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Asymmetric synthesis of α-chiral dihydrocinnamates by catalytic reductive aldol coupling and subsequent dehydroxylation

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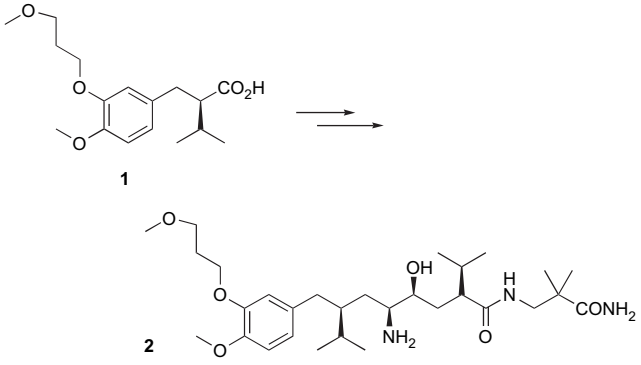
Abstract—Optically active dihydrocinnamate derivatives bearing the chiral carbon center at α-position were synthesized by Rh(Phebox)-catalyzed asymmetric reductive aldol coupling reaction with substituted cinnamates and benzaldehyde derivatives and subsequent dehydroxylation reaction.

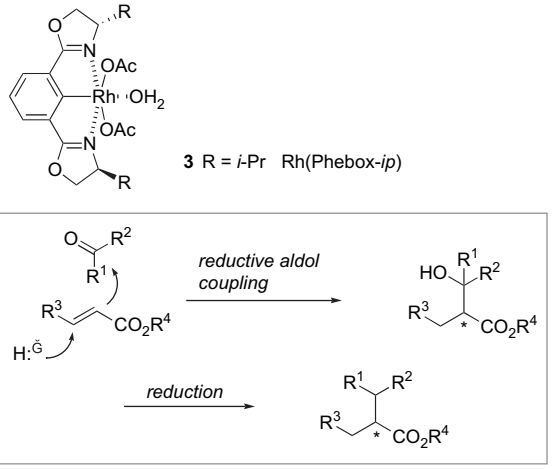
1. Introduction

Optically active dihydrocinnamates have been recognized as important material or intermediates for synthesis of bioactive compounds.[1] For example, the renin inhibitor SPP10 (**2**) can be synthesized via the substituted dihydrocinnamic acid **1** (Scheme 1).[1a,b] Recently, one approach by asymmetric hydrogenation reaction of substituted cinnamates was reported to attain high enantioselectivity.[2] Here, we propose an alternative method, which is comprised of reductive aldol coupling and subsequent dehydroxylation using commercially available carbonyl acceptors and α,β-unsaturated esters such as cinnamates and acrylate derivatives.



Scheme 1. Optically active dihydrocinnamates.

We have developed the enantioselective reductive aldol coupling of α,β-unsaturated esters and carbonyl compounds with chiral Rh(Phebox) catalysts (**3** and **4**) to provide β-hydroxyl esters.[3,4] Where, we think that even the β-hydroxyl group is removed, the products are still synthetically useful retaining high enantiomeric excess at α-position (Scheme 2). The transformation can become credible synthetic method providing optically active dihydrocinnamates or related esters.



Scheme 2. Rh(Phebox) complex and synthetic route to dihydrocinnamates.

2. Results and discussion

Firstly, we adopted the coupling of acetone (**4**) and ethyl *p*-methoxycinnamate (**5**) with Rh(Phebox) catalyst **1** (1 mol %) and $MePh_2SiH$. Although the coupling reaction readily provided β-hydroxyester **A** in 89%, reductive dehydroxylation from the intermediate **A** was unsuccessful with Et_3SiH in CF_3CO_2H, step (b).[5] Therefore, we examined dehydration and hydrogenation via **B** to obtain the desired

