Stereoselective Reduction of β,δ-Diketo Esters. A Novel Strategy for the Synthesis of Artificial HMG-CoA Reductase Inhibitors

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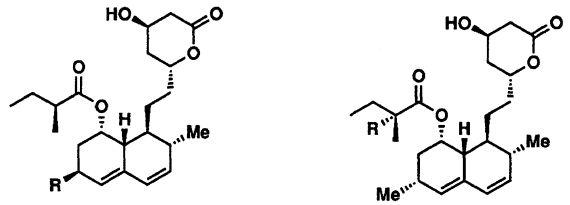
Condensation of *N*-methoxy-*N*-methyl amides with the dianions of acetoacetates gives in good yields β,δ-diketo esters, which are reduced with Et_2BOMe–$NaBH_4$ in tetrahydrofuran–methanol highly selectively to give *syn*-β,δ-dihydroxy esters in one step. Similarly, the β,δ-diketo esters of the Taber's chiral alcohol or its enantiomer respectively are reduced to give *syn*-β,δ-dihydroxy esters of moderate enantiomeric excess. Higher diastereo- and enantioselectivity were achieved by reduction of the β,δ-diketo esters of the Taber's chiral alcohol or its enantiomer successively with diisobutylalane and with Et_2BOMe–$NaBH_4$. The resulting *syn*-diol esters were hydrolyzed and lactonized to give various types of β-hydroxy-δ-lactones commonly found in artificial HMG-CoA reductase inhibitors.

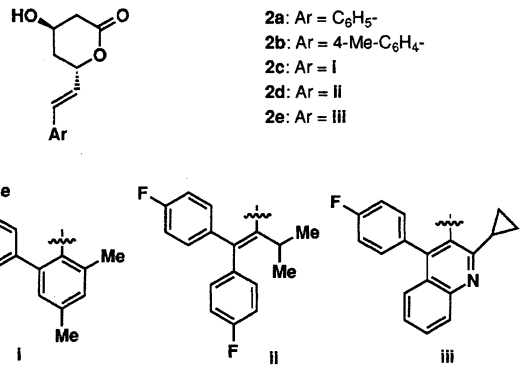
Hyperlipidemia and hypercholesterolemia are diseases that are very common in developed countries.[1] For clinical treatment of these diseases, natural products have been extensively screened, and compactin (**1a**) and lovastatin (**1b**) were discovered independently by the research groups of Sankyo and Merck to be highly potent inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase, a key enzyme of cholesterol biosynthesis.[2] These findings stimulated synthetic and biological studies, and various types of structural analogs have since been designed, synthesized, and tested.[3] Among them, pravastatin (**1c**) and simvastatin (**1d**) are on the market at present for medicinal use (Chart 1).[4] Further worldwide studies have been done to find agents showing comparable or higher activity and have yielded a series of compounds of type **2** having a *trans*-β-hydroxy-δ-lactone moiety in common (Chart 2).[3] We here report a novel method for the synthesis of *trans*-β-hydroxy-δ-lactones based on stereoselective reduction of β,δ-diketo esters.[5] Applications of the new method to several target molecules will be discussed also.



1a: R = H, compactin
1c: R = OH, pravastatin
(Na salt of the seco acid)

1b: R = H, lovastatin
1d: R = Me, simvastatin

Chart 1.



2a: Ar = C_6H_5-
2b: Ar = 4-Me-C_6H_4-
2c: Ar = i
2d: Ar = ii
2e: Ar = iii

Chart 2.

Retrosynthesis

Retrosynthetic analysis of **2** led us readily to its seco acid derivative **3**, which would be derived directly from

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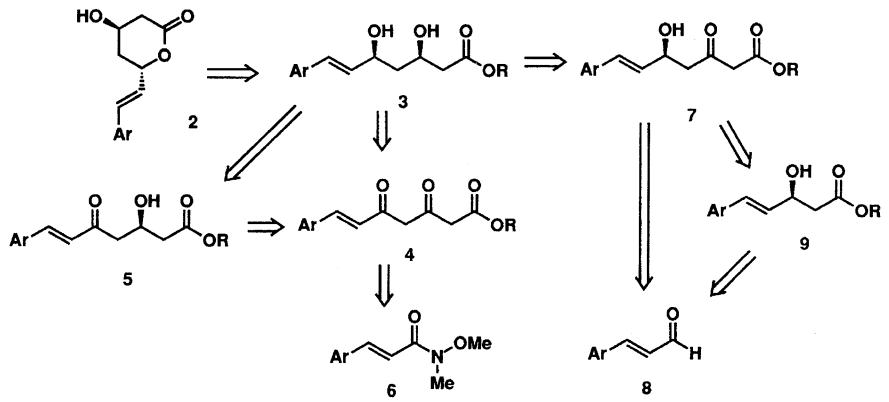


Scheme 1. Retrosynthetic analysis.

the β,δ-diketo ester **4** or alternatively from β-hydroxy-δ-keto ester **5**. The diketo ester **4** was considered to be derived from a β-aryl-substituted acrylic acid derivative (e.g. **6**) by the reaction with the dianion of acetoacetate or its synthetic equivalent. The hydroxy keto ester **5** would be prepared by selective mono-reduction of **4**. Another precursor of **3** should be δ-hydroxy-β-keto ester **7**, which might be prepared by the condensation of β-hydroxy ester **9** with the enolate of an acetic acid derivative. The intermediate **9**, in turn, should be prepared from cinnamaldehyde analog **8** by condensation with the enolate of an acetic acid derivative. The δ-hydroxy-β-keto ester **7** might be prepared by the aldol addition of **8** with an acetoacetate derivative.

Of course, synthesis involving the Wittig-type olefination also is possible. This process will be discussed in the following paper.[6]

At the time we started our study, the synthetic routes had been mainly concerned with the asymmetric aldol route **8**→**9** using an enolate of an acetate of a chiral alcohol.[7] The stepwise aldol route appeared to be tedious to us, because the carbon–carbon bond forming reactions should be repeated under strict control of stereo- and chemoselectivity. The other approach known at the outset of our study involved a strategy based on the synthesis of 1,3-*syn*-diol derivatives followed by the Wittig-type olefination.[6] The chiral *syn*-1,3-diol derivatives are often derived from natural products such as sugars, glutamic acid, or ascorbic acid.[8,9] As the transformation from these natural sources requires in general multi-step synthesis, we considered this approach was not practical. Accordingly, the retrosynthetic analysis, particularly **3**⇒**4** discussed in Scheme 1, was considered to be straightforward.

Synthesis of β,δ-Diketo Esters. Since β,δ-diketo esters are versatile synthetic intermediates of polyketide synthesis, we first used the well-studied procedure, namely, the reaction of the dianion of acetoacetate esters with *N*,*N*-dimethylcinnamamide.[10] Contrary to our expectation, only 1 : 2 reaction products were isolated. Possibly, conjugate addition of the dianion first took place before the desired condensation. To enhance the reactivity, we modified the amide functionality to ester, acid chloride, or acylimidazole but with totally unsuccessful results. Finally we found that *N*-methoxy-*N*-methyl amides **6** of cinnamic acid gave the desired 1 : 1 products.[5a] Results summarized in Table 1 clearly show that this method is applicable to a wide variety of α,β-unsaturated amides. In addition to the compounds listed in Table 1, **4h** and **4i** were also obtained in high yields (Chart 3). Thus, it is obvious that the condensation reaction using *N*-methoxy-*N*-methyl amide is highly effective for the synthesis of (poly)ene diketo esters. Conjugated addition products were not detected at all.

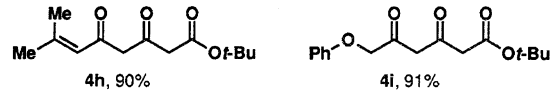
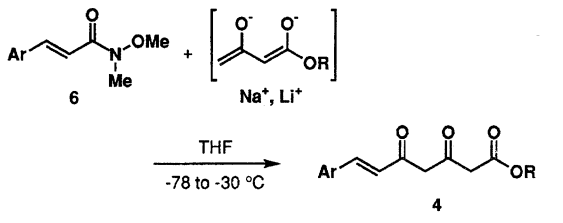


Chart 3.

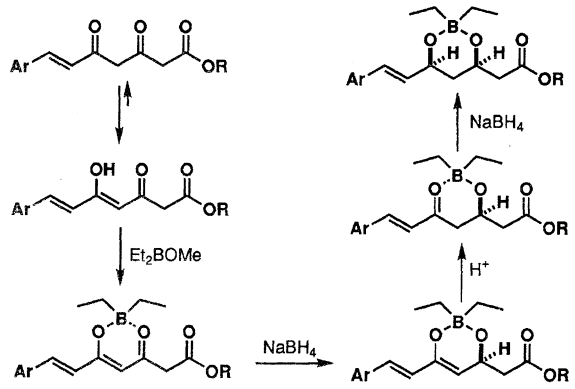


(1)

The structure of **4** is worth noting. The δ-keto group was found to be enolized as evidenced by ^{1}H NMR (see Scheme 2 and Experimental). Thus, conjugation of the adjacent C=C and C=O bonds through the enol moiety appears to stabilize the diketo ester structure.

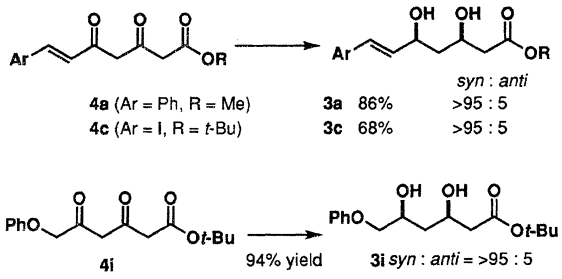
Table 1. Condensation of **6** with the Dianion of Acetoacetate

Ar	R		Yield/% of **4**	
C_6H_5	Me	**6a**	**4a**	57
C_6H_5	Et	**6a′**	**4a′**	49
C_6H_5	*t*-Bu	**6a″**	**4a″**	49
i	*t*-Bu	**6c**	**4c**	75
Me	*t*-Bu	**6f**	**4f**	42
(*E*)-MeCH=CH	*t*-Bu	**6g**	**4g**	79



Scheme 2. One-pot *syn*-reduction of *β*,*δ*-diketo esters.

***Syn*-Reduction of *β*,*δ*-Diketo Esters.** The next synthetic problem is a stereoselective one-step reduction of **4** to the *syn*-diols **3**.[11] Since the *δ*-carbonyl group is enolized, we considered that, to achieve the reduction in one step, a proton source should be required. Thus, sodium borohydride reduction in alcoholic media appeared promising, and, after several experiments, Prasad's procedure[11a,11b] met our criteria. Thus, the diketo esters were reduced with sodium borohydride in combination with diethyl(methoxy)borane in a mixed solvent system of THF–methanol (4 : 1) at −78 °C to give *syn*-*β*,*δ*-dihydroxy esters **3** with high diastereoselectivities (usually >95 : 5) and in good yields.[12] Stereochemical assignment is based on ^{1}H NMR of the acetonides derived from the diols **3a** and **3i**. Results using **4a**, **4c** and **4i** are shown below in the equation.



(2)

conditions: $NaBH_4$-Et_2BOMe, THF-MeOH (4 : 1), -78 °C to r.t.

(3)

Since the enolized *δ*-keto group resists the reduction, the *β*-keto group should be reduced first. Protonation followed by tautomerization gives a boron chelate of **5**. Further reduction finally gives rise to a boron chelate of **3**.

