Synthesis of Artificial HMG-CoA Reductase Inhibitors Based on the Olefination Strategy

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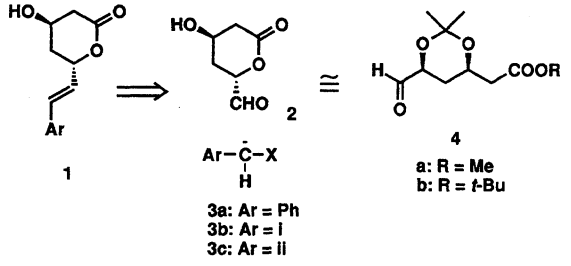
Synthetic methods were studied for optically active 6-oxo-3,5-isopropylidenedioxyhexanoate esters (**4**), which could be used as a key precursor of various kinds of artificial analogs of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. An enantiomer (+)-**4** was prepared by asymmetric reduction of β,δ-diketo esters derived from the Taber's alcohol or L-tartrate followed by a series of chemical transformations, and the desired enantiomer (−)-**4** was prepared by the same asymmetric reduction starting from D-tartrate. The key intermediate (−)-**4** was finally converted into a highly potent HMG-CoA reductase inhibitor, NK-104.

As discussed in our preceding paper,[1] potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase have been explored, which lower the cholesterol level in blood with less side effects and are shown to have a common structure, **1**.[2] For its convergent synthesis, it is desirable to find a general synthetic method which allows various structural modifications. Herein we focus on a synthetic method based on the Wittig-type olefination (Scheme 1).[3] The synthetic strategy shown in Scheme 1 involves connection of a β-hydroxy-δ-lactone unit with various kinds of aryl moiety through an (*E*)-1,2-vinylene bridge. Thus, 6-oxo-3,5-dihydroxyhexanoic acid 1,5-lactone (**2**) appeared to be a common building block for artificial HMG-CoA reductase inhibitors. The (*E*)-1,2-vinylene unit might be constructed by the Wittig-type olefination using an appropriate reagent, **3**. A protected form of **2** is equivalent to its acetal **4**.[3] Accordingly, we studied enantioselective synthesis of **4** and report herein two methods based on asymmetric reduction of β,δ-diketo esters[4] (Chart 1).



Scheme 1. Retrosynthesis.

Stereoselective Reduction of β,δ-Diketo Esters of the Taber's Alcohol. As discussed in our previous paper,[1] reduction of β,δ-diketo esters of the Taber's alcohol gave *syn*-β,δ-dihydroxy esters of high enantiomeric excess (ee). The particular substrate **5** having phenyl group at the olefin terminal is easily prepared by the condensation of *N*-methoxy-*N*-methyl cinnamamide and acetoacetate of the Taber's alcohol[5] and selectively reduced to *syn*-diol **6** by reduction[1] with $HAl(i\text{-}Bu)_2$ (DIBAL) and then with $NaBH_4$–Et_2BOMe (Scheme 2).[6] The chiral auxiliary was easily recovered by alkaline hydrolysis, and the resulting β,δ-dihydroxy carboxylic acid was esterified with excess diazomethane to give ester **7***. The free 1,3-diol moiety was protected as an acetonide to give **8*** in 81% yield. The C=C bond

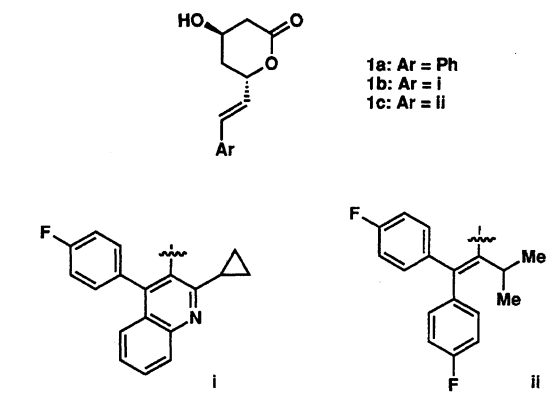


Chart 1.

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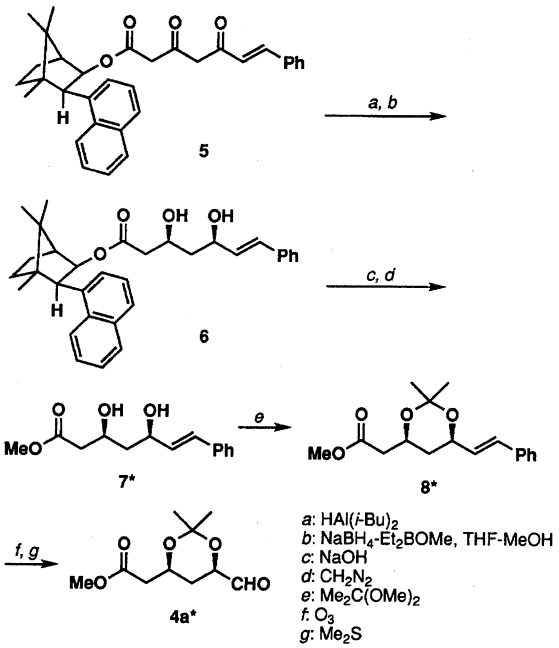


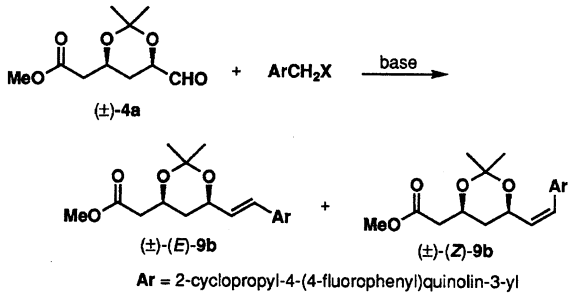
Scheme 2.

was cleaved by ozonolysis to give unstable aldehyde **4a*** showing (+) optical rotation. This was shown to be an enantiomer of **4a**.

We next studied the Wittig-type olefination of (±)-**4a** prepared from (±)-**7** (cf. Scheme 2), using 1 mol equivalent of a Wadsworth–Emmons-type olefination reagent **3b** ($X=P(O)(OEt)_2$)[7,8] under various conditions (Scheme 3). Results summarized in Table 1 were unsatisfactory in respect to efficiency and selectivity. The Wittig reagent **3b** ($X=PPh_3^+$) was effective but stereochemically unsatisfactory. However, a Warren-type reagent **3b** ($X=P(O)Ph_2$)[8] was found to be excellent to do the olefination highly selectively in high yields. Particularly, a hindered lithium amide like lithium 2,2,6,6-tetramethylpiperidide as a base nicely gave (±)-(*E*)-**9b** of high purity.

The best conditions were applied to **4a*** prepared as above, and we obtained **9b***, an enantiomeric precursor of our target **1b**. Since excellent % ee was attained by this approach, we have only to start with the enantiomer of the Taber's alcohol to prepare **4** and then **1** with the correct configuration (Chart 2).

The potential of this strategy is demonstrated again



Scheme 3.

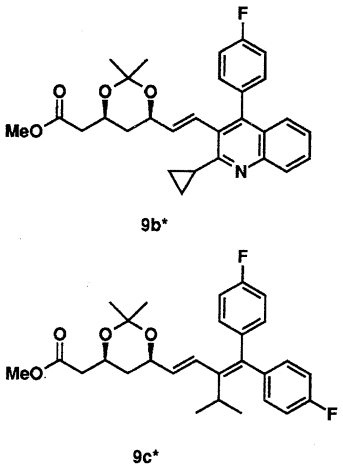
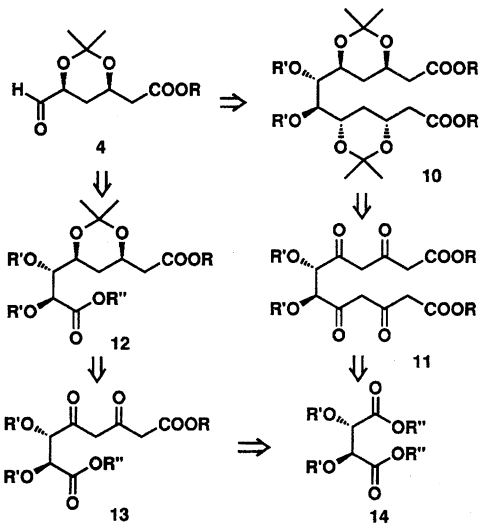


Chart 2.

by the synthesis of the precursor of **1c**. Thus, the aldehyde **4a*** was condensed with an appropriate reagent **3c** ($X=P(O)Ph_2$) to give **9c*** in good yield with high (*E*)-selectivity (Chart 2).