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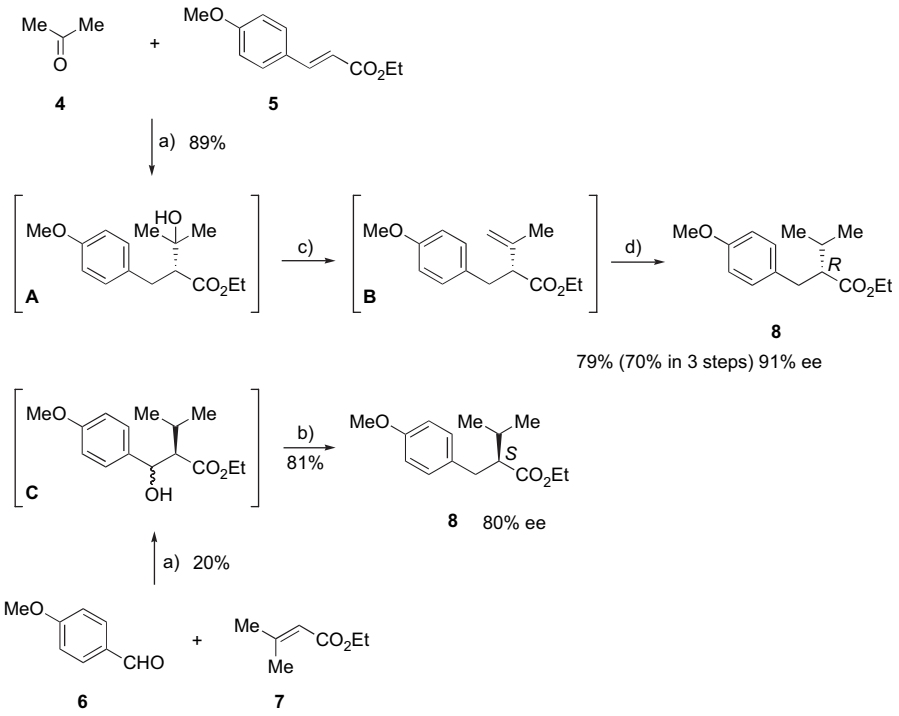
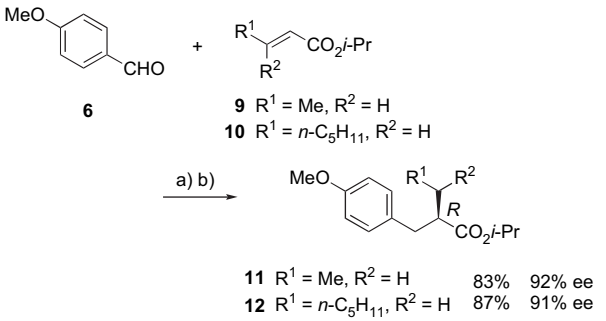


Scheme 3. Synthetic route to dihydrocinnamate; (a) 1 mol % Rh(Phebox-*ip*), $MePh_2SiH$, then KF; (b) Et_3SiH, CF_3CO_2H; (c) MsCl, Et_3N; (d) H_2 (1 atm), Pd/C (15%), MeOH.

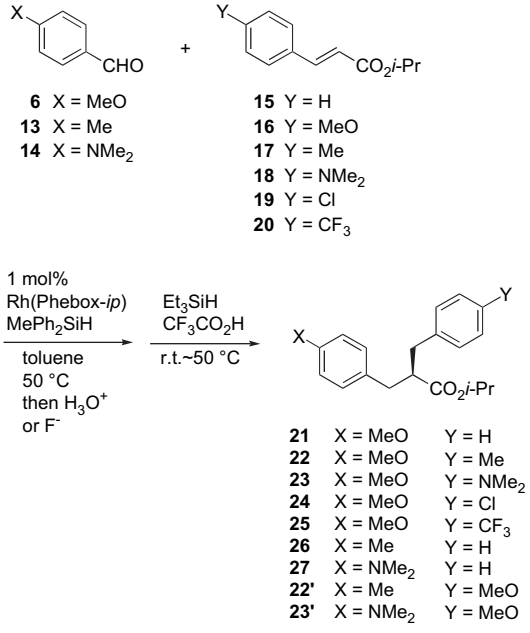
product **8** in 79% in two steps with 91% ee (*R*). Secondly, the coupling using *p*-anisaldehyde (**6**) and ethyl β-methyl crotonate (**7**) was examined but to furnish only 20% of the intermediate **C**. However, it was subjected to reductive dehydroxylation with Et_3SiH in CF_3CO_2H to give the product **8** in 81% with 80% ee (*S*) (Scheme 3).[6]

