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Synthesis of an Enantiocomplementary Catalyst of β-Isocupreidine (β-ICD) from Quinine

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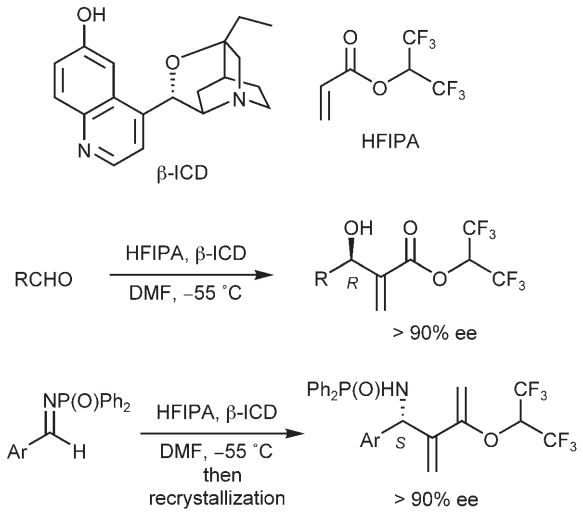
Abstract: Compound **20**, a pseudoenantiomer of β-isocupreidine (β-ICD), was synthesized from quinine employing a Barton reaction of nitrosyl ester **13** and acid-catalyzed cyclization of carbinol **18** as key steps. The Baylis–Hillman reaction of benzaldehyde, *p*-nitrobenzaldehyde, and hydrocinnamaldehyde with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) using **20** as a chiral amine catalyst was found to give the corresponding *S*-enriched adducts in high optical purity (>91% ee) in contrast to the β-ICD-catalyzed reaction which affords *R*-enriched adducts. This result suggests that compound **20** can serve as an enantiocomplementary catalyst of β-ICD in the asymmetric Baylis–Hillman reaction of aldehydes with HFIPA.

Keywords: asymmetric catalysis; Baylis–Hillman reaction; β-isocupreidine; organic catalysis; quinine

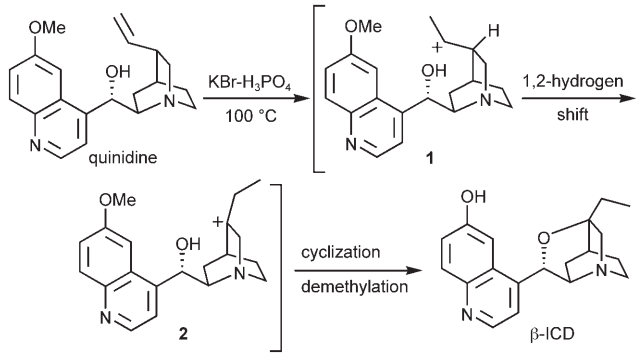
Introduction

The Baylis–Hillman reaction has attracted considerable interest due to the fascinating tandem Michael-aldol sequence catalyzed by a Lewis base and the promising utility of the multifunctional products. Recent literature continues to record impressive progress in rate acceleration as well as asymmetric induction based on imaginative ideas.[1] Recently, we have developed a highly enantioselective asymmetric Baylis–Hillman reaction of aldehydes[2] as well as imines[3] by use of β-isocupreidine (β-ICD)[4,5] as a chiral Lewis base catalyst and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as an activated alkene. In addition, we have successfully demonstrated the synthetic utility of this reaction *via* syntheses of biologically intriguing natural products.[6] This β-ICD-HFIPA method has remarkable advantages in terms of the high enantioselectivity, the broad applicability, and the availability of both β-ICD and HFIPA. However, one serious drawback is that this method cannot be applied to the synthesis of the products with the opposite absolute configuration because the required enantiomer of β-ICD is not easily available.[7] As one solution to this problem, we investigated the synthesis of an enantiocomplementary catalyst of β-ICD.

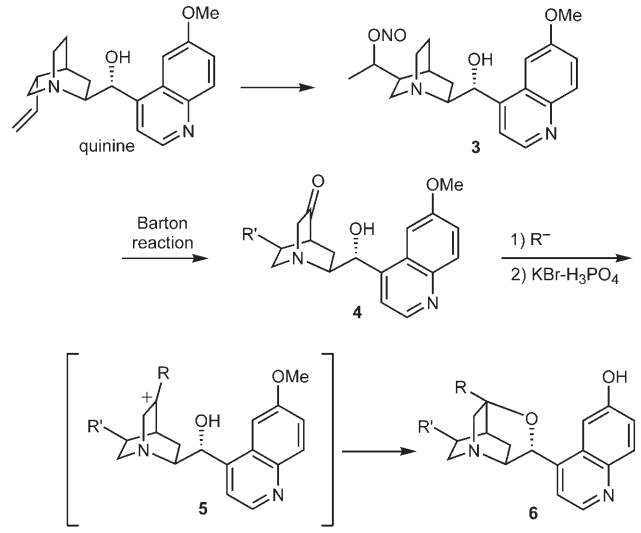
β-ICD can be prepared in one step from quinidine by treatment with aqueous KBr-H_3PO_4 at 100 °C.[2] In this process, together with demethylation, acid-induced cycloisomerization of quinidine takes place *via* carbocations **1** and **2** as reported by Hoffmann et al. (Scheme 2).[4] This transformation suggests that if carbocation **5** is accessible from quinine, a pseudoenantiomer of quinidine, then the synthesis of **6**, a pseudoenantiomer of β-ICD, would also become possible. Thus, we envisaged ketone **4** as a precursor of carbocation **5** and postulated that this intermediate could be accessed *via* a Barton reaction[8,9] of nitrosyl ester **3**, accessible from quinine *via* a suitable functionalization of the C-3 vinyl group involving epimerization of the stereocenter (Scheme 1).



Scheme 1. The β-ICD-HFIPA method.



Scheme 2. Cycloisomerization of quinidine leading to β-ICD.

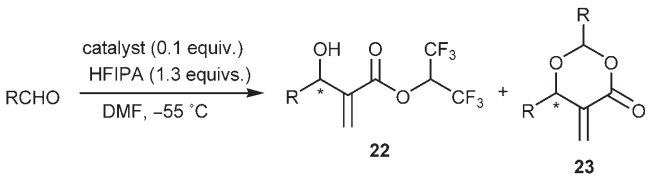


Scheme 3. Strategy for the synthesis of a pseudoenantiomer of β-ICD from quinine.

