Enantioselective Synthesis of the Key Intermediate of the Acyl-CoA: Cholesterol Acyltransferase (ACAT) Inhibitor (R-106578) Using 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)–Ru(OAc)$_2$ as a Catalyst

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Acidic segment of an acyl-CoA: cholesterol acyltransferase (ACAT) inhibitor, R-106578 was synthesized by enantioselective hydrogenation of the *Z*-olefine (9-(*Z*)) using (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)–Ru(OAc)$_2$ as a catalyst in methanol at 100 °C, 5 kgf/cm^2 of H$_2$ pressure. The requisite *Z*-olefine was prepared regioselectively *via* coumarin derivative (5).

Key words enantioselective hydrogenation; (*R*)-BINAP–Ru(OAc)$_2$; coumarin derivative; ACAT inhibitor

Targeting the inhibition of acyl-CoA: cholesterol acyltransferase (ACAT) in the absorption process of cholesterol in the small intestines is currently being undertaken widely all over the world in the research and development of new medicine with potential hypolipidemic and anti-atherosclerotic activities. Several compounds have been reported as promising ones such as CI-1011,[2] F-1394[3] or YM-750.[4] Along these lines we also devoted ourselves to discover our own compound, R-106578 (**1**).[5] Here, we would like to describe our synthesis of the key intermediate (**2**)[6] in the optically active form using a ruthenium(II) complex of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as a catalyst. At the starting point of this work the optical form of the acid intermediate (**2**) was prepared by chromatographic separation of the diastereomeric mixture of 3-[2-(2,4-dimethoxyphenyl)heptanoyl]-4(*S*)-benzyl-2-oxazolinone followed by lithium aluminum hydride (LAH) reduction, cyanation and then alkaline hydrolysis, or the optical resolution of the *dl* form of the acid (**2**) using (*S*)-(−)-α-methylbenzylamine as a chiral base.[5]

Therefore, the aim of the present work is to develop an efficient and practical method for the preparation of the desired chiral acid (**2**). The key features of our approach are the asymmetric hydrogenation with the BINAP–Ru(OAc)$_2$ catalyst and the regiospecific synthesis of *Z*-olefin (**4**) *via* coumarin analogue **5** (Charts 1, 2).

At first, we prepared α,β-unsaturated carboxylic acid derivatives (**8**-(*E*),-(*Z*), **9**-(*E*),-(*Z*)) to investigate the enantioselectivities of the hydrogenation of their olefinic bonds. Friedel–Crafts acylation[7] of 1,3-dimethoxybenzene (**6**) followed by Horner–Emmons olefination gave the α,β-unsaturated carboxylate (**8**). The (*E*)/(*Z*)-selectivity of this olefination was *ca.* 1/3, and each **8**-(*E*) and **8**-(*Z*) was separated by silica gel column chromatography. Alkaline hydrolysis of the isolated **8**-(*E*) and **8**-(*Z*) yielded the corresponding acids **9**-(*E*) and **9**-(*Z*) respectively.

With the requisite olefins (**8**-(*E*) and **8**-(*Z*), and **9**-(*E*) and **9**-(*Z*)) in hand we examined the asymmetric hydrogenation. Although varied conditions are generally applied in pilot plant scale synthesis, we performed the hydrogenation reaction under fixed conditions using (*S*)- or (*R*)-BINAP–Ru(OAc)$_2$ as a catalyst in methanol at 100 °C, 5 kgf/cm^2 of H$_2$ pressure.[8] The results are shown in Table 1, in which the asymmetric hydrogenation of **9**-(*Z*) is satisfactory (>97% ee), but the other three have poor selectivity (**9**-(*E*)) or poor reactivity (**8**-(*E*), **8**-(*Z*)). Furthermore, when this reaction was conducted in methanol, the methyl ester of **9**-(*Z*) was produced in a small quantity. To avoid this side reaction a mixed solvent of 2-propanol and water (9 : 1) was used expecting the steric effect to form fewer amount of the isopropyl ester. The ee of this reaction proved to be over 97%. When this reaction was performed in 2-propanol, the ee was *ca.* 96%. From these experiments, it became clear that the best result was obtainable from **9**-(*Z*) using (*R*)-BINAP–Ru(OAc)$_2$ as a