Next, crotonate **9** and 2-octenoate **10** were subjected to the coupling with *p*-anisaldehyde (**6**) as an acceptor followed by reduction to give the α-ethyl and α-*n*-pentyl dihydrocinnamates **11** and **12** in high yields 83 and 87%, respectively (Scheme 4). The high enantioselective synthesis of the corresponding dihydrocinnamates with over 90% ee was thus attained.



Scheme 4. The coupling of *p*-anisaldehyde and crotonate and octenoate; (a) 1 mol % Rh(Phebox-*ip*), $MePh_2SiH$, then KF; (b) Et_3SiH, CF_3CO_2H.

We extended the method of the coupling and reduction sequence to the coupling between aromatic aldehydes and isopropyl cinnamates to furnish a variety of α-benzyl substituted cinnamates in 63–92% yields (Scheme 5, Table 1).[7] We have thus attained 88–93% of high enantioselectivity without separation of *anti*, *syn*-diastereomers by two-step manipulation.



Scheme 5. The coupling of aromatic aldehydes and cinnamates.

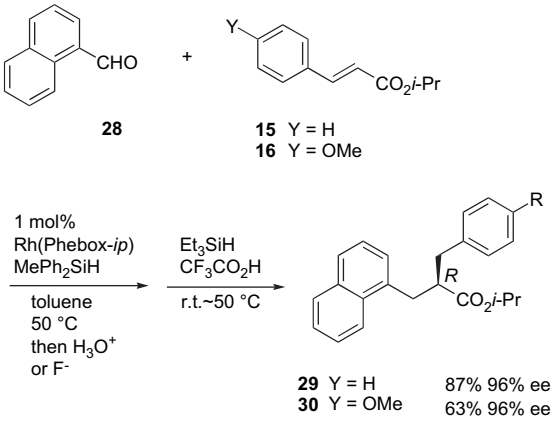
α-Naphthoaldehyde (**28**) was employed as an acceptor to give the coupling product in which β-hydroxy group could be removed by reduction with Et_3SiH to form the desired cinnamates **29** and **30** in 87 and 63% yields, respectively (Scheme 6). The highest ees of 96% were observed.

Table 1. Asymmetric synthesis of dihydrocinnamates with aryl aldehydes and cinnamates Rh(Phebox) catalyst **3**[a]

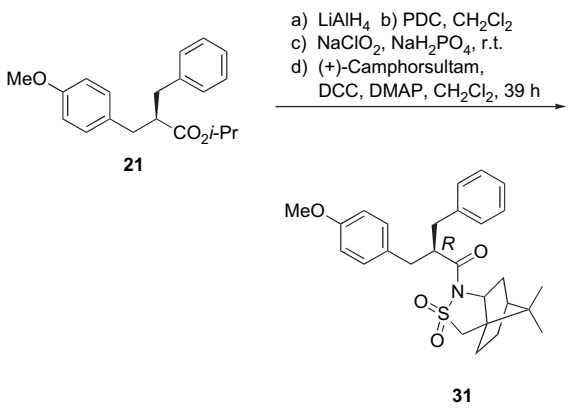
Entry	Aldehyde	Cinnamate	Product	Yield (%)	ee (%)
1[b]	**6**	**15**	**21**	92	93
2	**6**	**17**	**22**	84	92
3	**6**	**18**	**23**	76	93
4	**6**	**19**	**24**	71	92
5	**6**	**20**	**25**	76	88
6	**13**	**15**	**26**	82	93
7	**14**	**15**	**27**	72	89
8	**13**	**16**	**22′**	63	92
9	**14**	**16**	**23′**	70	91

[a] Reaction condition: cat. Rh(Phebox-*ip*) (1 mol %), aldehyde (0.5 mmol), cinnamate (0.75 mmol), $MePh_2SiH$ (0.8 mmol), toluene (0.5 mL), 50 °C, 0.5 h.

