Anti-AIDS Agents. 60.† Substituted 3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP) Analogues as Potent Anti-HIV Agents

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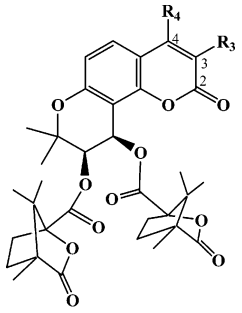
Synthesis of positional isomers is a commonly used technique in drug design. Accordingly, based on prior SAR studies of 3′*R*,4′*R*-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**) analogues, a series of mono- and disubstituted chromone derivatives of 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP, **4**) were designed and synthesized. Together with **1** and 4-methyl DCK (**2**), all newly synthesized DCP analogues (**4**−**21**) were screened for anti-HIV-1 activity against a non-drug-resistant strain in H9 lymphocytes and a multiple reverse transcriptase (RT) inhibitor-resistant strain in the MT4 cell line. Several DCP analogues (**4**, **5**, **7**, **8**, **13**, and **17**) exhibited extremely high anti-HIV activity in the non-drug-resistant strain assay, with EC_{50} values ranging from 0.00032 to 0.0057 μM and remarkable therapeutic indexes (TI) ranging from 5.6×10^3 to 1.16×10^5, which were similar to those of **2** (EC_{50} 0.0059 μM, TI > 6.6×10^3) and better than those of **1** (EC_{50} 0.049 μM, TI > 328). Even more promisingly, some DCP analogues also showed activity against a multi-RT inhibitor-resistant strain, HIV-1 RTMDR1, whereas most DCK analogues did not. The most significant compound was **8**, with an EC_{50} value of 0.06 μM and TI of 718 against the multi-RT inhibitor-resistant HIV-1 strain. Compounds **9** and **10** also showed good activity with an EC_{50} value of 0.14 μM, and TIs of 272 and >111, respectively. 2-Ethyl DCP (**8**) exhibited the best anti-HIV activity in both assays. Further development of **8**-related compounds as clinical trial candidates is warranted.

Introduction

Since first reported in the 1980s, acquired immunodeficiency syndrome (AIDS), which is caused by the human immunodeficiency virus (HIV) and results in life-threatening opportunistic infections and malignancies, has spread rapidly through the human population and become a major worldwide pandemic.[1,2] The global AIDS epidemic claimed more than three million lives in 2003, and ca. 40 million people were living with HIV or AIDS at the end of that same year.[3]

In our previous studies, 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**) and 4-methyl DCK (**2**) (Figure 1) were discovered to be potent against HIV-1_{IIIB} replication in H9 lymphocytes with remarkable EC_{50} values of 2.56×10^{-4} μM and 1.83×10^{-6} μM, and TI values of 1.37×10^5 and 6.89×10^7, respectively.[4−7] Structure−activity relationship (SAR) study results with DCK analogues indicated that 3′*R*,4′*R* configurations and planarity of the coumarin nucleus are essential structural features for anti-HIV activity; alkyl/*O*-alkyl substituents at the 3-, 4-, and 5-positions on the coumarin nucleus are favorable for enhanced anti-HIV activity and decreased toxicity; and two bulky (*S*)-(−)-camphanoyl groups at the 3′- and 4′-positions are preferred to other substituents.



1. R_3=R_4=H, DCK
2. R_3=H, R_4=CH_3
3. R_3=CH_2OH, R_4=CH_3

Figure 1. DCK (**1**), 4-methyl DCK (**2**), and hydroxymethyl DCK analogue (**3**).

However, our recent screening determined that most DCK analogues lack potency against multi-RT inhibitor-resistant HIV strains. This observation together with poor water solubility presented two main obstacles to the development of DCK-related drug candidates. We recently reported the design and synthesis of **3**, which is more water soluble than **1** and has moderate bioavailability (F = 15%).[8] However, as with most DCK analogues, compound **3** did not show antiviral activity against the multi-RT inhibitor-resistant strain at the tested concentrations. Therefore, further modification was necessary to overcome these problems.

