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Synthesis of an Artificial HMG-CoA Reductase Inhibitor NK-104 via a Hydrosilylation–Cross-Coupling Reaction

Kyoko Takahashi,[#] **Tatsuya Minami,**[##] **Yoshio Ohara,**[†] **and Tamejiro Hiyama**[*,††]

Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229

†Central Research Institute, Nissan Chemical Industries Ltd., 722-1 Tsuboi-cho, Funabashi, Chiba 274

††Research Laboratory of Resources Utilization, Tokyo Institute of Technology,
4239 Nagatsuta, Yokohama, Kanagawa 226

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The hydrosilylation of *t*-butyl (3*R*,5*S*)-3,5-isopropylidenedioxy-6-heptynoate with $ClMe_2SiH$ and a platinum catalyst, *t*-$Bu_3P \cdot Pt(CH_2{=}CHSiMe_2)_2O$, gave an (*E*)-vinylsilane in high yield with high regioselectivity. A subsequent cross-coupling reaction with an aryl halide afforded *t*-butyl (3*R*,5*S*,6*E*)-7-aryl-3,5-isopropylidenedioxy-6-heptenoate. This sequence was applied to the synthesis of a potent HMG-CoA reductase inhibitor, NK-104.

The inhibition of cholesterol biosynthesis contributes to a lowering of the serum cholesterol level.[1)] A rate-limiting step of cholesterol biosynthesis converts β-hydroxy-β-methylglutaryl CoA (HMG-CoA) into mevalonic acid using HMG-CoA reductase. Since compactin and lovastatin, natural products that efficiently inhibit HMG-CoA reductase, were discovered, many synthetic and semisynthetic analogs have been developed; some of these are now used for treating hypercholesterolaemia and hyperlipemia. Studies on the structure-activity relationship have revealed that (3*R*,5*S*)-3,5-dihydroxy-6-alkenoic acid 1,5-lactone is essential for inhibiting the enzyme.[2)] Consequently, various kinds of synthetic analogs have been reported,[3)] which have a rather simple aromatic part in lieu of the complex *trans*-decalin moiety. Most of these have a common structure **1**.[4)] We have been studying convergent synthetic methods of **1**,[5)] and have found a new strategy (Scheme 1) which is based on a hydrosilylation–cross-coupling reaction. The strategy, as applied to (3*R*,5*S*)-3,5-isopropylidenedioxy-6-heptynoate **3**, is highly effective for the synthesis of a key intermediate **2**. We report herein on the experimental details and an application to the synthesis of a potent HMG-CoA reductase inhibitor, NK-104 (**1b**).[6,7)]

For a typical hydrosilylation reaction, chlorosilane or dialkoxymethylsilane is generally employed together with $H_2PtCl_6 \cdot 6H_2O$ as a catalyst of the first choice.[8)] Before applying hydrosilylation to the highly functionalized substrate **3**, we tested the feasibility of the sequence of the reactions using a model substrate, 3-(2-tetrahydropyranyloxy)-1-butyne **4**. The hydrosilylation of **4** was carried out under the standard conditions using dialkoxymethylsilane as a hydrosilylating agent and H_2PtCl_6 catalyst. After all of the acetylenic substrate was consumed, the resulting mixture of vinylsilanes **5** and **5′** was subjected to a cross-coupling reaction with iodobenzene using a (η^3-allylPdCl)$_2$ catalyst and a tetrabutylammonium fluoride (TBAF) promoter (Scheme 2).[8)] We could isolate regioisomeric coupling products **6** and **6′** in moderate to good yields. As expected, the terminal coupling product **6** predominated with *E*-configuration.

The results summarized in Table 1 show that $(EtO)_2MeSiH$ exhibited moderate reactivity to give **6** and **6′** in 68% yield with a ratio of 91:9. The hydrosilylation proceeded perfectly in *syn*-addition, and the coupling reaction was carried out while retaining the configuration of the olefinic part. Thus, no trace of (*Z*)-olefin was detected. When a bulkier $(i\text{-}PrO)_2MeSiH$ was used, although the selectivity of the desired **6** increased to 95:5, the total yield decreased. Other hydrosilanes, like $(AcO)_2MeSiH$ or $(Et_2N)_2MeSiH$, gave a complex mixture of products without any formation of the desired coupled product. As the coupling partner, iodide reacted satisfactorily, but phenyl triflate failed to give the desired product. For the coupling of **5** and **5′**, triethyl phosphite ligand was effective in improving the coupling yields.[8d)]

Since chlorosilanes are presumably more reactive in hydrosilylation, we next examined the reaction using $ClMe_2SiH$, Cl_2MeSiH or Cl_3SiH and various metal catalysts. The results given in Table 1 demonstrate that the best results were obtained with $ClMe_2SiH$ and a *t*-

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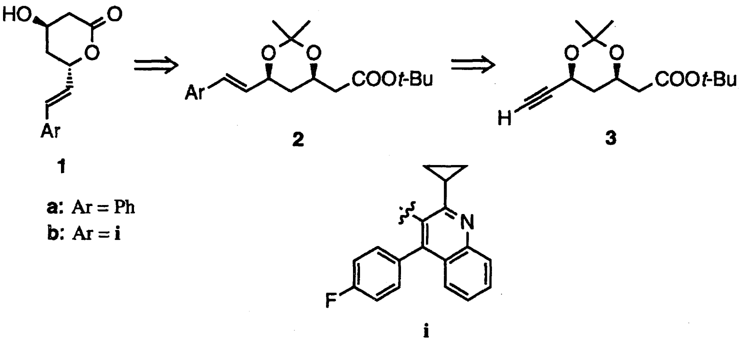
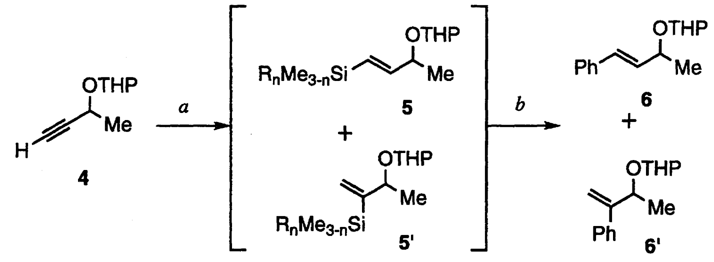
[#] Present address: Kyoritsu College of Pharmacy, 1-5-30 Shibakoen, Minato-ku, Tokyo 105.

[##] Present address: Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920.



