hydrogenation of type **D** trisubstituted alkenes would give products that are chemically related to **C**, but these types of transformations tend to be difficult to achieve using RhP_2 complexes because the double bonds are hindered.[12] In fact, the preferred catalysts for the trisubstituted alkenes **D** tend to be IrN,P complexes, that is, chiral analogs of Crabtree's catalyst.[12] Consequently, the work described here was undertaken to use our particular chiral analog of Crabtree's

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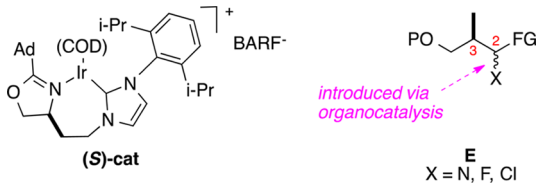
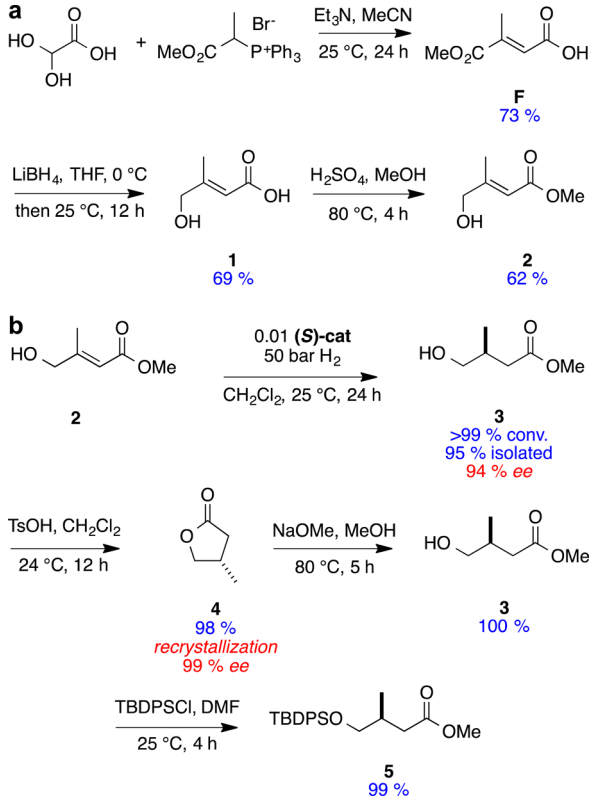
catalyst, **cat**,[13,14] to reduce **D**-type substrates via scalable transformations. We also set out to establish that all stereoisomeric forms of the 2-substituted chirons **E** could be obtained via organocatalytic modifications of the homo-Roche ester derivatives **B**. Similar reactions of achiral substrates are well-known, but finding appropriate organocatalysts to overcome the stereochemical bias exerted by the C^3 chiral center was an open issue.



RESULTS AND DISCUSSION

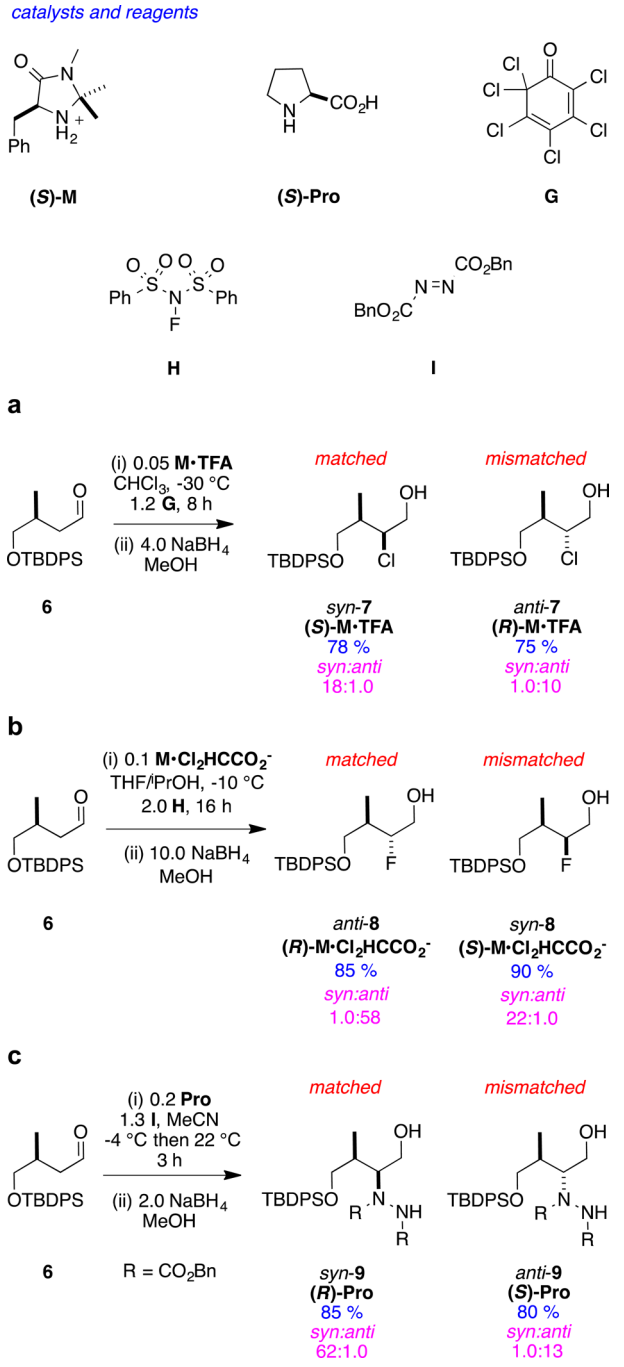
There is a literature procedure for conversion of glyoxylic acid monohydrate into the α,β-unsaturated ester **F**.[15] The first new step in this work was to chemoselectively reduce the ester group of **F** in the presence of its carboxylic acid functionality[16] to give the hydroxyacid **1**,[17,18] which was isolated via acid−base extraction (in this manuscript, numbers are given to compounds obtained via a new route, even if they are known); this procedure seems to be superior to both the established routes to **1**.[17,18] Subsequently, the hydroxyacid **1** was esterified to give the known[19] hydroxyester **2**. None of the steps described in Scheme 1a involve column chromatography, and the synthesis can give tens of grams of the product **2**.