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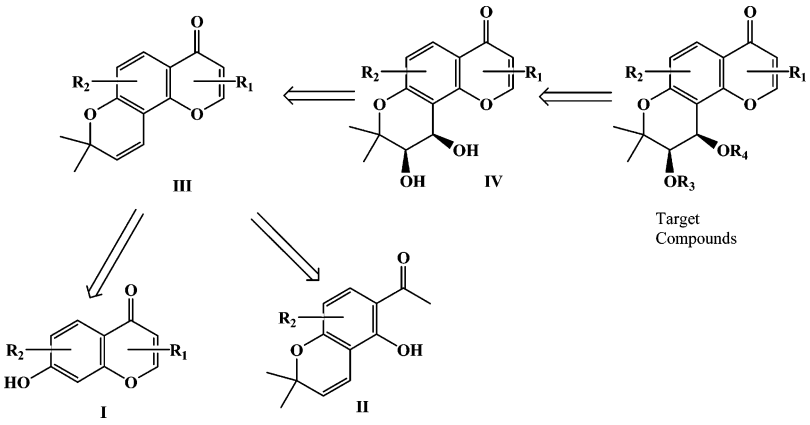
Scheme 1. Retrosynthetic Strategy for Substituted DCP Derivatives



In the current study, we modified the coumarin skeleton in order to identify new drug candidates with potent anti-HIV activity against drug-resistant strains. This paper reports their design, syntheses, and bioassay data.

Design

It is not fully clear why DCK analogues show remarkably reduced activity against drug-resistant viral strains. Mutations of the viral RT could cause conformational changes directly on the binding sites or other regions that affect binding. Accordingly, DCK might dissociate more rapidly from or not fit into the putative mutated target. Our goal is to improve activity against drug-resistant strains by modifying the coumarin skeleton. Preparing ring position isomers is a common principle of analogue design, as such a change may alter electron distribution in an aromatic ring system or affect the complementarity toward in vivo receptors.

In 2003, we first reported that the DCK-related compound 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP, **4**), a positional isomer of DCK, showed potent in vitro anti-HIV activity in acutely HIV-1_{IIIB}-infected H9 lymphocytes, a non-drug-resistant strain, with an EC_{50} of 6.78×10^{-4} μM and TI of 14500, values similar to those of DCK.[9] Thus, the carbonyl group, which is at position 4 in DCP, is not restricted to position 2, as found in DCK.

Our next goals were to continue our SAR study on both DCK and DCP series, explore the structural requirements of the pyranochromone derivatives as new anti-HIV agents, and increase the anti-HIV activity in drug-resistant strains. In our prior modification studies in the DCK series, incorporating small alkyl group(s) on the coumarin skeleton led to retained or increased activity. Thus, in the current study, several analogous new DCP analogues with chromone ring substitutions were designed and synthesized asymmetrically by the same approaches.

On the basis of the structural difference between the A rings of DCK (**1**) and DCP (**4**), we mainly focused our continued modifications on the chromone A ring. Thus, 3-methyl (**5**), 3-phenyl (**6**), 2-methyl (**7**), 2-phenyl (**12**), and 2,3-dimethyl (**13**) DCP analogues were synthesized to investigate the impact of different substituents at these positions (Figure 2). After reviewing bioassay results, we have now introduced different alkyl groups, i.e., ethyl, propyl, isopropyl, and ethoxymethyl, at the

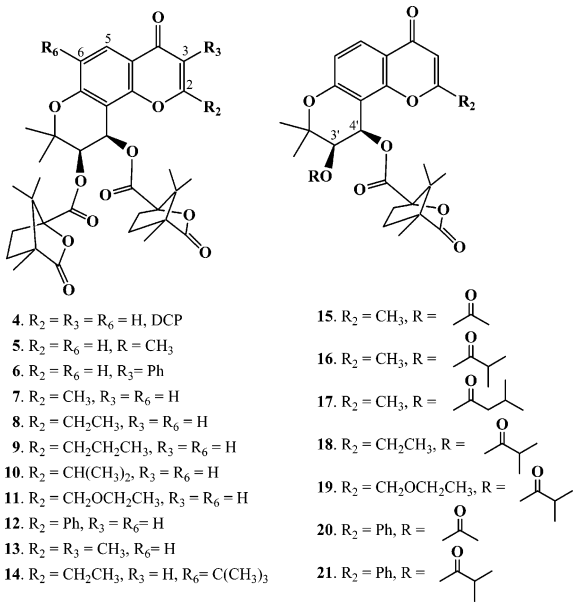
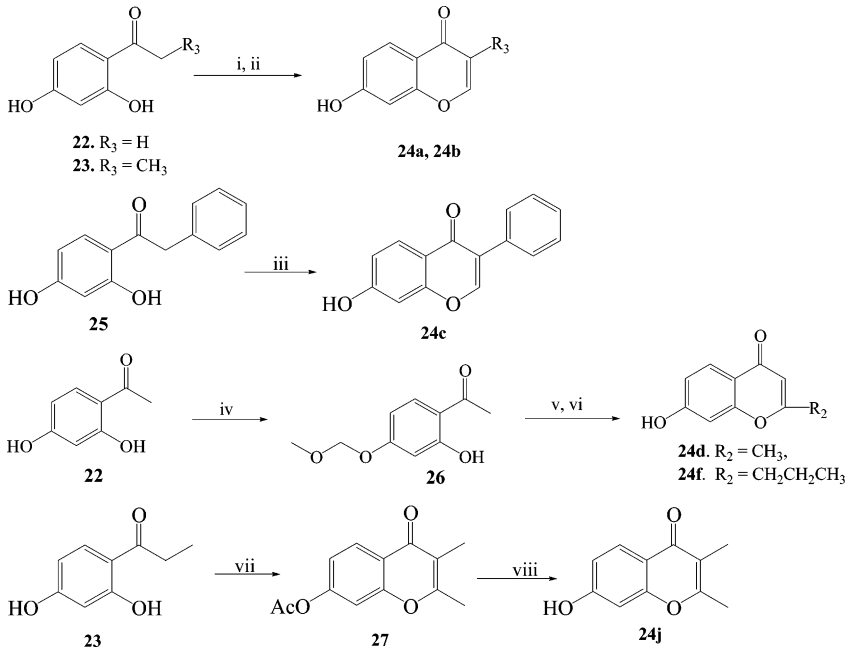