Results and Discussion

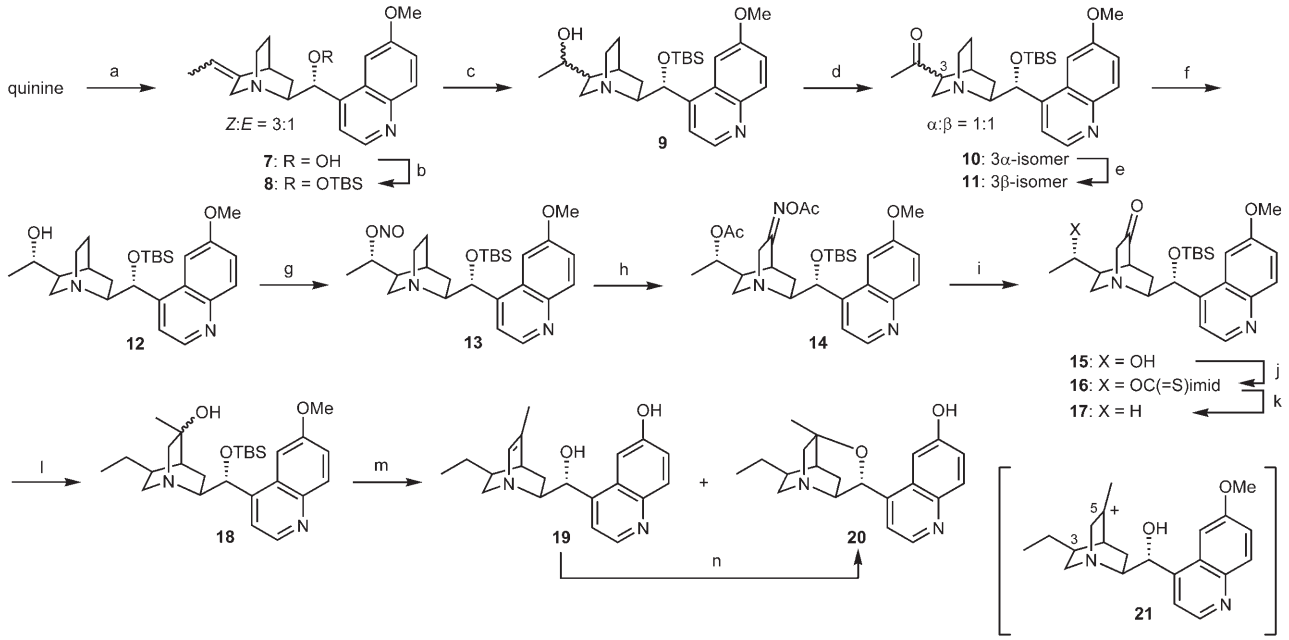
Scheme 4 illustrates the synthetic route to compound **20** which has the enantiomeric skeleton of β-ICD. $RhCl_3$-catalyzed isomerization[10] of quinine followed by protection of the C-9 hydroxy group as its *tert*-butyldimethylsilyl ether gave **8** as a 3:1 *Z*/*E*-isomeric mixture in 77% yield. Without separation, hydroboration of **8** with thexylborane followed by oxidation of the resulting alkylboranes with trimethylamine *N*-oxide[11] afforded **9** as a 6:3:2:1 mixture of four diastereomers in 91% yield. Swern oxidation of **9** followed by treatment with K_2CO_3 in methanol afforded a 1:1 mixture of methyl ketones **10** and **11**. After separation, the undesired isomer **10** was subjected to a recycling sequence involving the above-mentioned epimerization and separation. After repeating this sequence four times, methyl ketone **11** was obtained in 85% total yield from **9**. Gratifyingly, it was found that, upon treatment of **11** with $NaBH_4$ in methanol at 0 °C, reduction occurred with almost perfect diastereoselectivity to give alcohol **12** in 85% yield. For the subsequent Barton reaction, **12** was subjected to nitrosylation[12] using nitrosyl chloride in the presence of finely ground K_2CO_3 in CH_2Cl_2 to give nitrate **13** almost quantitatively. Upon irradiation of **13** in benzene-toluene using a medium-pressure mercury lamp[9] and acetylation of the photo-products, oxime acetate **14** was obtained in 35% yield. Hydrolysis[13] of **14** with $TiCl_3$ in aqueous acetone followed by deacetylation with K_2CO_3 in methanol furnished ketone **15** in 90% yield. To remove the hydroxy group used for the nitrosyl transfer process, **15** was subjected to a Barton–McCombie procedure[14] *via* **16** to give ketone **17** in 87% yield. After Grignard reaction of **17** with methylmagnesium bromide, the resulting carbinol **18** was directly exposed to

Table 1. Baylis-Hillman reactions of aldehydes with HFIPA using β-ICD and **20**.



Entry	R	Time [h]	Catalyst	Yield [%]:[a] config. [% ee][b]	
				22	**23**
1	Ph	24	**20**	69: *S* (91)	0
2	*p*-$NO_2C_6H_4$	1.5	**20**	53: *S* (91)	14: *S* (33)
3	Ph$(CH_2)_2$	15	**20**	54: *S* (98)	14: *R* (45)
4	Ph	48	β-ICD	75: *R* (97)	0
5	*p*-$NO_2C_6H_4$	1.5	β-ICD	57: *R* (95)	17: *R* (49)
6	Ph$(CH_2)_2$	15	β-ICD	40: *R* (98)	22: *S* (3)

[a] Isolated yield.
[b] Determined by HPLC analysis using a chiral column of the corresponding methyl ester obtained by methanolysis.