Scheme 1.



a: $R_nMe_{3-n}SiH$ (1.2 eq), catalyst
b: PhX (1.1 eq), (n-Bu)$_4$NF (1.5 eq), (η^3-allylPdCl)$_2$ (2.5 mol%), {(EtO)$_3$P (5.0 mol%)}

Scheme 2.

Table 1. Hydrosilylation–Cross-Coupling Reaction of **4** Using $R_nMe_{3-n}SiH$

Run	$R_nMe_{3-n}SiH$	X	Catalyst	Yield/%	**6** : **6'**
1	$(EtO)_2MeSiH$	I	H_2PtCl_6	68[a)]	91 : 9
2	$(EtO)_2MeSiH$	OTf	H_2PtCl_6	[a,b)]	—
3	$(i\text{-}PrO)_2MeSiH$	I	H_2PtCl_6	43[a)]	95 : 5
4	$ClMe_2SiH$	I	$t\text{-}Bu_3P\cdot Pt(CH_2{=}CHSiMe_2)_2O$	82	93 : 7
5	$ClMe_2SiH$	OTf	$t\text{-}Bu_3P\cdot Pt(CH_2{=}CHSiMe_2)_2O$	[b)]	—
6	Cl_3SiH	I	$t\text{-}Bu_3P\cdot Pt(CH_2{=}CHSiMe_2)_2O$	[b)]	—
7	Cl_3SiH	I	$RuCl_2(PPh_3)_3$	[b)]	—

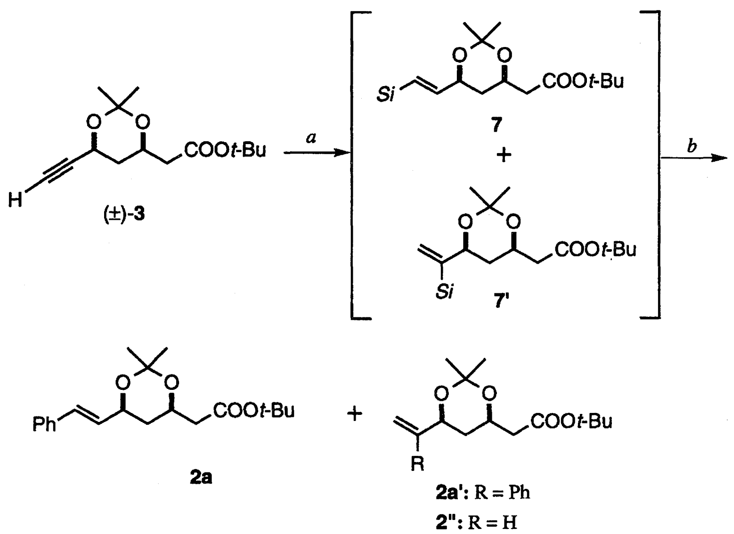
a) Cross-coupling was carried out in the presence of $(EtO)_3P$ (5 mol%). b) A complex mixture of products resulted.

$Bu_3P\cdot Pt(CH_2{=}CHSiMe_2)_2O$ catalyst.[9)] Hereby, the hydrosilylation reaction proceeded smoothly; the following cross-coupling reaction gave the desired (E)-1-phenyl-1-butene derivative **6** in 82% yield with **6** : **6'**=93 : 7. Metal complexes H_2PtCl_6, $RhH(PPh_3)_4$, $RhCl(PPh_3)_3$, $RuCl_2(PPh_3)_3$ or $Pt[(CH_2{=}CHSiMe_2)_2O]_n$ failed to catalyze the hydrosilylation. Although Cl_3SiH showed the highest reactivity, the resulting vinylsilane was found to be too unstable to polymerize before the subsequent coupling reaction.

Because the model reaction of Scheme 2 demonstrates that hydrosilylation with $(EtO)_2MeSiH$, $(i\text{-}PrO)_2MeSiH$ and $H_2PtCl_6\cdot 6H_2O$ catalyst or with $ClMe_2SiH$ and $t\text{-}Bu_3P\cdot Pt(CH_2{=}CHSiMe_2)_2O$ catalyst was satisfactory with respect to the reactivity and selectivity, we applied these conditions to *t*-butyl ($3S^*$,$5R^*$)-3,5-isopropylidenedioxy-6-heptynoate ((±)-**3**) (Scheme 3). The results are summarized in Table 2.

Compared with the model substrate **4**, (±)-**3** exhibited sufficient reactivity to be converted into a mixture of vinylsilane **7** and **7'**. Without any purification the mixture was allowed to react with iodobenzene in the presence of a Pd catalyst and TBAF to give **2a**, **2a'**, and **2''** (Table 2).[10)] Since the ratio of **7** : **7'** was closely related to that of **2a** : (**2a'**+**2''**), we assumed that **7** was quantitatively transformed to **2a**, whereas the undesired regioisomer **7'** was less reactive to give, along with **2a'**, a protodesilylation product **2''**. To suppress the formation of **2''**, we used tris(diethylamino)sulfur difluorotrimethylsilicate; this, however, turned out to be less efficient and gave **2a** in only 28% yield.

Table 2 clearly shows that hydrosilylation of (±)-**3** with $(EtO)_2MeSiH$ and the H_2PtCl_6 catalyst proceeded smoothly, and that the subsequent coupling reaction also was effective, though the regioselectivity was inferior to that of **4** (Run 1). The bulky substituent on



a: *Si*-H (1.2 eq) (see Table 2), catalyst, r.t., 1 h
b: PhX, (*n*-Bu)$_4$NF, (η^3-allylPdCl)$_2$, {(EtO)$_3$P}, THF, 60 °C, 0.5 h

Scheme 3.