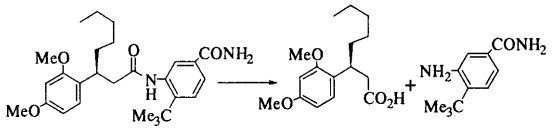

Chart 1

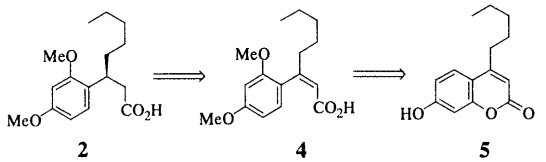

Chart 2

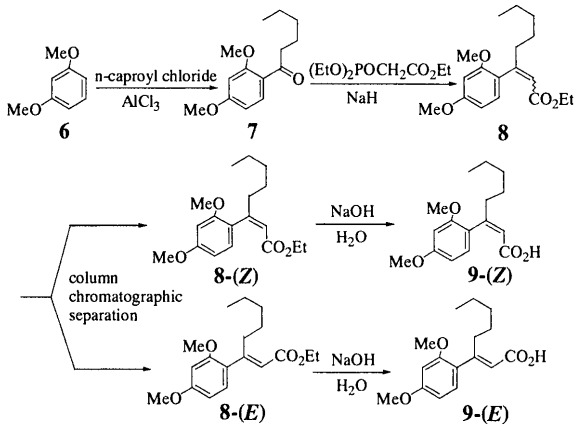

Chart 3

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Dedicated to the memory of Dr. Kyosuke Tsuda.

Table 1. Hydrogenation of the Olefinic Starting Materials

Starting Substrate	BINAP–$Ru(OAc)_2$	ee[a] (%)	Rxn time	Abs. config.[a]	Yield[b]
8-(*E*)	*S*	44.3	7 h	*S*	3%
8-(*Z*)	*S*	92.8	14 h	*R*	64%
9-(*E*)	*S*	3.7	2 h	*S*	Quant.
9-(*Z*)	*S*	97.0	2 h	*R*	Quant.
9-(*Z*)	*R*	97.0	1 h	*S*	Quant.

a) The absolute configuration and enantiomeric excesses (ee) were determined by HPLC analysis (CHIRALCEL OD by Daicel) after the optically active carboxylic acid was converted to the methyl ester by $TMSCHN_2$. Column, Daicel Chiralcel OD (ϕ4.6×250 mm); eluent, *n*-hexane/2-propanol (99 : 1); flow rate, 1.0 ml min^{-1}; oven, 25 °C; detect, UV (280 nm); t_R of (*R*)-methyl ester 8.5 min, t_R of (*S*)-methyl ester 17.1 min, t_R of (*R*)-ethyl ester 6.9 min, t_R of (*S*)-ethyl ester 10.7 min. *b*) Yields were determined by the above HPLC analysis.

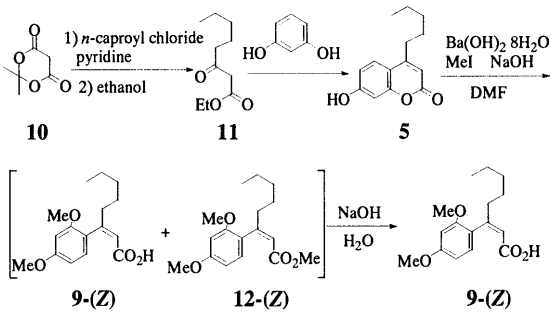

Chart 4

catalyst.

The above described route to the starting acid (**9**-(*Z*)) is multi-step using column chromatography for the separation of the isomers (**8**-(*E*)) and (**8**-(*Z*)), and consequently is unrealistic for large scale production of the desired acid (**2**). Therefore, we developed a new regiospecific synthetic method for the acid **9**-(*Z*) *via* the coumarin analogue (**5**).

According to the documented procedure[9] ethyl *n*-hexanoylacetate (**11**) was easily synthesized from Meldrum's acid (**10**) and *n*-caproyl chloride followed by refluxing in ethanol. Treatment of **11** and resorcinol in the presence of Amberlyst® 15[10] or *p*-toluenesulfonic acid afforded the coumarin derivative (**5**).[11] The lactone ring of this coumarin derivative (**5**) was cleaved with $Ba(OH)_2$ $8H_2O$, excess NaOH (flake) and excess methyl iodide in *N*,*N*-dimethylformamide (DMF)[12] to yield a mixture of the acid (**9**-(*Z*)) and methyl ester (**12**-(*Z*)). This mixture was further hydrolyzed under basic conditions to the desired (**9**-(*Z*)), mp 51—52 °C.