Figure 2. Substituted DCP derivatives 4−21.

2-position of the chromone nucleus (a beneficial position) to give 2-substituted DCP analogues **8**−**11**. Also, a 6-*tert*-butyl substitution was introduced into compound **8**, the most active compound, to produce analogue **14**. Finally, we designed a series of 2-substituted-3′*R*-acyl-4′*R*-camphanoyl pyranochromone derivatives (**15**−**21**) (Figure 2). Acyl groups with smaller volumes replaced the 3′-camphanoyl group in order to explore the requirements at this position for anti-HIV activity.

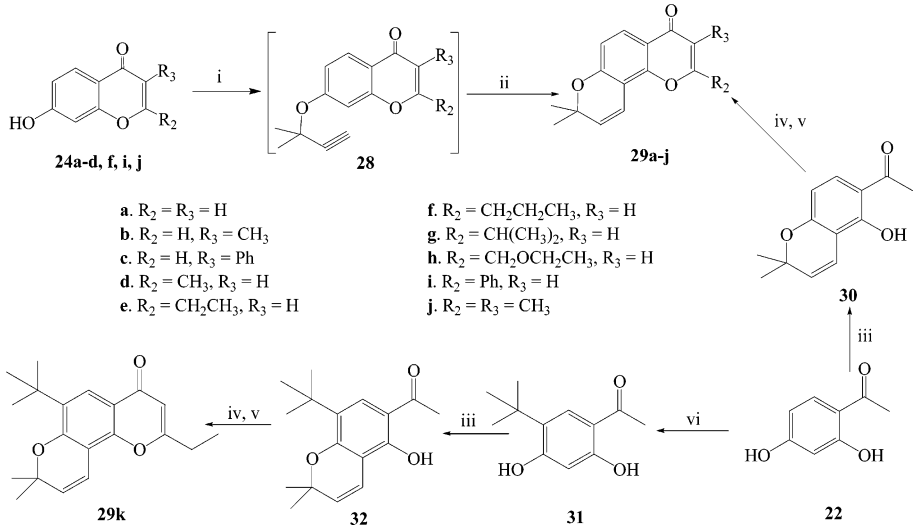
For all designed target compounds (**4**-**21**), our first synthetic strategy was to consecutively (a) prepare variously substituted 7-hydroxychromones (**I**) from 2,4-dihydroxyacetophenone and its substituted derivatives, (b) produce substituted pyranochromones (**III**), (c) asymmetrically synthesize dihydroxypyranochromones with required 3′*R*,4′*R* configurations (**IV**), and (d) finally, produce substituted DCP derivatives (Scheme 1). A second synthetic strategy for some 2-substituted DCPs was to begin with 2,2-dimethyl-5-hydroxy-6-ethanone-2*H*-chromene (**30**) and its derivatives (**II**) rather than the 7-hydroxychromones (**I**). All target compounds were tested in vitro for suppression of HIV-1_{IIIB} replication in H9 lymphocytes (non-drug-resistant strain), as well as against the HIV-1 RTMDR1 multi-RT inhibitor-resistant viral strain in MT4 cells.