Table 2. Hydrosilylation–Cross-Coupling Sequence of (±)-**3** with PhI

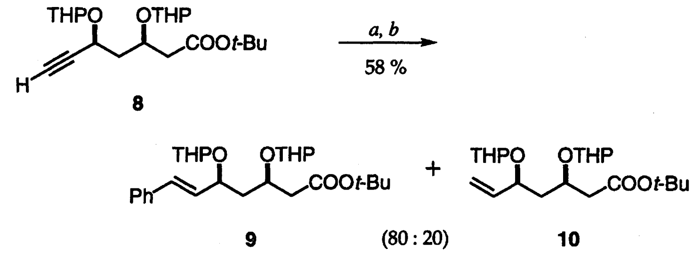
Run	*Si*-H[a)]	Catalyst[b)]	Ph-X[c)]	TBAF equiv	$P(OEt)_3$ mol%	Total yield %	**2a** : **2a′** : **2″** [d)]
1	$(EtO)_2MeSi$-H	**A**	Ph-I	1.5	5	91	70 : 28 : 2
2	(*i*-PrO)$_2$MeSi-H	**A**	Ph-I	1.5	5	77	72 : 18 : 10
3	$(EtO)_2MeSi$-H	**B**	Ph-I	1.5	5	80	89 : 1 : 10
4	$ClMe_2SiH$	**B**	Ph-I	2.0	—	78	96 : 4 : 0
5	$ClMe_2SiH$	**B**	Ph-Br	2.0	—	82	95 : 5 : 0
6	$ClMe_2SiH$	**B**	Ph-I	1.0	—	81	96 : 4 : 0

a) Amount of *Si*-H was 1.2 mol equivalents. b) Catalyst **A**: $H_2PtCl_6\cdot H_2O$ in 2-propanol, catalyst **B**: *t*-Bu$_3$P·Pt(CH$_2$=CHSiMe$_2$)$_2$O (0.5 mol%). c) Ph-X (1.1 mol equivalents) and Pd catalyst (2.5 mol% Pd) were used for cross-coupling reaction. d) Determined by ^{1}H NMR.

Si lowered the whole efficiency. In contrast, the reaction using $ClMe_2SiH$ and *t*-Bu$_3$P·Pt(CH$_2$=CHSiMe$_2$)$_2$O catalyst proceeded in good yields with excellent regioselectivities (Runs 4—6). Furthermore, the coupling reaction could be carried out even with bromobenzene (Run 5). The good regioselectivity remained throughout the coupling reaction. It is worth noting that no trace of **2″** was produced in these cases. Therefore, $ClMe_2SiH$ was concluded to be a favorable hydrosilylating agent, particularly for the requisite substrate **3**. Another point which we should mention here is that one equivalent of TBAF was sufficient for a coupling reaction with iodobenzene (Run 6). This observation indicates that a pentacoordinate intermediate $[RSiMe_2FCl]^-$ for a substitution reaction is sufficiently reactive to undergo transmetalation, and, thus, a cross-coupling reaction. This finding was a particular example only with iodobenzene, because bulky heteroaryl iodide required two mol equivalents of TBAF (vide infra).

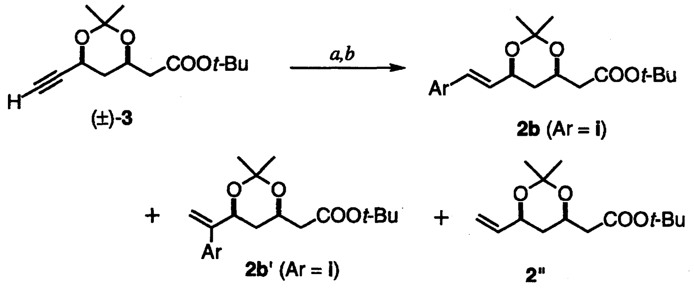
We next studied the possibility of improving the regioselectivity of the reaction of (±)-**3** with $(EtO)_2MeSiH$ by changing the diol protecting group. We expected that an attack of Si to the undesired internal acetylenic carbon (C-6) should be retarded by the steric bulk of the protecting group; we thus prepared bis-THP-protected acetylene **8**, and subjected it to the sequence of reactions described above. Indeed, the regioselectivity was improved by up to 80 : 20, though the reaction proceeded very slowly to afford **9** in 58% overall yield along with a fair amount of protodesilylation product **10** (Scheme 4).

Finally, we studied the synthesis of NK-104 (**1b**), a potent inhibitor of HMG-CoA, in a racemic form. Hereby, we employed 2-cyclopropyl-4-(4-fluorophenyl)-3-iodoquinoline (Ar-I, Ar=**i**)[15)] as the coupling partner. We were delighted to find that, in spite of the steric hindrance of the Ar moiety, the results were satisfactory, as was the case of iodobenzene, except for the fact that two equivalents of TBAF were required. The reaction with $(EtO)_2MeSiH$ and H_2PtCl_6 catalyst gave **2b** in 88% yield with 72% regioselectivity (Table 3), whereas the hydrosilylation of (±)-**3** with $ClMe_2SiH$ and *t*-Bu$_3$P·Pt(CH$_2$=CHSiMe$_2$)$_2$O catalyst, followed by cross-coupling, gave **2b** in 83% yield along with only a trace amount of the undesired regioisomer **2b′** (Scheme 5).



a: $(EtO)_2MeSiH$ (1.2 eq), H_2PtCl_6 catalyst
b: PhI (1.2 eq), $(n\text{-}Bu)_4NF$ (1.5 eq), $(\eta^3\text{-allylPdCl})_2$ (2.5 mol%), $(EtO)_3P$ (5 mol%)

Scheme 4.



a: *Si*-H, catalyst, r.t., 1 h (cf. Table 3)
b: Ar-I (Ar = i), $(n\text{-}Bu)_4NF$, $(\eta^3\text{-allylPdCl})_2$, (2.5 mol%), [$(EtO)_3P$ (5 mol%)], THF, 60 °C, 0.5 h

Scheme 5.

Table 3. Hydrosilylation–Cross-Coupling Sequence of (±)-**3** with ArI

Run	*Si*-H[a)]	Catalyst[b)]	Ar-I[c)] equiv	TBAF equiv	$P(OEt)_3$ mol%	Total yield %	**2b** : **2b′** : **2″** [d)]
1	$(EtO)_2MeSiH$	**A**	1.1	1.5	2.5	88	72 : 11 : 17
2	$ClMe_2SiH$	**B**	1.0	2.0	—	83	96 : 4 : 0

a) Amount of *Si*-H was 1.2 mol equivalents. b) Catalyst **A**: $H_2PtCl_6\cdot H_2O$ in 2-propanol, catalyst **B**: $t\text{-}Bu_3P\cdot Pt(CH_2{=}CHSiMe_2)_2O$. c) The amount of Pd catalyst for coupling reaction was 2.5 mol% on Pd atom base. d) Determined by ^1H NMR.

The advantages of the synthetic strategy based on the hydrosilylation–cross-coupling reaction described here are as follows: (1) both of the reactions proceed rapidly in high yields under mild conditions; (2) various types of artificial HMG-CoA reductase inhibitors are readily accessible from the common intermediate **3** that is stable enough to be stored at ambient temperatures for prolonged time; (3) the resulting coupling products **2** are easily transformed to final targets **1** by an acid treatment.