Scheme 1. (a) Synthesis of the Hydrogenation Substrate 2 and (b) Asymmetric Hydrogenation of Alkene 2



Hydrogenation of alkene **2** is the key transformation in this paper. Under the conditions shown in Scheme 1b, approximately 15 g of the hydroxyester **2** can be hydrogenated with complete conversion to give **3** (a type **B** chiron), and the catalysts is still active at the end of this transformation. High, but not perfect, enantioselectivities are obtained in this process, and the acyclic product **3** can be lactonized to **4** then efficiently recrystallized to give optically pure material. For subsequent applications of these products (here and perhaps elsewhere), the lactone **4** was converted to two other potentially useful acyclic chirons, the alcohol **3** (now as one enantiomer) and the silyl ether **5**.

Scheme 2. Asymmetric Transformations of Substrates 6: (a) Chlorination; (b) Fluorination; and (c) Amination[a]



[a]Throughout, selectivities were determined via analytical HPLC on a Chiralcel-OD column.

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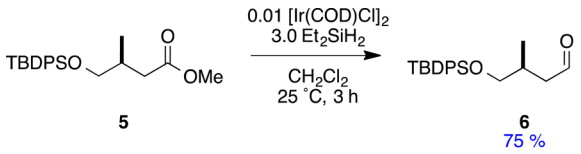
The next task was to convert ester **5** to the corresponding aldehyde **6** (reaction 1); Brookhart's catalytic silylation/hydrolysis procedure[20] was used for this transformation. This reduction afforded the aldehyde **6** for elaboration via organocatalytic processes involving iminium and enamine intermediates.

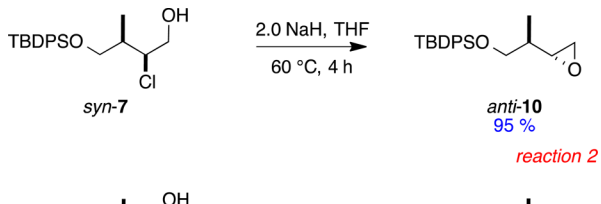


5 **6** 75 %

reaction 1

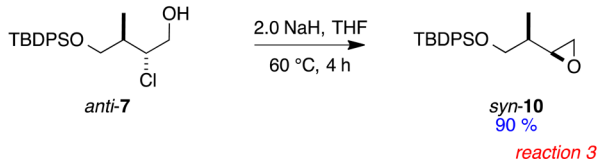
To the best of our knowledge, organocatalytic transformations of the homo-Roche aldehydes **6** have not been reported before. However, there is precedent for electrophilic α-substitutions of β-chiral aldehydes,[21] and, of course, a great deal of literature for the parent reactions of acyclic nonchiral aldehydes.[22] Scheme 2 shows the data accumulated for the organocatalytic transformations of aldehyde **6**. Part **a** refers to chlorinations performed using MacMillan's catalyst **M•TFA**[23] (a commercial sample of the hydrochloride catalyst did not work in this reaction, so it was converted to the trifluoroacetate, that is, the salt used by MacMillan's group). It emerged that the (*S*)-enantiomer of the catalyst matched[24] the substrate bias and gave an excellent stereoselectivity for the *syn*-isomer of **7** after borohydride reduction. However, in the mismatched case (*R*)-**M•TFA** overwhelmed the substrate bias hence a 10:1.0 ratio in favor of *anti*-**7** was observed. Similarly, MacMillan's fluorination procedure[25] using (*R*)-**M•Cl$_2$HCCO$_2^-$** gave even better matched and mismatched selectivities in catalyst-controlled reactions to give the 2-fluoroalcohols **8** after reduction. For amination reactions it was desirable to use dibenzyl azocarboxylate rather than other alkyl derivatives for the reasons indicated below (Scheme 3), so we used List's procedure that described application of exactly that electrophile.[26] Just as in the chlorination and fluorination reactions, the aminations were catalyst-controlled. These transformations gave superb selectivity in the matched case for *syn*-**9**, and a 13:1.0 ratio for the *anti*-isomer via the mismatched process.

Reactions 2 and 3 show how the isomeric 2-chloroalcohols **7** were efficiently ring closed to the corresponding epoxides **10**. These reactions were performed because the epoxides **10** are valuable chirons, but their use has been limited by the fact that syntheses of these materials require multiple steps and some routes are only practical for one or two of the four possible stereoisomers.[27−29]



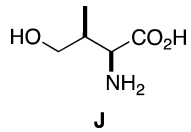
syn-**7** *anti*-**10** 95 %

reaction 2



anti-**7** *syn*-**10** 90 %

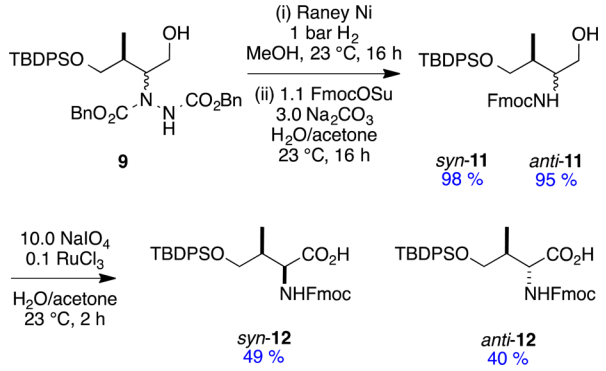
reaction 3



J

Finally, derivatives of γ-hydroxyvaline **J** were prepared to illustrate how the amination products **9** could be used in a novel short synthesis. γ-Hydroxyvalines are naturally occurring amino acids that have been associated with stimulation of insulin secretion.[30] Hydrogenolysis of the benzyl protecting groups of **9** and simultaneous homolysis of the N−N bond gave the *N*-protected amino alcohols **11** after addition of Fmoc (Scheme 3). Catalytic oxidation of those alcohols gave the *N*-Fmoc-γ-silyl protected amino acid **12**. All four stereoisomers of **12** could be obtained by this route, and one enantiomer of each of the *syn*- and *anti*-forms was made to prove this. The final products **12** are suitably protected for many peptide synthesis strategies, so no attempt was made to obtain the corresponding γ-hydroxyvalines since we have no immediate application for these. The synthesis of the 2*S*,3*S*-*syn*-isomer was performed on a large enough scale to obtain 0.42 g of product. Previous syntheses of γ-hydroxyvaline derivatives required either 12 steps to obtain an enantiomer of the *N*-BOC-*O*-PMB-protected form of the reduced product (i.e., alcohol not carboxylic acid),[31] or via multistep routes to *syn*,*anti*-mixtures of various protected derivatives that were then separated (via crystallization of diastereomeric copper complexes,[32] or via column chromatography[33]).