Synthetic Strategy Starting with Tartrate. Another strategy is summarized in Scheme 4. The requisite aldehyde **4** having a correct configuration may be derived by glycol cleavage of a bis-acetonide **10**. The bis-acetonide **10** may be prepared by *syn*-reduction of tetraketo diester **11**, which would be prepared by the reaction of D-tartrate and 2 mol of the dianion of acetoacetate. During the reduction of **11** to **10**, two six-membered chelates should be formed, each blocking one face of the other chelate and thus achieving double asymmetric reduction. To realize this concept, we attempted to prepare **11** by using various protecting group R′ in **14** and by activating the ester carbonyl in different ways. However, all our attempts to obtain **11** failed. Instead, a 1:1 product **13** was isolated in good yields. Therefore, we changed our strategy to the one starting with **13** as the key intermediate, namely, **4**⇒**12**⇒**13**⇒**14**.



Scheme 4.

Table 1. Olefination of (±)-**4a** with reagent **3b**

Preparation of **3b**			Olefination			
X	Base (1 equiv)	Conditions	Temperature	Yield/%	*E* : *Z*	Recovered $ArCH_2X$
$P(O)(OEt)_2$	*n*-BuLi	THF, 0 °C	−78 °C—r.t.	28	68 : 32	40
	n-BuLi	THF–HMPA, −78 °C	−78 °C—r.t.	36	44 : 56	27
	t-BuLi	THF, −78 °C	−78 °C—r.t.	41	68 : 32	46
	t-BuLi	THF, r.t.	r.t.	19	87 : 13	67
$P(O)Ph_2$	*n*-BuLi	THF, r.t.	r.t.	64	99 : 1	8
	n-BuLi	Et_2O, r.t.	r.t.	35	99 : <1	58
	n-BuLi	THF, 0 °C	0 °C—r.t.	51	98 : 2	38
	$LiN(i\text{-}Pr)_2$	THF, r.t.	r.t.	54	98 : 2	34
	$LiN(SiMe_3)_2$	THF, r.t.	r.t.	47	98 : 2	14
	$LiN(CMe_2CH_2)_2CH_2$	THF, r.t.	r.t.	76	98 : 2	16

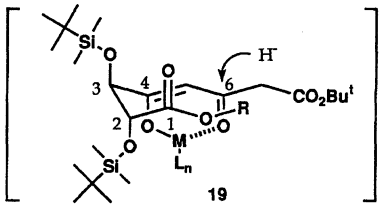
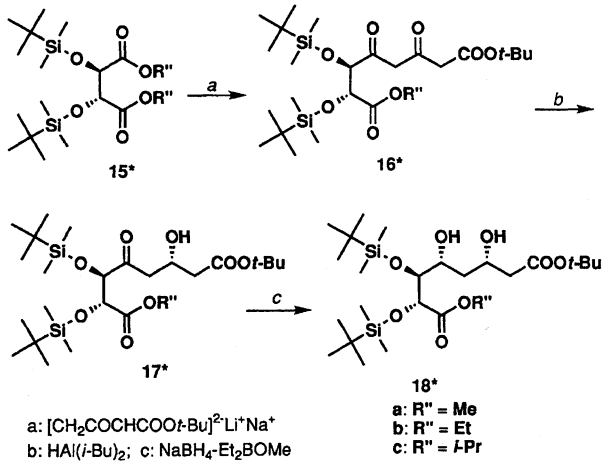


Chart 3.

(Scheme 4)

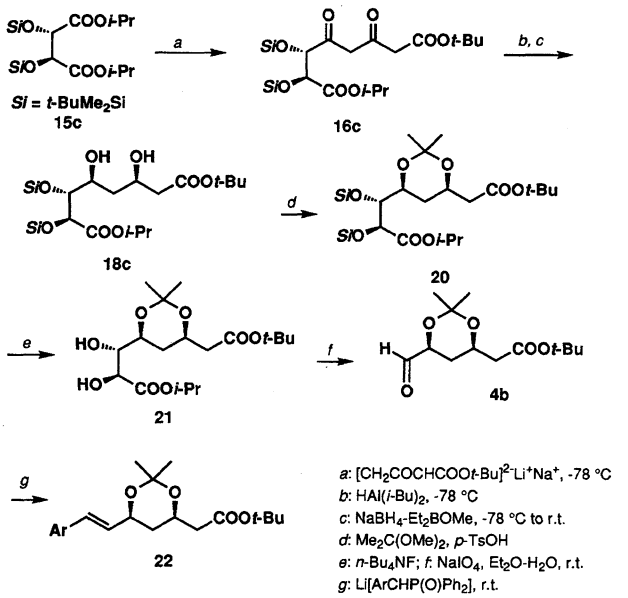
This strategy was done starting with naturally abundant L-tartaric acid at first. The glycol moiety of L-tartaric acid ester was protected by 2,2-dimethoxypropane, and the resulting acetonide was allowed to react with the dianion of *t*-butyl acetoacetate to give **13** ($R'_2=Me_2C$, R=*t*−Bu). Reduction of this diketo diester under a variety of conditions proceeded without any selectivity. We finally found that a bis(*t*-butyldimethylsilyl) group was a nice protecting group to attain high selectivity for carbonyl reduction. Thus, **15*** was allowed to react with the dianion of *t*-butyl acetoacetate to give **16*** in good yields. Although reduction of **16*** with $NaBH_4$–Et_2BOMe in MeOH–THF was not selective enough to give *syn*-diol **18*** in one step, reduction with DIBAL was highly selective to give **17***



Scheme 5.

Table 2. Reduction of **16*** with DIBAL to Give **17***

	R″	Yield/%	Diastereoselectivity
a	Me	51	89 : 11
b	Et	56	97 : 3
c	*i*-Pr	61	99 : 1



Scheme 6. Synthesis of NK-104.

(Scheme 5). Stereochemical assignment was effected by further reduction with $NaBH_4$–Et_2BOMe, protection of the 1,3-diol as acetonide, followed by glycol cleavage with $NaIO_4$ to give **4b***, an enantiomer of **4b**. Noteworthy is that the selectivity of the DIBAL reduction depended on the bulkiness of R″ group. By increasing bulkiness from Me, Et to *i*-Pr, the diastereoselectivity was improved as summarized in Table 2.

The stereochemical results may be understood in terms of a transition state **19** (Chart 3). ^1H NMR spectra of **16*** showed that the C(4)-carbonyl was enolized in organic solvent. Thus 1 mol of DIBAL is consumed to form a chelate shown in **19**. The conformation of the chelated compound is assumed to be fixed as **19**

by the silyl-protected glycol part so that these bulky silyloxy groups orient anti due to steric repulsion.[9] In addition, dipole repulsion between 1- and 6-oxo groups is expected to be operating to give **19** predominantly. Thus, hydride attacks C(6)-carbonyl preferentially from the *si*-face, opposite to the C(1) ester part. This model explains how the diastereoselectivity is improved by a bulky R, i.e. isopropyl group.

To obtain the requisite aldehyde **4** having a correct absolute configuration, we started with the silyl-protected diisopropyl D(−)-tartrate (**15c**). Reaction of **15c** with the dianion of *t*-butyl acetoacetate gave the requisite β,δ-diketo ester **16c**, which upon reduction with DIBAL and then with $NaBH_4$–Et_2BOMe gave *syn*-diol **18c**. Protection of the 1,3-diol moiety as acetonide gave **20** (Scheme 6). Desilylation of **20** with tetrabutylammonium fluoride gave **21**, which was oxidized with periodate to afford the desired aldehyde **4b** in good yield. The Warren-type olefination of **4b** afforded **22** highly selectively with (*E*)-configuration.[10]

Conclusion. We have demonstrated that the olefination route is an alternative convergent strategy for the synthesis of various types of artificial inhibitors of HMG-CoA reductase. This route allows us to prepare the aldehyde **4b** from diisopropyl D-(−)-tartrate and combine the aldehyde **4b** with a reagent having a general structure $Li[ArCHP(O)Ph_2]$. Since this strategy is apparently convergent and highly efficient, a variety of synthetic designs based on this method will be possible.