Scheme 4. *Reagents and Conditions*: (a) $RhCl_3 \cdot 3\,H_2O$ (3 mol %), H_2SO_4, EtOH, reflux (95%); (b) TBSCl, imidazole, DMF, 100 °C (81%); (c) (i) thexylborane, THF, 0 °C, (ii) $Me_3N(O)$, diglyme, reflux (91%); (d) (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to room temperature, (ii) K_2CO_3, MeOH, reflux, (iii) separation; (e) (i) K_2CO_3, MeOH, reflux, (ii) separation (85% from **8** after 4 cycles); (f) $NaBH_4$, MeOH, 0 °C (85%); (g) NOCl, K_2CO_3, CH_2Cl_2, 0 °C; (h) (i) hv, benzene-toluene (3:1), 4 °C; (ii) Ac_2O, pyridine, 0 °C (35% from **11**); (i) (1) aqueous $TiCl_3$, acetone, (2) K_2CO_3, MeOH, (90%); (j) 1,1-thiocarbonyldiimidazole,THF, reflux; (k) Bu_3SnH, cat AIBN, toluene, reflux, (87%, from **13**); (l) MeMgBr, THF, 0 °C (86%); (m) KBr, 85% H_3PO_4, 100 °C, 10 days (**19**:**20** = 3:2, 54%); (n) KBr, 85% H_3PO_4, 100 °C, 3 days (**19**:**20** = 3:2, 72%).

the conditions employed for the synthesis of β-ICD from quinidine. Thus, treatment of **18** with aqueous KBr-H_3PO_4 at 100 °C for 10 days afforded a 3:2 mixture of uncyclized enamine **19** and the desired compound **20** in 54% yield. After chromatographic separation, enamine **19** was treated again with aqueous KBr-H_3PO_4 at 100 °C for 3 days to give a 3:2 mixture of **19** and **20** in 72% yield. As a result, compound **20** was obtained in 31% yield from **17**. In this particular case, the preferential production of **19** rather than **20** can be explained by the difficulty of cyclization of carbocation **21**, possibly due to severe steric hindrance between the C-3 ethyl and the C-5 methyl groups. In fact, the cyclization of carbocation **2** having no substituent at the C-3 position proceeded rather smoothly to produce β-ICD in higher yield (61%).[2]

In order to evaluate the ability of **20** as a chiral amine catalyst complementary to β-ICD, we examined the Baylis–Hillman reaction of benzaldehyde, *p*-nitrobenzaldehyde, and hydrocinnamaldehyde with HFIPA using **20** as a catalyst (Table 1). As a result, it was found that compound **20** catalyzed the Baylis–Hillman reaction as effectively as β-ICD and resulted in opposite enantioselectivity. This result suggests that the C-3 and C-5 substituents on the quinuclidine ring exert little effect on the catalytic ability.

Conclusion

We have synthesized chiral amine **20** starting from quinine and proved that it behaves as an enantiocomplementary catalyst to β-ICD in the asymmetric Baylis–Hillman reaction of aldehydes with HFIPA. Efforts toward improving the synthetic route are now underway in this laboratory.

Experimental Section

General Remarks

Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere. All extracts were dried over K_2CO_3 and concentrated by rotary evaporation below 30 °C at *ca.* 25 Torr unless otherwise noted. Analytical and preparative thin-layer chromatography were performed with Merck F-254 TLC plates. Column chromatography was performed employing silica gel 60 (230–400 mesh ASTM, Merck). 1,1,1,3,3,3-Hexafluoroisopropyl acrylate (HFIPA) was purchased from Tokyo Chemical Industry (Tokyo Kasei) Co. Ltd. and used without purification. β-Isocupreidine (β-ICD) was prepared according to the procedure we had established earlier.[2] Commercial reagents and solvents were used as supplied with the following exceptions. Anhydrous tetrahydrofuran (THF) (stabilizer free) and diethyl ether (Et_2O) were pur-

chased from Kanto Chemical Co., Inc. Dichloromethane (CH_2Cl_2), triethylamine, dimethyl sulfoxide (DMSO), and *N*,*N*-dimethyformamide (DMF) were distilled from CaH_2. Benzene and toluene were distilled from P_2O_5. Infrared spectra were measured on a JASCO FT/IR-230 spectrometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter at ambient temperature. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 300 or a Varian Unity plus 500 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) in δ units and coupling constants are given in Hertz. TMS was defined as 0 ppm for ^1H NMR spectra and the center of the triplet of $CDCl_3$ was defined as 77.10 ppm for ^{13}C NMR spectra. HR-MS (EI) spectra were measured on a JEOL JMS-DX303 or a JEOL JMS-700N. Note that ^1H NMR and ^{13}C NMR spectra of all compounds except for **7** and **20** were complex because rotational isomers at the C-9 center were present.

(8*S*,9*R*)-3-Ethylidene-6′-methoxyrubane (7) (3:1 *Z*/*E*-Mixture)

To a solution of quinine (5.56 g, 17.1 mmol) in EtOH (110 mL) was added concentrated H_2SO_4 (1.83 mL) and the mixture was stirred for 10 min at room temperature. $RhCl_3 \cdot 3\,H_2O$ (136 mg, 0.517 mmol) was added and the mixture was refluxed for 2 h. After evaporation of the EtOH, the reaction mixture was diluted with $CHCl_3$, basified with 10% K_2CO_3, washed with brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 20/1) gave **7**, a white amorphous solid, as a 3:1 *Z*/*E*-mixture; yield: 5.30 g (95%). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.3 Hz, 1H), 7.88 (d = 9.3 Hz,1H), 7.49 (d, *J* = 4.3 Hz, 1H), 7.24 (dd, *J* = 2.7, 9.6 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 0.7H), 7.15 (d, *J* = 2.4 Hz, 0.3H), 5.71 (br s, 1H), 5.52–5.04 (m, 2H), 3.83 (s, 3H), 3.78–3.61 (m, 1H), 3.54–3.32 (m, 2H), 3.10 (br t, *J* = 7.5 Hz, 1H), 2.84–2.66 (m, 1H), 2.33 (br s, 1H), 1.97 (br dd, *J* = 9.0, 12.0 Hz, 1H), 1.85–1.77 (m, 1H), 1.65–1.24 (m, 2H), 1.53 (d, *J* = 6.9 Hz, 0.8H), 1.41 (d, *J* = 6.9 Hz, 2.2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 148.1, 147.2, 143.8, 139.7, 131.1, 126.4, 121.4, 118.5, 118.4, 115.1, 101.4, 70.9, 60.8, 58.8, 56.5, 55.7, 44.0, 33.2, 27.5, 12.4; FT-IR (neat): ν = 3162, 1621, 1509, 1241, 1228, 1029 cm^{-1}; HR-MS (EI): calcd. for $C_{20}H_{24}O_2N_2$ (M^+): 324.1838; found: 324.1833.