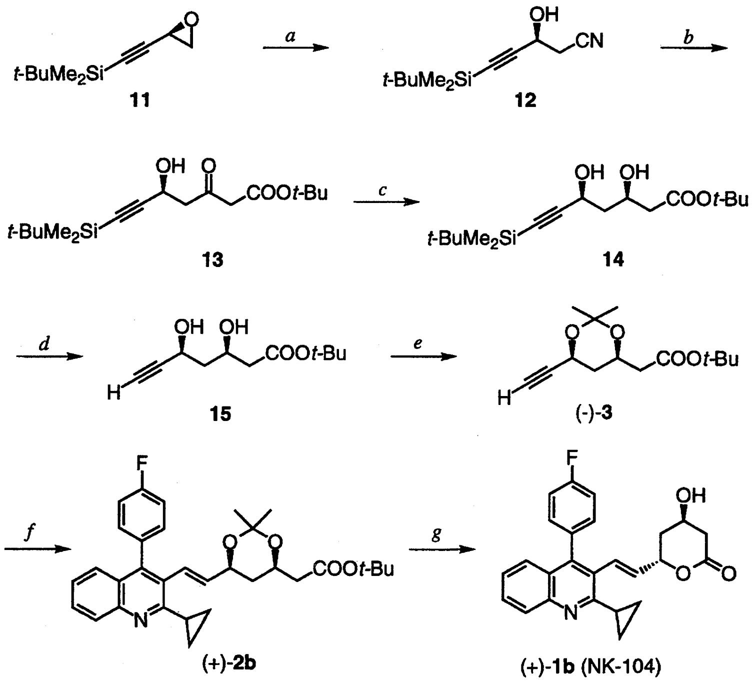
Our next problem was how to prepare an optically active form of **3**. We did this by starting with epoxide **11**, which was prepared in 7 steps from (+)-diethyl tartrate (Scheme 6).[11)] The epoxide was transformed to β-hydroxy nitrile **12** by a regioselective addition of KCN in an ethanol-buffer solution.[12)] A subsequent Blaze reaction[13)] gave δ-hydroxy-β-keto ester **13**, which was reduced with sodium borohydride in the presence of diethylmethoxyborane[14)] to give dihydroxy ester **14**. Desilylation and diol-protection gave the desired optically active acetylene (−)-**3**.

Now, having obtained (−)-**3**, we subjected the substrate to the hydrosilylation–cross-coupling sequence discussed above, and obtained, after deprotection and lactonization, (+)-**1b**, NK-104. The enantiomeric excess was determined to be over 98%.

Conclusion. The strategy discussed in this paper for the synthesis of NK-104 (**1b**) allows us to combine an Ar part and a β-hydroxy-δ-lactone moiety through the hydrosilylation–cross-coupling sequence of reactions. An advantage of this method is that various kinds of aryls can be introduced at the very late stage of synthesis, and, thus, should be useful for the synthesis of a variety of HMG-CoA reductase inhibitors.

Experimental

All of the temperatures are uncorrected. The melting points were measured with a Yanako MP-J3 instrument. ^1H NMR spectra (Me_4Si as an internal standard in $CDCl_3$, unless otherwise noted) were obtained with a Bruker AM-



a: KCN (2 eq), EtOH, pH 7.0 buffer solution, r.t., 16 h, 58%
b: $BrCH_2CO_2t$-Bu (4 eq), Zn (5 eq), THF, reflux, 1 h; HCl *aq*, 0.5 h, 60%
c: $NaBH_4$ (4 eq), Et_2BOMe (1.1 eq), THF-MeOH, -78 °C, 6 h, 82%
d: $(n\text{-Bu})_4NF$ (cat.), THF (H_2O), 0 °C, 2 h, 81%
e: $Me_2C(OMe)_2$, *p*-TsOH (5%), r.t., 2 h, 95%
f: $ClMe_2SiH$ (1.2 eq), $t\text{-Bu}_3P{\bullet}Pt(CH_2{=}CHSiMe_2)_2O$ (0.5 mol%), r.t., 1 h;
Ar-I (Ar = **i**, 1.0 eq), $(n\text{-Bu})_4NF$ (2.0 eq), $(\eta^3\text{-allylPdCl})_2$ (2.5 mol%), THF, 60 °C, 0.5 h, 80%
g: CF_3COOH (15 eq), CH_2Cl_2, r.t., 16 h, 67%, 98% ee

Scheme 6.

400 or Bruker AC-200P spectrometer, the chemical shifts being given in ppm units. The IR spectra were recorded with a JASCO A-202 spectrometer in neat liquid, unless otherwise noted. The specific rotation was measured with a Horiba SEPA-200 spectrometer. MS were recorded with an RMU-6MG instrument and HRMS with a Hitachi M-80A spectrometer. HPLC analyses were performed with a Tosoh OCPM chromatograph with a UV detector. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica Gel 60 F_{254}. Column chromatography was performed with a Wakogel C-200 or Merck Si 60. Tetrahydrofuran (THF) was distilled immediately before use from benzophenone ketyl under an argon atmosphere. Dichloromethane was distilled from calcium hydride before use.

General Method for Hydrosilylation–Cross-Coupling Reaction of 3-(2-Tetrahydropyranyloxy)-1-butyne (4). A catalyst (0.5 mol%) was added to a mixture of **4** (0.100 g, 0.65 mmol) and a hydrosilane (1.2 equiv) in a sealed tube; the mixture was stirred at room temperature for 1—18 h. Completion of the reaction and the ratio of regioisomers were assayed by ^{1}H NMR. If needed, the catalyst was filtered off before removing the excess hydrosilane in vacuo. This crude vinylsilane was first dissolved in THF (1 ml), and then mixed with iodobenzene (147 mg, 0.72 mmol), TBAF (1.0 M THF solution, 1.5—2.0 equiv), $(\eta^3\text{-allylPdCl})_2$ (0.016 mmol, 6.7 mg), and $P(OEt)_3$ (5 mol%), if needed (1 M=1 mol dm^{-3}). The whole mixture was stirred at 60—80 °C for 0.5—1 h, cooled to room temperature, diluted with diethyl ether (5 ml) and dichloromethane (0.5 ml), and stirred for 15 min. The precipitated material was filtered through a Celite pad, and the filtrate was concentrated in vacuo. Purification by short column chromatography (hexane, then hexane–ethyl acetate 20 : 1) gave a mixture of **6** and **6′**. The regioisomeric ratios were measured by ^{1}H NMR based on the following absorptions. **6**: $\delta=6.06$ (dd, $J=7.9$, 15.9 Hz, 0.5 H), 6.30 (dd, $J=6.3$, 15.9 Hz, 0.5 H), 6.53 (d, $J=15.9$ Hz, 0.5 H), 6.58 (d, $J=15.9$ Hz, 0.5 H); **6′**: $\delta=5.29$ (m, 1 H), 5.33 (d, $J=1.6$ Hz, 0.5 H), 5.45 (t, $J=1.5$ Hz, 0.5 H). Separation of **6** and **6′** was done by column chromatography (hexane–ethyl acetate 200 : 1).