Attempted Asymmetric Reduction Using Chiral Borane Reagent. As the *syn*-reduction is based on the boron chelate involving the two ketone carbonyls (Scheme 2), we then studied asymmetric reduction of **4a** using chiral borane reagents **10a**—**10d** in place of Et_2BOMe. We prepared these reagents as described in the literature[13—16] and used without further purification. Using **10a**—**10c**, the reduction of **4a** took place without any selectivity: chemical yield and *syn*: *anti* ratio of the product **3a** were 67%, 1 : 1; 90%, 1 : 1.2; 34%, 2 : 1 respectively. In case of **10d** only, the chemical yield and the selectivity were satisfactory (70%, >95 : 5), but $[\alpha]_D$ of **3a** was nearly zero (Chart 4). In any event, reduction with **10d** was applied to **4c** and after the same sequence of transformations, we obtained **2c**[13] which exhibited $[\alpha]_D^{20}$ −3.09° [lit,[17] +39° (*c* 1, $CHCl_3$)]. Thus, ee appeared to be at best 8% with the wrong absolute configuration. Accordingly, we stopped studying this further. However, recently this kind of asymmetric reduction using a chiral amino alcohol as a ligand is reported to give *syn*-diols of high ee's.[18]

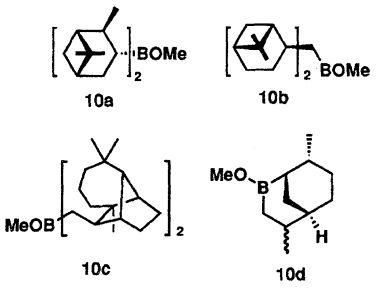


Chart 4.

One-Pot Reduction of *β*,*δ*-Diketo Esters of the Taber's Chiral Alcohol. The failure of asymmetric reduction using a chiral borane chelating agent may be attributed to the symmetric structural feature of the substrate **4a**. The boron diketonate chelate (Scheme 2) looks almost planar with a sterically similar substituent on each carbonyl, namely, CH_2COOR and CH=CHAr respectively. Thus, discrimination of the *re* or *si* face of the *β*-carbonyl by the chiral borane reagents **10a**—**10d** turned out to be very difficult. Accordingly, we concluded it would be essential to create a dissymmetric environment around the diketo ester moiety by reducing the conformational freedom of the molecule **4**. To fulfil these criteria, we have chosen *β*,*δ*-diketo esters derived from the Taber's chiral alcohol **11***[19] or its enantiomer **11**. The naphthalene ring acts as a steric shield of one face of carbonyls and the *gem*-dimethyl group behaves as a conformational anchor.[5b]

As described in the literature,[19b] we prepared the Taber's chiral alcohol **11*** and its enantiomer **11** from D-(+)-camphor and L-(−)-camphor, respectively (Charts 5 and 6). Both **11*** and **11** were converted into the corresponding acetoacetates **12*** and **12**, respectively, by transesterification with methyl acetoacetate. The acetoacetates **12*** and **12** were converted as before into the corresponding *β*,*δ*-diketo esters **13*** and **13** respectively by the condensation with an *N*-methoxy-*N*-methyl cinnamamide derivative. Although the chemical yields were not high, those based on the consumed acetoacetate were acceptable.

The diketo ester **13a*** was first reduced under the conditions discussed above to give *β*,*δ*-dihydroxy ester **14a*** in 85% yield (Table 2, Entry 1). Since the stereochemical assignment was hard at this stage, the diol ester **14a*** was hydrolyzed with dil NaOH aq so-

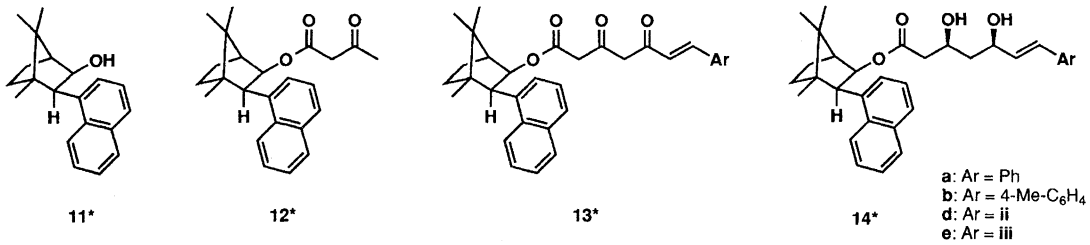


Chart 5.

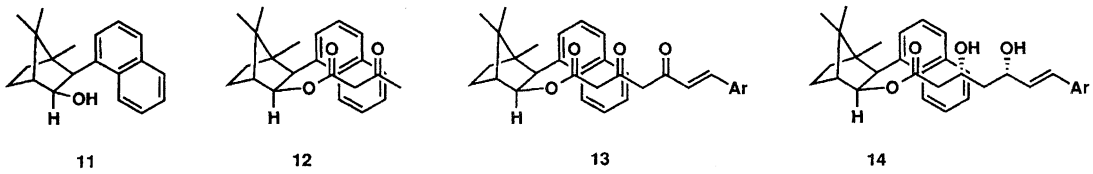
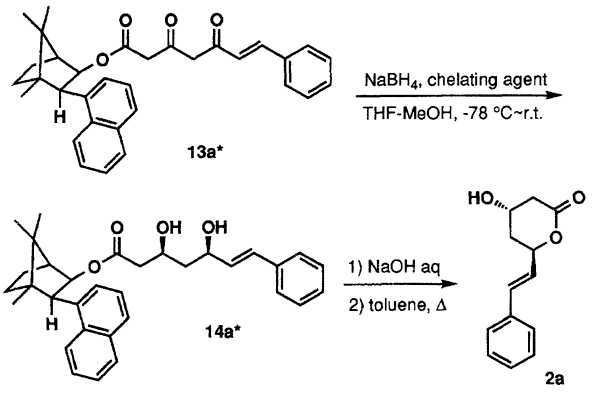


Chart 6.

Table 2. Asymmetric Reduction of β,δ-Diketo Ester **13a***

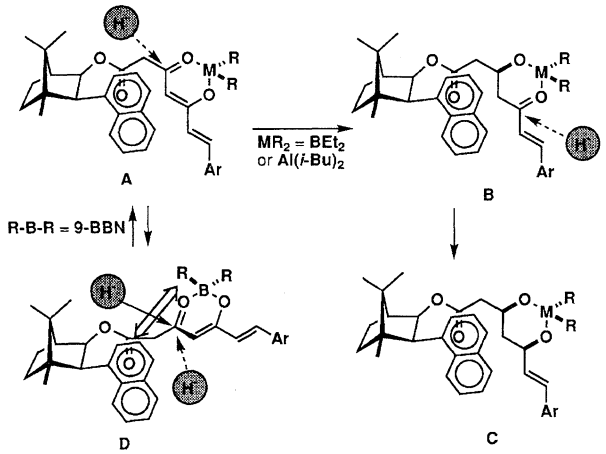
Entry	Chelating agent	**14a***	**2a**			
		Yield/%	Yield/%	*trans* : *cis*	Config.	% ee
1	Et_2BOMe	85	76	95 : <5	3*S*, 5*R*	49
2	Et_2BOMe (2 equiv)	78	50	95 : 5	3*S*, 5*R*	37
3	9-MeO-9-BBN	31	66	97 : 3	—	0
4	Me_2BOEt	90	61	76 : 24	3*R*, 5*S*	42
5	Me_2BBr	35	61	70 : 30	3*R*, 5*S*	58

lution and lactonized by heating in toluene to give β-hydroxy-δ-lactone **2a**. ^{1}H NMR assay showed the diastereomeric ratio was over 95 : 5. HPLC analysis, however, disclosed the enantiomeric excess (ee) was 49%. The absolute configuration was proved to be (3*S*, 5*R*) by comparing $[\alpha]_D$ with that of an authentic compound of known configuration.[20] Use of 2 equivalents of Et_2BOMe (Entry 2) did not change the selectivity. A bulkier borane chelating agent, 9-MeO-9-BBN, was proved to be more diastereoselective but enantiomerically nonselective (Entry 3). To our surprise, asymmetric induction with Me_2BOEt or Me_2BBr gave the opposite enantioselectivity (Entries 4 and 5).



(4)

Reagent systems like $NaBH_4$–$AlCl_3$ or $Zn(BH_4)_2$–$ZnCl_2$ were less selective diastereomerically or enantiomerically.



Scheme 3. Stereochemical course of hydride reduction of **13***.

The stereochemical outcome may be understood in terms of a chelate shown in Scheme 3. The boron chelating agent interacts with the β,δ-diketo moiety, thereby leaving the ester carbonyl free (**A**) and allowing the hydride to attack the β-carbonyl from the face opposite to the naphthyl ring (**B** and **C**). This corresponds to the enantioselectivity observed in Taber's β-keto ester reductions, which were assumed to proceed through an *anti* conformation. The absence of asymmetric induc-

Table 3. Two-Step Reduction of **13*** or **13** and Synthesis of Lactone **2*** or **2**

Entry	Diketo ester	Hydroxy keto ester (yield/%)		Isomer ratio	Dihydroxy ester (yield/%)		Lactone yield/%		*trans* : *cis*	config	% ee
1	**13a***	**16a***	(85)	>95 : 5	**14a***	(80)	**2a***	(53)	100 : 0	3*S*, 5*R*	>95
2	**13a**	**16a**	(70)	>95 : 5	**14a**	(78)	**2a**	(56)	99 : 1	3*R*, 5*S*	>97
3	**13b***	**16b***	(78)	>95 : 5	**14b***	(81)	**2b***	(60)	100 : 0	3*S*, 5*R*	>92
4	**13e***	**16e***	(56)	>95 : 5	**14e***	(85)	**2e***	(45)	96 : 4	3*S*, 5*R*	>93

tion using 9-MeO-9-BBN (Entry 3) may be attributed to steric repulsion between 9-BBN and the naphthalene ring and/or *gem*-dimethyls of the chiral alcohol, thus forcing the β,δ-diketo ester away from the face-blocking naphthalene ring and thereby giving equal opportunity for the hydride attack from both sides of the β-carbonyl group (**D**). Accordingly, the reduction, though diastereoselective, was not enantioselective. The inverse asymmetric induction with Me_2BOEt or Me_2BBr may be ascribed to the less bulkier Me_2B group, which may allow additional interaction with the ester carbonyl to induce a *sny* conformation responsible for the 3*R* configuration of **14a***.

The asymmetric reduction was applied to the synthesis of the diene lactone **2d**.[21] Starting with **11***, we prepared **13d***, which upon reduction with $NaBH_4$–Et_2BOMe gave the *syn*-dihydroxy ester **14d***. Hydrolysis followed by lactonization gave **2d*** with (3*S*, 5*R*) configuration, *trans*: *cis*=82 : 18, 66% ee. Since **2d*** is an enantiomer of **2d**, we prepared **13d** from **12** and **6d**. After the same sequence of reactions, we obtained (3*R*, 5*S*)-**2d** (*trans*: *cis*=79 : 21, 64% ee).

In a similar manner, the sequence of transformations was applied to the synthesis of **2e*** and **2e**.[22] The reaction of **12*** with **6e** gave **13e***, which was reduced to the *syn*-dihydroxy ester **14e***. Hydrolysis followed by lactonization gave **2e*** (*trans*: *cis*=77 : 23, 58% ee). Reduction of **13e*** with $NaBH_4$–Me_2BOEt resulted again in the inverse of asymmetric induction to give **15e**, which was transformed to **2e** (*trans*: *cis*=64 : 36, 37% ee) by hydrolysis and lactonization (Chart 7).

Two-Step Reduction of β,δ-Diketo Esters of the Taber's Chiral Alcohol. Although we have established a one-pot procedure for 1,3-stereoselective reduction of the diketo esters **13** or **13***, there is still room for improving the stereoselectivity. Thus we further studied stepwise reduction and found diisobutylalane (DIBAL) reduction gives **16*** or **16** with high selectivity (Chart 8). Subsequent *syn*-reduction with $NaBH_4$–Et_2BOMe was highly stereoselective, thus net transformation to **2*** being over 92% ee. The results are summarized in Table 3. As readily seen, the two-step procedure is extremely powerful and effective for the synthesis of **2** of high % ee. The stereochemical outcome can be understood again by the model shown in Scheme 3. To obtain the correct enantiomer of **2**, we have only to start with **11**.

Attempted Aldol Route. The dianion of **12*** was allowed to react with cinnamaldehyde under various conditions in the presence or absence of metal salt like $ZnCl_2$. The aldol product **17a*** was found to be a ca. 1 : 1 diastereomeric mixture in any case. Thus, the aldol reaction using **12*** appears to be totally nonselective. Probably, the nucleophilic γ-carbon is so far away from the control elements (*gem*-dimethyls and naphthalene ring) that it allows the γ-carbon to attack the aldehyde carbonyl in a non-selective manner.