Scheme 3. Syntheses of α-*N*-γ-*O*-Protected Forms of γ-Hydroxyvaline



9 *syn*-**11** 98 % *anti*-**11** 95 %

syn-**12** 49 % *anti*-**12** 40 %

CONCLUSIONS

The pivotal observation in this paper is that we may use type-**D** trisubstituted alkenes, specifically **2**, to give the same product that would be formed from hydrogenation of itaconic acid (or the diester) *and* differentiation of the two carboxylate groups (then reduction). Key to this is the fact that chiral Crabtree's analogs like **cat** can mediate hydrogenations of trisubstituted alkenes without suitable coordinating functional groups (CFGs) for binding Rh-centers. Fortunately, the starting material **2** is also easy to make and this facilitates the whole process.

Prior to our studies, Alexakis and Mazet elegantly combined enantioselective iridium-mediated isomerization reactions[34−37] with organocatalytic functionalization of aldehydes to form two chiral centers.[21] The work we have performed here is conceptually similar except that it is based on production of a particularly high-value chiron, the homo-Roche ester, and elaboration of that in distinct steps. Moreover, the initial chiral center is established here via hydrogenation rather than isomerization reactions.

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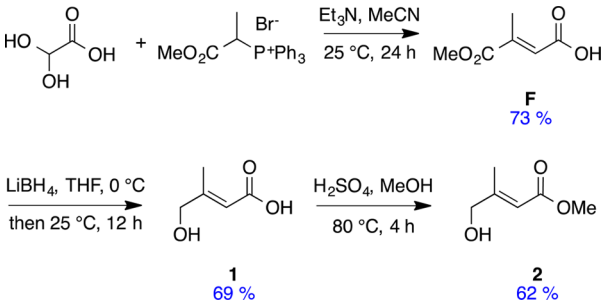
EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under an air atmosphere unless it stated. Glassware for anhydrous reactions was dried in an oven at 140 °C for minimum 6 h prior to use. Dry solvents were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at a high commercial quality (typically 97% or higher) and used without further purification, unless otherwise stated. High field NMR spectra were recorded at 400 MHz for ^{1}H, and 100 MHz for ^{13}C. Chemical shifts of ^{1}H and ^{13}C spectra were referenced to the NMR solvents. Flash chromatography was performed using silica gel (230−600 mesh). Thin layer chromatography was performed using glass plates coated with silica gel 60 F254. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double double doublet, dq = double quartet, m = multiplet, br = broad.

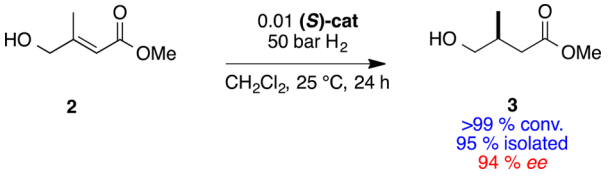
Preparation of (*E*)-Methyl 4-Hydroxy-3-methylbut-2-enoate (2).



(E)-4-Methoxy-3-methyl-4-oxobut-2-enoic Acid (F).[15] To a solution of (1-methoxy-1-oxopropan-2-yl)triphenylphosphonium bromide (42.9 g, 100 mmol) in dry MeCN (300 mL) was added triethylamine (13.2 mL, 95 mmol) and glyoxylic acid monohydrate (8.74 g, 95 mmol) at 0 °C. The solution was further stirred at 0 °C for 2 h and at room temperature overnight. Half of the solvent was removed under reduced pressure, and ethyl acetate (100 mL) was added. The resulting solution was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 50 mL), acidified (pH 1 - 2) at 0 °C with concentrated HCl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were evaporated to dryness, yielding a clear oil **F** (10.5 g, 73%) which was used for the next reaction without further purification.

(E)-4-Hydroxy-3-methylbut-2-enoic Acid (1).[16] $LiBH_4$ (400 mmol) was added to (*E*)-4-methoxy-3-methyl-4-oxobut-2-enoic acid **F** (200 mmol) in THF (200 mL) at 0 °C. The reaction mixture was then allowed to ambient temperature and stirred for 12 h. The mixture was poured into 1N HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed under reduced pressure to yield the product **1** as a white solid (16 g, 69%), which was used for the next reaction without further purification.

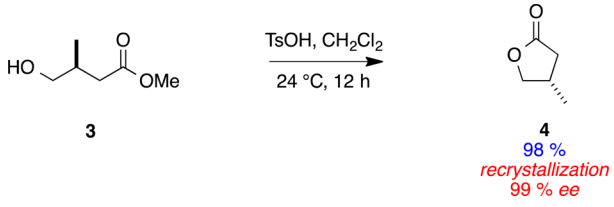
(E)-Methyl 4-Hydroxy-3-methylbut-2-enoate (2). To a solution of H_2SO_4 in 50 mL of MeOH, (*E*)-4-hydroxy-3-methylbut-2-enoic acid **1** (150 mmol) was added at room temperature. The mixture was stirred and refluxed for 4 h. After cooling to ambient temperature, solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2. The organic layer was washed with $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure to obtain product **2** as a clear oil (12 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, J = 4.7 Hz, 1H), 3.96 (s, 2H), 3.63 (s, 3H), 1.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 132.3, 119.7, 67.2, 58.3, 26.2. HRMS (ESI, TOF): m/z = 131.0711, calcd For $C_6H_{11}O_3$ $[M+H]^+$ 131.0708.



Catalytic Hydrogenation. (*E*)-Methyl 4-hydroxy-3-methylbut-2-enoate **2** (120 mmol) and **(*S*)-cat** (1 mol %) were dissolved in CH_2Cl_2 (0.5 M). The resulting mixture was degassed by three cycles of freeze−pump−thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 24 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 10−30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC analysis.

Methyl (S)-4-Hydroxy-3-methylbutanoate (3). Colorless oil, 15.2 g (95% isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3H), 3.35 (dd, J = 6.6, 12 Hz, 2H), 2.48 (m, 2H), 2.07 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 68.5, 62,1, 37.8, 32.5, 14.7. HRMS (ESI, TOF): m/z = 133.0864, calcd For $C_6H_{13}O_3$ $[M+H]^+$ 133.0865.

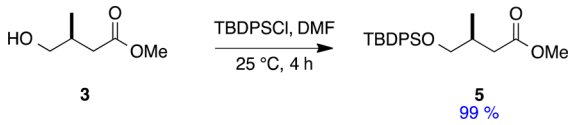
Preparation of (*S*)-4-Methyldihydrofuran-2(3*H*)-one (4). To a solution of methyl (*S*)-4-hydroxy-3-methylbutanoate (12 g, 90 mmol)



in 30 mL of CH_2Cl_2, TsOH (0.95 equiv) was added at room temperature. The mixture was stirred for 6 h, then the organic layer was washed with H_2O (3 × 30 mL), brine and dried over Na_2SO_4. Solvent was removed under reduced pressure to yield product as colorless oil (9.8 g, 98%).