[b] Aldehyde (1.0 mmol), cinnamate (1.5 mmol), $MePh_2SiH$ (1.6 mmol), toluene (1.0 mL), 50 °C, 0.5 h.



Scheme 6. The coupling of α-naphthoaldehyde and cinnamates.



Scheme 7. Transformation of dihydrocinnamate **21** to the sulfonamide **31**.

In order to determine the absolute configuration of the products, the dihydrocinnamate **21** was converted in four steps to the corresponding sulfonamide **31** (Scheme 7). The α-carbon atom of **27** proved to be *R*-absolute configuration. On the basis of the analysis, the absolute configurations for other products were assigned similarly. In addition, we propose the hypothetical stereochemical course of the reaction via cyclic transition state of the *E*(*O*)-enolate, where *Si*-face of the enolate may attack to the carbonyl group to form the *R*-absolute configuration at the 2-position of the corresponding aldol product (Figs. 1 and 2).

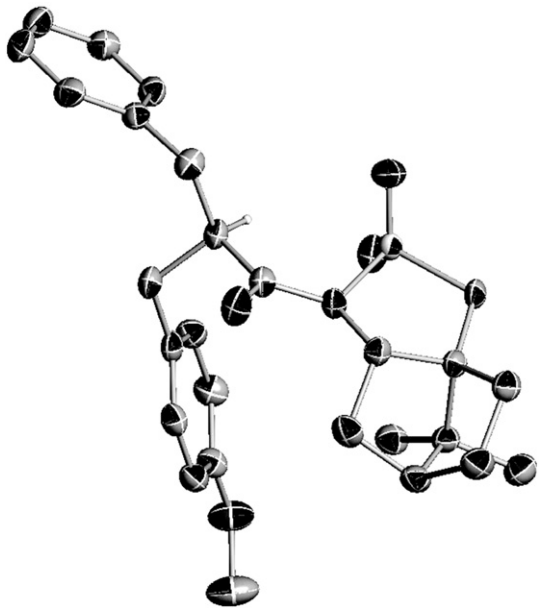


Figure 1. Molecular structure of **31**.

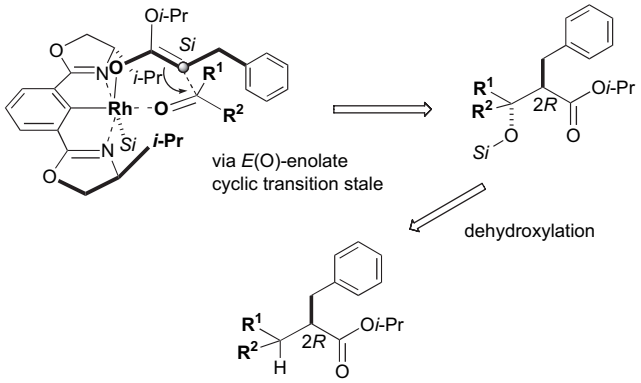


Figure 2. Hypothetical stereochemical course.

3. Conclusion

We have demonstrated that asymmetric reductive aldol reaction and dehydroxylation sequence with chiral Rh(Phebox) catalyst can give optically active α-substituted cinnamate derivatives with high enantioselectivity. This synthetic method can provide a new route to biologically active compounds having chirality at α-carbon atoms of esters and related compounds.

4. Experimental

4.1. General

NMR spectra were obtained in $CDCl_3$ solution at 25 °C on a 300 spectrometer (^1H, 300 MHz; ^{13}C, 75 MHz). ^1H NMR chemical shifts are reported in δ units, in parts per million relative to the singlet at 7.26 ppm for chloroform. The Rh(Phebox) catalyst was synthesized by the method reported by us, see, Ref. 8. Absolute toluene was used, and the cinnamates **5**, **15**, the aldehydes, and the silanes were

commercially available. Other cinnamates and the unsaturated esters were prepared from the corresponding acid chloride or acids with alcohols.