In conclusion, we succeeded in discovering a very efficient synthetic method for the optically active 3-(*S*)-(2,4-dimethoxyphenyl)octanoic acid by asymmetric hydrogenation (using (*R*)-BINAP–$Ru(OAc)_2$) of 3-(2,4-dimethoxyphenyl)-2-octenoic acid (**9**-(*Z*)), which was prepared regiospecifically *via* the coumarin derivative (**5**).

Experimental

Melting points were determined on a melting point instrument, FP62 (Mettler) and are uncorrected. Infrared (IR) spectra were recorded on an FT-IR spectrometer, Spectrum 2000 (Perkin Elmer). ^{1}H-NMR spectra were recorded on a FT-NMR system, JNM-LA400 (400 MHz) (JEOL). Coupling constants are reported in hertz (Hz) and chemical shift in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a JEOL JMS-BU20 or JMS-700 spectrometer. Optical rotations were measured with a high sensitive polarimeter, SEPA-3000 (Horiba). Column chromatography was performed on silica gel (Microbeads 4B, 100—200 mesh, Fuji silysia). All chemicals were obtained from commercial sources and were used without further purification.

1-(2,4-Dimethoxyphenyl)hexan-1-one (7) To a slurry of $AlCl_3$ (10.6 g) in CH_2Cl_2 (50 ml) were added 1,3-dimethoxybenzene (**6**, 10.4 ml) and then *n*-caproyl chloride (11.1 ml) while maintaining the reaction temperature at 0—10 °C. The whole mixture was stirred at 0—5 °C for an additional 2.5 h. Water (50 ml) was added to the reaction mixture and the product was separated. The organic layer was washed with saturated aq. $NaHCO_3$, 20% aq. NaCl, and then the solvent was removed *in vacuo*. *n*-Hexane (50 ml) was added to the residue, and then cooled to 0—5 °C for 0.5 h. The precipitate was filtered and dried *in vacuo* to afford 16.94 g of **7** (90%). mp 36.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=3.9 Hz), 1.20—1.40 (4H, m), 1.66 (2H, t, J=7.6 Hz), 2.92 (2H, t, J=7.3 Hz), 3.85 (3H, s), 3.87 (3H, s), 6.40—6.55 (2H, m), 7.78 (1H, d, J=8.5 Hz). IR (KBr) cm^{-1}: 2938, 1662, 1597. Electron ionization (EI)-MS *m/z*: 236 (M^+). *Anal.* Calcd for $C_{14}H_{20}O_3$; C, 71.16; H, 8.53; O, 20.31. Found: C, 71.22; H, 8.30; O, 20.36.

Ethyl (*E*)- and (*Z*)-3-(2,4-Dimethoxyphenyl)-2-octenate (8) In a 500 ml four-necked flask, 60% oil dispersion of NaH (10.2 g) was washed with *n*-hexane (20 ml) and then tetrahydrofuran (THF, 240 ml) was added. Triethyl phosphonoacetate (62.9 g) was added dropwise to the slurry solution at −10 °C and then a solution of ketone (**7**) (30.0 g) in THF (60 ml) was added successively. The whole mixture was refluxed for 7 h. After cooling, saturated aq. NH_4Cl (120 ml), water (50 ml) and diethyl ether (150 ml) were added with careful stirring. The organic layer was separated and washed with 20% aq. NaCl three times, dried over anhydrous Na_2SO_4, and then the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (2 l). Elution with *n*-hexane/ethyl acetate (10/1—8/2) gave the less polar **8**-(*E*) (9.30 g, 24%) as oil and the more polar **8**-(*Z*) (27.82 g, 72%) as oil. **8**-(*E*): ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7.1 Hz), 1.13—1.45 (9H, m), 3.02 (2H, t, J=8.0 Hz), 3.78 (3H, s), 3.82 (3H, s), 4.20 (2H, q, J=7.8 Hz), 5.79 (1H, s), 6.46 (2H, m), 7.03 (1H, m). **8**-(*Z*): ^{1}H-NMR ($CDCl_3$, 400 MHz, ppm) δ: 0.86 (3H, t, J=7.1 Hz), 1.09 (3H, t, J=7.1 Hz), 1.25—1.40 (6H, m), 2.40 (2H, t, J=7.6 Hz), 3.74 (3H, s), 3.79 (3H, s), 4.00 (2H, q, J=7.1 Hz), 5.90 (1H, s), 6.47 (2H, m), 6.90 (1H, m).