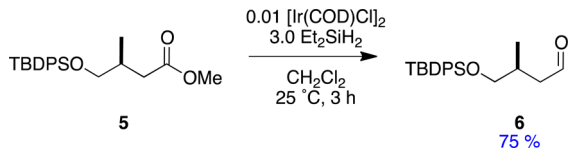
Procedure for Recrystallization. (*S*)-4-Methyldihydrofuran-2(3*H*)-one **4** was dissolved in EtOAc and hexane and the mixture was cooled to −20 °C. After getting precipitation, solvent was decanted in low temperature and washed with cold hexane.

Preparation of Methyl (*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-3-methylbutanoate (5). To a solution of methyl (*S*)-4-hydroxy-3-



methylbutanoate **3** (5.5 g, 42 mmol) in 30 mL of DMF, TBDPSCl (0.95 equiv) was added at room temperature. The mixture was stirred for 4 h, then solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O (3 × 30 mL), brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude was purified by chromatography using 5% EtOAc/hexane as eluent to obtain product **5** as a clear oil (15 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.30 (m, 10H), 3.69 (s, 3H), 3.59 (dd, J = 3.3, 12 Hz, 2H), 2.63−2.60 (m, 2H), 2.32−2.20 (m, 1H), 1.09 (s, 9H), 1.02 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 137.8, 133.8, 129.7, 126.9, 68.7, 51.9, 38.7, 26.8, 19.7, 16.1. HRMS (ESI, TOF): m/z = 371.0222, calcd For $C_{22}H_{31}O_3Si$ $[M+H]^+$ 371.0242.

Preparation of (*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methylbutanal (6). A modification of reported procedure[20] was used.



Under an atmosphere of argon, to an oven-dried flask was added $[Ir(COD)Cl]_2$ (10.1 mg, 0.015 mmol) and 1.5 mL of CH_2Cl_2. Then diethyl silane (529 mg, 6.0 mmol) was added and the resulting mixture was stirred at 23 °C for 1 min. After addition of methyl (*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutanoate **5** (3.0 mmol), the mixture

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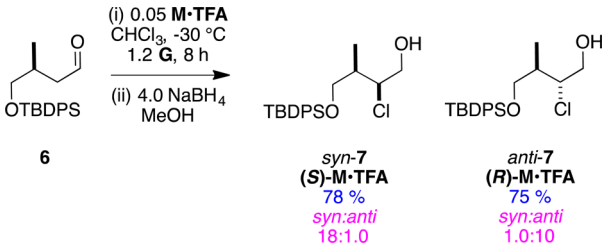
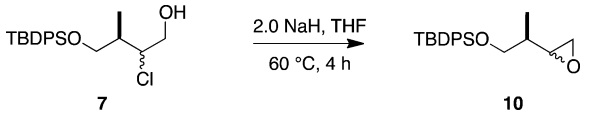
was stirred at 23 °C for 1 h. Then add another portion of [Ir(COD)-Cl]$_2$ (10.1 mg, 0.015 mmol) and diethyl silane (265 mg, 3.0 mmol) to the mixture and allow it to stir 23 °C for 2 h. The reaction was diluted with diethyl ether and quenched by 0.1 M HCl. After stirring for 20 min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel, eluting with ∼10−15% CH_2Cl_2/hexanes gave the desired aldehyde **6** as colorless oil (766 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (t, J = 2.1 Hz, 1H), 7.81−7.74 (m, 4H), 7.54−7.47 (m, 6H), 3.70 (dd, J = 9.9, 5.1 Hz, 1H), 3.57 (dd, J = 9.9, 6.9 Hz, 1H), 2.69 (ddd, J = 15.9, 5.7, 2.1 Hz, 1H), 2.48−2.39 (m, 1H), 2.35 (ddd, J = 15.9, 7.2, 2.1 Hz, 1H), 1.18 (s, 9H), 1.05 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 135.6, 135.6, 133.6, 133.5 129.8, 127.8, 68.5, 48.2, 31.3, 27.0, 19.3, 16.9. IR (CH_2Cl_2) νcm^{-1}) 3070, 2931, 2858, 2360, 1724, 1469, 1427, 1111, 806.3, 740.7, 702.1. HRMS (ESI, TOF): m/z = 347.2021, calcd for $C_{21}H_{28}O_2SiLi$ [M+H]$^+$ 347.2019.

Typical Procedure for α-Chlorination of the Aldehyde. A modification of reported procedure[23] was used. 5-Benzyl-2,2,3,-

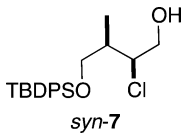


trimethylimidazolidin-4-one trifluoroacetic acid salt (13.5 mg, 0.05 mmol) in chloroform (1 mL) is cooled to −30 °C for five minutes prior to addition of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (181 mg, 0.6 mmol). The aldehyde **6** (170 mg, 0.5 mmol) was added to the yellow mixture. The resulting mixture was stirred at −30 °C for 8 h. The reaction was then warmed to 0 °C and MeOH (1 mL) was added to the mixture, followed by $NaBH_4$ (80 mg, 2 mmol). After stirring at 0 °C for 5 min, the reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 2.5% ∼ 5.0% EtOAc/hexanes gave the desired alcohol as colorless oil.

Typical Procedure for Preparation Epoxides. Under Ar, to a solution of **7** (75.4 mg, 0.2 mmol) in anhydrous THF was added NaH



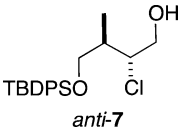
(10.0 mg, 0.4 mmol) and the mixture was stirred at 60 °C for 4 h. The reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with CH_2Cl_2 three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with CH_2Cl_2/hexanes (20%) gave the desired epoxide as a colorless oil.



syn-**7**

(2S,3R)-4-((tert-Butyldiphenylsilyl)oxy)-2-chloro-3-methylbutan-1-ol (syn-7). The compound was prepared according to the typical α-chlorination procedure catalyzed by (*S*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one trifluoroacetic acid salt. Purification by flash chromatography afforded *syn*-7 as a colorless oil (147 mg, 78% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) 7.81−7.75 (m, 4H), 7.54−7.44 (m, 6H), 4.49−4.45 (m, 1H), 3.88−3.86 (m, 2H), 3.71−3.62 (m, 2H), 2.34 (br, 1H), 2.22−2.16 (m, 1H), 1.12 (s, 9H), 1.05 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.6, 133.2, 129.8, 127.8, 66.5, 65.7, 65.7, 38.8, 26.9, 19.3, 11.8. IR (CH_2Cl_2) νcm^{-1}) 3356, 3071, 2932, 2859, 2361, 1470, 1427, 1377, 1111, 822. HRMS (ESI, TOF): m/z = 377.1718, calcd For $C_{21}H_{30}ClO_2Si$ [M+H]$^+$ 377.1704. The diastereoselectivity was 18:1.0, determined by ^{1}H NMR and confirmed by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), t_r 11.7 min (major diastereomer), t_r 12.7 min (minor diastereomer).