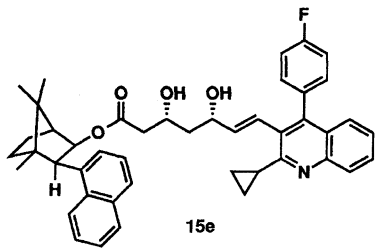


Chart 7.

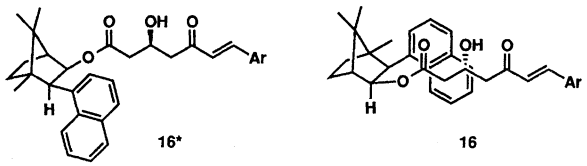
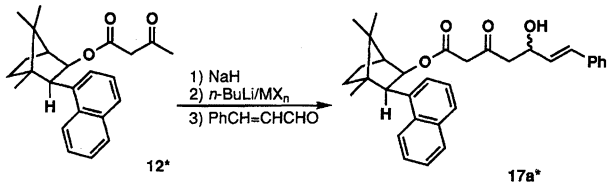


Chart 8.



(5)

Conclusion. We have demonstrated that stereoselective reduction of β,δ-diketo esters is a straightforward process for the synthesis of *syn*-β,δ-dihydroxy esters. Application of this method to the β,δ-diketo esters of chiral alchol **11*** or **11** was shown to be useful for the synthesis of a variety of optically active artificial HMG-CoA reductase inhibitors.

Experimental

Melting points and boiling points are uncorrected. ^1H NMR spectra (Me_4Si as an internal standard) were obtained with a Bruker AM-400 spectrometer, chemical shifts being given in ppm units. IR were recorded with a JASCO A-202 instrument. Specific rotations were measured with a Horiba SEPA-200. MS were recorded with an RMU-6MG

instrument and HRMS with a Hitachi M-80A spectrometer. HPLC analyses were done with a Tosoh CCPM using a UV detector. Recycling preparative HPLC was done using a Japan Analytical Industry LC-908. TLC analyses were done on commercial plates bearing a 0.25-mm layer of Merck silica gel 60 F_{254}. Preparative TLC plates were prepared with Merck Kiesel-gel PF_{254}. Column chromatography was done with silica gel (Wacogel C-200 or Merck Si 60) at atmospheric pressure. Tetrahydrofuran (THF) was distilled right before use from benzophenone ketyl under an argon atmosphere. Dichloromethane was distilled from calcium hydride before use. All the reactions were done under an argon atmosphere.

***N*-Methoxy-*N*-methylcinnamamide (6a).** Pyridine (10.5 ml, 0.13 mol) was added to a chloroform (400 ml) solution of cinnamoyl chloride (9.35 g, 56 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (5.76 g, 59 mmol) at 0 °C under an argon atmosphere. The resulting mixture was stirred at room temperature for 2 h and quenched by addition of sat NaCl aq solution. The organic layer was separated, and the aq layer was extracted with dichloromethane. The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane–ethyl acetate 2:1) to give **6a** (8.12 g, 76% yield). Mp 37—38 °C. IR (KBr) 1650, 1610, 1380, 1000, 990, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.30 (s, 3 H), 3.76 (s, 3 H), 7.02 (d, J=15.8 Hz, 1 H), 7.30—7.70 (m, 5 H), 7.74 (d, J=15.8 Hz, 1 H). Found: C, 68.89; H, 6.86; N, 7.25%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%.

***N*-Methoxy-*N*-methyl(phenoxy)acetamide (6i).** Pyridine (2.0 ml, 25 mmol) was added to a chloroform (40 ml) solution of MeN(OMe)H·HCl (0.90 g, 9.2 mmol) and phenyoxylacetyl chloride (1.27 ml, 9.2 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. Workup followed by silica gel column chromatography gave the desired amide (1.42 g, 79% yield) as a viscous oil. IR (neat) 2950, 1690, 1600, 1500, 1220, 980, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.23 (s, 3 H), 3.75 (s, 3 H), 4.80 (s, 2 H), 6.8—7.5 (m, 5 H). MS m/z (rel intensity) 195 (46, M^+), 107 (56), 79 (25), 77 (90), 74 (100), 51 (24), 42 (19). Found: m/z 195.0866. Calcd for $C_{10}H_{13}NO_3$: M, 195.0893.

(*E*)-*N*-Methoxy-*N*-methyl-3-(4′-fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)propenamide (6c). Oxalyl chloride (0.091 ml, 1.1 mmol) was added to a dry benzene (5 ml) solution of (*E*)-3-(4′-fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)propenoic acid (0.158 g, 0.55 mmol), and the mixture was heated at 70 °C for 1 h. All the volatile material was evaporated in vacuo, and the residue was dissolved in dry chloroform (10 ml). To this solution were added MeN(OMe)H·HCl (0.100 g) and then pyridine (0.14 ml) at 0 °C. The mixture was gradually warmed to room temperature and stirred for 12 h before quenching with sat. NaCl aq solution. Workup followed by preparative TLC (silica gel, hexane–ethyl acetate 2:1) gave **6c** (0.144 g, 80% yield). Mp 78—80 °C. IR (KBr) 2950, 1650, 1620, 1500, 1420, 1380, 1240, 1180, 990, 860, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.26 (d, J=1.75 Hz, 3 H), 2.32 (s, 3 H), 2.41 (s, 3 H), 3.17 (s, 3 H), 3.39 (s, 3 H), 6.21 (d, J=16 Hz, 1 H), 6.9—7.3 (m, 5 H), 7.74 (d, J=16 Hz, 1 H); MS m/z (rel intensity) 328 (M^++1, 21), 327 (M^+, 100), 239 (9), 226 (12), 225 (68), 224 (21), 209 (12). Found: C, 73.30; H, 6.78; N, 4.25%. Calcd for $C_{20}H_{22}FNO_2$: C, 73.37; H, 6.77; N, 4.28%.

Following amides were prepared by the similar procedure.

(*E*)-*N*-Methoxy-*N*-methyl-2-butenamide (6f). IR (neat): 2980, 2950, 1675, 1640, 1460, 1390, 1190, 1010, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.92 (dd, J=1.5, 6.6 Hz, 3 H), 3.23 (s, 3 H), 3.70 (s, 3 H), 6.42 (dq, J=15.4, 1.5 Hz, 1 H), 7.03 (dq, J=15.4, 6.6 Hz, 1 H); MS m/z (rel intensity) 129 (M^+, 5), 69 (100), 41 (57), 39 (22), 28 (11). Found: m/z 129.0783. Calcd for $C_6H_{11}NO_2$: M, 129.0788.

(*E,E*)-*N*-Methoxy-*N*-methyl-2,4-hexadienamide (6g). IR (neat) 2975, 2950, 1660, 1630, 1610, 1410, 1380, 1180, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.84 (d, J=5.5 Hz, 3 H), 3.24 (s, 3 H), 3.70 (s, 3 H), 6.1—6.5 (m, 3 H), 7.1—7.5 (m, 1 H); MS m/z (rel intensity) 155 (M^+, 7), 95 (100), 67 (59), 41 (33), 39 (18). Found: m/z 155.0939. Calcd for $C_8H_{13}O_2N$: M, 155.0944.

***N*-Methoxy-*N*,3-dimethyl-2-butenamide (6h).** IR (neat) 2975, 2950, 1660, 1440, 1370, 1000, 840, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.90 (d, J=1.1 Hz, 3 H), 2.13 (d, J=0.9 Hz, 3 H), 3.20 (s, 3 H), 3.67 (s, 3 H), 6.12 (br s, 1 H); MS m/z (rel intensity) 143 (M^+, 3), 83 (100), 55 (57), 39 (14), 29 (20), 27 (11). Found: m/z 143.0929. Calcd for $C_7H_{13}NO_2$: M, 143.0945.

***N*-Methoxy-*N*-methyl-(*E*)-3-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]propenamide (6e). One-Step Procedure.** Butyllithium (1.64 M hexane solution (1 M=1 mol dm^{-3}), 11.5 ml, 18.8 mmol) was added to *N*-methoxy-*N*-methyl(diethylphosphono)acetamide (4.5 g, 18.8 mmol) dissolved in THF (30 ml) at −78 °C, and the mixture was stirred for 30 min. To this reaction mixture was added a THF (70 ml) solution of 2-cyclopropyl-4-(4-fluorophenyl)-3-formylquinoline[22] (4.5 g, 15.5 mmol), and the resulting mixture was gradually warmed under stirring from −78 °C to room temperature over a period of 3 h before quenching by addition of water. Workup followed by column chromatography (silica gel, hexane–ethyl acetate 4:1) gave **6e** (5.4 g, 92% yield) as a colorless crystals. Mp 141 °C, R_f 0.52 (hexane–ethyl acetate 2:1), IR ($CHCl_3$) 3000, 1650, 1610, 1515, 1490, 1415, 1385, 1220, 1090, 1025, 840, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.05—1.09 (m, 2 H), 1.37—1.40 (m, 2 H), 2.40 (m, 1 H), 3.21 (s, 3 H), 3.49 (s, 3 H), 6.46 (d, J=16.1 Hz, 1 H), 7.16—7.27 (m, 4 H), 7.30—7.37 (m, 2 H), 7.62 (dd, J=6.2, 2.0 Hz, 1 H), 7.89 (d, J=16.1 Hz, 1 H), 7.96 (d, J=8.2 Hz, 1 H); MS m/z (rel intensity) 376 (M^+, 9), 316 (48), 288 (51), 260 (12), 185 (14), 129 (11), 43 (100). Found: C, 73.25; H, 5.74; N, 7.33%. Calcd for $C_{23}H_{21}FN_2O_2$: C, 73.39; H, 5.62; N, 7.44%.

Alternative Synthesis of 6e. Two-Step Procedure. Butyllithium (1.64 M hexane solution, 7.54 ml, 12.4 mmol) was added to a THF (4 ml) solution of diisopropylamine (1.25 g, 12.4 mmol) at −78 °C, and the mixture was stirred for 15 min. To the lithium diisopropylamide solution was added a THF (20 ml) solution of *N*-methoxy-*N*-methylacetamide (1.27 g, 12.3 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 15 min. To this mixture was added a THF (40 ml) solution of 2-cyclopropyl-4-(4-fluorophenyl)-3-formylquinoline (3.00 g, 10.3 mmol). The reaction mixture was stirred at −78 °C to room temperature over a period of 3 h before quenching with water and extraction with diethyl ether. The ethereal extracts were washed with sat. NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was puri-

fied by column chromatography (hexane–ethyl acetate 2:1) to give *N*-methoxy-*N*-methyl-3-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-2-yl]-3-hydroxypropanamide (3.70 g, 91% yield). R_f 0.30 (hexane–ethyl acetate 2:1). IR ($CHCl_3$) 3450, 3000, 1640, 1515, 1490, 1420, 1230, 1070, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.02—1.16 (m, 3 H), 1.74—1.79 (m, 1 H), 2.66 (d, J=17.2 Hz, 1 H), 3.17 (s, 3 H), 3.16—3.24 (m, 1 H), 3.52 (dd, J=17.2, 11.3 Hz, 1 H), 3.62 (s, 3 H), 4.14 (d, J=2.4 Hz, 1 H), 5.35 (dt, J=11.3, 2.4 Hz, 1 H), 7.12—7.35 (m, 6 H), 7.58 (dd, J=6.8, 1.4 Hz, 1 H), 7.92 (dq, J=8.4, 0.6 Hz, 1 H); MS m/z (rel intensity) 394 (M^+, 11), 363 (M^+ − OMe, 46), 334 (58), 292 (100), 274 (38), 263 (37).

A dichloromethane (10 ml) solution of methanesulfonyl chloride (1.44 g, 12.6 mmol) was added to a dichloromethane (40 ml) solution of *N*-methoxy-*N*-methyl-3-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3-hydroxypropanamide (3.30 g, 8.4 mmol) and triethylamine (1.27 g, 12.6 mmol). The resulting mixture was stirred at 0 °C for 30 min and at room temperature for 3 h before treatment with triethylamine (1.27 g, 12.6 mmol). The mixture was heated to reflux for 3 h, quenched with sat. $NaHCO_3$ aq solution and extracted with dichloromethane. The organic layer was washed with sat. NaCl aq solution, dried ($MgSO_4$), and then concentrated. The residue was purified by column chromatography (hexane–ethyl acetate 3:1) to give **6e** (2.52 g, 80% yield). Spectral and physical data were identical with those prepared by the One-Step procedure.