(*E*)-1-Phenyl-3-(2-tetrahydropyranyloxy)-1-butene (6). The preparation of **6** was peroformed in the way described above, except for the substrate and reagent. Hydrosilylation was effected using **4** (200 mg, 1.30 mmol), $ClMe_2SiH$ (145 mg, 0.24 mmol), and $t\text{-Bu}_3P{\cdot}Pt(CH_2{=}CHSiMe_2)_2O$ (3.8 mg, 0.5 mol%), at room temperature for 1 h. The cross-coupling reaction was carried out using iodobenzene (295 mg, 1.44 mmol), TBAF (1.0 M THF solution, 1.9 mmol, 1.9 ml), $(\eta^3\text{-allylPdCl})_2$ (0.033 mmol, 13 mg) in THF (1 ml), at 60 °C for 0.5 h. A workup and purification by column chromatography (hexane, then hexane–ethyl acetate 10 : 1) gave a mixture of **6** and **6′** (204 mg, 68%, **6** : **6′**=93 : 7), each product as a mixture of diastereomers. The full ^{1}H NMR spectra of **6** were δ=1.32 (d, J=6.4 Hz, 1.5 H), 1.38 (d, J=6.5 Hz, 1.5 H), 1.51—1.93 (m, 6 H), 3.46—3.54 (m, 1 H), 3.89—3.96 (m, 1 H), 4.41—4.48 (m, 1 H), 4.68 (m, 0.5 H), 4.79 (m, 0.5 H), 6.06 (dd, J=7.9, 15.9 Hz, 0.5 H), 6.30 (dd, J=6.3, 15.9 Hz, 0.5 H), 6.53 (d, J=15.9 Hz, 0.5 H), 6.58 (d, J=15.9 Hz, 0.5 H), 7.25—7.45 (m, 5 H).

***t*-Butyl (3*S**,5*R**,6*E*)-7-Phenyl-3,5-isopropylidenedioxy-6-heptenoate (2a). Method A:** To a mixture of (±)-**3** (100 mg, 0.39 mmol) and $(EtO)_2MeSiH$ (63 mg, 0.47 mmol) in a sealed tube was added 1 drop of $H_2PtCl_6 \cdot H_2O$ (0.1 M 2-propanol solution). The whole mixture was stirred at room temperature for 1 h, filtered through a Celite pad, and concentrated. The residue was dissolved in THF (0.8 ml) and mixed with iodobenzene (88 mg, 0.43 mmol), $P(OEt)_3$ (3 mg, 0.02 mmol), $[(\eta^3\text{-allyl})PdCl]_2$ (4 mg, 0.01 mmol), and TBAF (1.0 M THF solution, 0.59 ml, 0.59 mmol), successively; the reaction mixture was then stirred at 60 °C for 0.5 h. The workup and the following short column chromatography (hexane, then hexane–ethyl acetate 10 : 1) gave a mixture of **2a**, **2a′** and **2″** (120 mg, 91%, **2a** : **2a′** : **2″**=70 : 28 : 2). The regioisomeric ratios were measured by ^{1}H NMR of the mixture. The following spectra were assigned, respectively. **2a**: δ=6.16 (dd, J=6.3, 15.9 Hz, 1 H), 6.60 (d, J=15.9 Hz, 1 H), **2a′**: δ=5.34 (m, 1 H), 5.42 (m, 1 H); **2″**: δ=5.14 (dt, J=1.3, 10.5 Hz, 1 H), 5.32 (dt, J=1.4, 17.3 Hz, 1 H), 5.81 (ddd, J=5.9, 10.5, 17.3 Hz, 1 H). Purification by column chromatography (hexane–ethyl acetate 200 : 1) gave **2a** (82 mg, 63%) as colorless needles, mp 99 °C. IR (KBr) 3057, 2993, 2972, 2937, 2908, 1720, 1381, 1363, 1309, 1282, 1261, 1201, 1174, 1157, 1134, 1087, 987, 939, 746, 696 cm^{-1}; ^{1}H NMR δ=1.41 (dt, J=11.7, 12.9 Hz, 1 H), 1.45 (s, 3 H), 1.46 (s, 9H), 1.54 (s, 3 H), 1.71 (dt, J=2.5, 12.9 Hz, 1 H), 2.34 (dd, J=6.2, 15.2 Hz, 1 H), 2.48 (dd, J=7.0, 15.2 Hz, 1 H), 4.31—4.40 (m, 1 H), 4.54—4.59 (m, 1 H), 6.16 (dd, J=6.3, 15.9 Hz, 1 H), 6.60 (d, J=15.9 Hz, 1 H), 7.20—7.40 (m, 5 H); MS m/z (rel intensity) 332 (M^{+}; trace), 276 (1), 218 (1), 201 (3), 159 (2), 158 (5), 131 (2), 115 (3), 104 (11), 57 (100).

Method B: To a mixture of (±)-**3** (25 mg, 0.10 mmol) and $ClMe_2SiH$ (11 mg, 0.12 mmol) was added $t\text{-}Bu_3P \cdot Pt(CH_2{=}CHSiMe_2)_2O$ (0.3 mg, 0.5 mol%); the resulting mixture was stirred at room temperature for 1 h in a sealed tube. Removal of the excess hydrosilane in vacuo gave a 96 : 4 mixture of **7** and **7′**. The following ^{1}H NMR absorptions are assigned to **7** (*Si*=$ClMe_2Si$); δ=0.48 (s, 6 H), 1.42 (s, 3 H), 1.45 (s, 9 H), 1.48 (s, 3 H), 1.55—1.74 (m, 2 H), 2.31 (dd, J=6.3, 15.3 Hz, 1 H), 2.46 (dd, J=6.8, 15.3 Hz, 1 H), 4.24—4.49 (m, 2 H), 5.95 (d, J=18.8 Hz, 1 H), 6.22 (dd, J=4.4, 18.8 Hz, 1 H). This compound was treated with iodobenzene (13 μl, 0.11 mmol), $(\eta^3\text{-allylPdCl})_2$ (1 mg, 2.5 mol%), TBAF (1.0 M THF solution, 0.10 ml, 0.10 mmol) in THF (0.4 ml), and the whole mixture was stirred at 60 °C for 0.5 h before dilution with diethyl ether (5 ml) and dichloromethane (0.5 ml). The mixture was stirred for 15 min, and all the precipitated material was removed by filtration. Concentration of the filtrate and purification by column chromatography (hexane–ethyl acetate 20 : 1) gave **2a** (27 mg, 81% yield) and its regioisomer **2a′** in a ratio of 96 : 4.