The product was converted to the epoxide according to the typical procedure for preparation epoxides. Purification by flash chromatography afforded (2*R*,3*R*)-4-*tert*-butyldiphenylsilyloxy-1,3-epoxy-3-methylbutane (*anti*-**10**) as a colorless oil (67.5 mg, 95% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.49−7.38 (m, 6H), 3.66 (dd, J = 6.3, 1.6 Hz, 2H), 2.90−2.87 (m, 1H), 2.79 (dd, J = 4.9, 4.1 Hz, 1H), 2.63 (dd, J = 5.0, 2.8 Hz, 1H), 1.65−1.56 (m, 1H), 1.09 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.6, 129.7, 127.7, 66.4, 55.1, 46.8, 39.1, 26.8, 19.2, 13.3. IR (CH_2Cl_2) νcm^{-1}) 3070, 2927, 2859, 2338, 1462, 1427, 1389, 1362, 1111, 933.6, 887.3, 821.7. HRMS (ESI, TOF): m/z = 347.2020, calcd For $C_{21}H_{28}O_2SiLi$ [M+Li]$^+$ 347.2019.



anti-**7**

(2R,3R)-4-((tert-Butyldiphenylsilyl)oxy)-2-chloro-3-methylbutan-1-ol (anti-7). The compound was prepared according to the typical chlorination procedure catalyzed by (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one trifluoroacetic acid salt. Purification by flash chromatography afforded *anti*-7 as colorless oil (141 mg, 75% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.68 (m, 4H), 7.51−7.39 (m, 6H), 4.26−4.22 (m, 1H), 3.95 (dd, J = 12.2, 4.5 Hz, 1H), 3.87 (dd, J = 12.2, 6.5 Hz, 1H), 3.78 (dd, J = 10.4, 5.9 Hz, 1H), 3.72 (dd, J = 10.4, 4.3 Hz, 1H), 2.54 (br, 1H), 2.27−2.16 (m, 1H), 1.10 (s, 2H), 1.06 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.1, 129.8, 127.8, 67.4, 65.5, 65.1, 39.4, 26.9, 19.2, 14.6. IR (CH_2Cl_2) νcm^{-1}) 3383, 3071, 2932, 2859, 2361, 1470, 1427, 1389, 1111. HRMS (ESI, TOF): m/z = 377.1710, calcd For $C_{21}H_{30}ClO_2Si$ [M+H]$^+$ 377.1704. The diastereoselectivity was 1.0:10 determined by ^{1}H NMR and confirmed by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), t_r 11.8 min (minor diastereomer), t_r 12.8 min (major diastereomer).

The product was then converted to the epoxide according to the typical procedure for preparation epoxides. Purification by flash chromatography afforded (2*S*,3*R*)-4-*tert*-butyldiphenylsilyloxy-1,3-epoxy-3-methylbutane (*syn*-**10**) as colorless oil (61.3 mg, 90% isolated yield). The relative stereochemistry was determined by comparing with a known epoxide, which was reported previously.[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.66 (m, 4H), 7.48−7.38 (m, 6H), 3.75 (qd, J = 9.9, 5.1 Hz, 2H), 3.02−2.99 (m, 1H), 2.81−2.75 (m, 1H), 2.57 (dd, J = 5.0, 2.8 Hz, 1H), 1.68−1.60 (m, 1H), 1.10 (s, 9H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.8, 129.6, 127.6, 66.2, 54.0, 45.6, 38.5, 26.9, 19.3, 12.6. IR (CH_2Cl_2) νcm^{-1}) 3071, 2928, 2859, 1470, 1427, 1389, 1362, 1111, 933.6, 875.7, 821.7. HRMS (ESI, TOF): m/z = 347.2003, calcd For $C_{21}H_{28}O_2SiLi$ [M+Li]$^+$ 347.2019.

Relative stereochemistry determination of 7: the ^{1}H NMR data of *syn*-**10** matched with reported data[29] and differs from that of *anti*-**10**. Therefore, the relative stereochemistry assignment was confirmed.

Typical Procedure for α-Fluorination of the Aldehyde. A modification of reported procedure[25] was used. 5-Benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt (38.0 mg, 0.1 mmol) and *N*-fluorobenzenesulfonimide (315 mg, 1.0 mmol) was dissolved in THF (4.5 mL) and ^{i}PrOH (0.5 mL). The mixture was cooled to −10 °C prior to addition of the aldehyde (170 mg, 0.5 mmol). The resulting mixture was stirred at −10 °C for 16 h and

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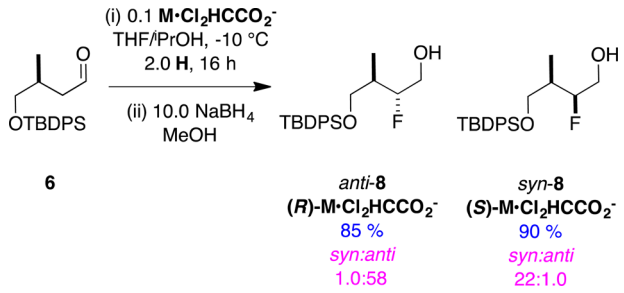
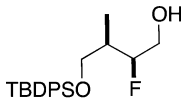
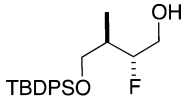


was then warmed to 0 °C. To the mixture at 0 °C was added 1 mL MeOH and $NaBH_4$ (200 mg, 5 mmol). After stirring at 0 °C for 5 min, the reaction was quenched by 1 M $KHSO_4$. The mixture was diluted with water and the aqueous solution was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. The residue was redissolved in dichloromethane and the solid was filtered off on a small silica pad. The mixture was concentrated again *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with ∼5−10% EtOAc/hexanes gave the desired alcohol as colorless oil.