Methyl (*E*)-7-Phenyl-3,5-dioxo-6-heptenoate (4a). A Typical Procedure for the Synthesis of β,δ-Diketo Esters. Methyl acetoacetate (12.1 ml, 0.113 mol) was added to a stirred slurry of NaH (60% in oil, 4.5 g, 0.113 mol) in THF (250 ml) at 0 °C. The mixture was stirred for 10 min before cooling at −10 °C. A 1.48 M hexane solution of butyllithium (76 ml, 0.113 mol) was added to this solution, and the resulting mixture was stirred for 10 min and then cooled at −78 °C. The amide obtained above (7.2 g, 38 mmol) was added to the dianion solution, and the whole was stirred for 30 min at −78 to −30 °C before quenching with dil hydrochloric acid. Workup followed by chromatographic purification gave **4a** (5.3 g, 57% yield). Mp 52—53 °C. IR (KBr) 3420, 1740, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.45 (s, 2 H), 3.76 (s, 3 H), 5.75 (s, 1 H, enol =C*H*–), 6.47 (d, J=15.8 Hz, 1 H), 7.25—7.70 (m, 5 H), 7.63 (d, J=15.8 Hz, 1 H), 14.83 (br s, 1 H, enol O*H*); MS m/z (rel intensity) 246 (M^+, 12), 173 (49), 145 (34), 144 (33), 131 (100), 103 (45), 77 (30), 69 (21). Found: C, 68.22; H, 5.93%. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%.

***t*-Butyl 3,5-Dioxo-6-phenoxyhexanoate (4i).** This (161 mg, 91% yield) was prepared from **6i** (118 mg, 0.61 mmol), *t*-butyl acetoacetate (0.28 ml, 1.71 mmol), NaH (60% in oil, 68 mg, 1.71 mmol), THF (5 ml), and *n*-BuLi (1.57 M hexane solution, 1.09 ml, 1.71 mmol) as a viscous oil. IR (neat) 3000, 2950, 1735, 1600, 1500, 1370, 1250, 1150, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.44 (s, 9 H), 3.27 (s, 2 H), 4.60 (s, 2 H), 6.00 (s, 1 H, enol =C*H*–), 6.80—7.55 (m, 5 H), 11.4 (br s, 1 H, enol O*H*). MS m/z (rel intensity) 292 (M^+, 4), 129 (53), 107 (21), 77 (32), 57 (100). Found: m/z 292.1324. Calcd for $C_{16}H_{20}O_5$: M, 292.1309.

Similarly, followings were prepared.

***t*-Butyl (*E*)-3,5-Dioxo-6-octenoate (4f).** IR (neat) 3000, 2950, 1730, 1660, 1590, 1150, 960, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (s, 9 H), 1.91 (dd, J=1.5, 7.0 Hz, 3 H), 3.29 (s, 2 H), 5.56 (s, 1 H), enol =C*H*–), 5.87 (dq, J=15.6, 1.8 Hz, 1 H), 6.85 (dq, J=15.6, 7.0 Hz, 1 H), 14.9 (br s, 1 H, enol O*H*); MS m/z (rel intensity) 226 (M^+, 4), 171 (24), 170 (23), 155 (23), 153 (23), 111 (55), 69 (69), 57 (100). Found: m/z 226.1197. Calcd for $C_{12}H_{18}O_4$: M, 226.1203.

***t*-Butyl (*E*,*E*)-3,5-Dioxo-6,8-decadienoate (4g).** Mp 55—56 °C. IR (KBr) 3000, 2950, 1730, 1630, 1590, 1430, 1365, 1325, 1280, 1260, 1150, 990, 970, 870, 800, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.70 (s, 9 H), 1.86 (d, J=5.1 Hz, 3 H), 3.30 (s, 2 H), 5.60 (s, 1 H, enol =C*H*–), 5.6—6.3 (m, 3 H), 7.0—7.4 (m, 1 H), 14.9 (br s, 1 H, enol O*H*); MS m/z (rel intensity) 252 (M^+, 8), 196 (51), 181 (41), 179 (21), 137 (62), 136 (25), 121 (32), 109 (78), 95 (78), 67 (28), 57 (100). Found: C, 66.77; H, 7.99%. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99%.

***t*-Butyl 7-Methyl-3,5-dioxo-6-octenoate (4h).** Colorless oil, IR (neat) 3000, 2950, 1730, 1640, 1590, 1370, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.46 (s, 9 H), 1.91 (s, 3 H), 2.17 (s, 3 H), 3.25 (s, 2 H), 5.50 (s, 1 H, enol =C*H*–), 5.5—5.7 (m, 1 H), 15.5 (br s, 1 H, enol O*H*); MS m/z (rel intensity) 240 (M^+, 3), 184 (21), 169 (65), 125 (47), 83 (100), 82 (31), 57 (85), 41 (27). Found: C, 64.74; H, 8.50%. Calcd for $C_{12}H_{20}O_4$: C, 64.98; H, 8.39%.

Methyl (*E*,3*S,5*R**)-3,5-Dihydroxy-7-phenyl-6-heptenoate (3a).** Diethyl(methoxy)borane (0.015 ml, 0.112 mmol) was added to the solution of methyl (*E*)-7-phenyl-3,5-dioxo-6-heptenoate (**4a**, 23 mg, 0.093 mmol) in THF (1 ml) and methanol (0.25 ml) at −78 °C. The mixture was once warmed to room temperature and cooled again at −78 °C, treated with $NaBH_4$ (18 mg, 0.47 mmol), gradually warmed to room temperature and then quenched with acetic acid (3 ml). The whole mixture was stirred for 30 min and then extracted with ethyl acetate. The combined extracts were washed with sat. $NaHCO_3$ aq solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was treated with methanol and then concentrated. This procedure was repeated 10 times. Purification by preparative TLC (hexane–ethyl acetate 1:1) gave **3a** (20 mg, 86% yield). ^1H NMR ($CDCl_3$) δ=1.68—1.85 (m, 2 H), 2.45—2.60 (m, 2 H), 3.40 (br s, 1 H), 3.71 (s, 3 H), 3.83 (br s, 1 H), 4.28—4.37 (m, 1 H), 4.53—4.63 (m, 1 H), 6.21 (dd, J=15.7 and 6.5 Hz, 1 H), 6.61 (d, J=15.9 Hz, 1 H), 7.20—7.40 (m, 5 H).

Methyl(3*S,5*R**)-3,5-Isopropylidenedioxy-7-phenyl-6-heptenoate.** A dichloromethane (1 ml) solution of **3a** (ca. 3:1 diastereomeric mixture, 14.3 mg, 0.058 mmol) was stirred with 2-methoxypropene (11 μl. 0.12 mmol), molecular sieves 4A, and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) at room temperature for 1.5 h. Filtration, neutralization with sat. $NaHCO_3$ aq solution, extraction, followed by preparative TLC (dichloromethane–acetone 30:1), gave the desired acetonide in 75% total yield. A less polar minor isomer (3.2 mg) turned out to be a ca. 1:1 mixture of two conformational isomers of *anti*-diol: ^1H NMR ($CDCl_3$) δ=1.43 (s, 1.5 H), 1.44 (s, 1.5 H), 1.44 (s, 1.5 H), 1.53 (s, 1.5 H), 1.6—2.0 (m, 2 H), 2.4—2.7 (m, 2 H), 3.69 (s, 3 H), 4.2—4.7 (m, 2 H), 6.08 (dd, J=16.0, 5.9 Hz, 0.5 H), 6.26 (dd, J=16.0, 6.2 Hz, 0.5 H), 6.58 (dd, J=16.0, 0.9 Hz, 0.5 H), 6.61 (dd, J=16.0, 0.9 Hz, 0.5 H), 7.2—7.6 (m, 5 H). A more polar major isomer (9.2 mg) was concluded to be the acetonide of *syn*-diol as a single isomer. ^1H NMR

($CDCl_3$) δ=1.36 (s, 6 H), 1.8—2.1 (m, 2 H), 2.70 (d, J=4.6 Hz, 2 H), 3.22 (s, 3 H), 4.2—4.5 (m, 1 H), 6.23 (dd, J=16.0, 6.2 Hz, 1 H), 6.71 (d, J=16.0 Hz, 1 H), 7.2—7.6 (m, 5 H).

***t*-Butyl (3*S**,5*R**)-3,5-Dihydroxy-6-phenoxyhexanoate (3i).** Reduction of **4i** (67 mg, 0.23 mmol) with $NaBH_4$ and Et_2BOMe in THF–methanol gave **3i** (64 mg, 94% yield). Mp 96—97 °C. IR (neat) 3450, 2980, 2930, 1720, 1600, 1500, 1370, 1240, 1150, 750, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (s, 9 H), 1.6—1.9 (m, 2 H), 2.45 (d, J=6.2 Hz 2 H), 3.4—4.5 (m, 6 H), 6.8—7.5 (m, 5 H); MS m/z (rel intensity) 296 (M^+, 2), 147 (28), 129 (33), 115 (42), 111 (27), 94 (88), 77 (22), 57 (10). Found: C, 64.55; H, 8.21%. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16%.

***t*-Butyl(3*S**,5*R**)-3,5-Isopropylidenedioxy-6-phenoxyhexanoate.** A dichloromethane (1 ml) solution of **3i** (15 mg, 0.05 mmol) was treated with 2-methoxypropene (10 μl, 0.1 mmol), molecular sieves 4A and a catalytic amount of PPTS at room temperature for 2 h. Workup followed by preparative TLC (dichloromethane–acetone 15 : 1) gave the desired acetonide of **3i** (12 mg, 70% yield) as a single isomer. ^1H NMR ($CDCl_3$) δ=1.25—1.40 (m, 1 H), 1.41 (s, 3 H), 1.45 (s, 9 H), 1.51 (s, 3 H), 1.77 (dt, J=2.5, 12.5 Hz, 1 H), 2.34 (dd, J=6.0, 15.2 Hz, 1 H), 2.46 (dd, J=7.1, 15.2 Hz, 1 H), 3.83 (dd, J=5.5, 9.5 Hz, 1 H), 4.03 (dd, J=5.5, 9.5 Hz, 1 H), 4.2—4.4 (m, 2H), 6.8—7.0 (m, 3 H), 7.2—7.4 (m, 2 H).

***t*-Butyl (*E*)-7-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)-3,5-dioxo-6-heptenoate (4c).** To a suspension of NaH (60% in oil, 47.1 mg, 1.18 mmol) in THF (2 ml) *t*-butyl acetoacetate (0.195 ml, 1.17 mmol) was added at 0 °C. The mixture was stirred for 10 min and then cooled at −78 °C. A hexane solution of butyllithium (1.53 M, 0.77 ml, 1.17 mmol) was added to the reaction mixture, and the resulting mixture was stirred 10 min before the addition of a THF (1 ml) solution of **6c** (121 mg, 0.37 mmol) at −78 °C. The reaction mixture was then gradually warmed to −60 °C, quenched with citric acid aq solution and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed (silica gel, hexane–ethyl acetate 20 : 1) to give **4c** (117 mg, 75% yield) as a viscous oil. IR (neat) 3000, 2950, 1735, 1635, 1580, 1500, 1240, 1150, 1120, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (s, 9 H), 2.28 (d, J=1.98 Hz, 3 H), 2.34, (s, 3 H), 2.42 (s, 3 H), 3.27 (s, 2 H), 5.44 (s, 1 H, enol =C*H*–), 5.75 (d, J=16.3 Hz, 1 H), 6.9—7.2 (m, 5 H), 7.59 (d, J=16.3 Hz, 1 H), 12.24 (br s, 1 H, enol O*H*); MS m/z (rel intensity) 424 (M^+, 1), 368 (21), 350 (10), 309 (16), 267 (16), 240 (63), 239 (100), 238 (59), 225 (93), 224 (44), 223 (19), 129 (50), 111 (22), 59 (23), 57 (64). Found: m/z 424.2063. Calcd for $C_{26}H_{29}FO_4$: M, 424.2049.