Experimental[1]

Methyl (3*S*, 5*R*, 6*E*)-7-Phenyl-3,5-dihydroxy-6-heptenoate (7*). Sodium hydroxide aq solution (1 M, 0.2 ml, 1 M=1 mol dm^{-3}) was added to (4*R*)-4,7,7-trimethyl-3-exo-(1-naphthyl)bicyclo[2.2.1]heptan-2-exo-yl (3*S*, 5*R*, 6*E*)-7-phenyl-3,5-dihydroxy-6-heptenoate (**6**)[1] (0.21 g, 0.42 mmol) in methanol (1 ml), and the resulting solution was stirred at room temperature for 12 h. The methanol was removed under reduced pressure, and the residue was diluted and extracted with diethyl ether. The aq layer was acidified with aq HCl and extracted with diethyl ether. The ethereal layer was treated with excess diazomethane ethereal solution. The excess diazomethane was quenched with acetic acid, and the reaction mixture was washed with sat. $NaHCO_3$ aq solution, dried ($MgSO_4$), and concentrated. Purification by column chromatography (silica gel, hexane–ethyl acetate 2:1) gave **7*** (92 mg, 87% yield) as a colorless oil. $[\alpha]_D^{20}$ +8.23° (*c* 1.19, $CHCl_3$), R_f 0.08 (hexane–ethyl acetate 2:1). IR ($CHCl_3$) 3475, 3005, 1720, 1490, 1435, 1205, 1110, 1070, 1030, 775, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.73 (dt, *J*=14.3 and 3.1 Hz, 1 H), 1.80 (dt, *J*=14.3 and 9.4 Hz, 1 H), 2.52 (dd, *J*=17.4 and 16.5 Hz, 1 H), 2.54 (dd, *J*=19.8 and 16.5 Hz, 1 H), 3.24 (s, 1 H), 3.72 (s, 3H), 3.74 (s, 1 H), 4.43 (m, 1 H), 4.59 (m, 1 H), 6.21 (dd, *J*=15.7 and 6.4 Hz, 1 H), 6.62 (d, *J*=15.7 Hz, 1 H), 7.24 (tt, *J*=7.2 and 1.3 Hz, 1 H), 7.31 (t, *J*=7.2 Hz, 2 H), 7.38 (d, *J*=7.2 Hz, 2 H); MS *m/z* (rel intensity) 250 (M^+, 3), 232 (M^+-H_2O, 4), 218 (4), 215 (4), 200 (15), 158 (60), 104 (100). Found: *m/z* 250.1244. Calcd for $C_{14}H_{18}O_4$: M, 250.1222.

Methyl (3*S*, 5*R*, 6*E*)-7-Phenyl-3,5-isopropylidenedioxy-6-heptenoate (8*). A solution of **7*** (90 mg, 0.36 mmol) and *p*-toluenesulfonic acid (5 mg) in 2,2-dimethoxypropane (1.0 ml) was stirred at room temperature for 6 h before dilution with diethyl ether. The whole was washed with sat. $NaHCO_3$ aq solution and then with sat. NaCl aq solution, dried ($MgSO_4$), and concentrated. Column chromatography of the residue (silica gel, hexane–ethyl acetate 10:1) gave **8*** (97 mg, 92% yield). $[\alpha]_D^{20}$ +6.66° (*c* 1.11, $CHCl_3$), R_f 0.78 (hexane–ethyl acetate 2:1). IR ($CHCl_3$) 3000, 1735, 1440, 1380, 1200, 1160, 1085, 1030, 770, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.40 (dd, *J*=11.4 and 10.2 Hz, 1 H), 1.45 (s, 3 H), 1.54 (s, 3 H), 1.74 (dt, *J*=12.3 and 2.5 Hz, 1 H), 2.52 (dd, *J*=15.6 and 6.2 Hz, 1 H), 2.60 (dd, *J*=15.6 and 6.9 Hz 1 H), 3.70 (s, 3 H), 4.40 (m, 1 H), 4.57 (m, 1 H), 6.16 (dd, *J*=15.6 and 6.2 Hz, 1 H), 6.60 (d, *J*=15.6 Hz, 1 H), 7.24 (tt, *J*=7.2 and 1.3 Hz, 1 H), 7.29 (t, *J*=7.2 Hz, 2 H), 7.37 (d, *J*=7.2 Hz, 2 H); MS *m/z* (rel intensity) 290 (M^+, 3), 232 (4), 215 (15), 158 (50), 104 (100). Found: *m/z* 290.1496. Calcd for $C_{17}H_{22}O_4$: M, 290.1498.

Methyl (3*S*, 5*R*)-3,5-Isopropylidenedioxy-6-oxohexanoate (4a*). Ozone was introduced into a methanol (ca. 2 ml) solution of **8*** (0.120 g, 0.41 mmol) at −78°C until the blue color persisted. Excess ozone was removed by flushing with nitrogen, and the resulting ozonide was quenched with dimethyl sulfide (0.5 ml) at −78°C. The whole mixture was stirred at room temperature overnight. Concentration followed by column chromatography afforded **4a*** (49 mg, 90% yield) as a relatively unstable colorless oil. $[\alpha]_D^{20}$ +20.00° (*c* 1.30, $CHCl_3$), R_f 0.14 (hexane–ethyl acetate 2:1). IR ($CHCl_3$) 2950, 1735, 1435, 1380, 1080, 1030, 775, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.35 (dt, *J*=12.9 and 12.0 Hz, 1 H), 1.46 (s, 3 H), 1.50 (s, 3 H), 1.86 (dt, *J*=12.9 and 2.7 Hz, 1 H), 2.44 (dd, *J*=15.8 and 6.0 Hz, 1 H), 2.58 (dd, *J*=15.8 and 7.0 Hz, 1 H), 3.70 (s, 3 H), 4.33 (m, 1 H), 4.38 (m, 1 H), 9.58 (s, 1 H); MS *m/z* (rel intensity) 201 (M^+-Me, 24), 129 (31), 97 (36), 59 (100).

2- Di(4- fluoropheny)methylidene- 3- methylbutyl-(diphenyl)phosphine Oxide. To lithium diisopropylamide (42.2 mmol), prepared form butyllithium (1.68 M hexane solution, 25.1 ml, 42.2 mmol) and diisopropylamine (4.27 g, 42.2 mmol) in THF (100 ml) at −78°C and by stirring for 15 min, was added ethyl 3-methylbutyrate (5.0 g, 38.4 mmol) in THF (50 ml) at −78°C, and the resulting solution was stirred for 30 min at −78°C before addition of a THF (50 ml) solution of 4,4′-difluorobenzophenone (9.20 g, 42.2 mmol) at −78°C. The whole mixture was stirred at −78°C for 2 h and at 0 °C for 10 min and was then quenched with NH_4Cl aq solution. Workup gave a crude aldol product, which was dissolved along with *p*-toluenesulfonic acid (0.20 g) in toluene (100 ml) and heated under reflux for 12 h. Neutralization with sat. $NaHCO_3$ aq solution followed by workup afforded a crude α,β-unsaturated ester, which was dissolved in dichloromethane (100 ml) and reduced with DIBAL (21.2 ml, 0.119 mol dissolved in dichloromethane 100 ml) at 0 °C for 2 h. The excess aluminium reagent was quenched with dil aq HCl, and the reaction mixture was extracted with dichloromethane. Workup afforded 2-di(4-fluorophenyl)methylene-3-methyl-1-butanol (11.3 g, quantitative yield), which exhibited ^{1}H NMR ($CDCl_3$) δ=1.11 (d, *J*=6.9 Hz, 6 H), 1.30 (t, *J*=5.5 Hz, 1 H), 2.75 (m, *J*=7.0

Hz, 1 H), 4.13 (d, J=5.0 Hz, 2 H), 6.95—7.02 (m, 4 H), 7.07—7.12 (m, 2 H), 7.18—7.23 (m, 2H).