syn-**8**

(2S,3R)-4-((tert-Butyldiphenylsilyl)oxy)-2-fluoro-3-methylbutan-1-ol (syn-8). The compound was prepared according to the typical α-fluorination procedure catalyzed by (*S*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt. Purification by flash chromatography afforded *syn*-**8** as a colorless oil (162 mg, 90% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.69 (m, 4H), 7.51−7.39 (m, 6H), 4.66 (dtd, *J* = 48.4, 6.2, 3.0 Hz, 1H), 3.96−3.68 (m, 4H), 2.22−2.01 (m, 2H), 1.11 (s, 9H), 1.04 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (d, *J* = 2.3 Hz), 133.5 (d, *J* = 3.1 Hz), 129.7 (d, *J* = 1.3 Hz), 127.7 (s), 95.4 (d, *J* = 170.3 Hz), 64.5 (d, *J* = 6.1 Hz), 63.3 (d, *J* = 22.2 Hz), 37.1 (d, *J* = 18.9 Hz), 26.9 (s), 19.3 (s), 13.0 (d, *J* = 6.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −194.48 (dtd, *J* = 40.0, 25.3, 14.5 Hz). IR (CH_2Cl_2) νcm^{-1}) 3364, 3071, 2928, 2855, 2361, 1470, 1427, 1393, 1362, 1111, 1049. HRMS (ESI, TOF): *m*/*z* = 361.2021, calcd For $C_{21}H_{30}FO_2Si$ $[M+H]^+$ 361.1999. The diastereoselectivity was ^{19}F NMR and confirmed by 22:1.0 determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), t_r 16.05 min (major diastereomer), t_r 23.68 min (minor diastereomer).

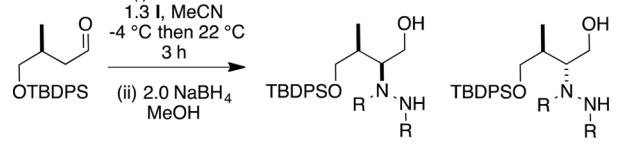


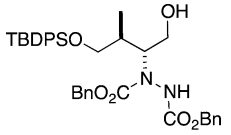
anti-**8**

(2R,3R)-4-((tert-Butyldiphenylsilyl)oxy)-2-fluoro-3-methylbutan-1-ol (anti-8). The compound was prepared according to the typical α-fluorination procedure catalyzed by (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt. Purification by flash chromatography afforded *anti*-**8** as a colorless oil (153 mg, 85% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.69 (m, 4H), 7.51−7.41 (m, 6H), 4.72 (dtd, *J* = 48.8, 6.4, 3.1 Hz, 1H), 3.97−3.75 (m, 2H), 3.67−3.64 (m, 2H), 2.28 (br, 1H), 2.11−2.00 (m, 1H), 1.12 (s, 9H), 0.99 (dd, *J* = 7.0, 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (d, *J* = 4.5 Hz), 133.3 (d, *J* = 8.2 Hz), 129.8 (s), 127.8 (d, *J* = 1.6 Hz), 95.4 (d, *J* = 171.0 Hz), 65.2 (d, *J* = 6.0 Hz), 63.7 (d, *J* = 22.6 Hz), 37.4 (d, *J* = 19.6 Hz), 26.9 (s), 11.7 (d, *J* = 5.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −198.46 to −198.93 (m). IR (CH_2Cl_2) νcm^{-1}) 3356, 3071, 2932, 2859, 2361, 1470, 1427, 1389, 1362, 1111, 1034. HRMS (ESI, TOF): *m*/*z* = 361.2035, calcd For $C_{21}H_{30}FO_2Si$ $[M+H]^+$ 361.1999. The diastereoselectivity was 1.0:58, determined by ^{19}F NMR and confirmed by Chiral HPLC (Chiralcel OD, Hex/iPrOH 99:1, 1 mL/min, 25 °C), 3t_r 16.05 min (minor diastereomer), t_r 23.68 min (major diastereomer).

Relative stereochemistry determination of **8**: since both catalyst and reaction condition are identical to what has been reported, and the reaction is catalyst controlled; the stereochemistry was assigned according to MacMillan's fluorinated product. The product cannot be easily converted to any known structure.

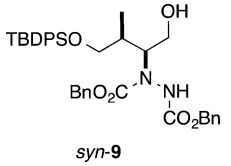
Typical Procedure for the α-Amination of the Aldehyde. A modification of reported procedure[38] was used. Dibenzyl azodicarboxylate (90%, 1.29 g, 3.9 mmol) and proline (70 mg, 0.6 mmol) in MeCN (10 mL) were cooled down to −3 °C. The aldehyde (1.02 g 3.0 mmol) was then added and the mixture was stirred at −3 °C for 2 h. The reaction was gradually warmed to 20 °C within *ca.* 1 h. The mixture was then cooled to 0 °C, treated with MeOH (3 mL) and $NaBH_4$ (240 mg, 6.0 mmol) and was stirred for 5 min at 0 °C. The reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 15% EtOAc/hexanes gave the desired alcohol as white foamy solid.





anti-**9**

Dibenzyl 1-((2R,3S)-4-((tert-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)hydrazine-1,2-dicarboxylate (anti-9). The compound was prepared according to the typical α-amination procedure catalyzed by (*S*)-Proline. Purification by flash chromatography afforded *anti*-**9** as a white foamy solid (1.54 g, 80% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.50−7.27 (m, 16H), 6.85 (d, *J* = 31.1 Hz, 1H), 5.37−5.10 (m, 4H), 4.45−4.12 (m, 2H), 3.80−3.41 (m, 4H), 1.95−1.66 (m, 1H), 1.12−1.09 (m, 9H), 0.99−0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 157.4, 135.6, 133.3, 133.2, 129.6, 129.8, 128.7, 128.6, 128.2, 127.9, 127.8, 127.7, 68.6, 65.9, 65.6, 60.4, 35.6, 26.9, 19.3, 15.1. IR (CH_2Cl_2) νcm^{-1}) 3356, 3032, 2928, 1717, 1454, 1408, 1265, 1227, 1111, 1057. HRMS (ESI, TOF): *m*/*z* = 641.3078, calcd For $C_{37}H_{45}N_2O_6Si$ $[M+H]^+$ 641.3047. The diastereoselectivity was 1.0:13, determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 93:7, 1 mL/min, 25 °C), t_r 10.3 min (minor diastereomer), t_r 14.4 min (major diastereomer).



syn-**9**

Dibenzyl 1-((2S,3S)-4-((tert-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)hydrazine-1,2-dicarboxylate (syn-9). The compound was prepared according to the typical α-amidation procedure catalyzed by (*R*)-Proline. Purification by flash chromatography afforded *syn*-**9** as a white foamy solid (1.63 g, 85% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.62 (m, *J* = 13.5, 6.6 Hz, 4H),