***t*-Butyl (3*S**,5*R**,6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-isopropylidenedioxy-6-heptenoate (2b).** The preparation of **2b** was made in the same way as described for **2a**, except for the substrate and the reagent. Hydrosilylation was effected using (±)-**3** (50 mg, 0.20 mmol), $ClMe_2SiH$ (23 mg, 0.24 mmol), and $t\text{-}Bu_3P \cdot Pt(CH_2{=}CHSiMe_2)_2O$ (0.6 mg, 0.5 mol%). The cross-coupling reaction was carried out using 2-cyclopropyl-4-(4-fluorophenyl)-3-iodoquinoline (77 mg, 0.20 mmol), $(\eta^3\text{-allylPdCl})_2$ (2 mg, 2.5 mol%), TBAF (1.0 M THF solution, 0.39 ml, 0.39 mmol) in THF (0.8 ml). The workup and purification by column chromatography (hexane–ethyl acetate 20 : 1) gave **2b** (84 mg, 83%). IR ($CHCl_3$) 3000, 1720, 1605, 1510, 1490, 1380, 1230, 1165, 1090, 1025, 840 cm^{-1}; ^{1}H NMR δ=1.04 (dd, J=3.3, 8.1 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, 12 H), 2.35 (dd, J=6.4, 15.6 Hz, 1 H), 2.43 (m, 1 H), 2.54 (dd, J=6.7, 15.6 Hz, 1 H), 4.25—4.32 (m, 1 H), 4.33—4.38 (m, 1 H) 5.57 (dd, J=6.1, 16.3 Hz, 1 H), 6.55 (dd, J=1.2, 16.3 Hz, 1 H), 7.15—7.37 (m, 6 H), 7.58 (dd, J=1.6, 6.6 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).

***t*-Butyl (3*S**,5*R**,6*E*)-7-Phenyl-3,5-di(2-tetrahydropyranyloxy)-6-heptenoate (9).** To a mixture of **8** (a mixture of diastereomers, 100 mg, 0.26 mmol) and $(EtO)_2MeSiH$ (42 mg, 0.31 mmol) in a sealed tube was added 2 drops of $H_2PtCl_6 \cdot H_2O$ (0.1 M 2-propanol solution). The whole mixture was stirred at room temperature for 1 h, filtered through a Celite pad, and concentrated. The residue was dissolved in THF (0.5 ml) and mixed with iodobenzene (59 mg, 0.29 mmol), $P(OEt)_3$ (2.2 mg, 0.01 mmol), $[(\eta^3\text{-allyl})PdCl]_2$ (2.7 mg, 0.007 mmol), and TBAF (1.0 M THF solution, 0.39 ml, 0.39 mmol), successively; the reaction mixture was then stirred at 60 °C for 0.5 h. The workup as above, followed by column chromatography (hexane–ethyl acetate 10 : 1), gave a mixture of **9** and **10**, each as a mixture of diastereoisomers (70 mg, 58%). IR (KBr) 2941, 2870, 1730, 1367, 1259, 1201, 1155, 1132, 1076, 1024, 989, 869 cm^{-1}; ^{1}H NMR δ=1.40—1.86 (m+2s (δ=1.42 and 1.43), 22 H), 1.97—2.23 (m, 1 H), 2.42—2.57 (m, 1.5 H), 2.71—2.77 (m, 0.5 H), 3.42—3.52 (m, 2 H), 3.86—3.98 (m, 2 H), 4.03—4.25 (m, 1 H), 4.34—4.49 (m, 1 H) 4.63—4.78 (m, 1 H), 5.98—6.08 (m, 0.2 H), 6.22—6.31 (m, 0.8 H), 7.19—7.39 (m, 5 H); MS m/z (rel intensity) 461 (M^{+}+1; trace), 291 (trace), 235 (2), 201 (1), 85 (100).

(3*S*)-5-(*t*-Butyldimethylsilyl)-3-hydroxy-4-pentynenitrile (12). Phosphate buffer (pH 7.0, 0.4 ml) and sodium cyanide (26 mg, 0.4 mmol) were added to a solution of (3*R*)-3,4-epoxy-1-(*t*-butyldimethylsilyl)-1-butyne[11] (**11**, 36 mg, 0.2 mmol) in EtOH (0.4 ml). The resulting mixture was first stirred at room temperature for 16 h, then diluted with diethyl ether (5 ml), washed with NaCl aq solution, dried (Ns_2SO_4), and filtered. Concentration followed by column chromatography (hexane–ethyl acetate 10 : 1) afforded **12** (24 mg, 58%) as a pale yellow oil. $[\alpha]^{D}_{20}$ −39.1 (c 1.01, $CHCl_3$). IR 3428, 2955, 2932, 2890, 2859, 2259, 2180, 1723, 1471, 1404, 1252, 1071, 839, 810, 777 cm^{-1}; ^{1}H NMR δ=0.13 (s, 6 H), 0.95 (s, 9 H), 2.28 (d, J=5.7 Hz, 1 H), 2.74 (dd, J=6.0, 16.5 Hz, 1 H), 2.79 (dd, J=5.6, 16.5 Hz, 1 H), 4.67 (ddd, J=5.6, 5.7, 6.0 Hz, 1 H); MS m/z (rel intensity) 152 (M^{+}−C_4H_9; 43), 111 (100). HRMS Found: m/z 152.0522. Calcd for $C_7H_{10}NOSi$: M^{+}−C_4H_9, 152.0531.