Scheme 2. Synthesis of 7-Hydroxychromones (**24**)[a]



[a] Reagents and conditions: (i) 70% perchloric acid, triethyl orthoformate, 40 min; (ii) H_2O, reflux, 5 min; (iii) methanesulfonyl chloride/DMF; (iv) chloromethyl methyl ether, K_2CO_3, anhydrous acetone/N_2, rt; (v) NaH, ethyl alkanoate, anhydrous THF/Ar; (vi) Amberlyst 15, 2-propanol, reflux; (vii) Ac_2O, NaOAc, reflux; viii. $NaHCO_3$/MeOH (1:1, v:v) rt.

Scheme 3. Synthesis of Substituted Pyranochromones (**29**)[a]



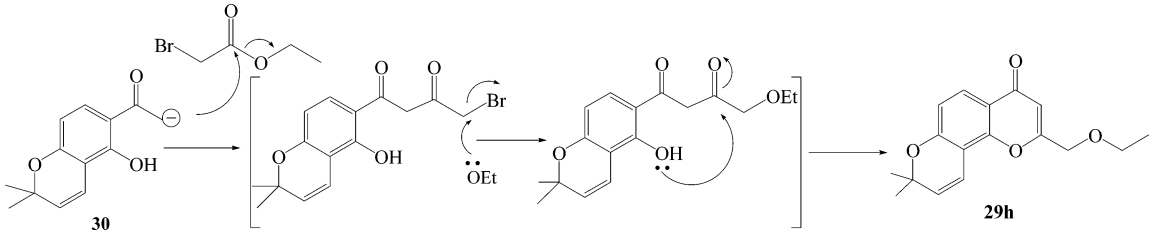
[a] Reagents and conditions: (i) 3-chloro-3-methyl-1-butyne; K_2CO_3, kI, DMF/80 °C; (ii) *N*,*N*-diethylaniline, reflux; (iii) 4,4-dimethoxy-2-methyl-2-butanol, anhydrous pyridine, 140 °C; (iv) NaH, ethyl alkanoate, anhydrous THF/Ar; (v) Amberlyst 15, 2-propanol, reflux; (vi) *tert*-butyl alcohol, H_3PO_4, P_2O_5, 80 °C.

Chemistry

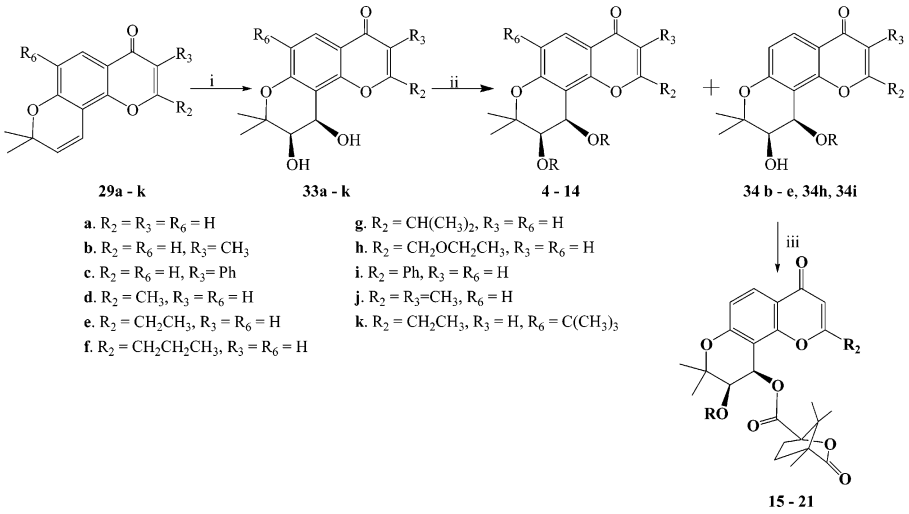
The synthesis of **4** was previously described without full experimental details, which are presented herein. Scheme 2 shows the syntheses of substituted 7-hydroxychromones (**24a**−**d**, **24f**, and **24j**). Commercially available 2,4-dihydroxyacetophenone (**22**) or propiophenone (**23**) was treated with triethyl orthoformate and 70% perchloric acid, followed by hydrolysis in boiling water to afford 7-hydroxychromone (**24a**) or 7-hydroxy-3-methylchromone (**24b**).[10] 7-Hydroxy-3-phenylchromone (**24c**) was synthesized from benzyl 2,4-dihydroxyphenyl ketone (**25**) by treatment with methanesulfonyl chloride in dry DMF.[11] 2-Substituted-7-hydroxychromones (**24d** and **24f**) were synthesized in three steps from **22**. Compound **22** was first protected as the C-4 methoxymethyl (MOM) ether (**26**); the C-2 hydroxy group is unlikely to react because of intramolecular H-bonding with the adjacent carbonyl moiety. Compound **26** and ethyl acetate or ethyl butyrate were treated with sodium hydride in anhydrous THF under nitrogen. Subsequent hydrolysis of the intermediate mixture with Amberlyst 15 resin in 2-propanol gave 2-methyl- (**24d**) and 7-hydroxy-2-propylchromone (**24f**).[12] 2,3-Dimethyl-7-hydroxychromone (**24j**) was synthesized in two steps. A mixture of **23**, Ac_2O, and anhydrous NaOAc was heated under reflux to afford **27**, which was hydrolyzed in a 1:1 mixture of MeOH and saturated aqueous $NaHCO_3$ at room temperature to provide **24j**.[13]