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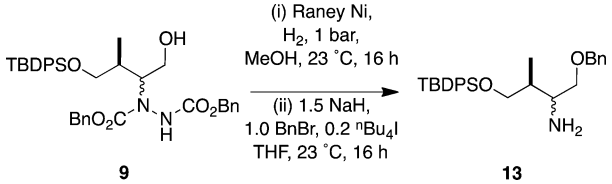
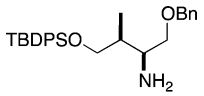
7.50−7.24 (m, 16H), 6.96 (s, 1H), 5.30−5.22 (m, 3H), 5.13 (dd, J = 12.1, 9.6 Hz, 1H), 4.36−4.16 (m, 2H), 3.86−3.70 (m, 2H), 3.59−3.44 (m, 2H), 1.80 (br, 1H), 1.11−1.08 (m, 9H), 0.93−0.90 (m, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 158.6, 158.2, 156.8, 156.5, 135.9, 135.6, 135.5, 135.4, 133.0, 130.1, 129.9, 128.6, 128.5, 128.1, 127.9, 127.8, 68.3, 64.0, 63.2, 60.6, 35.5, 27.0, 19.2, 14.9. IR (CH_2Cl_2) νcm^{-1}) 3356, 3032, 2959, 1724, 1470, 1408, 1261, 1223, 1111, 1053. HRMS (ESI, TOF): m/z = 641.3063 calcd For $C_{37}H_{45}N_2O_6Si$ [M+H]$^+$ 641.3047. The diastereoselectivity was 62:1.0, determined by Chiral HPLC (Chiralcel OD, Hex/iPrOH 93:7, 1 mL/min, 25 °C), t_r 10.2 min (minor diastereomer), t_r 14.3 min (major diastereomer).

Typical Procedure for the Hydrogenolysis and Benzylation of the Alcohol. To Raney−Nickel (∼0.3 g, prewashed with dry

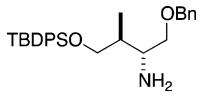


MeOH) in MeOH (1 mL), was added AcOH (0.3 mL) and a solution of **9** (64.0 mg, 0.1 mmol) in MeOH (1 mL). The solution was degassed and stirred under a slightly positive pressure of hydrogen (balloon) at 23 °C for 16 h. The reaction was then filtered through a short pad of Celite, and washed with CH_2Cl_2. The mixture was concentrated *in vacuo* and the residue was redissolved in CH_2Cl_2 and was neutralized by anhydrous Na_2CO_3. The solvent was removed by vacuum and the crude product was subjected to benzyl protection without further purification. Under Ar atmosphere, to a solution of the hydrogenated crude product (0.15 mmol) in anhydrous THF was added NaH (4.8 mg, 0.4 mmol). After stirring for 5 min, BnBr (19 μL, 0.15 mmol) and ^{n}Bu$_4$NI (11.1 mg, 0.03 mmol) was added and the mixture was stirred at 23 °C for 16 h. The reaction was quenched by 1 M $KHSO_4$. The aqueous solution was extracted with EtOAc (three times). The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with ∼1.0−2.5% MeOH/CH_2Cl_2 gave the desired product as a white foamy solid.



syn-**13**

(2S,3S)-1-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-3-methylbutan-2-amine (syn-13). The compound was prepared according to the typical hydrogenolysis and benzylation procedure. Purification by flash chromatography afforded *syn*-**13** as a white foamy solid (22.2 mg, 50% yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.65 (m, 4H), 7.48−7.28 (m, 11H), 4.55 (d, J = 4.8 Hz, 2H), 3.77−3.60 (m, 3H), 3.47 (dd, J = 9.3, 7.6 Hz, 1H), 3.18 (td, J = 7.2, 3.4 Hz, 1H), 2.80 (br, 2H), 1.90−1.79 (m, 1H), 1.08 (s, 9H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.6, 133.4, 133.3, 129.7, 128.4, 127.8, 127.7, 73.3, 72.8, 66.8, 53.9, 38.1, 27.0, 19.2, 13.9.

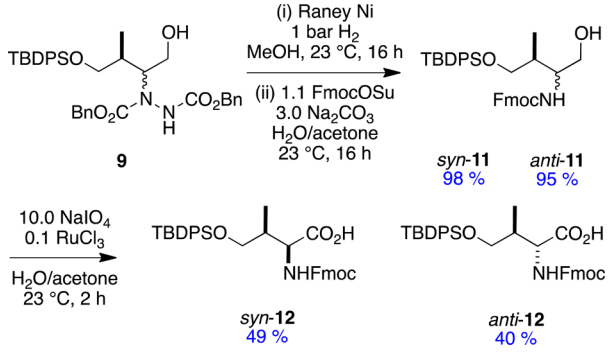


anti-**13**

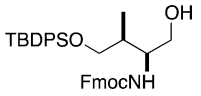
(2R,3S)-1-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-3-methylbutan-2-amine (anti-13). The compound was prepared according to the typical hydrogenolysis and benzylation procedure. Purification by flash chromatography afforded *anti*-**13** as a white foamy solid (22.3 mg, 50% yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.49−7.28 (m, 11H), 4.54 (s, 2H), 3.68−3.58 (m, 2H), 3.56−3.49 (m, 1H), 3.38 (dd, J = 10.2, 6.5 Hz, 1H), 3.26 (br, 1H), 1.83 (br, 1H), 1.51 (br, 2H), 1.08 (s, 9H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 135.6, 133.8, 133.7, 129.6, 128.4, 127.7, 127.6, 74.3, 73.2, 66.8, 29.7, 26.9, 19.3, 11.7.

Relative stereochemistry determination of **9**: the ^{13}C NMR data of *syn*-**13** matched with reported data[39] and differ from that of *anti*-**13**. Therefore, the relative stereochemistry assignment was confirmed.