***t*-Butyl (5*S*)-7-(*t*-Butyldimethylsilyl)-5-hydroxy-

3-oxo-6-heptynoate (13). To activated Zn powder (44 mg, 0.65 mmol) suspended in THF (0.1 ml) was added *t*-butyl bromoacetate (22 μl, 0.13 mmol); the resulting mixture was stirred at 80 °C for 0.5 h. To the mixture were added **12** (28 mg, 0.13 mmol) and *t*-butyl bromoacetate (64 μl, 0.39 mmol), and stirring was continued for 0.5 h. The reaction mixture was quenched with 2 M hydrochloric acid (0.1 ml) and stirred for additional 0.5 h. After extraction with diethyl ether, the combined organic layer was first washed with $NaHCO_3$ aq solution, and then with NaCl aq solution successively, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue (hexane–ethyl acetate 7:1) gave **13** (26 mg, 60%) as a colorless oil with recovered **12** (10 mg, 36%). **13** exhibited $[\alpha]_{20}^{D}$ −25.9 (*c* 1.01, $CHCl_3$). IR 3437, 2955, 2932, 2887, 2858, 2173, 1716, 1651, 1471, 1408, 1394, 1369, 1323, 1251, 1147, 1045, 839, 812, 777, 684 cm^{-1}; ^1HNMR δ=0.10 (s, 6 H), 0.93 (s, 9 H), 1.48 (s, 9 H), 2.78 (d, *J*=5.3 Hz, 1 H), 2.93 (dd, *J*=3.8, 17.5 Hz, 1 H), 3.02 (dd, *J*=8.0, 17.5 Hz, 1 H), 3.40 (s, 2 H), 4.83 (ddd, *J*=3.8, 5.3, 8.0 Hz, 1 H); MS *m/z* (rel intensity) 253 ($M^+-OC_4H_9$; 1), 213 ($M^+-C_4H_9-C_4H_8$; 16), 195 ($M^+-C_4H_9-C_4H_8-H_2O$; 10), 153 (8), 151 (11), 109 (31), 85 (24), 75 (38), 57 (100). HRMS Found: *m/z* 253.1228. Calcd for $C_{13}H_{21}O_3Si_1$: $M^+-OC_4H_9$, 253.1259.

***t*-Butyl (3*R*,5*S*)-7-(*t*-Butyldimethylsilyl)-3,5-dihydroxy-6-heptynoate (14).** Diethylmethoxyborane (21 μl, 0.17 mmol) was added to a solution of **13** (50 mg, 0.15 mmol) in THF (1.2 ml) and methanol (0.3 ml) at −78 °C under an argon atmosphere. The mixture was first stirred for 10 min, and then warmed to room temperature in order to dissolve the borane complex, and cooled again at −78 °C. Sodium borohydride (23 mg, 0.60 mmol) was added to the mixture. The resulting reaction mixture was stirred for 3 h, gradually warmed to room temperature over 3 h, quenched with acetic acid (0.5 ml), treated with H_2O and $NaHCO_3$ aq solution, and extracted with diethyl ether. The ethereal extract was washed with NaCl aq solution, dried ($MgSO_4$), and concentrated. The residue was first dissolved in methanol (5 ml) and then concentrated under reduced pressure. The methanol treatment operation was repeated 8 times in order to decompose the borane complex. Column chromatography of the residue (hexane–ethyl acetate 6:1) gave **14** (40 mg, 82%) as a colorless solid. $[\alpha]_{20}^{D}$ −9.33 (*c* 0.62, $CHCl_3$). IR (KBr) 3346, 2955, 2930, 2858, 2175, 1726, 1367, 1311, 1278 cm^{-1}; ^1HNMR δ=0.11 (s, 6 H), 0.93 (s, 9 H), 1.47 (s, 9 H), 1.82 (ddd, *J*=3.2, 4.8, 14.1 Hz, 1 H), 1.96 (ddd, *J*=8.2, 9.5, 14.1 Hz, 1 H), 2.45 (d, *J*=6.2 Hz, 2 H), 2.91 (d, *J*=3.4 Hz, 1 H), 3.51 (br d, *J*=2.4 Hz, 1 H), 4.25 (m, 1 H), 4.67 (ddd, *J*=3.4, 4.8, 8.2 Hz, 1 H); MS *m/z* (rel intensity) 237 ($M^+-OC_4H_9-H_2O$; trace), 215 ($M^+-C_4H_9-C_4H_8$; 16), 197 ($M^+-C_4H_9-C_4H_8-H_2O$; 8), 145 (22), 111 (17), 109 (16), 101 (46), 75 (60), 57 (100). HRMS Found: *m/z* 237.1293. Calcd for $C_{13}H_{21}O_2Si$: $M^+-OC_4H_9-H_2O$, 237.1310.

***t*-Butyl (3*R*,5*S*)-3,5-Dihydroxy-6-heptynoate (15).** To a THF (1.5 ml) solution of **14** (21 mg, 0.064 mmol) was added TBAF (1 M THF solution, 10 μl) at 0 °C. The mixture was stirred for 2 h before quenching with H_2O, and then extracted with diethyl ether. The combined organic layer was washed with NaCl aq solution, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue (hexane–ethyl acetate 10:1) gave **15** (13 mg, 81%) as a pale yellow oil. $[\alpha]_{20}^{D}$ −22.6 (*c* 0.77, $CHCl_3$). IR 3400, 3302, 2980, 2930, 2116, 1720, 1369, 1302, 1257, 1153, 1080, 842, 758, 665 cm^{-1}; ^1HNMR δ=1.47 (s, 9 H), 1.83 (dddd, *J*=1.2, 3.0, 4.8, 14.1 Hz, 1 H), 1.97 (ddd, *J*=8.2, 9.9, 14.1 Hz, 1 H), 2.44 (br d, *J*=6.0 Hz, 2 H), 2.48 (d, *J*=2.2 Hz, 1 H), 3.07 (d, *J*=3.2 Hz, 1 H), 3.62 (dd, *J*=1.1, 3.2 Hz, 1 H), 4.21—4.30 (m, 1 H), 4.66—4.71 (m, 1 H); MS *m/z* (rel intensity) 141 ($M^+-OC_4H_9$; 4), 123 (3), 99 (3), 98 (6), 89 (13), 57 (100). HRMS Found: *m/z* 141.0534. Calcd for $C_7H_9O_3$: $M^+-OC_4H_9$, 141.0551.