(8*S*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-3-ethylidene-6′-methoxyrubane (8) (3:1 *Z*/*E*-Mixture)

To a solution of **7** (1.07 g, 3.30 mmol) in DMF (5 mL) was added imidazole (450 mg, 6.62 mmol) and *tert*-butyldimethylsilyl chloride (745 mg, 4.98 mmol) and the mixture was the heated at 100 °C for 3 h. The reaction mixture was diluted with Et_2O, washed with water and brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 20/1) gave **8**, a yellow oil, as a 3:1 *Z*/*E*-mixture; yield: 1.17 g (81%). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.8 Hz, 0.8H), 8.64 (d, *J* = 3.9 Hz, 0.2H), 7.99 (d, *J* = 9.0 Hz, 0.8H), 7.97 (d, *J* = 7.8 Hz, 0.2H), 7.84 (d, *J* = 2.4 Hz, 0.2H), 7.49 (d, *J* = 4.8 Hz, 0.8H), 7.35 (dd, *J* = 2.4, 9.0 Hz, 0.8H), 7.30–7.22 (m, 1H). 7.12 (d, *J* = 4.8 Hz, 0.2H), 5.76 (br s, 0.8H), 5.21–5.00 (m , 1H), 4.84 (d, *J* = 9.3 Hz, 0.2H), 3.96, 3.94, 3.88 (3 s,3H), 3.90–3.00 (m, 3.2H), 3.00–2.54 (m, 2H), 2.33 (br s, 0.8H), 2.10 (br t, *J* = 8.4 Hz, 0.8H), 1.85–1.50 (m, 2.2H), 1.45 (d, *J* = 6.9 Hz, 0.7H), 1.32 (d, *J* = 6.9 Hz, 2.3H), 1.35–1.18 (m, 1H), 0.96 (s, 6H), 0.89 (s, 1H), 0.87 (s, 2H), 0.16 (s, 2H), 0.02, −0.06 (2 s, 1H), −0.38 (s, 2H), −0.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 147.6, 147.0, 145.3, 144.2, 141.5, 121.5, 118.5, 100.4, 72.0, 61.8, 56.6, 55.7, 43.6, 33.2, 27.6, 27.0, 22.9, 12.2, −4.4, −5.3; FT-IR (neat); ν = 1619, 1257, 1240 cm^{-1}; HR-MS (EI): calcd. for $C_{26}H_{38}O_2N_2Si$ (M^+): 438.2703; found: 438.2696.

(8*S*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-10,11-dihydro-10-hydroxy-6′-methoxycinchonane (9) (6:3:2:1 Diastereoisomeric Mixture)

To a stirred solution of **8** (13.91 g, 31.7 mmol) in THF (40 mL) at −40 °C was added dropwise thexylborane-THF, freshly prepared from BH_3 (1 M in THF, 220 mL, 220 mmol) and 2,3-dimethyl-2-butene (26.4 mL, 269 mmol). After being stirred at 0 °C for 16 h, the mixture was concentrated. The residue was dissolved in diglyme (168 mL) and trimethylamine *N*-oxide (70.9 g, 945 mmol) was added. After being refluxed for 14 h, the reaction mixture was concentrated, extracted with $CHCl_3$, washed with 10% K_2CO_3 and brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 10/1) gave **9**, a white amorphous solid, as a 6:3:2:1 mixture of four diastereomers; yield: 13.20 g (91%).

(3*S*,8*S*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-10,11-dihydro-6′-methoxycinchonan-10-one (11)

To a solution of oxalyl chloride (8.26 mL, 86.9 mmol) in CH_2Cl_2 (160 mL) was added DMSO (12.3 mL, 180 mmol) at −78 °C. After stirring for 30 min at −78 °C, a solution of **9** (13.18 g, 28.86 mmol) in CH_2Cl_2 (40 mL) was added, and stirring was continued at −78 °C for 1 h. The reaction mixture was treated with triethylamine (36.4 mL, 261 mmol) and allowed to warm to room temperature, and stirred for 1 h. The reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, dried, and concentrated to give a 1:1 mixture of 3α-isomer **10** and 3β-isomer **11** as a yellow oil; yield: 15.2 g. To a solution of this mixture (15.2 g) in MeOH (200 mL) was added K_2CO_3 (4.0 g, 28.9 mmol) and the mixture was refluxed for 1 h. After evaporation of the MeOH, the residue was extracted with $CHCl_3$, washed with 10% K_2CO_3, dried, and concentrated. Purification of the residue by column chromatography on silica gel (*t*-BuOMe/MeOH = 50/1) gave **10** (yield: 4.54 g) and **11** (yield: 3.76 g). This epimerization-separation sequence was repeated four times to afford additional **11** (yield: 7.34 g).

Compound **11** (11.10 g, 85% total yield) was obtained as a white amorphous solid: $[\alpha]_D^{26}$: −151.5° (*c* 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 4.8 Hz, 0.8H), 8.65 (d, *J* = 3.9 Hz, 0.2H), 8.04 (d, *J* = 9.3 Hz, 1H), 7.86 (d, *J* = 3.0 Hz, 0.2H), 7.54 (d, *J* = 4.5 Hz, 0.8H), 7.38 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 0.8H), 7.10 (d, *J* = 4.5 Hz, 0.2H), 5.63 (br s, 0.8H), 4.82 (d, *J* = 9.6 Hz , 0.2H), 3.95 (s, 2.4H), 3.92 (s, 0.6H), 3.41 (m, 1H), 3.22 (dd, *J* = 7.5, 13.5 Hz, 0.8H), 3.06–2.81 (m, 2H), 2.80–2.68 (m, 0.8H), 2.61 (br s, 0.8H), 2.49 (br t, *J* = 8.7 Hz, 0.8H), 2.30–2.18 (m, 0.1H), 2.08

(s, 3H), 2.05–1.98 (m, 1H), 1.80–1.18 (m, 3.7H), 0.98 (s, 7.2H), 0.85 (s, 1.8H), 0.14 (s, 2.4H), 0.10 (s, 0.6H), −0.34 (s, 2.4H), −0.44 (s, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 147.5, 144.4, 132.0, 126.2, 121.7, 121.3, 118.7, 108.2, 100.6, 72.7, 77.3, 61.2, 55.9, 51.8, 49.0, 43.6, 29.3, 25.8, 22.3, 18.2, −4.2, −5.1; FT-IR (neat): ν = 1705, 1622, 1508, 1466, 1362, 1250, 1119, 1038, cm^{-1}; HRMS (EI): calcd. for $C_{26}H_{38}O_3N_2Si$ (M^+): 454.2652; found: 454.2652.