4.2. Typical reactions

4.2.1. The coupling of *p*-anisaldehyde (6) and isopropyl cinnamate (15) and subsequent reductive dehydroxylation (entry 1, Table 1). The rhodium complex **3** [Rh(Phebox-*ip*)$(OAc)_2(H_2O)$] (5.4 mg, 0.01 mmol), isopropyl cinnamate (**15**) (285 mg, 1.5 mmol), and *p*-anisaldehyde (136 mg, 1.0 mmol) were placed in a 10 mL-flask. Under an argon atmosphere, toluene (1.0 mL) was added at room temperature, and then methyldiphenylsilane (317 mg, 1.6 mmol) was slowly added at 50 °C by syringe. The mixture was stirred for 0.5 h. The reaction was monitored by TLC examination. After concentration, THF (1.0 mL), MeOH (1 mL), aq HCl (1 mL, 4 *N*), and KF (232 mg, 4.0 mmol) were added at 0 °C, and the mixture was stirred at room temperature for 24 h. TLC, R_f=0.33 for *syn*-aldol product and R_f=0.24 for *anti*-aldol product (eluent: EtOAc/hexane=1:3). The mixture was treated with aq $NaHCO_3$ (ca. 15 mL), and was extracted with EtOAc (5 mL×3). The combined organic layer was washed with saturated brine (5 mL), and then dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography with EtOAc/hexane as eluent to give the aldol product in 93% yield (307 mg, 0.93 mmol) as colorless oil; *anti*/*syn*=90:10, by ^{1}H NMR. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) *anti*: δ 0.93 (d, J=6.3 Hz, 3H), 1.04 (d, J=6.0 Hz, 3H), 2.74 (dd, J=13.2, 5.4 Hz, 1H), 2.85–3.05 (m, 2H), 3.81 (s, 3H), 4.78 (d, J=6.6 Hz, 1H), 4.88 (m, 1H), 6.88 (d, J=8.7 Hz, 2H), 7.11–7.30 (m, 7H); for *syn*: δ 0.83 (d, J=6.3). IR (neat) ν 3475, 1715 (C=O) cm^{-1}. EI-HRMS: [M^+] *m*/*z*, found: 328.1678; calcd ($C_{20}H_{24}O_4$): 328.1675. Chromatography: DAICEL CHIRALPAK AS-H, eluent: hexane/2-propanol (90:10) (1.0 mL/min), retention time; 5.8 min (*syn*, major), 6.5 min (*syn*, minor), 7.2 min (*anti*, minor), 9.5 min (*anti*, major), *syn* 81% ee, *anti* 95% ee.

To a solution of the aldol mixture (256 mg, 0.78 mmol) in trifluoroacetic acid (0.58 mL) was added triethylsilane (0.27 mL, 1.7 mmol) at 0 °C. The mixture was stirred for 0.5 h at room temperature. The reaction was monitored by TLC examination; R_f=0.68 (eluent: EtOAc/hexane=1:3). The mixture was treated with aq $NaHCO_3$ (ca. 15 mL), and was extracted with EtOAc (5 mL×3). The combined organic layer was washed with saturated brine (5 mL), and then dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography with EtOAc/hexane as eluent to give the desired product **21** in 97 % yield (236 mg, 0.76 mmol) as colorless oil (92% for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J=6.2 Hz, 3H), 0.99 (d, J=6.2 Hz, 3H), 2.72–2.97 (m, 5H), 3.78 (s, 3H), 4.83 (sept, J=6.2 Hz, 1H), 6.79 (d, J=8.5 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 7.16–7.27 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 21.8, 37.7, 38.4, 50.0, 55.3, 67.4, 113.5, 126.1, 128.1, 128.7, 129.7, 131.0, 139.0, 157.8, 174.1. IR (neat) ν 1726 (C=O) cm^{-1}. EI-HRMS: [M^+] *m*/*z*, found: 312.1721; calcd ($C_{20}H_{24}O_3$): 312.1725. Chromatography: DAICEL CHIRALCEL OJ-H, eluent: hexane/2-propanol (90:10) (0.7 mL/min), retention time; 11.1 min (major), 12.3 min (minor), 93% ee; $[\alpha]_D^{25}$ +3.2 (*c* 2.1, $CHCl_3$).