Reduction of 4c with 10d. To a THF (1.6 ml) solution of **4c** (34 mg, 0.079 mmol) was added **10d** (prepared by methanol treatment of LimBCl[16] and distilled, 33 μl, ca. 0.2 mmol), and the mixture was stirred at room temperature for 15 min and then cooled at −78 °C. To this mixture were added dry methanol (0.4 ml) and $NaBH_4$ (15 mg, 0.40 mmol) at −78 °C, and the whole was gradually warmed to room temperature, quenched with citric acid aq solution and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in a mixture of methanol (3 ml), a pH=7 buffer (2 ml) and 30% H_2O_2 (1 ml). The mixture was stirred for 12 h at room temperature and extracted with dichloromethane. Workup and preparative TLC (silica gel, dichloromethane–acetone 9 : 1) gave *t*-butyl (*E*)-7-(4′-fluoro-3,3′,5-trimethy[1,1′-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoate **3c** (23.2 mg, 68%). ^1H NMR ($CDCl_3$) δ=1.3—1.6 (m, 2 H), 1.50 (s, 9 H), 2.27 (d, J=1.98 Hz, 3 H), 2.31 (s, 3 H), 2.34 (s, 3 H), 2.2—2.4 (m, 2 H), 3.1 (br s, 1 H), 3.73 (br s, 1 H), 4.0—4.2 (m, 1 H), 4.3—4.4 (m, 1 H), 5.37 (dd, J=6.4 and 16.2 Hz, 1 H), 6.44 (d, J=16.2 Hz, 1 H), 6.9—7.2 (m, 5 H). MS m/z (rel intensity) 428 (M^+, 0.7), 372 (50), 354 (33), 336 (41), 252 (72), 251 (78), 240 (80), 239 (95), 227 (94), 226 (95), 225 (98), 224 (51), 214 (54), 211 (50). Found: m/z 428.2371. Calcd for $C_{26}H_{33}FO_4$: M, 428.2361.

The dihydroxy ester **3c** was dissolved in methanol (1 ml) and 1 M NaOH aq solution (0.11 ml), and the mixture was stirred at room temperature for 1 h before acidification with dil HCl and concentration. The residue was dissolved in water and extracted with ethanol–chloroform (1 : 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in toluene (2 ml) and heated at 90 °C for 8 h. Concentration followed by preparative TLC (dichloromethane–acetone 9 : 1) gave **2c** (7.1 mg, 37%), $[\alpha]_D^{20}$ = −3.09° (*c* 0.71, $CHCl_3$). ^1H NMR ($CDCl_3$) δ=1.7—2.0 (m, 2 H), 1.97 (br s, 1 H), 2.29 (d, J=1.9 Hz, 3 H), 2.33 (s, 3 H), 2.34 (s, 3 H), 2.5—2.8 (m, 2 H), 4.2—4.3 (m, 1 H), 5.1—5.2 (m, 1 H), 5.38 (dd, J=6.7, 16.2 Hz, 1 H), 6.52 (d, J=16.2 Hz, 1 H), 6.9—7.1 (m, 5 H).

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*)-7-Phenyl-3,5-dioxo-6-heptenoate (13a*). A THF (40 ml) solution of (4*R*)-4,7,7-trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl acetoacetate[19] (**12*** 3.45 g, 9.5 mmol) was added to NaH (0.38 g, 60% in oil, 9.5 mmol) suspended in THF (40 ml) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and cooled at −10 °C. To the mixture was added *n*-BuLi (1.55 M hexane solution, 6.1 ml, 9.5 mmol). The reaction mixture was stirred for 10 min and then cooled at −78 °C. A THF (20 ml) solution of **6a** (1.62 g, 9.5 mmol) was added to the reaction mixture at −78 °C, and the resulting mixture was warmed to room temperature over a period of 4 h. The reaction was quenched with dil HCl, and the resulting was extracted with ether. The organic layer was washed with sat. NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (silica gel, hexane–ethyl acetate 10 : 1) afforded, along with the recovered acetoacetate **12*** (0.29 g, 8% yield, R_f 0.56 (hexane–ethyl acetate 5 : 1)), the desired diketo ester **13a***. R_f 0.44 (hexane–ethyl acetate 5 : 1), $[\alpha]_D^{20}$ −141.0° (*c* 1.90, $CHCl_3$). ^1H NMR ($CDCl_3$) δ=1.00 (s, 3H), 1.21 (s, 3H), 1.29 (s, 3H), 1.42—1.60 (m, 2H), 1.76 (dt, J=5.0, 12.0 Hz, 1 H), 1.91—2.02 (m, 2H), 2.60 (d, J=15.0 Hz, 1 H), 2.66 (d, J=15.0 Hz, 1 H), 4.06 (d, J=8.5 Hz, 1 H), 4.78 (s, 1H), 5.56 (d, J=8.5 Hz, 1 H), 6.24 (d, J=16.0 Hz, 1 H), 7.37 (dd, J=16.0, 7.5 Hz, 1 H), 7.40—7.58 (m, 8 H), 7.60 (d, J=7.5 Hz, 1 H), 7.66 (d, J=8.5 Hz, 1 H), 7.77 (dd, J=8.0 and 1.0 Hz, 1 H), 8.02 (d, J=8.5 Hz, 1 H), 14.48 (br, 1 H); IR ($CHCl_3$) 3060, 2950, 1735, 1640, 1600, 1590, 1575, 1445, 1320, 1160, 1120, 1020, 985 cm^{-1}; MS m/z (rel intensity) 494 (M^+, 3), 263 (5), 247 (6), 215 (19), 179 (13), 173 (49), 171 (16), 170 (100), 165 (23), 152 (9), 142 (12), 141 (39), 131 (48), 121 (12). Found: m/z 494.2472. Calcd for $C_{33}H_{34}O_4$: M, 494.2457.

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-

[2.2.1]heptan-2-*exo*-yl (*E*,3*S*,5*R*)-3,5-Dihydroxy-7-phenyl-6-heptenoate (14a*). One-Pot Procedure. Diethyl(methoxy)borane (62 ml, 0.44 mmol) was dissolved in a THF (2.0 ml)–methanol (0.5 ml) solution of **13a*** (0.20 g, 0.40 mmol) at −78 °C, and the solution was stirred at −78 °C for 10 min and gradually warmed up to room temperature over a period of 15 min and then recooled at −78 °C. Sodium borohydride (77 mg, 2.0 mmol) was added to the mixture, and the reaction mixture was stirred at −78 °C for 6 h and warmed gradually to room temperature over 12 h before quenching with acetic acid. Extraction with ether, drying the ethereal extracts ($MgSO_4$), and concentration gave a residue, which was dissolved in methanol (10 ml) and then concentrated again. This last procedure was repeated 10 times to cleave O–B bonds. The final residue was purified by column chromatography (silica gel, hexane–ethyl acetate 7:3) to give **14a*** (0.17 g, 85% yield) as a viscous oil. Pure **14a*** was obtained by HPLC purification. R_f 0.27 (hexane–ethyl acetate 2:1). ^{1}H NMR ($CDCl_3$) δ=1.01 (s, 3 H), 1.26 (s, 3 H), 1.33 (s, 3 H), 1.84—2.18 (br m, 11 H), 3.07—3.13 (m, 1 H), 4.08 (d, J=8.8 Hz, 1 H), 4.13—4.18 (m, 1 H), 5.53 (d, J=8.8 Hz, 1 H), 6.00 (dd, J=6.2 and 15.9 Hz, 1 H), 6.51 (d, J=15.9 Hz, 1 H), 7.21—7.52 (m, 8 H), 7.66 (d, J=7.4 Hz, 1 H), 7.73 (d, J=8.2 Hz, 1 H), 7.84 (d, J=8.2 Hz, 1 H), 8.05 (d, J=8.5 Hz, 1 H); IR ($CHCl_3$) 3550, 2950, 1730, 1600, 1395, 1250, 1180, 1085, 1015, 965, 785 cm^{-1}; MS m/z (rel intensity) 498 (M^+, weak), 480 (weak), 463 (weak), 264 (19), 263 (79), 262 (13), 235 (34), 207 (32), 201 (21), 170 (100), 155 (39), 141 (84), 131 (42), 115 (33), 104 (16), 95 (19), 91 (33), 71 (28), 55 (24), 43 (27). Found: m/z 498.2775. Calcd for $C_{33}H_{38}O_4$: M, 498.2770.

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-[2.2.1]heptan-2-*exo*-yl (*E*,3*S*)-3-Hydroxy-5-oxo-7-phenyl-6-heptenoate (16a*). DIBAL (0.97 M toluene solution, 0.153 ml, 0.148 mmol) was added to **13a*** (33 mg, 0.067 mmol) in THF (1 ml), and the resulting mixture was stirred at −78 °C for 4 h before quenching with 1 M HCl. The mixture was extracted with ethyl acetate (50 ml), and the combined extracts were washed with 5% $NaHCO_3$ aq solution, dried ($MgSO_4$) and concentrated to give a crude product (34 mg), which was purified by preparative TLC (silica gel, hexane–ethyl acetate 3:2) to afford **16a*** (28 mg, 85% yield). $[\alpha]_D^{20}$ −99.17° (c 1.45, $CHCl_3$), R_f 0.49 (hexane–ethyl acetate 2:1). HPLC (silica gel 60, hexane–ethanol 80:1) showed an isomer ratio of 95.3:4.7. ^{1}H NMR ($CDCl_3$) δ=1.00 (s, 3 H), 1.25 (s, 3 H), 1.35 (s, 3 H), 1.54—2.17 (m, 10 H), 3.54—3.61 (m, 1 H), 4.09 (d, J=8.7 Hz, 1 H), 5.56 (d, J=8.7 Hz, 1 H), 6.53 (d, J=16 Hz, 1 H), 7.37—7.6 (m, 13 H); IR ($CHCl_3$) 3580, 2950, 2925, 1725, 1680, 1650, 1605, 1390, 1120, 1090, 780 cm^{-1}; MS m/z (rel intensity) 396 (M^+, 1), 478 (2), 350 (8), 262 (12), 240 (26), 199 (17), 179 (10), 171 (14), 170 (100), 169 (10), 165 (16), 146 (17), 145 (12), 141 (28), 131 (53), 103 (27), 77 (19), 71 (14), 55 (10), 43 (28).

(4*R*)-4,7,7,-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-[2.2.1]heptan-2-*exo*-yl (*E*,3*S*,5*R*)-3,5-Dihydroxy-7-phenyl-6-heptenoate (14a*). To a mixture of **16a*** (15 mg, 0.03 mmol) in THF (1 ml) and methanol (0.1 ml) was added Et_2BOMe (4.3 ml, 0.031 mmol) at −78 °C. The resulting mixture was stirred at room temperature for 15 min and cooled again at −78 °C. To this mixture was added $NaBH_4$ (4 mg, 0.11 mmol). The reaction mixture was then stirred at −78 °C for 3 h and at room temperature for 10 h. Workup and purification gave **14a*** (12 mg, 80% yield). HPLC analysis (Si 60, hexane–ethanol 40:1) showed a single peak. $[\alpha]_D^{20}$ −86.51° (c 0.55, $CHCl_3$). All other spectra were identical with those of the sample prepared by One-Step Procedure and purified by preparative HPLC.