(3*S*,8*S*,9*R*,10*S*)-9-(*tert*-Butyldimethylsilyloxy)-10,11-dihydro-6′-methoxycinchonan-10-ol (12)

To a solution of **11** (11.1 g, 24.4 mmol) in MeOH (200 mL) was added $NaBH_4$ (4.61 g, 121.9 mmol) at −78 °C and the mixture was stirred at −78 °C for 16 h. After evaporation of the MeOH, the residue was extracted with $CHCl_3$, washed with 10% K_2CO_3 and brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 10/1) gave **12** as a yellow oil; yield: 9.49 g (85%); $[\alpha]_D^{21}$: −148.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.8 Hz, 0.8H), 8.61 (d, *J* = 4.5 Hz, 0.2H), 8.00 (d, *J* = 9.3 Hz, 0.8H), 7.97 (d, *J* = 9.3 Hz, 0.2H), 7.86 (d, *J* = 2.4 Hz, 0.2H), 7.52 (d, *J* = 4.8 Hz, 0.8H), 7.35 (dd, *J* = 2.7, 9.9 Hz, 0.8H), 7.08 (d, *J* = 4.5 Hz, 0.2H), 5.64 (br s, 0.8H), 4.80 (d, *J* = 9.3 Hz, 0.2H), 3.95 (br s, 2.4H), 3.84 (br s, 0.6H), 3.75–3.23 (m, 2H), 2.90 (br s, 1.6H), 2.60–1.90 (m, 5.4H), 1.65 (br t, *J* = 9.8 Hz, 1H), 1.35–1.45 (m, 1.6H), 1.23–0.60 (m, 2.4H), 1.06 (t, *J* = 6.9 Hz, 2.4H), 1.03 (t, *J* = 6.9 Hz, 0.6H), 0.96 (s, 7.2H), 0.82 (s, 1.8H), 0.14 (s, 2.4H), 0.09 (s, 0.6H), −0.37 (s, 2.4H), −0.45 (s, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 147.4, 146.9, 144.0, 131.5, 126.2, 121.7, 118.7, 100.7, 72.3, 67.6, 60.7, 60.5, 55.9, 54.8, 53.9, 43.9, 43.4, 32.9, 25.9, 22.8, 21.8, 21.3, −4.3, −5.2; FT-IR (neat): ν = 3160, 1621, 1509, 1257, 1242 cm^{-1}; HR-MS (EI): calcd. for $C_{26}H_{40}O_3N_2Si$ (M^+): 456.2808; found: 456.2814.

(3*S*,8*S*,9*R*,10*S*)-10-Acetoxy-9-(*tert*-butyldimethylsilyloxy)-10,11-dihydro-6′-methoxycinchonan-5-one Oxime Acetate (14)

Nitrosyl chloride was freshly generated by adding dropwise 33% aqueous $NaNO_2$ (24 mL) to concentrated HCl (32 mL) at 0 °C and introduced to a mixture of **12** (3.29 g, 7.20 mmol) and K_2CO_3 (50.0 g, 362 mmol) in CH_2Cl_2 (350 mL) at 0 °C over 3 h. The organic layer was separated, washed with water and brine, dried, and concentrated to afford crude **13** (3.16 g) as a yellow oil which was used for the next reaction without purification.

Crude nitrate **13** (3.16 g) was dissolved in benzene (240 mL) and toluene (80 mL) and argon was introduced into the solution for 10 min. This mixture was then irradiated using a high-pressure mercury lamp at 2 °C for 3 h. The reaction mixture was diluted with AcOEt, washed with 10% K_2CO_3 and brine, dried, and concentrated to give crude oxime (1.74 g). To a solution of the oxime in pyridine (20 mL) was added acetic anhydride (6 mL, 63.5 mmol) at 0 °C and the mixture was stirred for 12 h. After removal of the pyridine, the residue was extracted with CH_2Cl_2, washed with 10% Na_2CO_3 and brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 50/1) gave **14** as a yellow oil; yield: 385 mg (35%); $[\alpha]_D^{21}$: −101.5° (*c* 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 4.5 Hz, 0.8H), 8.67 (d, *J* = 4.5 Hz, 0.2H), 8.06 (d, *J* = 9.3 Hz, 0.8H), 8.02 (d, *J* = 9.3 Hz, 0.2H), 7.82 (d, *J* = 2.8 Hz, 0.2H), 7.44 (d, *J* = 4.5 Hz, 1H), 7.40 (dd, *J* = 2.8, 9.3 Hz, 1H), 7.15 (br s, 0.8H), 7.10 (d, *J* = 4.5 Hz, 0.2H), 5.73 (br s, 0.8H), 4.72 (d, *J* = 9.2 Hz, 0.2H), 4.60–4.45 (m, 1H), 4.34 (d, *J* = 19.2 Hz, 0.8H), 4.08 (m, 0.2H), 3.99 (s, 2.4H), 3.91 (s, 0.6H), 3.76 (d, *J* = 19.2 Hz, 0.2H), 3.51 (d, *J* = 19.2 Hz, 0.8H), 3.33 (d, *J* = 19.2 Hz, 0.2H), 3.20–2.91 (m, 2.6H), 2.30 (br dt, *J* = 2.3, 12.9 Hz, 2H), 2.12, 2.08, 1.98 (3 s, 6H), 1.95–1.85 (m, 1H), 1.49–1.37 (m, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.93 (s, 9H), −0.02 (s, 2.4H), −0.06 (s, 0.6H), −0.37 (s, 2.4H), −0.46 (s, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 169.7, 168.1, 157.9, 147.1, 146.3, 144.0, 131.8, 125.5, 121.4, 118.3, 100.2, 71.8, 59.2, 55.5, 54.1, 49.1, 40.7, 31.6, 25.6, 24.3, 20.8, 17.9, 17.7, −4.38, −5.40; FT-IR (neat): ν = 1619, 1508, 1241 cm^{-1}; HRMS (EI): calcd. for $C_{29}H_{40}O_6N_3Si$ [$(M - CH_3)^+$]: 554.2686; found: 554.2677.