4.2.2. The coupling of α-naphthoaldehyde (28) and isopropyl cinnamate (15) and subsequent dehydroxylation (Scheme 6). The rhodium complex **3** [Rh(Phebox-*ip*)$(OAc)_2(H_2O)$] (2.7 mg, 0.005 mmol), isopropyl cinnamate (**15**) (143 mg, 0.75 mmol), and *p*-anisaldehyde (78 mg, 0.5 mmol) were placed in a 10 mL-flask. Under an argon atmosphere, toluene (0.5 mL) was added at room temperature, and then methyldiphenylsilane (159 mg, 0.8 mmol) was slowly added at 50 °C by syringe. The mixture was stirred for 0.5 h. The reaction was monitored by TLC examination. EtOH (1.0 ml) was added and the mixture was concentrated. Then, THF (1.0 mL), MeOH (1 mL), TBAF (0.5 mL, 1 M in THF), and KF (290 mg, 5.0 mmol) were added at 0 °C, and the mixture was stirred at 50 °C for 48 h. TLC, R_f=0.45 for aldol product (eluent: EtOAc/hexane=1:3). The mixture was extracted with EtOAc (5 mL×3). The combined organic layer was washed with saturated brine (5 mL), and then dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography with EtOAc/hexane as eluent to give the crude aldol mixture (169 mg, 0.48 mmol); *anti*/*syn*=>99:<1 by ^{1}H NMR. To a solution of the aldol mixture (169 mg) in trifluoroacetic acid (0.36 mL) was added triethylsilane (0.15 mL, 0.96 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature. The reaction was monitored by TLC examination; R_f=0.75 (eluent: EtOA/hexane=1:3). The mixture was treated with aq $NaHCO_3$ (ca. 12 mL), and was extracted with EtOAc (5 mL×3). The combined organic layer was washed with saturated brine (5 mL), and then dried over $MgSO_4$. After concentration, the residue was purified by silica gel column chromatography with EtOAc/hexane as eluent to give the desired product **29** in 87% yield (145 mg, 0.44 mmol) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J=6.3 Hz, 3H), 0.95 (d, J=6.3 Hz, 3H), 2.87 (m, 1H), 3.04–3.15 (m, 2H), 3.28 (m, 1H), 3.39 (m, 1H), 4.81 (sept, J=6.3 Hz, 1H), 7.17–7.38 (m, 6H), 7.43–7.49 (m, 2H), 7.71 (m, 1H), 7.78–7.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 21.7, 35.4, 38.8, 49.0, 67.5, 123.3, 125.1, 125.2, 125.7, 126.2, 126.9, 127.0, 128.1, 128.5, 128.8, 131.6, 133.6, 135.0, 138.8, 174.2. IR (neat) ν 1725 (C=O) cm^{-1}. EI-HRMS: [M^+] *m*/*z*, found: 332.1772; calcd ($C_{23}H_{24}O_2$): 332.1776. Chromatography: DAICEL CHIRALCEL OD-H, eluent: hexane/2-propanol (90:10) (0.7 mL/min), retention time; 7.5 min (minor), 8.2 min (major), 96% ee; $[\alpha]_D^{23}$ −21.8 (*c* 2.1, $CHCl_3$).