(*E*,3*S*,5*R*)-3,5-Dihydroxy-7-phenyl-6-heptenoic Acid 1,5-Lactone (2a*). To **14a*** (prepared by One-Step Procedure and purified by preparative HPLC, 18 mg, 0.036 mmol) dissolved in methanol (0.5 ml) was added aq NaOH solution (1 M, 60 μl, 0.06 mmol). The mixture was stirred for 36 h at room temperature, diluted with water and extracted with diethyl ether. The aqueous layer was acidified with 5 M HCl and extracted with diethyl ether (10 ml×3 times). The ethereal layer was washed with sat. NaCl aq solution and dried ($MgSO_4$). Concentration in vacuo gave a dihydroxy acid (8 mg) which was dissolved in dry toluene (2 ml) and heated under reflux for 9 h. Evaporation of the toluene under reduced pressure followed by preparative TLC afforded **2a*** (6.1 mg, 76% yield). Mp 114 °C. R_f 0.24 (dichloromethane–acetone 9:1), $[\alpha]_D^{20}$ −11.33° (c 0.41, $CHCl_3$). The enantiomeric ratio measured by a CHIRALCEL OA column (hexane–isopropyl alcohol 9 :1) was 97:3 (94% ee). ^{1}H NMR ($CDCl_3$) δ=1.94 (ddd, J=14.0, 10.8, and 3.1 Hz, 1 H), 2.12 (dm, J=14.0 Hz, 1 H), 2.5—2.8 (br, 1 H), 2.67 (ddd, J=17.8, 4.0, and 1.6 Hz, 1 H), 2.78 (dd, J=17.8 and 4.9 Hz, 1 H), 4.4—4.3 (m, 1 H), 5.37 (dddd, J=10.7, 6.0, 3.0, and 1.0 Hz, 1 H), 6.21 (dd, J=6.0 and 15.9 Hz, 1 H), 6.71 (dd, J=15.9 and 0.9 Hz, 1 H), 7.24—7.45 (m, 5 H); IR (KBr) 3440, 3080, 3050, 2975, 2940, 1725, 1600, 1500, 1425, 1395, 1375, 1245, 1165, 1075, 1035, 980, 755, 695 cm^{-1}; MS m/z (rel intensity) 218 (M^+, 15), 200 (13), 172 (10), 131 (21), 130 (20), 129 (24), 114 (21), 104 (100), 91 (40), 77 (21), 68 (34), 51 (15), 43 (32). Found: m/z 218.0956. Calcd for $C_{13}H_{14}O_3$: M, 218.0943. Found: C, 71.36; H, 6.51%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46%.

The dihydroxy ester **14a*** obtained by the One-Step Procedure was, without HPLC purification, similarly hydrolyzed, and lactonized as above to give **2a*** of 49% ee.

(4*S*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-[2.2.1]heptan-2-*exo*-ol: This was prepared from L-(−)-camphor according to the literature procedure[19b] Mp 151—152 °C, $[\alpha]_D^{20}$ +179.88° (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=0.83—2.06 (br m, 5 H), 1.00 (s, 3 H), 1.23 (s, 3 H), 1.40 (s, 3 H), 3.95 (d, J=8 Hz, 1 H), 4.48 (d, J=8 Hz, 1 H), 7.36—8.37 (br m, 7 H); IR (KBr) 3610, 3540, 2980, 2910, 1605, 1515, 1490, 1460, 1400, 1100, 1065, 1045, 800 cm^{-1}; MS m/z (rel intensity) 280 (M^+, 6), 171 (13), 170 (100), 169 (13), 165 (11), 142 (21), 141 (20), 41 (14).

(4*S*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-[2.2.1]heptan-2-*exo*-yl (*E*)-7-Phenyl-3,5-dioxo-6-heptenoate (13a): R_f 0.25 (hexane–ethyl acetate 10:1), $[\alpha]_D^{20}$ +130.55° (c 0.80, $CHCl_3$).

(4*S*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-[2.2.1]heptan-2-*exo*-yl (*E*,3*R*)-3-Hydroxy-5-oxo-7-phenyl-6-heptenoate (16a). R_f 0.49 (hexane–ethyl acetate 2:1), $[\alpha]_D^{20}$ +103.7° (c 0.96, $CHCl_3$). HPLC (Si 60) showed the diastereomeric ratio to be >95:5.

(4*S*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-[2.2.1]heptan-2-*exo*-yl (*E*,3*R*,5*S*)-3,5-Dihydroxy-7-phenyl-6-heptenoate (14a). R_f 0.29 (hexane–ethyl acetate 2:1), $[\alpha]_D^{20}$ +84.54° (c 0.44, $CHCl_3$).

(*E*,3*R*,5*S*)-3,5-Dihydroxy-7-phenyl-6-heptenoic Acid 1,5-Lactone (2a). R_f 0.24 (dichloromethane–acetone 10:1), $[\alpha]_D^{20}$ +10.66° (*c* 0.15, $CHCl_3$); lit,[20] $[\alpha]_D^{27}$ +9.86 (*c* 0.80, $CHCl_3$). HPLC (CHIRALCEL OA, hexane–2-propanol 9:1) showed a diastereomeric ratio of 99:1 and >97% ee.

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*)-8-Bis(4-fluorophenyl)-methylidene-9-methyl-3,5-dioxo-6-decenoate (13d*). (4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]-heptan-2-*exo*-yl acetoacetate (**12***, 0.91 g, 2.5 mmol) was converted into the dianion with NaH (2.6 mmol) and *n*-BuLi (2.5 mmol) in THF (7 ml). This dianion was allowed to react with *N*-methoxy-*N*-methyl-4-bis(4-fluorophenyl)methylidene-5-methyl-2-hexenamide (prepared from the corresponding acid chloride, 0.93 g, 2.5 mmol) at −10 °C to room temperature. Workup followed by purification by column chromatography gave, along with recovered **12*** (0.38 g, 42%), **13d*** (0.66 g, 38% yield, 67% based on the consumed starting material) as a semisolid. R_f 0.27 (hexane–dichloromethane 1:1), $[\alpha]_D^{20}$ −116.23° (*c* 0.85, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ=0.76—2.13 (m, 11 H), 1.00 (s, 3 H), 1.33 (s, 3 H), 1.37 (s, 3 H), 2.53 (s, 2 H), 2.84—3.24 (m, 1 H), 4.08 (d, J=9 Hz, 1 H), 4.75 (s, 1 H), 5.57 (d, J=9 Hz, 1 H), 5.92 (d, J=16.5 Hz, 1 H), 6.73—8.10 (m, 16 H), 14.5 (br, 1 H); IR (KBr) 3060, 2980, 2900, 1735, 1605, 1505, 1395, 1320, 1225, 1160, 1095, 1015, 835, 785 cm^{-1}; MS *m/z* (rel intensity) 674 (M^+, 2), 412 (4), 394 (13), 263 (14), 207 (11), 203 (14), 171 (14), 170 (100), 169 (14), 165 (13), 142 (20), 141 (26), 111 (28), 109 (12), 69 (27), 43 (22). Found: *m/z* 674.3195. Calcd for $C_{44}H_{44}F_2O_4$: M, 674.3208.

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*,3*S*,5*R*)-8-Bis(4-fluorophenyl)methylidene-3,5-dihydroxy-9-methyl-6-decenoate (14d*). R_f 0.39 (hexane–ethyl acetate 2:1), $[\alpha]_D^{20}$ −93.32° (*c* 5.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=0.79—0.98 (m, 2 H), 1.00 (s, 3 H), 1.05 (d, J=5.8 Hz, 3 H), 1.07 (d, J=5.8 Hz, 3 H), 1.26 (s, 3 H), 1.32 (s, 3 H), 1.45—1.54 (m, 1H), 1.56 (br s, 1 H, OH), 1.59—1.63 (m, 2 H), 1.72—1.85 (m, 2 H), 1.92—2.00 (m, 2 H), 2.77—2.85 (m, 1 H), 2.94—2.99 (m, 1 H), 3.82—3.86 (m, 1 H), 4.08 (d, J=8.8 Hz, 1 H), 5.38 (dd, J=6.35 and 16.2 Hz, 1 H), 5.51 (d, J=8.8 Hz, 1 H), 6.04 (dd, J=1.1 and 16.2 Hz, 1 H), 6.86 (m, 8 H), 7.38—8.05 (m, 7 H); IR ($CHCl_3$) 3575, 2960, 2875, 1725, 1600, 1500, 1465, 1400, 1175, 1090, 1010, 1000, 835 cm^{-1}; MS *m/z* (rel intensity) 678 (M^+, trace), 660 (trace), 643 (trace), 617 (trace), 416 (4), 269 (13), 264 (22), 263 (100), 207 (44), 170 (22), 141 (39), 109 (20).

(*E*,3*S*,5*R*)-8-Bis(4-fluorophenyl)methylidene-3,5-dihydroxy-9-methyl-6-decenoic Acid 1,5-Lactone (2d*). A mixture of **14d*** (55 mg, 0.081 mmol), 1 M NaOH (0.16 ml) and methanol (2 ml) was stirred at room temperature for 29 h before dilution with water (5 ml) and extraction with diethyl ether (5 ml×2 times). The aqueous layer was acidified with 1 M HCl (1 ml) and extracted with diethyl ether (15 ml×3 times). The combined ethereal extracts were washed with sat. NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in toluene (3 ml) and heated at 110 °C for 5 h. Concentration and preparative TLC (dichloromethane–acetone 40:1) gave **2d*** (21 mg, 65% yield). R_f 0.63 (dichloromethane–acetone 10:1). This material was found to be an 83:17 mixture of *trans* (60% ee) and *cis* isomers by HPLC (CHIRALCEL AD, hexane–2-propanol 40:1). $[\alpha]_D^{20}$ −91.03 (*c* 0.36, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=1.09 (d, J=7.0 Hz, 3 H), 1.11 (d, J=7.0 Hz, 3 H), 1.61 (ddd, J=13.8, 10.4, and 3.3 Hz, 1 H), 1.75—1.81 (m, 1H), 2.56 (ddd, J=17.7, 4.2, and 1.6 Hz, 1 H), 2.70 (dd, J=5.0 and 17.7 Hz, 1 H), 2.82—2.91 (m, 1 H), 4.22—4.26 (m, 1 H), 4.52—4.59 (m, 1 H), 5.01—5.06 (m, 1 H), 5.55 (dd, J=16.2 and 6.8 Hz, 1 H), 6.23 (dd, J=16.2 and 1.2 Hz, 1 H), 6.91—7.09 (m, 8 H); IR ($CHCl_3$) 3650, 2940, 2875, 1735, 1605, 1505, 1405, 1365, 1260, 1235, 1160, 1130, 1095, 1060, 1040, 970, 835, 800 cm^{-1}. Found: *m/z* 398.1671. Calcd for $C_{24}H_{24}F_2O_3$: M, 398.1691.

(4*S*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*)-8-Bis(4-fluorophenyl)-methylidene-9-methyl-3,5-dioxo-6-decenoate (13d). Obtained starting from **11** in 38% yield or 75% yield based on the acetoacetate consumed. R_f 0.28 (hexane–dichloromethane 1:1), $[\alpha]_D^{20}$ +112.45° (*c* 1.05, $CHCl_3$).

(4*S*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*,3*R*,5*S*)-8-Bis(4-fluorophenyl)methylidene-3,5-dihydroxy-9-methyl-6-decenoae (14d). $[\alpha]_D^{20}$ +84.32° (*c* 1.25, $CHCl_3$).

(*E*,3*R*,5*S*)-8-Bis(4-fluorophenyl)methylidene-3,5-dihydroxy-9-methyl-6-decenoic Acid 1,5-Lactone (2d). Obtained as a 79:21 mixture of *trans* and *cis* isomers. Pure *trans* lactone isolated by preparative TLC (dichloromethane–acetone 4:1) was 64% ee. R_f 0.36 (dichloromethane–acetone 10:1), $[\alpha]_D^{20}$ +113.4° (*c* 0.67, $CHCl_3$).

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*)-7-(4-Methylphenyl)-3,5-dioxo-6-heptenoate (13b*). R_f 0.17 (hexane–dichloromethane 1:1), $[\alpha]_D^{20}$ −145.36° (*c* 0.63, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=0.80—2.1 (m, 5 H), 1.00 (s, 3 H), 1.22 (s, 3 H), 1.30 (s, 3 H), 2.40 (s, 3 H), 2.63 (s, 2 H), 4.08 (d, J=9 Hz, 1 H), 4.80 (s, 1 H), 5.58 (d, J=9 Hz, 1 H), 6.22 (d, J=15 Hz, 1 H), 7.13—8.13 (m, 12 H), 14.5 (br, 1 H); IR ($CHCl_3$) 2925, 2850, 1720, 1625, 1570, 1500, 1475, 1425, 1325, 1245, 1150, 1115, 1075, 1005, 960, 800 cm^{-1}; MS *m/z* (rel intensity) 508 (M^+, 7), 398 (2), 280 (4), 262 (11), 229 (44), 187 (62), 170 (100), 169 (13), 165 (12), 145 (45), 142 (13), 141 (27), 115 (15), 41 (13).