(3*S*,8*S*,9*R*,10*S*)-9-(*tert*-Butyldimethylsilyloxy)-10,11-dihydro-10-hydroxy-6′-methoxycinchonan-5-one (15)

To a solution of **14** (933 mg, 1.64 mmol) in acetone (30 mL) was added aqueous $TiCl_3$ (1.3 M, 2.91 mL, 3.78 mmol) at room temperature and the mixture was stirred for 3 h. After the reaction was quenched with 10% K_2CO_3, the reaction mixture was stirred until it became a white suspension and filtered through a pad of Celite. The filtrate was extracted with CH_2Cl_2, washed with brine, dried, and concentrated. The residue was dissolved in MeOH (20 mL) and K_2CO_3 (500 mg, 3.62 mmol) was added. After being stirred at room temperature for 6 h, most of the MeOH was removed under vacuum and the residue was extracted with $CHCl_3$. The extract was washed with water and brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 50/1) gave **15**; yield: 697 mg (90%); $[\alpha]_D^{21}$: −103.5° (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 4.5 Hz, 0.8H), 8.67 (d, *J* = 4.5 Hz, 0.2H), 8.06 (d, *J* = 9.2 Hz, 0.8H), 8.00 (d, *J* = 9.2 Hz, 0.2H), 7.55 (d, *J* = 9.2 Hz, 0.2H), 7.48 (d, *J* = 4.5 Hz, 0.8H), 7.40 (dd, *J* = 2.7, 9.2 Hz, 1H), 7.16 (br s, 0.8H), 7.08 (br s, 0.2H), 5.70 (br s, 0.8H), 4.72 (d, *J* = 9.5 Hz, 0.2H), 4.20–3.88 (m, 1H), 3.96 (s, 2.4H), 3.93 (s, 0.6H), 3.52–3.36 (m, 1H), 3.21–1.86 (m, 8H), 1.58 (ddd, *J* = 4.2, 8.4, 12.0 Hz, 0.8H), 1.52–1.41 (m, 0.2H), 1.19 (br d, *J* = 3.3 Hz, 0.6H), 1.11 (d, *J* = 6.3 Hz, 2.4H), 0.99 (s, 1.8H), 0.93 (s, 7.2H), 0.13 (s, 2.4H), 0.05 (s, 0.6H), −0.34 (s, 2.4H), −0.47 (s, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.9, 158.1, 147.4, 144.2, 132.0, 125.9, 121.5, 118.5, 100.5, 79.1, 72.3, 68.9, 59.5, 55.5, 55.0, 45.8, 42.0, 25.9, 24.3, 21.2, 18.0, −4.32, −5.11; FT-IR (neat): ν = 3343, 2931, 2857, 1729, 1621, 1508, 1257 cm^{-1}; HR-MS (EI): calcd. for $C_{26}H_{38}O_4N_2Si$ (M^+): 470.2601; found: 470.2611.

(3*S*,8*S*,9*R*)-9-*tert*-Butyldimetylsilyloxy-10,11-dihydro-6′-methoxycinconan-5-one (17)

To a solution of **15** (697 mg, 1.48 mmol) in THF (60 mL) was added *N*,*N*-thiocarbonyldiimidazole (1.63 g, 8.89 mmol) at room temperature and the mixture was refluxed for 42 h. The reaction mixture was diluted with CH_2Cl_2, washed with 10%

Na_2CO_3 and brine, dried, and concentrated to give crude thiocarbamate **16** (1.50 g).

To a solution of crude **16** (1.50 g) in toluene (120 mL) were added 2,2-azobisisobutyronitrile (36.5 mg, 0.222 mmol) and tributyltin hydride (1.23 mL, 4.44 mmol). After being refluxed for 30 min, the reaction mixture was diluted with AcOEt, washed with saturated KF, 10% K_2CO_3, and brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 100/1) gave **17** as a white amorphous solid; yield: 590 mg (87%); $[\alpha]_D^{21}$: −147.2° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 4.4 Hz, 0.8H), 8.67 (d, *J* = 3.9 Hz, 0.2H), 8.05 (d, *J* = 9.1 Hz, 0.8H), 7.86 (brs, 0.2H), 7.47 (d, *J* = 4.4 Hz, 1H), 7.40 (dd, *J* = 2.4, 9.1, 1H), 7.25 (brs, 0.8H), 7.08 (d, *J* = 4.5 Hz, 0.2H), 6.20–5.56 (m, 0.8H), 4.73 (d, *J* = 9.3 Hz, 0.2H), 4.07–4.18 (m, 0.8H), 3.99 (s, 2.4H), 3.92 (s, 0.6H), 3.56–2.81 (m, 3.2 H), 2.50–1.79 (m, 3H), 1.58 (ddd, *J* = 4.1, 9.3, 13.5, 1H), 1.35–1.13 (m, 3H), 0.94 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.18 (s, 2.4H), 0.06 (s, 0.6H), −0.33 (s, 2.4H), −0.47 (s, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 147.4, 144.4, 132.1, 125.9, 121.9, 118.6, 104.6, 100.4, 80.4, 71.8, 59.4, 58.4, 56.2, 45.8, 45.6, 40.1, 28.3, 25.9, 18.1, 11.5, −4.3, −5.0; FT-IR (neat): ν = 1731, 1619, 1255 cm^{-1}; HR-MS (EI): calcd. for $C_{26}H_{38}O_3N_2Si$ (M^+): 454.2652; found: 454.2626.