Phosphorus tribromide (2.0 ml, 1.69 mmol) was added to a solution of 2-di(4-fluorophenyl)methylene-3-methyl-1-butanol (3.0 g, 10.4 mmol) in toluene (20 ml) and dichloromethane (20 ml) at room temperature, and the whole was stirred for 2 h before neutralization with $NaHCO_3$ aq solution. Extractive workup gave a crude bromide which was dissolved in toluene (30 ml) and heated along with ethyl diphenylphosphinite (4.79 g, 20.8 mmol) to reflux for 18 h. All the volatile material was removed in vacuo, and the residue was purified by column chromatography (silica gel, hexane–ethyl acetate 4 : 1) to give 2-di(4-fluorophenyl)methylidene-3-methylbutyl(diphenyl)phosphine oxide (4.9 g, 94% yield). Mp 185 °C, R_f 0.11 (hexane–ethyl acetate 5 : 1). IR ($CHCl_3$) 3600, 2950, 1600, 1500, 1220, 1160, 1100, 1030, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.99 (d, J=6.9 Hz, 6 H), 2.78 (heptet, J=6.9 Hz, 1 H), 3.38 (d, J=14.5 Hz, 2 H), 6.75 (td, J=8.7 and 1.9 Hz, 2 H), 6.94 (tt, J=8.7 and 1.9 Hz, 4 H), 7.06 (dd, J=8.7 and 5.5 Hz, 2 H), 7.34—7.53 (m, 10 H). Found: C, 75.97; H, 5.71%. Calcd for $C_{30}H_{27}F_2OP$: C, 76.26; H, 5.76%.

Methyl (3*S*, 5*R*, 6*E*)-8-di(4-fluorophenyl)methylidene-3,5-isopropylidenedioxy-9-methyl-6-decenoate (9c*). To lithium 2,2,6,6-tetramethylpyperidide (0.26 mmol), prepared by treating 2,2,6,6-tetramethylpyperidine (37 mg, 0.26 mmol) in THF (2.0 ml) with butyllithium (1.62 M hexane solution, 0.16 ml, 0.26 mmol) at −78°C for 15 min, was added at −78°C 2-di(4-fluorophenyl)methylidene-3-methylbutyl(diphenyl)phosphine oxide (0.122 g, 0.26 mmol) in THF (4.0 ml), and the mixture was stirred at room temperature for 30 min. To the carbanion **3c** thus prepared was added a THF (2.0 ml) solution of **4a*** (50 mg, 0.23 mmol), and the whole mixture was stirred at room temperature for 3 h before quenching with sat. $NaHCO_3$ aq solution. Workup followed by purification by column chromatography gave **9c*** (75 mg, 72% yield) which was shown to be a mixture of (*E*) : (*Z*)=98 : 2 by ^1H NMR. $[\alpha]_D^{20}$ +120.00° (*c* 1.00, $CHCl_3$), R_f 0.38 (hexane–ethyl acetate 5 : 1). IR ($CHCl_3$) 3000, 1730, 1600, 1500, 1440, 1380, 1220, 1160, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.10 (d, J=7.1 Hz, 3 H), 1.12 (d, J=7.1 Hz, 3 H), 1.36 (s, 3 H), 1.44 (s, 3 H), 2.34 (dd, J=15.6 and 6.4 Hz, 1 H), 2.53 (dd, J=15.6 and 6.7 Hz, 1H), 2.86 (heptet, J=7.1 Hz, 1 H), 3.69 (s, 3 H), 4.22—4.31 (m, 2H), 5.59 (dd, J=16.3 and 6.5 Hz, 1 H), 6.11 (d, J=16.3 Hz, 1 H), 6.89—7.08 (m, 8H); MS m/z (rel intensity) 470 (M^+, 9), 412 (8), 369 (40), 241 (100), 155 (15). Found: m/z 470.2265. Calcd for $C_{28}H_{32}F_2O_4$: M, 470.2266.

[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl(diphenyl)phosphine Oxide. To 2-cyclopropyl-4-(4-fluorophenyl)-3-(hydroxymethyl)quinoline[10,11] (6.0 g, 20.5 mmol) in dichloromethane (20 ml) and toluene (40 ml) was added phosphorus tribromide (4.0 ml, 42.1 mmol) at room temperature, and the resulting mixture was stirred for 3 h at room temperature before quenching with sat. $NaHCO_3$ aq solution. Workup gave the corresponding bromide (7.2 g, 98%) which showed ^1H NMR ($CDCl_3$) δ= 1.12—1.16 (m, 2 H), 1.37—1.41 (m, 2 H), 2.51 (m, 1 H), 4.59 (s, 2 H), 7.40 (m, 6 H), 7.62 (dd, J=6.8 and 1.6 Hz, 1 H), 7.97 (d, J=8.9 Hz, 1 H) and used for the next reaction without purification.

A toluene (20 ml) solution of 3-bromomethyl-2-cyclopropyl-4-(4-fluorophenyl)quinoline (1.00 g, 2.80 mmol) and ethyl diphenylphosphinite (1.30 g, 5.65 mmol) was heated under reflux for 12 h. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, hexane–ethyl acetate 1 : 1) to give the title compound (1.38 g, quantitative yield) as a colorless solid. R_f 0.11 (hexane–ethyl acetate 2 : 1). IR ($CHCl_3$) 2950, 1605, 1510, 1490, 1435, 1210, 1110, 1025, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (dd, J=8.8 and 3.1 Hz, 2 H), 1.20—1.24 (m, 2 H), 2.55—2.61 (m, 1 H), 4.04 (d, J=14.0 Hz, 2 H), 6.78 (d, J=5.5 Hz, 1 H), 6.80 (d, J=5.5 Hz, 1 H), 6.97 (d, J=8.7 Hz, 1 H), 6.99 (d, J=8.7 Hz, 1 H), 7.05 (d, J=8.4 Hz, 1 H), 7.24 (td, J=7.0 and 1.2 Hz, 1 H), 7.33—7.51 (m, 10 H), 7.57 (t, J=7.2 Hz, 1 H), 7.95 (d, J=8.3 Hz, 1 H); MS m/z (rel intensity) 477 (M^+, 3), 449 (0.1), 352 (4), 246 (8), 201 (50), 124 (25), 77 (100).

Diethyl [2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methylphosphonate. A toluene (30 ml) solution of 3-bromomethyl-2-cyclopropyl-4-(4-fluorophenyl)-quinoline (4.00 g, 10.2 mmol) and triethylphosphite (3.50 ml, 20.4 mmol) was heated under reflux for 12 h. Concentration followed by column chromatography gave the title phosphonate reagent (4.14 g, quantitative yield) as colorless solid. Mp 80 °C, R_f 0.09 (hexane–ethyl acetate 5 : 1). IR ($CHCl_3$) 2950, 1600, 1510, 1490, 1435, 1240, 1145, 1020, 970, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.09 (dd, J=8.0 and 3.1 Hz, 2 H), 1.19 (t, J=7.0 Hz, 6 H), 1.29—1.33 (m, 2 H), 2.61—2.67 (m, 1 H), 3.43 (d, J=22.5 Hz, 2 H), 3.84—4.01 (m, 4 H), 7.17—7.35 (m, 6 H), 7.59 (dt, J=7.0 and 1.2 Hz, 1 H), 8.95 (d, J=8.4 Hz, 1 H); MS m/z (rel intensity) 413 (M^+, 63), 385 (4), 356 (4), 328 (5), 276 (100).

[2-Cyclopropy-4-(4-fluorophenyl)quinolin-3-yl]methyltriphenylphosphonium Bromide. Triphenylphosphine (2.81 g, 10.7 mmol) was added to a toluene solution (50 ml) of 3-bromomethyl-2-cyclopropyl-4-(4-fluorophenyl)quinoline (4.00 g, 10.2 mmol), and the mixture was heated under reflux for 5 h. The precipitates were collected by filtration, washed with toluene, and dried to give the phosphonium salt (6.80 g, quantitative yield) as a white powder. Mp 245 °C (decomp). IR ($CHCl_3$) 3300, 3050, 1600, 1520, 1495, 1440, 1320, 1220, 1150, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.3—0.7 (m, 2 H), 1.2—0.9 (m, 2 H), 2.5—2.0 (m, 1 H), 5.5 (d, J=14.4 Hz, 2 H), 8.0—8.6 (m, 23 H).