Typical Procedure for the Preparation of α-Amino Acid. To Raney−Nickel (∼1.5 g, prewashed with dry MeOH) in MeOH (10 mL),



was added AcOH (3 mL) and a solution of **9** (1.44 g, 2.25 mmol) in MeOH (10 mL). The solution was degassed and stirred under a slightly positive pressure of hydrogen (balloon) at 23 °C for 16 h. The reaction was then filtered through a short pad of Celite, and washed with CH_2Cl_2. The mixture was concentrated *in vacuo* and the residue was redissolved in CH_2Cl_2 and was neutralized by anhydrous Na_2CO_3. The solvent was removed by vacuum and the crude product was subjected to Fmoc-protection without further purification. To a solution of the above crude product in H_2O (10 mL) and acetone (10 mL) was added FmocOSu (830 mg, 2.5 mmol) and Na_2CO_3 (715 mg, 6.7 mmol). The reaction was stirred at 23 °C for 16 h. The mixture was extracted with EtOAc three times. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 10% ∼ 20% EtOAc/hexanes gave **11** as a white foamy solid. To a solution of $RuCl_3$ (29 mg, 0.14 mmol) and $NaIO_4$ (2.95 g, 13.8 mmol) in water was added **11** (800 mg, 1.38 mmol). The mixture was stirred at 23 °C for 2 h, and then added MeOH (2 mL). The reaction was stirred until solid precipitation occurred. The solid was filtered on Celite and washed it with EtOAc. One M $KHSO_4$ (3 mL) was added to the filtrate. Then, the aqueous phase was extracted by EtOAc. The combined organic layers were dried with $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with ∼15−50% EtOAc/hexanes gave the desired acid **12** as a white foamy solid.



syn-**11**

(9H-Fluoren-9-yl)methyl ((2S,3S)-4-((tert-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)carbamate (syn-11). Purification by flash chromatography afforded *syn*-**11** as a white foamy solid (1.28 g, 98% yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.74 (m, 6H), 7.66 (dd, J = 7.3, 3.6 Hz, 2H), 7.55−7.40 (m, 8H), 7.34 (t, J = 7.4 Hz, 2H), 6.05 (d, J = 6.7 Hz, 1H), 4.50 (d, J = 6.5 Hz, 2H), 4.28 (t, J = 6.8 Hz, 1H), 3.93−3.74 (m, 4H), 3.69 (dd, J = 10.4, 4.5 Hz, 1H), 3.31 (br, 1H), 2.05 (br, 1H), 1.19 (s, 9H), 1.13 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 144.1, 141.4, 135.7, 132.9, 130.0, 127.9, 127.7, 127.1, 125.2, 120.0, 66.9, 66.0, 64.6, 56.7, 47.4, 35.7, 27.0, 19.2, 15.3. IR (CH_2Cl_2) νcm^{-1}) 3402, 3067, 2928, 1701, 1508, 1450, 1327, 1227, 1111, 1042. HRMS (ESI, TOF): m/z = 580.2874, calcd For $C_{36}H_{42}NO_4Si$ [M+H]$^+$ 580.2883.

(9H-Fluoren-9-yl)methyl ((2R,3S)-4-((tert-Butyldiphenylsilyl)oxy)-1-hydroxy-3-methylbutan-2-yl)carbamate (anti-11). Purification by flash chromatography afforded *anti*-**11** as a white foamy solid (1.24 g, 95% yield in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.77

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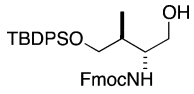
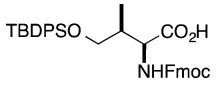


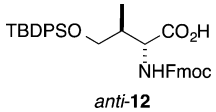
anti-**11**

(m, 2H), 7.74 (dd, J = 7.7, 6.7 Hz, 4H), 7.64 (d, J = 7.4 Hz, 2H), 7.55−7.39 (m, 8H), 7.33 (td, J = 7.5, 1.0 Hz, 2H), 5.85 (d, J = 8.3 Hz, 1H), 4.51−4.43 (m, 2H), 4.26 (t, J = 6.9 Hz, 1H), 3.90 (dd, J = 11.2, 4.2 Hz, 1H), 3.83−3.80 (m, 1H), 3.78−3.69 (m, 2H), 3.63 (dd, J = 10.7, 7.2 Hz, 1H), 3.34 (br, 1H), 2.11−2.10 (m, 1H), 1.15 (s, 9H), 0.97 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 144.0, 141.4, 135.7, 132.8, 130.1, 127.9, 127.7, 127.1, 125.1, 120.0, 66.8, 66.1, 63.0, 56.3, 47.4, 37.2, 27.0, 19.2, 14.1. IR (CH_2Cl_2) νcm^{-1}) 3368, 3067, 2928, 1701, 1512, 1450, 1242, 1111. HRMS (ESI, TOF): m/z = 580.2865, calcd For $C_{36}H_{42}NO_4Si$ $[M+H]^+$ 580.2883.



syn-**12**

(2S,3S)-2-(((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-((tert-butyldiphenylsilyl)oxy)-3-methylbutanoic acid (syn-12). Purification by flash chromatography afforded *syn*-**12** as a white foamy solid (0.42 g, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.60 (m, 8H), 7.55−7.29 (m, 10H), 6.41 (d, J = 8.4 Hz, 1H), 4.61−4.51 (m, 7H), 4.34 (t, J = 6.9 Hz, 1H), 3.88 (d, J = 8.5 Hz, 1H), 3.62 (dd, J = 10.7, 5.1 Hz, 1H), 2.49 (m, 1H), 1.25−1.09 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 156.9, 143.9, 141.3, 135.7, 132.6, 130.0, 127.9, 127.7, 127.1, 125.3, 120.0, 67.4, 66.1, 58.1, 47.1, 36.4, 26.9, 19.2, 14.7. IR (CH_2Cl_2) νcm^{-1}) 3399, 3067, 2928, 1717, 1508, 1450, 1427, 1219, 1111, 1034. HRMS (ESI, TOF): m/z = 616.2552, calcd For $C_{36}H_{39}NaNO_5Si$ $[M+Na]^+$ 616.2495.



anti-**12**

(2R,3S)-2-(((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-4-((tert-butyldiphenylsilyl)oxy)-3-methylbutanoic acid (anti-12). Purification by flash chromatography afforded *anti*-**12** as a white foamy solid (0.34 g, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.56 (m, 8H), 7.49−7.27 (m, 10H), 5.90 (d, J = 8.2 Hz, 1H), 4.69 (d, J = 6.2 Hz, 2H), 4.51−4.34 (m, 2H), 4.24 (t, J = 6.5 Hz, 1H), 3.70−3.57 (m, 2H), 2.43 (br, 1H), 1.09 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 143.8, 141.3, 135.6, 133.0, 129.8, 127.8, 127.7, 127.1, 125.1, 119.9, 67.3, 66.1, 56.1, 47.2, 37.9, 29.7, 26.8, 19.1. HRMS (ESI, TOF): m/z = 594.2752, calcd For $C_{36}H_{40}NO_5Si$ $[M+H]^+$ 594.2676.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of **2**, **3**, **5**−**13**, and GC traces after hydrogenation, recrystallization of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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