4.3. X-ray diffraction study

Single crystals of **31** suitable for X-ray diffraction study were obtained from hexane/ethyl acetate solution at 0 °C. The diffraction data were collected on a Brucker SMART APEX CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.71073 Å). An empirical absorption correction was applied by using SADABS. The structure was solved by direct method and refined by full-matrix least-square on F^2 using SHELXTL. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located on calculated positions and refined as rigid groups. Refinement details: empirical formula; $C_{27}H_{33}NO_4S$; M_r=467.60; temperature 173(2) K; crystal system: triclinic; space group: $P2_12_12_1$; a=10.617(4), b=12.996(4), c=17.630(6) Å, V=2432.4(14) Å^3, Z=4, ρ_{calcd}=1.277 Mg/m^3, μ=0.167 mm^{-1}, F(000)=1000, crystal size=0.50×0.20×0.10 mm^3, θ range=1.95 to 27.53°;

Index ranges: $-13\leq h\leq 13$, $-14\leq k\leq 16$, $-22\leq l\leq 16$; reflections collected 17,052, independent reflections 5579 [R(int)=0.0446], completeness to θ=27.53°, 99.6%; max/min transmission 1.000000/0.702521; data/restraints/parameters 5579/0/301; goodness-of-fit on F^2 1.072; final R indices [$I>2\sigma(I)$]: $R1$=0.0486, $wR2$=0.1011; R indices (all data): $R1$=0.0609, $wR2$=0.1058; largest diff. peak/hole 0.581 and −0.270 e Å^{-3}. CCDC 660609 contains the supplementary crystallographic data. The data can be obtained free of charge via http://www.ccdc.cam.au.ac.uk or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; deposit@ccdc.cam.au.uk.

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Supplementary data

Analysis for products, NMR, IR, MS, EA, optical rotations, LC charts, and synthetic procedure of the sulfonamide. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.055.

References and notes

1. For examples of bioactive dihydrocinnamates: for renin inhibitors, (a) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160; For vitronectin receptor antagonists, (b) Dondoni, A.; Lathauwer, G. D.; Perrone, D. *Tetraheron Lett.* **2001**, *42*, 4819; For γ-secretase inhibitors, (c) Churcher, I.; Ashton, K.; Butcher, J. W.; Clarke, E. E.; Harrison, H. D. L.; Owens, A. P.; Teall, M. R.; Williams, S.; Wrigley, J. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 179; For opioid antagonists, (d) Lu, Y.; Nguyen, T. M. D.; Weltrowska, G.; Berezowska, I.; Lemieux, C.; Chung, N. N.; Schiller, P. W. *J. Med. Chem.* **2001**, *44*, 3048; For dihydrocinnamate as a building block, (e) Chang, L. L.; Hannah, J.; Ashton, W. T.; Rasmusson, G. H.; Ikeler, T. J.; Patel, G. F.; Garsky, V.; Uncapher, C.; Yamanaka, G.; McClements, W. L.; Tolman, R. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1207.
2. Hoen, R.; Booers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meestsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4209.
3. (a) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972; (b) Ito, J.; Shiomi, T.; Nishiyama, H. *Adv. Synth. Catal.* **2006**, *348*, 1235.
4. Shiomi, T.; Nishiyama, H. *Org. Lett.* **2007**, *9*, 1651.
5. For the dehydroxylation with Et_3SiH in CF_3CO_2H, see: West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675. As an alternative reduction method, $InCl_3/Ph_2SiHCl$ was examined to give complicated products.
6. Several reduction method such as hydrogenolysis with Pd/C and other silane-based reductions were examined to result in very low yields. Electron donating group such as MeO group on C is important to accelerate dehydroxylation process.
7. The intermediate reductive aldol product, β-hydroxylester, derived from **6** and **15** with $MePh_2SiH$ (entry 1, Table 1) could be isolated in 90% yield and showed 90:10 of *anti*/*syn* ratio and high enantioselectivity, 95% ee for *anti* and 81% ee for *syn*. On the basis of our previous findings,[3,4] *syn*-product was expected to have 2*R* absolute configuration as same as that for *anti*-product. Therefore, the mixture was subjected to the reduction step to form the corresponding dehydroxyl cinnamate without severe decrease of ee. In place of $MePh_2SiH$, $(EtO)_2MeSiH$ was employed to decrease the ee for the *syn*-product; *anti*/*syn*=85:15, 83% ee for *anti* and 39% for *syn*.
8. Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. *Chem.—Eur. J.* **2006**, *12*, 63.