Methyl 7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-*syn*-isopropylidenedioxy-6-heptenoate ((±)-9b*). With the Phosphonate Reagent. A pentane solution of *t*-butyllithium (1.60 M, 0.15 ml, 0.24 mmol) was added to diethyl [2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methylphosphonate (0.100 g, 0.24 mmol) in THF (3.0 ml) at −78°C under an argon atmosphere, and the resulting mixture was stirred for 30 min before addition of (±)-**4a** (50 mg, 0.23 mmol) in THF (2.0 ml). The reaction mixture was gradually warmed from −78°C to 0 °C over 3 h and stirred at room temperature for 2 h. Workup followed by column chromatography (silica gel, hexane–ethyl acetate 10 : 1) gave methyl (*Z*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-*syn*-isopropylidenedioxy-6-heptenoate [(±)-(*Z*)-**9b**] (14 mg, 12% yield) and (±)-(*E*)-**9b** (31 mg, 29% yield) along with the recovered phosphonate (46 mg, 46%).

The (*Z*)-isomer showed R_f 0.40 (hexane–ethyl acetate

5:1). IR ($CHCl_3$) 3000, 1730, 1600, 1510, 1490, 1380, 1230, 1160, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.04 (dd, J=8.1 and 3.3 Hz, 2 H), 1.25—1.31 (m, 2 H), 1.37 (s, 3 H), 1.35—1.40 (m, 2 H), 1.46 (s, 3 H), 2.29 (dd, J=15.5 and 6.3 Hz, 1 H), 2.41—2.46 (m, 1 H), 2.48 (dd, J=15.5 and 6.8 Hz, 1 H), 3.64 (s, 3 H), 4.06—4.13 (m, 1 H), 4.30—4.38 (m, 1 H), 5.61 (dd, J=11.4 and 8.2 Hz, 1 H), 6.42 (d, J=11.4 Hz, 1 H), 7.15—7.37 (m, 6 H), 7.62 (dd, J=6.7 and 1.5 Hz, 1 H), 7.96 (d, J=8.2 Hz, 1 H); MS m/z 475 (M^+, 6), 416 (8), 400 (5), 344 (21), 288 (100), 275 (43).

The (*E*)-isomer exhibited mp 133 °C, R_f 0.33 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3000, 1730, 1605, 1510, 1490, 1380, 1230, 1160, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.04 (dd, J=8.1 and 3.3 Hz, 2 H), 1.25—1.31 (m, 2 H), 1.37 (s, 3 H), 1.35—1.40 (m, 2 H), 1.46 (s, 3H), 2.35 (dd, J=15.6 and 6.4 Hz, 1 H), 2.43 (m, 1 H), 2.54 (dd, J=15.6 and 6.7 Hz, 1 H), 3.71 (s, 3 H), 4.25—4.32 (m, 1 H), 4.33—4.38 (m, 1 H), 5.57 (dd, J=16.3 and 6.1 Hz, 1 H), 6.55 (dd, J=16.3 and 1.2 Hz, 1 H), 7.15—7.37 (m, 6 H), 7.58 (dd, J=6.6 and 1.6 Hz, 1 H), 7.95 (d, J=8.4 Hz, 1H); MS m/z (rel intensity) 475 (M^+, 6), 416 (8), 400 (5), 344 (21), 288 (100), 275 (43). Found: m/z 475.2133. Calcd for $C_{29}H_{30}FO_4N$, M, 475.2156.

With the Triphenylphosphonium Salt. Butyllithium (0.42 ml, 0.67 mmol) was added at −70°C to [2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyltriphenylphosphonium bromide (0.414 g, 0.67 mmol) in THF (15 ml), and the mixture was stirred at −78°C for 30 min. A THF (5 ml) solution of (±)-**4b** (0.21 g, 0.78 mmol) was added to the ylide solution at −78°C, and the mixture was stirred for 2 h at −78°C and gradually warmed to room temperature overnight. Workup followed by purification gave *t*-butyl (3*R*, 5*S*, *Z*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl-3,5-*syn*-isopropylidenedioxy-6-heptenoate (0.140 g, 40% yield) and its (*E*)-isomer (0.20 g, 58% yield). The (*Z*)-isomer exhibited R_f 0.40 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3450, 3000, 1720, 1595, 1560, 1510, 1490, 1380, 1310, 1260, 1220, 1200, 1160, 1100, 1030, 970, 950, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.8—1.7 (m, 21 H), 2.1—2.7 (m, 3 H), 3.7—4.2 (m, 2 H), 5.6 (dd, J=11.8 Hz, 1 H), 6.4 (d, J=11 Hz, 1 H), 7.0—8.1 (m, 8 H); MS m/z (rel intensity) 518 (M^++H, 100), 462, 404, 386, 344, 316, 288, 274, 262, 220, 173, 154, 136. The (*E*)-isomer exhibited mp 46 °C, R_f 0.33 (hexane–ethyl acetate 5:1). IR (KBr) 3450, 3000, 1720, 1600, 1560, 1510, 1490, 1380, 1310, 1260, 1220, 1200, 1160, 1100, 1030, 970, 950, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.85—1.7 (m, 21 H), 2.2—2.6 (m, 3 H), 4.0—4.5 (m, 2 H), 5.5 (dd, J=16.6 Hz, 1 H), 6.5 (d, J=16 Hz, 1 H), 7.0—8.0 (m, 8 H); MS m/z (rel intensity) 518 (M^++H, 100), 462, 404, 386, 344, 316, 288, 274, 262, 220, 173, 154, 136.

With the Diphenylphosphine Oxide Reagent. To lithium 2,2,6,6-tetramethylpiperidide (0.62 mmol), prepared from 2,2,6,6-tetramethylpiperidine (37 mg, 0.26 mmol) and butyllithium (1.62 M hexane solution, 0.16 ml, 0.26 mmol) in THF (2.0 ml) at −78°C, was added [2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]methyl(diphenyl)phosphine oxide (0.115 g, 0.24 mmol) in THF (4.0 ml) at −78°C, and the resulting mixture was stirred at room temperature for 30 min before treatment with (±)-**4a** (50 mg, 0.23 mmol) in THF (2.0 ml) at room temperature. The whole was stirred for 3 h at room temperature and worked up. Purification by column chromatography afforded a 98:2 mixture (^1H NMR) of (*E*)- and (*Z*)-(±)-**9b** (84 mg, 76% yield) along with the recovered phosphine oxide reagent (18 mg, 16%).

Similarly, **4a*** was converted into **9b***: $[\alpha]_D^{20}$ +19.2° (*c* 0.96, $CHCl_3$) and **9c***: $[\alpha]_D^{20}$ +120.0° (*c* 1.00, $CHCl_3$).

(3*R*, 5*S*, 6*E*)-7-{2-Cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl}-3,5-dihydroxy-6-heptenoic Acid 1,5-Lactone (1b*). A dichloromethane (5 ml) solution of **8b*** (0.26 g, 0.5 mmol) was added to a mixture of dichloromethane (2 ml) and trifluoroacetic acid (0.17 g, 1.5 mmol). The mixture was stirred at room temperature for 24 h and neutralized with $NaHCO_3$ aq solution under ice-cooling. Extraction (CH_2Cl_2), washing (sat. NaCl aq solution), drying (Na_2SO_4), concentration, followed by column chromatography (silica gel, hexane–ethyl acetate 5:1) gave **1b*** (0.15 g, 75% yield) as colorless crystals. Mp 139 °C, R_f 0.19 (hexane–ethyl acetate 2:1), $[\alpha]_D^{20}$ +9.0° (*c* 1.0, $CHCl_3$). 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, 1H), 1.78 (m, 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).