(3*S*,5*S*,8*S*,9*R*)-10,11-Dihydro-5,9-epoxy-6′-methoxy-5-methylcinconane (20)

To a stirred solution of **17** (312 mg, 0.686 mmol) in THF (8 mL) at 0 °C was added methylmagnesium bromide (3.0 M, 2.29 mL, 6.86 mmol). After being stirred at 0 °C for 1 h, the reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with 10% Na_2CO_3 and brine, dried, and concentrated to give **18** (330 mg) which was used for the next reaction without purification. Pure **18**, a white amorphous solid, was obtained as an epimeric mixture by preparative TLC ($CHCl_3$/MeOH = 10/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 4.5 Hz, 0.8H), 8.65 (d, *J* = 4.4 Hz, 0.2H), 8.00 (d, *J* = 10.0 Hz, 0.8H), 7.87 (d, *J* = 2.4 Hz, 0.2H), 7.52 (d, *J* = 4.4 Hz, 1H), 7.38 (dd, *J* = 10.0, 2.4 Hz, 1H), 7.18 (br s, 0.8H), 7.08 (d, *J* = 4.2 Hz, 0.2H), 5.67 (br s, 0.8H), 4.73 (d, *J* = 9.3 Hz, 0.2H), 3.96 (s, 2.4H), 3.93 (s, 0.6H), 3.57–3.38 (m, 1H), 3.17–2.30 (m, 4H), 1.99–1.28 (m, 8H), 1.19–1.04 (m, 2H), 0.95 (s, 7.2H), 0.83 (s, 1.8H), 0.79 (t, *J* = 7.5 Hz, 3H), 0.13–0.01 (m, 3H), −0.31 (s, 2.4H), −0.44 (s, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.4, 144.4, 132.0, 126.1, 121.7, 121.3, 118.8, 104.9, 100.5, 77.3, 73.2, 60.1, 59.1, 55.9, 39.5, 38.8, 28.6, 26.1, 25.8, 18.1, 12.9, −4.5, −4.7; FT-IR (neat): ν = 3354, 1620, 1508, 1468, 1255, 1111 cm^{-1}; HRMS (EI): calcd. for $C_{27}H_{42}O_3N_2Si$ (M^+): 470.2965; found: 470.2947.

A solution of crude **18** (322 mg) and KBr (816.3 mg, 6.86 mmol) in 85% aqueous H_3PO_4 (12.3 mL) was heated at 100 °C for 10days. The reaction mixture was basified to pH 9 with 2 M KOH, extracted with $CHCl_3$, washed with 10% K_2CO_3 and brine, dried, and concentrated. Purification of the residue by column chromatography on silica gel ($CHCl_3$/MeOH = 100/1) gave **19** (yield: 66.6 mg, 31%) and **20** (yield: 49.7 mg, 23%). Compound **19** (29.8 mg, 0.092 mmol) was again subjected to cyclization by heating with KBr (164 mg, 1.38 mmol) and 85% aqueous H_3PO_4 (2.5 mL) at 100 °C for 3 days. The reaction mixture was worked up and purified as mentioned above to give **19** (yield: 13.4 mg, 45%) and **20** (yield: 8.0 mg, 27%). As a result, the total yield of **20** from **17** is calculated to be 31%. Compound **20** is a colorless powder; $[\alpha]_D^{17}$: −21.4° (*c* 0.140, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 4.4 Hz, 1H), 8.00 (br s, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 4.4 Hz, 1H), 7.25 (dd, *J* = 2.4, 9.0 Hz, 1H), 6.01 (s, 1H), 3.74 (d, *J* = 12.6 Hz, 1H), 3.42 (br d, *J* = 6.3 Hz, 1H), 3.30–3.19 (m, 1H), 2.93 (d, *J* = 12.0 Hz, 1H), 2.89 (d, *J* = 12.0 Hz, 1H), 2.27–2.19 (m, 1H), 2.04 (dd, *J* = 6.6, 12.6 Hz, 1H), 1.79–1.49 (m, 3H), 1.38 (s, 3H), 1.09 (dd, *J* = 6.0, 12.6 Hz, 1H), 1.02 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 146.9, 143.3, 141.3, 131.4, 128.3, 127.0, 122.0, 118.9, 76.4, 74.3, 72.3, 55.5, 52.5, 40.1, 38.2, 37.2, 28.9, 26.5, 23.7, 12.6; FT-IR (neat): ν = 1469, 1238, 1062 cm^{-1}; HR-MS (EI): calcd. for $C_{20}H_{24}O_2N_2$ (M^+): 324.1838; found: 324.1848.

Baylis–Hillman Reaction of Aldehydes with HFIPA using 20 as a Catalyst

To a solution of the aldehyde (1.0 mmol) and **20** (31 mg, 0.1 mmol) in DMF (2 mL) at −55 °C was added HFIPA (220 μL, 1.3 mmol). After stirring at −55 °C for the time indicated in Table 1, the reaction was quenched by the addition of 0.1 M HCl (3 mL). The reaction mixture was extracted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and chromatographed (SiO_2, solvent system: EtOAc/hexane).

The optical purity and absolute configuration of **22** and **23** were determined by HPLC analysis using a chiral column of the corresponding methyl ester obtained as follows. A mixture of **22** or **23** (1.0 mmol) and triethylamine (0.7 mL) in MeOH (7 mL) was stirred at room temperature for 30 min and the reaction was quenched by the addition of Dowex 50 (H^+ form). The reaction mixture was filtered, concentrated, and chromatographed (SiO_2, solvent system: EtOAc/hexane).

1,1,1,3,3,3-Hexafluoroisopropyl (S)-3-hydroxy-3-phenyl-2-methylenepropanoate: colorless oil; $[\alpha]_D^{28}$: +50.5° (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5H), 6.60 (s, 1H), 6,24 (s, 1H), 5.75 (hept, *J* = 6.0 Hz, 1H), 5.63 (br s, 1H), 2.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6, 140.5, 140.0, 129.6, 128.8, 128.5, 126.8, 120.4 (q, $^1J_{C,F}$ = 305.6 Hz), 72.6, 66.8 (hept, $^2J_{C,F}$ = 35.3 Hz); FT-IR (neat): ν = 3375, 2970, 1755, 1387, 1298, 1132 cm^{-1}; HR-MS: calcd. for $C_{13}H_{10}NO_5F_6$ (M^+): 328.0534; found: 328.0538.

Methyl (S)-3-hydroxy-3-phenyl-2-methylenepropanoate: colorless oil (91% ee); $[\alpha]_D^{28}$: +93.2° (*c* 0.21, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 5H), 6.34 (s, 1H), 5.84 (s, 1H), 5.57 (d, *J* = 5.4 Hz, 1H), 3.73 (s, 3H), 3.02 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 142.1, 141.3, 128.5, 127.9, 126.6, 126.1, 73.3, 52.0; FT-IR (neat): ν = 3363, 3032, 2952, 1704, 1496, 1450 cm^{-1}; HR-MS: calcd. for $C_{11}H_{12}O_5$ (M^+): 192.0786; found: 192.0788. HPLC conditions: Daicel Chiralcel OJ, 2-propanol:hexane = 1:5 (0.5 mL/min), t_R = 26.4 min (*R*) and 32.4 min (*S*).