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*, 3*S*)-3-Hydroxy-5-oxo-7-(4-methylphenyl)-6-heptenoate (16b*). R_f 0.36 (hexane–ethyl acetate 3:1). HPLC analysis (Si 60, hexane–ethanol 80:1) had a diastereomeric ratio of 95.5:4.5. $[\alpha]_D^{20}$ −108.90° (*c* 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=1.80—2.33 (m, 10 H), 1.00 (s, 3 H), 1.23 (s, 3 H), 1.33 (s, 3 H), 2.40 (s, 3 H), 3.40—3.76 (m, 1 H), 4.10 (d, J=9 Hz, 1 H), 5.57 (d, J=9 Hz, 1 H), 6.50 (d, J=15.75 Hz, 1 H), 7.16—8.13 (m, 12 H); IR ($CHCl_3$) 3560, 2940, 2860, 1720, 1670, 1640, 1595, 1560, 1500, 1480, 1455, 1435, 1385, 1320, 1255, 1175, 1080, 1010, 970, 790 cm^{-1}; MS *m/z* (rel intensity) 510 (M^+, 1), 492 (1), 262 (14), 240 (26), 231 (19), 213 (22), 179 (10), 171 (13), 170 (100), 169 (11), 165 (15), 145 (92), 141 (29), 117 (17), 115 (20), 91 (13), 71 (13), 43 (21). Found: *m/z* 510.2775. Calcd for $C_{34}H_{38}O_4$: M, 510.2770.

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo[2.2.1]heptan-2-*exo*-yl (*E*,3*S*,5*R*)-3,5-Dihydroxy-7-(4-methylphenyl)-6-heptenoate (14b*). R_f 0.31 (hexane–ethyl acetate 2:1). HPLC (Si 60, hexane–ethanol

40:1) showed a single peak. $[\alpha]_D^{20}$ −87.00° (*c* 3.00, $CHCl_3$). ^1H NMR ($CDCl_3$) δ=1.01 (s, 3 H), 1.08—1.22 (m, 2 H), 1.27 (s, 3 H), 1.33 (s, 3 H), 1.45—1.53 (m, 1 H), 1.57—1.68 (m, 3 H), 1.73—1.84 (m, 2 H), 1.88—2.01 (m, 3 H), 2.33 (s, 3 H), 3.07—3.13 (m, 1 H), 4.09 (d, *J*=8.8 Hz, 1 H), 4.12—4.16 (m, 1 H), 5.53 (d, *J*=8.8 Hz, 1 H), 5.95 (dd, *J*=6.3 and 15.9 Hz, 1 H), 6.47 (d, *J*=15.9 Hz, 1 H), 7.12 (d, *J*=8.0 Hz, 2 H), 7.24 (d, *J*=8.0 Hz, 2 H), 7.41—7.53 (m, 3 H), 7.65 (d, *J*=7.4 Hz, 1 H), 7.73 (d, *J*=8.2 Hz, 1 H), 7.87 (dd, *J*=1.2 and 8.0 Hz, 1 H), 8.05 (d, *J*=8.5 Hz, 1 H); MS *m/z* (rel intensity) 512 (M^+, 1), 264 (16), 263 (68), 262 (16), 249 (31), 231 (23), 215 (17), 207 (41), 197 (16), 193 (13), 181 (14), 179 (22), 173 (14), 171 (16), 170 (100), 169 (28), 167 (24), 165 (23), 155 (35), 145 (43), 142 (16), 141 (73), 131 (24), 129 (35), 128 (15), 124 (14), 109 (23), 105 (37), 95 (20), 91 (17), 71 (20), 69 (17), 43 (22), 41 (32). Found: *m/z* 512.2911. Calcd for $C_{34}H_{40}O_4$: M, 512.2927.

(*E*,3*S*,5*R*)-3,5-Dihydroxy-7-(4-methylphenyl)-6-heptenoic Acid 1,5-Lactone (2b*). Mp 126—127 °C, R_f 0.32 (dichloromethane–acetone 10:1). HPLC (CHIRALCEL OA and AD) showed 92% ee. $[\alpha]_D^{20}$ −5.69° (*c* 0.65, $CHCl_3$). ^1H NMR ($CDCl_3$) δ=1.93—2.00 (m, 1 H), 2.08—2.15 (m, 1 H), 2.34 (s, 3 H), 2.64—2.70 (m, 1 H), 2.80 (dd, *J*=5.0 and 17.7 Hz, 1 H), 4.42—4.46 (m, 1 H), 5.33—5.38 (m, 1 H), 6.15 (dd, *J*=6.5 and 15.9 Hz, 1 H), 6.67 (d, *J*=15.9 Hz, 1 H), 6.67 (d, *J*=15.9 Hz, 1 H), 7.13 (d, *J*=8.0 Hz, 2 H), 7.28 (d, *J*=8.0 Hz, 2 H); IR (KBr) 3400, 2925, 2850, 1695, 1515, 1380, 1315, 1245, 1165, 1065, 1035, 975, 875, 800 cm^{-1}; MS *m/z* (rel intensity) 232 (M^+, 19), 214 (6), 145 (17), 131 (18), 129 (40), 128 (20), 119 (17), 118 (100), 117 (19), 115 (17), 105 (43), 91 (21), 44 (22), 43 (38). Found: *m/z* 232.1087. Calcd for $C_{14}H_{16}O_3$: M, 232.1100.

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicyclo-[2.2.1]heptan-2-*exo*-yl (*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl}-3,5-dioxo-6-heptenoate (13e*). To a suspension of NaH (60% in oil, 0.26 g, 6.5 mmol) in THF (20 ml) was added a solution of **12*** (2.37 g, 6.5 mmol) in THF (30 ml) at 0 °C, and the mixture was stirred for 15 min. To this mixture was added *n*-BuLi (1.64 M hexane solution, 4.00 ml, 6.55 mmol) at 0 °C, and the resulting mixture was cooled to −78 °C. To the mixture was added a THF (50 ml) solution of **4e*** (2.45 g, 6.51 mmol). The mixture was stirred at −78 °C to 0 °C over 3 h before hydrolysis with 1 M HCl (20 ml), neutralization with sat. $NaHCO_3$ aq solution and extraction with diethyl ether. The organic layer was washed with sat. NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (hexane–ethyl acetate 15:1) to give **13e*** (2.12 g, 48% yield) along with the recovered **12*** (0.60 g, 25%) and **6e** (1.22 g, 50%).

13e*: R_f 0.48 (hexane–ethyl acetate 5:1), $[\alpha]_D^{20}$ −106.60° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 2960, 1730, 1605, 1515, 1490, 1395, 1235, 1090, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (s, 3 H), 1.12 (dd, *J*=8.9 and 3.0 Hz, 2 H), 1.22 (s, 3 H), 1.24 (s, 3 H), 1.42—1.60 (m, 5 H), 1.72—1.79 (m, 1 H), 1.91—1.99 (m, 2 H), 2.41 (m, 1 H), 2.52 (d, *J*=14.8 Hz, 1 H), 2.57 (d, *J*=14.8 Hz, 1 H), 4.05 (d, *J*=8.7 Hz, 1 H), 4.69 (s, 1 H), 5.87 (d, *J*=16.2 Hz, 1 H), 7.20—7.47 (m, 10 H), 7.56 (m, 3 H), 7.72 (dd, *J*=8.0 and 1.1 Hz, 1 H), 7.98 (d, *J*=8.4 Hz, 1 H), 8.00 (d, *J*=8.4 Hz, 1 H), 14.3 (br, 1 H); MS *m/z* (rel intensity) 679 (M^+, 0.5), 401 (3), 399 (32), 356 (8), 288 (50), 274 (22), 170 (100).

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicylco-[2.2.1]heptan-2-*exo*-yl (3*S*,5*R*,6*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-dihydroxy-6-heptenoate (14e*). Diethyl(methoxy)borane (32 mg, 0.32 mmol) was added to a mixture of **13e*** (0.20 g, 0.29 mmol) in THF (2.0 ml) and methanol (0.5 ml) at −78 °C. The mixture was once warmed to room temperature under stirring over 15 min then cooled again at −78 °C. Thereto was added $NaBH_4$ (56 mg, 1.48 mmol). After stirring at −78 °C for 4 h and warming to room temperature over 8 h, the mixture was quenched with acetic acid (0.5 ml). Workup, methanol treatment (10 times), followed by column chromatography (hexane–ethyl acetate 15:1), gave **14e*** (0.181 g, 90% yield). R_f 0.36 (hexane–ethyl acetate 2:1), $[\alpha]_D^{20}$ −72.19° (*c* 1.00, $CHCl_3$). IR ($CHCl_3$) 3460, 3010, 2960, 1725, 1605, 1515, 1490, 1400, 1220, 1090, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.80 (br d, *J*=14.3 Hz, 1 H), 0.88—0.96 (m, 1 H), 1.02 (s, 3 H), 1.00—1.05 (m, 2 H), 1.27 (s, 3 H), 1.33 (s, 3 H), 1.31—1.37 (m, 2 H), 1.46—1.55 (m, 1 H), 1.57—1.63 (m, 2 H), 1.75—1.82 (m, 1 H), 1.83 (dd, *J*=15.4 and 9.4 Hz, 1 H), 1.92—1.98 (m, 1 H), 2.00 (d, *J*=4.8 Hz, 1 H), 2.39 (m, 1 H), 2.92—2.99 (m, 1 H), 3.03 (d, *J*=1.4 Hz, 1 H), 3.95—3.99 (m, 1 H), 4.08 (d, *J*=8.5 Hz, 1 H), 5.40 (dd, *J*=16.2 and 5.8 Hz, 1 H), 5.52 (d, *J*=8.5 Hz, 1 H), 6.50 (dd, *J*=16.2 and 1.4 Hz, 1 H), 7.07—7.18 (m, 4 H), 7.27—7.34 (m, 3 H), 7.38—7.44 (m, 2 H), 7.50 (dd, *J*=7.0 and 1.5 Hz, 1 H), 7.58 (dd, *J*=6.3 and 2.0 Hz, 1 H), 7.65 (d, *J*=7.3 Hz, 1 H), 7.69 (d, *J*=8.2 Hz, 1 H), 7.80 (dd, *J*=8.0 and 1.2 Hz, 1 H), 7.94 (d, *J*=7.7 Hz, 1 H), 8.04 (d, *J*=8.5 Hz, 1 H); MS *m/z* (rel intensity) 683 (M^+, 2), 644 (1), 420 (14), 288 (53), 275 (34), 170 (100).

(3*S*,5*R*,6*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl}-3,5-dihydroxy-6-heptenoic Acid 1,5-Lactone (2e*). Sodium hydroxide aq solution (1 M, 0.5 ml) was added to a methanol (5.0 ml) solution of **14e*** (70 mg, 0.10 mmol). The mixture was stirred at room temperature for 12 h, poured into sodium acetate–acetic acid buffer (pH 4—5, 15 ml) and extracted with ethyl acetate. The organic layer was washed with sat. NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was treated by preparative TLC (hexane–ethyl acetate 1:1) to separate **11*** (26 mg, 91% recovery) from the desired dihydroxy carboxylic acid, which was dissolved in toluene (25 ml) and heated under reflux for 12 h. Concentration under vacuum followed by preparative TLC (hexane–ethyl acetate 1:2) gave **2e*** (22 mg, 53% yield) as a colorless foam. HPLC analysis (CHIRALPACK AS, hexane–isopropyl alcohol 9:1) of **2e*** showed a *cis*:*trans* ratio of 77:23 and 58% ee. R_f 0.19 (hexane–ethyl acetate 2:1), $[\alpha]_D^{20}$ +14.77° (*c* 1.57, $CHCl_3$); IR ($CHCl_3$) 3440, 3005, 1730, 1600, 1560, 1510, 1490, 1410, 1230, 1155, 1060, 970, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.03—1.08 (m, 2 H), 1.30—1.40 (m, 2 H), 1.56—1.60 (m, 1 H), 1.78 (m, 1 H), 1.89 (br, 1 H), 2.38 (m, 1 H), 2.60 (ddd, *J*=7.4, 4.0, and 1.5 Hz, 1 H), 2.70 (dd, *J*=13.0 and 4.8 Hz, 1 H), 4.25 (m, 1 H), 5.18 and 4.66 (m, 1 H, ratio 77:23), 5.62 (dd, *J*=16.1 and 6.2 Hz, 1 H), 6.72 (dd, *J*=16.1 and 1.4 Hz, 1 H), 7.17—7.25 (m, 4 H), 7.30—7.37 (m, 2 H), 7.61 (dd, *J*=6.1 and 2.1 Hz, 1 H), 7.96 (d, *J*=8.3 Hz, 1 H); MS *m/z* (rel intensity) 403 (M^+, 9), 316 (11), 288 (100), 274 (12).