Tartrates Protected by Bis(*t*-butyldimethylsilyl) Group. A DMF (20 ml) solution of a tartrate (21.3 mmol), imidazole (4.36 g, 64.0 mmol), *t*-butyldimethylsilyl chloride (9.65 g, 64.0 mmol) was stirred at 60 °C for 12 h. The mixture was diluted with diethyl ether, washed with dil aq HCl and then with NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo to give the corresponding bis(*t*-butyldimethylsilyl) ether as colorless solid.

15a*: 88% yield, $[\alpha]_D^{20}$ +49.06° (*c* 2.03, $CHCl_3$). IR ($CHCl_3$) 1760, 1730, 1470, 1435, 1250, 1130, 1020, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.01 (s, 6 H), 0.08 (s, 6 H), 0.87 (s, 18 H), 3.72 (s, 6 H), 4.64 (s, 2 H). MS m/z (rel intensity) 349 (M^+−*t*-Bu, 72), 289 (33), 175 (9), 147 (36), 89 (42), 73 (100). Found: C, 53.3; H, 9.28%. Calcd for $C_{18}H_{38}O_6Si_2$: C, 53.16; H, 9.42%.

15b*: Quantitative yield, $[\alpha]_D^{20}$ +47.00° (*c* 1.76, $CHCl_3$). IR ($CHCl_3$) 2925, 2850, 1720, 1470, 1370, 1255, 1215, 1130, 1030, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.01 (s, 6H), 0.09 (s, 6H), 0.08 (s, 18 H), 1.29 (t, J=7.2 Hz, 6 H), 4.09—4.25 (m, 4 H), 4.62 (s, 2 H); MS m/z (rel intensity) 419 (M^+−Me, 2) 377 (M^+−*t*-Bu, 48), 231 (3), 189 (8), 161 (11), 133 (12), 73 (100). Found: m/z 419.2255. Calcd for $C_{19}H_{39}O_6Si_2$: M−CH_3, 419.2283.

15c*: Quantitative yields, $[\alpha]_D^{20}$ +50.06° (*c* 2.02, $CHCl_3$). IR ($CHCl_3$) 2925, 2850, 1750, 1705, 1470, 1370, 1250, 1130, 1100, 920, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.01 (s, 6 H), 0.08 (s, 6 H), 0.89 (s, 18 H), 1.26 (d, J=6.3 Hz, 12 H), 4.55 (s, 2H), 5.01 (heptet, J=6.3 Hz, 2 H); MS m/z (rel intensity) 463 (M^+, 1), 405 (5), 363 (9), 321 (32), 275 (16), 231 (12), 117 (32), 73 (100), 43 (53).

15c: Quantitative yield, $[\alpha]_D^{20}$ −50.10° (*c* 2.04, $CHCl_3$). Found: m/z 405.2135. Calcd for $C_{18}H_{37}O_4Si_2$: M−C_4H_9, 405.2127.

Isopropyl (2*S*,3*S*)-7-*t*-Butoxycarbonyl-2,3-bis(*t*-butyldimethylsilyloxy)-4,6-dioxoheptanoate (16c).

To the dianion of *t*-butyl acetoacetate (0.076 mmol), prepared by treatment of *t*-butyl acetoacetate (12.0 g, 0.076 mol) with NaH (60% in oil, 3.03 g, 0.076 mol) suspended in THF (150 ml) at −78°C and then with butyllithium (1.60 M hexane solution, 47.3 ml, 0.076 mol) at 0 °C for 5 min, was added a THF (50 ml) solution of **15c** (7.0 g, 15.1 mmol) at −78°C, and the mixture was stirred for 16 h before quenching with dil aq HCl. Workup followed by column chromatography (silica gel, hexane–ethyl acetate 20:1) afforded **16c** (6.2 g, 74% yield) as a colorless oil. R_f 0.64 (hexane–ethyl acetate 5:1), $[\alpha]_D^{20}$ −91.84° (*c* 2.04, $CHCl_3$). IR ($CHCl_3$) 2925, 2850, 1725, 1600, 1465, 1365, 1290, 1250, 1140, 1100, 915, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.09 (s, 3 H), 0.03 (s, 9 H), 0.86 (s, 9H), 0.91 (s, 9H), 1.25 (d, J=6.2 Hz, 6 H), 1.46 (s, 9 H), 3.25 (d, J=1.7 Hz, 1 H), 4.42 (d J=2.6 Hz, 1 H), 4.51 (d, J=2.6 Hz, 1 H), 5.00 (heptet, J=6.2 Hz, 1 H), 6.01 (s, 1 H), 14.98 (br s, 1 H); MS *m/z* (rel intensity) 561 (M^+, trace), 503 (M^+-t-Bu, 1), 447 (50), 407 (21), 387 (53), 315 (7), 273 (17), 185 (6), 129 (24), 73 (100).

Similarly, the following were prepared.

Methyl (2*R*, 3*R*)-7-*t*-Butoxycarbonyl-2,3-bis(*t*-butyldimethylsilyloxy)-4,6-dioxoheptanoate (16a*): 76% yield, $[\alpha]_D^{20}$ +94.54° (*c* 2.02, $CHCl_3$), R_f 0.61 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 2950, 2925, 2850, 1760, 1725, 1600, 1470, 1365, 1290, 1250, 1150, 1030, 915, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.09 (s, 3 H), 0.00 (s, 3 H), 0.03 (s, 6 H), 0.86 (s, 9 H), 0.90 (s, 9 H), 1.46 (s, 9 H), 3.25 (d, J=1.9 Hz, 1 H), 3.72 (s, 3 H), 4.52 (s, 2 H), 6.02 (s, 1 H), 14.99 (br s, 1 H); MS *m/z* (rel intensity) 532 (M^+, trace), 475 (M^+-t-Bu, 1), 419 (25), 349 (14), 289 (12), 231 (9), 227 (6), 147 (18), 73 (100). Found: *m/z* 419.1533. Calcd for $C_{17}H_{31}O_8Si_2$: $M-C_4H_9-C_4H_8$, 419.1556.

Ethyl (2*R*,3*R*)-7-*t*-Butoxycarbonyl-2,3-bis(*t*-butyldimethylsilyloxy)-4,6-dioxoheptanoate (16b*): 74% yield, $[\alpha]_D^{20}$ +94.09° (*c* 2.02, $CHCl_3$), R_f 0.68 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 2950, 2925, 2850, 1760, 1600, 1470, 1365, 1290, 1250, 1110, 1020, 910, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.09 (s, 3 H), 0.00 (s, 3 H), 0.02 (s, 3 H), 0.03 (s, 3 H), 0.85 (s, 9 H), 0.90 (s, 9 H), 1.28 (t, J=7.2 Hz, 3 H), 1.46 (s, 9 H), 3.30 (s, 1 H), 4.05—4.25 (m, 2 H), 4.49 (d, J=2.4 Hz, 1 H), 4.53 (d, J=2.4 Hz, 1 H), 6.02 (s, 1 H), 14.96 (br s, 1 H); MS *m/z* (rel intensity) 529 (M^+, trace), 489 (M^+-t-Bu, 1), 433 (29), 359 (4), 301 (7), 231 (11), 185 (5), 129 (13), 73 (100), 57 (91). Found: *m/z* 498.2353. Calcd for $C_{22}H_{41}O_8Si_2$: $M-C_4H_9$, 489.2338.

Isopropyl (2*R*, 3*R*)-7-*t*-Butoxycarbonyl-2,3-bis(*t*-butyldimethylsilyloxy)-4,6-dioxoheptanoate (16c*): 74% yield, $[\alpha]_D^{20}$ +91.89° (*c* 2.02, $CHCl_3$).