(*E*)-3-(2,4-Dimethoxyphenyl)oct-2-enoic Acid (9-(*E*)) To a solution of **8**-(*E*) (1.0 g) in ethanol (3 ml) was added 5 M aq. NaOH (0.78 ml) and the whole solution was heated at 60 °C for 5 h. After evaporation of the solvent *in vacuo*, 1 M aq. HCl (5 ml) was added to the residue and **9**-(*E*) was extracted with toluene (10 ml). Another toluene (10 ml) was added to the water layer and extracted again. The combined organic layer was washed with water (10 ml), and evaporated. *n*-Hexane (10 ml) was added to the residue, and cooled at 0—5 °C for 0.5 h. The resulting precipitate was filtered and dried *in vacuo* to afford the acid **9**-(*E*) (0.75 g, 82%). mp 95.8 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7.3 Hz), 1.20—1.40 (6H, m), 3.05 (2H, t, J=7.8 Hz), 3.80 (3H, s), 3.83 (3H, s), 5.85 (1H, s), 6.46 (2H, m), 7.06 (1H, m). IR (KBr) cm^{-1}: 2935, 1682, 1611, 1500. EI-MS *m/z*: 278 (M^+). *Anal.* Calcd for $C_{16}H_{22}O_4$; C, 69.04; H, 7.97; O, 22.99. Found: C, 68.79; H, 7.75; O; 23.01.

(*Z*)-3-(2,4-Dimethoxyphenyl)oct-2-enoic Acid (9-(*Z*)) from 8-(*Z*) To a solution of **8**-(*Z*) (1.0 g) in ethanol (3 ml) was added 5 M aq. NaOH (0.78 ml) and the whole was heated at 60 °C for 6 h. After evaporation the desired compound was isolated by the same procedure as in the case of the isomer (**9**-(*E*)) to give the desired **9**-(*Z*) (0.86 g, 95%). mp 84.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J=6.8 Hz), 1.20—1.40 (6H, m), 2.41 (2H, t, J=6.8 Hz), 3.71 (3H, s), 3.81 (3H, s), 5.88 (1H, s), 6.46 (2H, m), 6.90 (1H, m). IR (KBr) cm^{-1}: 2930, 1691, 1626, 1508. EI-MS *m/z*: 278 (M^+). *Anal.* Calcd for $C_{16}H_{22}O_4$; C, 69.04; H, 7.97; O, 22.99. Found: C, 68.93; H, 7.88; O; 23.09.

Ethyl 3-Oxooctanoate (11) According to the literature[7] a solution of *n*-caproyl chloride (40.0 g) in CH_2Cl_2 (100 ml) was added dropwise to a solution of Meldrum's acid (**10**) (39.7 g) in pyridine (50 ml) at 10 °C. The red solution was stirred for 4.5 h at room temperature and then 2 M aq. HCl (300 ml) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 ml). The combined organic layer was washed with water (100 ml), dried (Na_2SO_4), and evaporated to yield a red oil (67.63 g). A solution of the oil in ethanol (200 ml) was refluxed for 7 h and evaporated. The residue was distilled to give the title compound (**11**) (48.04 g, 94%), bp 84—86 °C (2 mmHg).

4-*n*-Pentyl-7-hydroxycoumarin (5) (Using Amberlyst® 15) To a solution of **11** (15.0 g) in toluene (150 ml) were added resorcinol (17.74 g) and Amberlyst® 15 (7.5 g), and the mixture was refluxed for 5.5 h with azeotropic removal of water and ethanol using Dean–Stark equipment. After filtration in the hot state, water (50 ml) was added carefully to the filtrate. The slurry formed was stirred for 0.5 h at 0—5 °C. The appeared precipitate was filtered, dried *in vacuo* to afford the coumarin derivative (**5**) (14.41 g, 81%). ^{1}H-NMR (CD_3OD) δ: 0.91 (3H, t, J=6.6 Hz), 1.30—1.50 (4H, m),

1.60—1.75 (2H, m), 2.76 (2H, t, J=7.8 Hz), 3.30 (3H, s), 6.06 (1H, s), 6.65—6.85 (2H, m), 7.61 (1H, m).