Scheme 3 illustrates the synthesis of the 2′,2′-dimethylpyranochromones (**29**). As described previously,[9]

Scheme 4. Possible Mechanism for Production of **29h**



Scheme 5. Synthesis of DCP Derivatives **4**−**21**[a]



[a] Reagents and conditions: (i) $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, $(DHQ)_2$-Phal, K_2CO_3, 0 °C; (ii) camphanoyl chloride, DMAP, pyridine/CH_2Cl_2; (iii) Ac_2O or acyl chloride, DMAP/CH_2Cl_2.

24a−**d**, **24f**, **24i**, and **24j** were converted to the corresponding pyranochromones (**29**) by alkylation with 3-chloro-3-methyl-1-butyne in DMF in the presence of K_2CO_3 and KI, followed by cyclization in refluxing *N*,*N*-diethylaniline. Alternatively, compound **22** was heated with 4,4-dimethoxy-2-methyl-2-butanol in anhydrous pyridine at 140 °C to afford **30**, which was reacted with various ethyl alkanoates and NaH in anhydrous THF, followed by hydrolysis with Amberlyst 15 resin in 2-propanol to afford **29e**, **29g**, and **29h**. The 6-*tert*-butyl analogue **29k** was prepared analogously from **31**, which was synthesized by reacting compound **22** with *tert*-butyl alcohol in the presence of H_3PO_4 and P_2O_5 at 80 °C. As shown in Scheme 4, when ethyl bromoacetate was reacted with **30**, the product was 2-ethoxymethyl-dimethylpyranochromone (**29h**), rather than 2-bromomethylpyranochromone as anticipated. Ethoxymethyl substitution could occur by attack of ethoxide and displacement of bromide, which is a good leaving group and adjacent to the carbonyl moiety.

According to Scheme 5, the asymmetric dihydroxylation of **29a**−**k** was accomplished using a catalytic Sharpless asymmetric dihydroxylation (AD),[14,15] in which $K_2OsO_2(OH)_4$ serves as catalyst and $(DHQ)_2$PYR or $(DHQ)_2$PHAL as chiral auxiliary.[14,16] After being dried in vacuo overnight, the diols (**33a**−**k**) were reacted with excess (*S*)-camphanoyl chloride in pyridine or DMAP and anhydrous methylene chloride at room temperature to afford target DCP derivatives (**4**−**14**).[6] Some 4′-camphanoyl-3′-hydroxy DCPs (**34b**−**e**, **34h**, and **34i**) were also isolated. The percent diasteromeric excesses (% de) ranged from 33 to 90%, as determined from the ^{1}H NMR spectra. These values probably differed due to the effect of the substituents on the molecular planarity of **29**. Compounds **34d**, **34e**, **34h**, and **34i** were reacted with various acid chlorides or anhydrides to afford 3′-acyl-4′-camphanoyl DCPs (**15**−**21**) with different *O*-acyl substitutions on the 3′ and 4′ positions.