Isopropyl (2*S*, 3*S*, 6*R*)-7-*t*-Butoxycarbonyl-2,3-bis(*t*-butyldimethylsilyloxy)-6-hydroxy-4-oxoheptanoate (17c): DIBAL (1.0 M in hexane, 2.2 ml, 2.20 mmol) was added drop by drop to **16c** (0.56 g, 1.00 mmol) in THF (5 ml) and hexane (3 ml) at −78°C, and the resulting mixture was stirred for 4 h at −78°C before quenching by dropwise addition of sat. Na_2SO_4 aq solution (10 drops). The organic layer was dried ($MgSO_4$) and filtered. Concentration followed by column chromatography (silica gel, hexane–ethyl acetate 20:1) afforded **17c** (0.33 g, 60% yield) as a colorless oil. $[\alpha]_D^{20}$ −37.45° (*c* 2.02, $CHCl_3$), R_f 0.57 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3525, 2925, 2850, 1710, 1470, 1365, 1290, 1250, 1145, 1100, 915, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.00 (s, 3 H), 0.01 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 9H), 1.25 (d, J=6.2 Hz, 6 H), 1.45 (s, 9 H), 2.41 (dd, J=16.0 and 7.6 Hz, 1 H), 2.46 (dd, J=16.0 and 5.1 Hz, 1 H), 2.82 (dd, J=18.7 and 7.5 Hz, 1 H), 2.92 (dd, J=18.7 and 4.8 Hz, 1 H), 3.38 (d, J=3.5 Hz, 1 H), 4.33 (d J=3.5 Hz, 1 H), 4.38—4.45 (m, 1 H), 4.43 (d, J=3.5 Hz, 1 H), 5.00 (heptet, J=6.2 Hz 1 H); MS *m/z* (rel intensity) 487 (M^+-H_2O-t-Bu, 4), 439 (5), 431 (5), 389 (9), 371 (4), 299 (4), 239 (7), 231 (7), 201 (5), 149 (10), 73 (100). Found: *m/z* 487.2579. Calcd for $C_{23}H_{43}O_7Si_2$: $M-C_4H_9-H_2O$, 487.2545.

In a similar way, the following hydroxy ketones **17a***—**17c*** were prepared.

17a*: $[\alpha]_D^{20}$ +43.08° (*c* 2.07, $CHCl_3$), R_f 0.57 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3475, 2925, 2850, 1710, 1470, 1365, 1290, 1250, 1145, 1100, 915, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.03 (s, 3 H), −0.03 (s, 3 H), 0.02 (s, 3 H), 0.03 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.43 (s, 9 H), 2.39 (dd, J=16.2 and 7.5 Hz, 1 H), 2.45 (dd, J=16.2 and 5.1 Hz, 1 H), 2.80 (dd, J=18.8 and 7.4 Hz, 1 H), 2.89 (dd, J=18.8 and 5.0 Hz, 1 H), 3.34 (d, J=3.6 Hz, 1 H), 3.69 (s, 3 H), 4.35 (d, J=2.9 Hz, 1 H), 4.36—4.41 (m, 1 H), 4.53 (d, J=2.9 Hz, 1 H); MS *m/z* (rel intensity) 536 (M^+, 2), 480 (M^+-t-Bu, 1), 462 (M^+-H_2O-t-Bu, 8), 402 (16), 356 (4), 289 (7), 271 (18), 201 (10), 147 (11), 73 (100). Found: *m/z* 459.2223. Calcd for $C_{21}H_{39}O_7Si_2$: $M-C_4H_9-H_2O$, 459.2232.

17b*: $[\alpha]_D^{20}$ +43.54° (*c* 2.03, $CHCl_3$), R_f 0.49 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3425, 2950, 2850, 1750, 1710, 1470, 1390, 1365, 1255, 1150, 1105, 1030, 915, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=−0.03 (s, 3 H), −0.02 (s, 3 H), 0.03 (s, 6 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.26 (t, J=7.2 Hz, 3 H), 1.44 (s, 9 H), 2.39 (dd, J=16.2 and 7.5 Hz, 1 H), 2.45 (dd, J=16.2 and 5.2 Hz, 1 H), 2.80 (dd, J=18.8 and 7.4 Hz, 1 H), 2.90 (dd, J=18.8 and 4.9 Hz, 1 H), 3.35 (d, J=3.5 Hz, 1 H), 4.06—4.23 (m, 2H), 4.35 (d, J=3.0 Hz, 1 H), 4.36—4.42 (m, 1 H), 4.50 (d, J=4.0 Hz, 1 H); MS *m/z* (rel intensity) 473 (M^+-H_2O-t-Bu, 4), 425 (3), 361 (15), 285 (34), 239 (17), 231 (16), 215 (14), 201 (8) 133 (100), 73 (100). Found: *m/z* 473.2377. Calcd for $C_{22}H_{41}O_7Si_2$: $M-C_4H_9-H_2O$, 473.2389.

17c*: $[\alpha]_D^{20}$ +37.39° (*c* 2.01, $CHCl_3$).

Isopropyl (2*S*,3*R*,4*S*,6*R*)-7-*t*-Butoxycarbonyl-2,3-bis(*t*-butyldimethylsilyloxy)-4,6-dihydroxyheptanoate (18c): Diethyl(methoxy)borane (0.81 ml, 6.2 mmol) was added to **17c** (3.17 g, 5.63 mmol) dissolved in THF (40 ml) and methanol (10 ml) at −78°C, and the mixture was once warmed up to room temperature, stirred for 15 min, and cooled again at −78°C. Sodium borohydride (0.85 g, 22.5 mmol) was added portionwise, and the reaction mixture was stirred at −78°C for 4 h and gradually warmed to room temperature over a period of 8 h before quenching with acetic acid (2.0 ml). Workup followed by column chromatography (silica gel, hexane–ethyl acetate 10:1) gave **18** (2.39 g, 75% yield) as a colorless oil. $[\alpha]_D^{20}$ +6.34° (*c* 2.10, $CHCl_3$), R_f 0.31 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3500, 2925, 2850, 1720, 1470, 1390, 1365, 1255, 1145, 1100, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.05 (s, 3 H), 0.07 (s, 3 H), 0.10 (s, 3 H), 0.12 (s, 3 H), 0.90 (s, 9 H), 0.92 (s, 9 H), 1.26 (d, J=6.3 Hz, 6 H), 1.45 (s, 9 H), 1.64—1.74 (m, 2 H), 2.38 (dd, J=15.7 and 5.1 Hz, 1 H), 2.43 (dd, J=15.7 and 7.7 Hz, 1 H), 3.01 (d, J=5.4 Hz, 1 H), 3.65 (dd, J=4.2 and 3.5 Hz, 1 H), 3.91 (d, J=1.8 Hz, 1 H), 4.01—4.07 (m, 1 H), 4.16 (d, J=4.2 Hz, 1 H), 4.20—4.26 (m, 1 H), 5.03 (m, J=6.3 Hz,

1 H); MS m/z (rel intensity) 509 ($M^+ - t$-Bu, trace), 491 ($M^+ - H_2O - t$-Bu, 1), 451 (4), 409 (2), 391 (11), 373 (4), 345 (5), 289 (4), 271 (5), 269 (5), 231 (16), 189 (14), 145 (38), 73 (100).

Isopropyl (2*S*, 3*R*, 4*S*, 6*R*)-7-*t*-Butoxycarbonyl-2, 3-bis(*t*-butyldimethylsilyloxy)-4,6-isopropylidenedioxyheptanoate (20): A mixture of **18c** (2.74 g, 4.85 mmol), 2,2-dimethoxypropane (5 ml), and *p*-toluenesulfonic acid (40 mg) was stirred at room temperature for 2 h and then was neutralized with sat. $NaHCO_3$ aq solution. Workup followed by column chromatography (silica gel, hexane–ethyl acetate 20:1) gave **20** (2.93 g, 99% yield) as colorless solid. Mp 82—83 °C, $[\alpha]_D^{20}$ −1.14° (*c* 2.11, $CHCl_3$), R_f 0.58 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3500, 2925, 1720, 1470, 1390, 1365, 1255, 1145, 1100, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.03 (s, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H), 0.08 (s, 3 H), 0.86 (s, 9 H), 0.90 (s, 9 H), 1.24 (d, J=6.3 Hz, 6 H), 1.35 (s, 3 H), 1.40 (s, 3H), 1.40 (s, 9 H), 1.77 (dt, J=12.7 and 2.4 Hz, 1 H), 2.29 (dd, J=15.0 and 5.7 Hz, 1 H), 2.40 (dd, J=15.0 and 7.3 Hz, 1 H), 3.74 (dd, J=7.3 and 2.9 Hz, 1 H), 3.93 (ddd, J=11.6, 7.3, and 2.4 Hz, 1 H), 4.18 (d, J=2.9 Hz, 1 H), 4.17—4.24 (m, 1H), 5.01 (m, J=6.3 Hz, 1 H); MS m/z (rel intensity) 547 ($M^+ - t$-Bu, 1), 491 (7), 433 (8), 373 (19), 317 (14) 261 (22), 259 (24), 173 (38), 73 (90), 57 (100).