5 (Using *p*-Toluenesulfonic Acid) To a solution of **11** (100 g) in toluene (1 l) were added resorcinol (118.24 g) and *p*-toluenesulfonic acid (10.21 g), and the mixture was refluxed for 1.5 h with azeotropic removal of water and ethanol with Dean–Stark equipment. Water (1 l) was added to the reaction mixture in hot state and cooled to 20 °C during 1 h. The slurry was stirred for 0.5 h at 0—5 °C. The appeared precipitates were filtered, dried *in vacuo* to afford the coumarin derivative **5** (105.91 g, 85%).

9-(*Z*) from 5 To a slurry of NaOH (flake, 86.1 g) and coumarin derivative (**5**) (100 g) in DMF (500 ml) was added $Ba(OH)_2$ $8H_2O$ (67.91 g) and MeI (221.5 ml) successively at 25—30 °C. The whole mixture was stirred at 30—33 °C for 2 h. Then toluene (1 l), water (1.5 l) and 36% aq. HCl (80 ml) were added successively. The organic layer was washed with water (1 l) twice, and evaporated to yield the mixture of **9**-(*Z*) and **12**-(*Z*) as orange-colored oil. Methyl ester (**12**-(*Z*)), ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.2 Hz), 1.20—1.50 (6H, m), 2.41 (2H, t, J=8.0 Hz), 3.54 (3H, s), 3.75 (3H, s), 3.83 (3H, s), 5.91 (1H, s), 6.47 (2H, m), 6.91 (1H, m). IR (KBr) cm^{-1}: 2930, 1691, 1626, 1508. To this mixture of **9**-(*Z*) and **12**-(*Z*) in toluene (200 ml), methanol (300 ml) and water (50 ml) was added NaOH (34.5 g), and the whole was refluxed for 2 h. Toluene (300 ml), water (300 ml) and 36% aq. HCl (80 ml) were added successively and the organic layer was washed with water (500 ml) and evaporated. The residue was dissolved in ethylcyclohexane at 70 °C, then cooled to 0—5 °C and the slurry was stirred for 0.5 h. The formed precipitate was filtered and dried *in vacuo* to give the desired (*Z*)-olefine (**9**-(*Z*)) (107.12 g, 89% from **5**).

(*S*)-3-(2,4-Dimethoxy)phenyloctanoic Acid (2) The (*Z*)-olefine (**9**-(*Z*)) (106.0 g), (*R*)-BINAP–$Ru(OAc)_2$ (53 mg), 2-propanol (85 ml) and water (21.3 ml) were bubbled with nitrogen for 2 h and then the whole was poured in the autoclave. After replacing the atmosphere with nitrogen and adjusting the pressure gauge with hydrogen at 5 kgf/cm^2, the yellowish solution was heated at 100 °C for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in methanol (318 ml). Water (114 ml) was added to this and the whole was cooled to 0—5 °C for 1 h. The resulting precipitates were filtered and dried *in vacuo* to yield the desired title (*S*)-acid (**2**) (103.63 g, 97%, content: 97.6%, 97.7% ee) which is identical with the reported data.[5] mp 52.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=6.8 Hz), 1.10—1.30 (6H, m), 1.50—1.70 (2H, m), 2.62 (2H, m), 3.39 (1H, quintet, J=7.5 Hz), 3.77 (3H, d, J=3.4 Hz), 3.79 (3H, d, J=3.4 Hz), 4.40—6.50 (2H, m), 7.01 (1H, dd, J=3.4, 9.0 Hz). IR (KBr) cm^{-1}: 2925, 1697, 1611, 1505, 1209, 1155, 830. EI-MS m/z: 280 (M^+). $[\alpha]_D^{27}$+6.1 (c=1.07, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{24}O_4$; C, 68.54; H, 8.63; O, 22.83. Found: C, 68.83; H, 8.41; O; 23.05.

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