1,1,1,3,3,3-Hexafluoroisopropyl (S)-3-hydroxy-3-(p-nitrophenyl)-2-methylenepropanoate: colorless oil (91% ee); $[\alpha]_D^{20}$: +45.9° (*c* 2.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 6.66 (s, 1H), 6.27 (s, 1H), 5.80–5.74 (m, 2H), 2.47 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 147.9, 147.5, 139.2, 130.9, 127.6, 123.9, 120.3 (q, $^1J_{C,F}$ = 281 Hz), 71.8, 66.9 (hept,

$^2J_{C,F}$ = 34.2 Hz); FT-IR (neat): ν = 3533, 1751, 1525, 1352, 1286, 1232, 1120, 1115 cm^{-1}; HR-MS: calcd. for $C_{13}H_9NO_5F_6$ (M^+): 373.0385; found: 373.0389.

(2S,6S)-2,6-Di(p-nitrophenyl)-5-methylene-1,3-dioxan-4-one: colorless oil (33% ee); $[\alpha]_D^{22}$: +1.0° (*c* 0.220, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.7 Hz, 2H), 8.31 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 2.7 Hz, 1H), 6.62 (s, 1H), 5.92 (br s, 1H), 5.42 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 149.0, 148.6, 144.2, 141.1, 135.2, 130.6, 128.8, 127.5, 124.3, 123.9, 99.5, 80.4; FT-IR (neat): ν = 3082, 2862, 1741, 1523, 1348, 1173 cm^{-1}; HR-MS: calcd. for $C_{17}H_{12}N_2O_7$ (M^+): 356.0644; found: 356.0663.

Methyl (S)-3-hydroxy-3-(p-nitrophenyl)-2-methylenepropanoate: colorless oil (91% ee); $[\alpha]_D^{23}$: +85.6° (*c* 0.54, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.58 (d, *J* = 6.9 Hz, 2H), 6.40 (s, 1H), 5.87 (s, 1H), 5.64 (d, *J* = 6.3 Hz, 1H), 3.75 (s, 3H), 3.30 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 147.8, 146.0, 127.9, 123.5, 71.5, 58.4, 53.0, 50.0; FT-IR (neat): ν = 3427, 2962, 1751, 1387, 1232, 1120 cm^{-1}; HR-MS (EI): calcd. for $C_{11}H_{11}NO_6$ (M^+): 253.0586; found: 253.0578. HPLC conditions: Daicel Chiralcel OJ, 2-propanol:hexane = 1:10 (0.5 mL/min), t_R = 29.0 min (*R*) and 32.4 min (*S*).

1,1,1,3,3,3-Hexafluoroisopropyl (S)-3-hydroxy-2-methylene-5-phenylpentanoate: colorless oil; $[\alpha]_D^{22}$: −10.4° (*c* 1.264, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 2H), 7.22–7.17 (m, 3H), 6.49 (s, 1H), 6.15 (s, 1H), 5.85 (hept, *J* = 6.0 Hz, 1H), 4.52 (dd, *J* = 3.6, 4.2 Hz, 1H), 2.85–2.66 (m, 2H), 2.24 (br s, 1H), 2.08–1.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 142.2, 140.6, 129.2, 128.6, 128.5, 126.2, 120.5 (q, $^1J_{C,F}$ = 282.3 Hz), 70.1, 66.7 (hept, $^2J_{C,F}$ = 34.7 Hz), 37.8, 32.0; FT-IR (neat): ν = 3427, 2962, 1751, 1387, 1232, 1120 cm^{-1}; HR-MS (EI): calcd. for $C_{15}H_{14}F_6O_3$ (M^+): 356.0847; found: 356.0863.

(6R)-2,6-Diphenethyl-5-methylene-1,3-dioxan-4-one (7:3 diastereoisomeric mixture): colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 4H), 7.23–7.17 (m, 10H), 6.49–6.47 (m, 1H), 5.58 (d, *J* = 2.1 Hz, 0.7H), 5.54 (d, *J* = 2.1 Hz, 0.3H), 5.45 (t, *J* = 5.1 Hz, 0.3H), 5.27 (d, *J* = 5.1 Hz, 0.7H), 4.71–4.67 (m, 0.3H), 4.51–4.46 (m, 0.7H), 2.93–2.65 (m, 4H), 2.22–1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 140.9, 140.6, 140.5, 136.8, 136.0, 128.7, 128.6, 128.5, 128.4, 126.8, 126.4, 126.2, 125.7, 101.1, 96.4, 77.5, 77.1, 76.7, 76.5, 74.2, 36.6, 35.8, 35.6, 35.3, 31.4, 30.8, 29.4, 29.3; FT-IR (neat): ν = 3028, 2931, 1730, 1446, 1379, 1234, 1161, 1030 cm^{-1}; HRMS (EI): calcd. for $C_{21}H_{22}O_3$ (M^+): 322.1569; found: 322.1567.

Methyl (S)-3-hydroxy-2-methylene-5-phenylpentanoate: colorless oil (98% ee): $[\alpha]_D^{22}$: −11.3° (*c* 0.654, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.15 (m, 5H), 6.24–6.23 (m, 1H), 5.81 (t, *J* = 0.9 Hz, 1H), 4.45–4.39 (m, 1H), 3.76 (s, 3H), 2.87–2.64 (m, 3H), 2.01–1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 142.2, 141.7, 128.5, 128.5, 126.0, 125.4, 71.2, 52.0, 37.7, 32.1; FT-IR (neat): ν = 3487, 3024, 2947, 1720, 1631, 1444, 1149, 1074 cm^{-1}; HR-MS (EI): calcd. for $C_{15}H_{16}O_3$ (M^+): 220.1099; found: 220.1123. HPLC conditions: Daicel Chiralcel OJ, 2-propanol:hexane = 5:1 (0.5 mL/min), t_R = 26.0 min (*R*), t_R = 27.7 min (*S*).

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