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicylco-[2.2.1]heptan-2-*exo*-yl (3*S*,6*E*)-7-{2-Cyclopropyl-4-

(4-fluorophenyl)quinolin-3-yl}-3-hydroxy-5-oxo-6-heptenoate (16e*). DIBAL (1.00 M hexane solution, 0.70 ml, 0.70 mmol) was added to a THF (5.0 ml) solution of **13e*** (0.200 g, 0.29 mmol) at −90 °C, and the whole was stirred at −90 °C for 24 h before quenching with sat. Na_2SO_4 aq solution (0.1 ml). The resulting mixture was diluted with ethyl acetate (20 ml), dried ($MgSO_4$), and then concentrated in vacuo. The crude product was purified by column chromatography (hexane–ethyl acetate 4 : 1) to give **16e*** (0.111 g, 56% yield) along with the recovered **13e*** (75 mg, 38% yield).

16e*: R_f 0.13 (hexane–ethyl acetate 5 : 1), $[\alpha]_D^{20}$ −77.75° (*c* 0.98, $CHCl_3$). IR ($CHCl_3$) 2950, 1720, 1600, 1550, 1510, 1490, 1390, 1230, 1210, 1090, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.01 (s, 3 H), 1.08 (dq, *J*=8.0 and 3.5 Hz, 2 H), 1.23—1.27 (m, 1 H), 1.24 (s, 3 H), 1.33 (s, 3 H), 1.39—1.42 (m, 2 H), 1.57—1.62 (m, 2 H), 1.72—1.81 (m, 1 H), 1.89 (dd, *J*=15.9 and 7.9 Hz, 1 H), 1.95—2.04 (m, 5 H), 2.30 (m, 1 H), 3.47—3.55 (m, 1 H), 4.08 (d, *J*=8.7 Hz, 1 H), 5.53 (d, *J*=8.7 Hz, 1 H), 6.15 (d, *J*=16.5 Hz, 1 H), 7.17—7.21 (m, 4 H), 7.32—7.47 (m, 5 H), 7.48 (d, *J*=16.5 Hz, 1 H), 7.63—7.77 (m, 3 H), 7.77 (dd, *J*=8.0 and 1.2 Hz, 1 H), 7.97 (d, *J*=8.4 Hz, 1 H), 8.03 (d, *J*=8.4 Hz, 1 H); MS *m/z* (rel intensity) 681 (M^+, 0.6), 663 (M^+-H_2O, 1), 402 (15), 384 (12), 350 (8), 331 (11), 316 (13), 288 (79), 240 (31), 170 (100).

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicylco-[2.2.1]heptan-2-*exo*-yl (3*S*,5*R*,6*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-dihydroxy-6-heptenoate (14e*). Diethyl(methoxy)borane (16 mg, 0.16 mmol) was added to a solution of **16e*** (0.102 g, 0.15 mmol) in THF (2.0 ml) and methanol (0.5 ml) at −78 °C. The mixture was once warmed to room temperature under stirring over 15 min then cooled again at −78 °C. To the mixture was added $NaBH_4$ (28 mg, 0.74 mmol). After stirring at −78 °C for 4 h and warming to room temperature over 8 h, the mixture was quenched with acetic acid (0.5 ml). The reaction mixture was treated with sat. $NaHCO_3$ aq solution and extracted with diethyl ether. The organic layer was washed with sat. NaCl aq solution, dried ($MgSO_4$) and then concentrated in vacuo. Methanol (10 ml) was added to dissolve the residue and then removed in vacuo. This operation was repeated 10 times to decompose and evaporate organoboron compounds. The resulting crude product was purified by column chromatography (hexane–ethyl acetate 15 : 1) to give **14e*** (87 mg, 85% yield). R_f 0.36 (hexane–ethyl acetate 2 : 1), $[\alpha]_D^{20}$ −73.78° (*c* 1.03, $CHCl_3$).

(3*S*,5*R*,6*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl}-3,5-dihydroxy-6-heptenoic Acid 1,5-Lactone (2e*). Sodium hydroxide aq solution (1 M, 0.1 ml) was added to a methanol (5.0 ml) solution of **14e*** (60 mg, 0.09 mmol), and the mixture was stirred at room temperature for 12 h and poured into sodium acetate-acetic acid buffer (pH 4—5, 15 ml) and extracted with ethyl acetate. The organic layer was washed with sat. NaCl aq solution, dried ($MgSO_4$) and concentrated in vacuo. The residue was treated by preparative TLC (hexane–ethyl acetate 1 : 1) to separate **11*** (22 mg, 90% recovery) from the desired dihydroxy carboxylic acid, which was dissolved in toluene (25 ml) and heated to reflux for 12 h. Concentration under vacuum followed by preparative TLC (hexane–ethyl acetate 1 : 2) gave **2e*** (16 mg, 45% yield) as a colorless foam. HPLC analysis (CHIRALPACK AS, hexane–isopropyl alcohol 9 : 1) of **2e*** showed a *cis* : *trans* ratio of 96 : 4 and 93% ee.

2e*: R_f 0.19 (hexane–ethyl acetate 2 : 1), $[\alpha]_D^{20}$ +6.98° (*c* 1.74, $CHCl_3$). IR ($CHCl_3$) 3440, 3005, 1730, 1600, 1560, 1510, 1490, 1410, 1230, 1155, 1060, 970, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.03—1.08 (m, 2 H), 1.30—1.40 (m, 2 H), 1.56—1.60 (m, 1 H), 1.78 (m, 1 H), 1.89 (br, 1 H), 2.38 (m, 1 H), 2.60 (ddd, *J*=7.4, 4.0, and 1.5 Hz, 1 H), 2.70 (dd, *J*=13.0 and 4.8 Hz, 1 H), 4.25 (m, 1 H), 5.18 (m, 1 H), 5.62 (dd, *J*=16.1 and 6.2 Hz, 1 H), 6.72 (dd, *J*=16.1 and 1.4 Hz, 1 H), 7.17—7.25 (m, 4 H), 7.30—7.37 (m, 2 H), 7.61 (dd, *J*=6.1 and 2.1 Hz, 1 H), 7.96 (d, *J*=8.3 Hz, 1 H); MS *m/z* (rel intensity) 403 (M^+, 9), 316 (11), 288 (100), 274 (12). Found: C, 74.16; H, 5.59; N, 3.39%. Calcd for $C_{25}H_{22}FNO_3$: C, 74.43; H, 5.50; N, 3.47%.

(4*R*)-4,7,7-Trimethyl-3-*exo*-(1-naphthyl)bicylco-[2.2.1]heptan-2-*exo*-yl (3*R*,5*S*,6*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl}-3,5-dihydroxy-6-heptenoate (15e*). Dimethyl(ethoxy)borane (14 mg, 0.16 mmol) was added to **13e*** (0.100 g, 0.15 mmol) in THF (2.0 ml) and methanol (0.5 ml) at −78 °C under an argon atmosphere. The mixture was once warmed to room temperature under stirring over 15 min and then cooled again at −78 °C. Thereto was added $NaBH_4$ (28 mg, 0.74 mmol). After stirring at −78 °C for 4 h and warming to room temperature over 8 h, the mixture was quenched with acetic acid (0.5 ml). Workup, methanol treatment (10 times), followed by column chromatography (hexane–ethyl acetate 15 : 1), gave **15e*** (95 mg, 94% yield). R_f 0.36 (hexane–ethyl acetate 2 : 1), $[\alpha]_D^{20}$ −75.29° (*c* 1.02, $CHCl_3$). IR ($CHCl_3$) 3460, 3010, 2960, 1725, 1605, 1515, 1490, 1400, 1220, 1090, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.75—0.96 (m, 2 H), 1.02 (s, 3 H), 1.00—1.05 (m, 2 H), 1.27 and 1.26 (s, 3 H), 1.33 and 1.32 (s, 3 H), 1.31—1.37 (m, 2 H), 1.46—1.55 (m, 1 H), 1.57—1.63 (m, 3 H), 1.75—1.82 (m, 1 H), 1.91—1.98 (m, 1 H), 2.00 (br, 2 H), 2.39 (m, 1 H), 2.92—2.99 (m, 1 H), 3.09 and 3.17 (m, 1 H), 3.90—4.00 (m, 1 H), 4.08 (br d, *J*=8.5 Hz, 1 H), 5.36—5.47 (m, 1 H), 5.51—5.58 (m, 1 H), 6.50 and 6.51 (dd, *J*=16.2 and 1.4 Hz, 1 H), 7.07—7.18 (m, 5 H), 7.27—7.52 (m, 5 H), 7.54—7.83 (m, 4 H), 7.94 (m, 1 H), 8.04 (m, 1 H); MS *m/z* (rel intensity) 683 (M^+, 12), 642 (0.3), 420 (41), 386 (13), 288 (78), 275 (34), 263 (100), 207 (74), 170 (93).

(3*R*,5*S*,6*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl}-3,5-dihydroxy-6-heptenoic 1,5-Lactone (2e). Sodium hydroxide aq solution (1 M, 0.1 ml) was added to a methanol (5.0 ml) solution of **15e*** (90 mg, 0.13 mmol). The mixture was stirred at room temperature for 12 h, poured into sodium acetate–acetic acid buffer (pH 4—5, 15 ml), and extracted with ethyl acetate. The organic layer was washed with sat. NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo. The residue was treated by preparative TLC (hexane–ethyl acetate 1 : 1) to separate **11*** (33 mg, 90% recovery) from the crude dihydroxy carboxylic acid, which was dissolved in toluene (25 ml) and heated to reflux for 12 h. Concentration under vacuum followed by preparative TLC (hexane–ethyl acetate 1 : 2) gave **2e** (26 mg, 48% yield) as a colorless foam. HPLC analysis (CHIRALPACK AS, hexane–isopropyl alcohol 9 : 1) of the product showed a *cis* : *trans* ratio of 96 : 4 and an optical purity of 37% ee. R_f 0.19 (hexane–ethyl acetate 2 : 1), $[\alpha]_D^{20}$ −20.90° (*c* 0.56, $CHCl_3$). IR ($CHCl_3$) 3440, 3005, 1730, 1600, 1560, 1510,

1490, 1410, 1230, 1155, 1060, 970, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.03—1.08 (m, 2 H), 1.30—1.40 (m, 2 H), 1.56—1.60 (m, 1 H), 1.78 (m, 1 H), 1.88 (br, 1 H), 2.38 (m, 1 H), 2.60 (ddd, J=7.4, 4.0, and 1.5 Hz, 1 H), 2.70 (dd, J=13.0 and 4.8 Hz, 1 H), 4.25 (m, 1 H), 5.18 and 4.66 (m, 1 H, ratio 64:36), 5.62 (dd, J=16.1 and 6.2 Hz, 1 H), 6.72 (dd, J=16.1 and 1.4 Hz, 1 H), 7.17—7.25 (m, 4 H), 7.30—7.37 (m, 2 H), 7.61 (dd, J=6.1 and 2.1 Hz, 1 H), 7.96 (d, J=8.3 Hz, 1 H); MS m/z (rel intensity) 403 (M^+, 9), 316 (11), 288 (100), 274 (12).

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