***t*-Butyl (3*R*,5*S*)-3,5-Isopropylidenedioxy-6-heptynoate ((−)-3).** To a mixture of **15** (16 mg, 0.07 mmol) and 2,2-dimethoxypropane (0.2 ml) was added *p*-toluenesulfonic acid (1 mg). The mixture was stirred for 2 h at room temperature, quenched with $NaHCO_3$ aq solution, and extracted with diethyl ether. The combined ethereal extract was washed with NaCl aq solution, dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (hexane–ethyl acetate 10:1) of the residue gave (−)-**3**. $[\alpha]_{20}^{D}$ −4.99 (*c* 1.00, $CHCl_3$). IR 3425, 3260, 2980, 2865, 1722, 1380, 1362, 1258, 1150, 1010, 840 cm^{-1}; ^1HNMR δ=1.42 (s, 3 H), 1.44 (s, 9 H), 1.47 (s, 3 H), 1.65 (dt, *J*=11.6, 12.9 Hz, 1 H), 1.82 (dt, *J*=2.6, 12.9 Hz, 1 H), 2.32 (dd, *J*=6.1, 15.4 Hz, 1 H), 2.45 (dd, *J*=7.0, 15.4 Hz, 1 H), 2.46 (d, *J*=2.1 Hz, 1 H), 4.26 (dddd, *J*=2.9, 6.1, 7.0, 11.6 Hz, 1 H), 4.68 (dt, *J*=2.5, 11.6 Hz, 1 H); MS *m/z* (rel intensity) 239 (M^+-CH_3), 183 ($M^+-CH_3-C_4H_8$). HRMS Found: *m/z* 239.1269. Calcd for $C_{13}H_{19}O_4$: M^+-CH_3, 239.1282.

***t*-Butyl (3*R*,5*S*,6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-isopropylidenedioxy-6-heptenoate ((+)-2b).** To a mixture of (−)-**3** (9.8 mg, 0.04 mmol) and chlorodimethylsilane (4.5 mg, 0.05 mmol) in a sealed tube was added $t\text{-}Bu_3P{\cdot}Pt(CH_2{=}CHSiMe_2)_2O$ (0.1 mg, 0.5 mol%); the mixture was stirred for 1 h at room temperature before removal of the excess chlorodimethylsilane in vacuo. This crude *t*-butyl (3*R*,5*S*,6*E*)-3,5-isopropylidenedioxy-7-chlorodimethylsilyl-6-heptenoate was dissolved in THF (0.08 ml) and mixed with 2-cyclopropyl-4-(4-fluorophenyl)-3-iodoquinoline[15] (15.3 mg, 0.04 mmol), (η^3-allylPdCl)$_2$ (0.4 mg, 0.001 mmol), TBAF (1.0 M THF solution, 78 μl, 0.078 mmol). The mixture was stirred at 60 °C for 0.5 h, diluted with diethyl ether (2 ml) and dichloromethane (0.1 ml), stirred at room temperature for 15 min, and filtered through a Celite pad. Concentration of the filtrate followed by column chromatography (hexane–ethyl acetate 20:1) gave (+)-**2b** (15.9 mg, 80% yield) as a colorless solid. Mp 140 °C. $[\alpha]_{20}^{D}$ +9.30 (*c* 1.01, $CHCl_3$); IR (KBr) 2978, 2941, 2910, 1720, 1602, 1570, 1512, 1489, 1379 cm^{-1}; ^1HNMR δ=1.04 (dd, *J*=3.3, 8.1 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, 12 H), 2.35 (dd, *J*=6.4, 15.6 Hz, 1 H), 2.43 (m, 1 H), 2.54 (dd, *J*=6.7, 15.6 Hz, 1 H), 4.25—4.32 (m, 1 H), 4.33—4.38 (m, 1 H), 5.57 (dd, *J*=6.1, 16.3 Hz, 1 H), 6.55 (dd, *J*=1.2, 16.3 Hz, 1 H), 7.15—7.37 (m, 6 H), 7.58 (dd, *J*=1.6, 6.6 Hz, 1 H), 7.95 (d, *J*=8.4 Hz, 1 H); MS *m/z* (rel intensity) 517 (M^+; 6), 461 ($M^+-C_4H_8$; 3), 448 ($M^+-CH_3-C_4H_8$; 8), 402 (12), 386 (22), 290 (52), 288 (56), 275 (50), 57 (100). Found: C, 74.27; H, 7.04; N, 2.51%. Calcd for $C_{32}H_{36}FNO_4$: C, 74.25; H, 7.01; N, 2.71%.

(3*R*,5*S*,6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6-heptenoic Acid 1,5-Lactone (NK-104, (+)-1b). Trifluoroacetic acid (23 μl, 0.3 mmol) was added to a solution of (+)-**2b** (10.9 mg, 0.02 mmol) in dichloromethane (0.2 ml). The reaction mixture was stirred for 16 h at room temperature, diluted with dichloromethane, washed with $NaHCO_3$ aq solution and with NaCl aq solution successively, and dried (Na_2SO_4). Concentration followed by column chromatography (hexane–ethyl acetate 5 : 1) gave (+)-**1b** (NK-104, 5.5 mg, 67% yield). Mp 135—137 °C. $[\alpha]^{\mathrm{D}}_{20}$ +8.80 (*c* 1.01, $CHCl_3$), >98% ee by HPLC (Daicel, Chiralpak AS, hexane–*i*-PrOH 9 : 1). IR (KBr) 3374, 3063, 3007, 2935, 1711, 1600, 1512, 1491, 1415 cm^{-1}; ^1HNMR δ=1.03—1.06 (m, 2 H), 1.30—1.40 (m, 2 H), 1.56—1.63 (m, 1 H), 1.75—1.81 (m, 1 H), 2.35—2.46 (m, 1 H), 2.59 (ddd, J=1.5, 4.1, 17.7 Hz, 1 H), 2.71 (dd, J=4.9, 17.7 Hz, 1 H), 4.22—4.27 (m, 1 H), 5.15—5.20 (m, 1 H), 5.62 (dd, J=6.2, 16.2 Hz, 1 H), 6.72 (dd, J=1.4, 16.2 Hz, 1 H), 7.17—7.25 (m, 4 H), 7.30—7.36 (m, 2 H), 7.61 (ddd, J=2.1, 6.1, 8.4 Hz, 1 H), 7.96 (d, J=8.4 Hz, 1 H); MS m/z (rel intensity) 403 (M^+; 18), 402 (M^+-1; 8), 341 (4), 316 (11), 315 (35), 314 (47), 288 (100). Found: C, 74.20; H, 5.54; N, 3.45%. Calcd for $C_{25}H_{22}FNO_3$: C, 74.43; H, 5.50; N, 3.47%.

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