Isopropyl (2*S*,3*R*,4*S*,6*R*)-7-*t*-Butoxycarbonyl-2,3-dihydroxy-4,6-isopropylidenedioxyheptanoate (21): Tetrabutylammonium fluoride (1.0 M in THF, 15.0 ml, 15.0 mmol) was added to **20** (2.93 g, 4.84 mmol) in THF (30 ml) at room temperature, and the mixture was stirred at room temperature for 3 h. Workup and column chromatography (silica gel, hexane–ethyl acetate 2:1) gave **21** (1.79 g, 99% yield) as a colorless solid. Mp 85 °C (hexane), R_f 0.59 (hexane–ethyl acetate 1:1), $[\alpha]_D^{20}$ +18.13° (*c* 2.00, $CHCl_3$). IR ($CHCl_3$) 3500, 2925, 1720, 1470, 1390, 1365, 1255, 1145, 1100, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20 (d, J=6.3 Hz, 6 H), 1.37 (s, 3 H), 1.44—1.47 (m, 1 H), 1.45 (s, 9 H), 1.46 (s, 3 H), 1.61 (dt, J=10.0 and 2.6 Hz, 1 H), 2.34 (dd, J=15.1 and 5.8 Hz, 1 H), 2.42 (dd, J=15.1 and 7.2 Hz, 1 H), 2.64 (d, J=5.8 Hz, 1 H), 3.15 (d, J=6.1 Hz, 1 H), 3.74 (ddd, J=8.5, 5.9, and 2.7 Hz, 1 H), 4.09—4.16 (m, 2 H), 4.27—4.33 (m, 1 H), 5.13 (m, J=6.3 Hz, 1 H); MS m/z (rel intensity) 361 ($M^+ -$ Me, 3), 305 ($M^+ -$ Me$-t$-Bu, 4), 433 (8), 263 (24), 173 (33), 115 (19), 59 (79), 57 (100). Found: C, 57.42; H, 8.40%. Calcd for $C_{18}H_{32}O_8$: C, 57.43; H, 8.57%.

***t*-Butyl (3*R*, 5*S*)-3,5-Isopropylidenedioxy-6-oxohexanoate (4b).** Water (3.0 ml) was added to a well-stirred mixture of sodium metaperiodate (0.23 g, 1.08 mmol) suspended in an ethereal (10 ml) solution of **21** (1.79 g, 0.53 mmol) at room temperature, and the mixture was stirred for 3 h. The ethereal layer was separated, washed with sat. NaCl aq solution, and dried ($MgSO_4$). Concentration followed by column chromatography (silica gel, hexane–ethyl acetate 2:1) gave **4b** (0.121 g, 85% yield) as a colorless oil. R_f 0.39 (hexane–ethyl acetate 1:1), $[\alpha]_D^{20}$ −27.14° (*c* 1.75, $CHCl_3$). IR ($CHCl_3$) 2950, 1735, 1435, 1389, 1080, 1030, 775, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40—1.48 (m, 1 H), 1.45 (s, 9 H), 1.45 (s, 3 H), 1.49 (s, 3 H), 1.83 (dt, J=12.9 and 2.8 Hz, 1 H), 2.35 (dd, J=15.4 and 5.9 Hz, 1 H), 2.46 (dd, J=15.4 and 7.1 Hz, 1 H), 4.29—4.37 (m, 2 H), 9.58 (d, J=0.5 Hz, 1 H); MS m/z (rel intensity) 201 ($M^+ -$ Me, 24), 129 (31), 97 (36), 59 (100).

***t*-Butyl (3*R*, 5*S*)-6-Hydroxy-3,5-isopropylidenedioxyhexanoate.** Sodium borohydride (50 mg, 1.29 mmol) was added to a methanol (5.0 ml) solution of **4b** (90 mg, 0.35 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Workup and column chromatography (hexane–ethyl acetate 1:1) gave the title alcohol (75 mg, 83% yield) as a colorless oil. R_f 0.44 (hexane–ethyl acetate 1:1), $[\alpha]_D^{20}$ −7.57° (*c* 2.00, MeOH) [lit, $[\alpha]_D^{20}$ −3.7° (*c* 14.9, MeOH);[12a] $[\alpha]_D^{20}$ −5.91° (*c* 2.0, MeOH)].[12b] IR ($CHCl_3$) 3585, 3000, 2940, 1720, 1455, 1380, 1365, 1315, 1255, 1230, 1200, 1150, 1080, 1020, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.39 (s, 3 H), 1.43—1.47 (m, 1 H), 1.46 (s, 9H), 1.48 (s, 3H), 1.50 (dt, J=12.8 and 2.6 Hz, 1 H), 2.10 (t, J=6.2 Hz, 1 H), 2.32 (dd, J=15.2 and 5.9 Hz, 1 H), 2.45 (dd, J=15.2 and 7.0 Hz, 1 H), 3.51 (ddd, J=11.4, 5.9, and 5.9 Hz, 1 H), 3.60 (ddd, J=11.4, 7.0, and 3.2 Hz, 1 H), 4.02 (ddd, J=11.8, 5.9, and 2.9 Hz, 1 H), 4.26—4.33 (m, 1 H); MS m/z (rel intensity) 246 (M^+, trace), 245 ($M^+ -$ H, 0.2), 229 (1), 205 (0.2), 189 (27), 129 (34), 111 (34), 59 (82), 57 (100).

***t*-Butyl (3*R*, 5*S*, 6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-isopropylidenedioxy-6-heptenoate (22).** To lithium 2,2,6,6-tetramethypiperidide, prepared by treatment of 2,2,6,6-tetramethylpiperidine (45 mg, 0.32 mmol) in THF (2.0 ml) with butyllithium (1.66 M hexane solution, 0.19 ml, 0.32 mmol) at −78°C for 15 min, was added [2-cyclopropy-4-(4-fluorophenyl)quinoline-3-yl]methyl(diphenyl)phosphine oxide (0.155 g, 0.32 mmol) dissolved in THF (4.0 ml) at −78°C, and the mixture was stirred at room temperature for 30 min before addition of **4** (75 mg, 0.29 mmol) dissolved in THF (2.0 ml) at room temperature. The mixture was stirred at room temperature for 3 h and quenched with sat. $NaHCO_3$ aq solution. Workup and column chromatography (silica gel, hexane–ethyl acetate 5:1) gave **22** (98 mg, 67% yield) as a colorless oil. The ratio of E/Z was found to be 99:1 by ^1H NMR. $[\alpha]_D^{20}$ +13.25° (*c* 1.25, $CHCl_3$), R_f 0.33 (hexane–ethyl acetate 5:1). IR ($CHCl_3$) 3000, 1720, 1605, 1510, 1490, 1380, 1230, 1165, 1090, 1025, 840 cm^{-1}; ^1H NNR ($CDCl_3$) δ=1.04 (dd, J=8.1 and 3.3 Hz, 2 H), 1.31—1.25 (m, 2 H), 1.37 (s, 3 H), 1.35—1.40 (m, 2 H), 1.46 (s, 12 H), 2.35 (ddd, J=15.6 and 6.4 Hz, 1 H), 243 (m, 1 H), 2.54 (dd, J=15.6 and 6.7 Hz, 1 H), 4.32—4.25 (m, 1 H), 4.38—4.33 (m, 1 H), 5.57 (dd, J=16.3 and 6.1 Hz, 1 H), 6.55 (dd, J=16.3 and 1.2 Hz, 1 H), 7.37—7.15 (m, 6 H), 7.58 (dd, J=6.6 and 1.6 Hz, 1 H), 7.95 (d, J=8.4 Hz, 1 H); MS m/z (rel intensity) 517 (M^+, 6), 461 (3), 448 (8), 402 (12), 386 (22) 290 (52), 288 (56), 275 (50), 57 (100).

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