Results and Discussion

The newly synthesized substituted DCPs (**4**−**21**) were tested in vitro for suppression of HIV-1_{IIIB} replication in H9 lymphocytes (non-drug-resistant strain), as well as against the HIV-1 RTMDR1 multi-RT inhibitor-resistant viral strain in MT4 cells. This latter viral strain contains several mutations in RT amino acid residues (L74V, M41L, V106A, and T215Y) and is resistant to AZT, ddI, nevirapine, and other nonnucleoside reverse transcriptase inhibitors (NNRTI).[17]

Against the non-drug-resistant strain, the EC_{50} and TI values of compounds **4**, **5**, **7**, **8**, and **13** were better than those of DCK and similar to or better than those of 4-methyl DCK, which were tested in parallel. Compounds **5** and **8** exhibited extremely high anti-HIV activity in this assay (Table 1), with EC_{50} values of 0.00099 μM and 0.00032 μM and remarkable therapeutic indexes (TI) of 1.48×10^4 and 1.16×10^5, respectively. DCP (**4**), 2-methyl DCP (**7**), and 2,3-dimethyl DCP (**13**) also showed potent anti-HIV activity with EC_{50} values of 0.0013, 0.0031, and 0.007 μM and TI values of 1.1×10^4, 8600, and 1500, respectively. 2-Propyl DCP (**9**) and 2-isopropyl DCP (**10**) exhibited moderate activity, with EC_{50} values of 0.02 μM and 0.07 μM, respectively. However, 2-ethoxymethyl DCP (**11**) and 2-phenyl DCP (**12**) were much less active (EC_{50} = 0.1 μM and 0.129 μM) and had lower therapeutic indexes (151 and 277) than DCK, and 3-phenyl DCP (**6**) showed only slight activity. As previously found with

Table 1. Anti-HIV Activity of DCP Analogues **4**−**14**[a]

	HIV_{IIIB}[b]			HIV-1 RTMDR1[c]		
compd	IC_{50} (μM)	EC_{50} (μM)	TI	IC_{50} (μM)	EC_{50} (μM)	TI
4[d]	14.20	0.0013	11100		NS	
5	14.70	0.00099	14800	3.14	1.28	2.5
6	>35.82	1.54	23.3		NS	
7	27.30	0.0031	8600	11.8	0.19	62.5
8	37.16	0.00032	116200	43.08	0.06	718
9	>37.65	0.020	1860	37.65	0.14	272
10	33.4	0.07	483	>15.04	0.14	>111.1
11	15.1	0.1	151	>12.5	0.37	>34
12	>35.82	0.129	>277	12.2	0.17	71
13	11.3	0.007	1500	4.72	0.31	15
14	35.4	1.62	22	>14.15	7.36	1.9
DCK (**1**)[e]	>16.1	0.049	>328	>16.1	12.06	1.3
4-MeDCK (**2**)[f]	>39.3	0.0059	>6660	>15.7	9.43	1.7
AZT	1872	0.044	42700	>37.5	0.1	>375

[a] All data presented in this table are averaged from at least two separate experiments. [b] This assay was performed in H9 lymphocytes by Panacos, Inc., Gaithersburg, MD. [c] This assay was performed in the MT-4 cell line by Dr. Chin-Ho Chen, Duke University, NC. [d] Previously obtained and published values: $EC_{50} = 0.00068$ μM and TI = 14500.[9] [e] Previously obtained and published values: $EC_{50} = 0.000256$ μM and TI = 1.37×10^5.[4] [f] Previously obtained and published values: $EC_{50} = 1.83 \times 10^{-6}$ μM and TI = $>6.89 \times 10^7$.[6] NS = no suppression at 10 μg/mL.

Table 2. Anti-HIV Activity of 3′-Acyl DCP Analogues **15**−**21**[a]

	HIV_{IIIB}[b]			HIV-1 RTMDR1[c]		
compd	IC_{50} (μM)	EC_{50} (μM)	TI	IC_{50} (μM)	EC_{50} (μM)	TI
15	>50	2.29	21.9	>40.2	2.2	18.2
16	40.7	0.88	46	17.1	0.30	56.3
17	>32.2	0.0057	5600	13.0	0.59	22
18	>46.3	0.25	182	>18.5	0.28	>66.7
19	>43.9	0.62	70	>17.5	1.09	>16.1
20	>44.6	2.24	20	6.25	4.46	1.4
21	>42.5	1.68	25.3		NS	
DCK (**1**) [e]	>16.1	0.049	>328	>16.1	12.06	1.3
4-MeDCK (**2**)[f]	39.3	0.0059	6600	>15.7	9.43	1.7
AZT	1872	0.044	42700	>37.5	0.1	>375

[a] See Table 1 footnotes.

DCK analogues, compound **14**, with *tert*-butyl on C-6, lost almost all activity. These data demonstrated that, in DCP analogues, introducing a small alkyl substituent (one or two carbons) at the chromone 2- and/or 3-position resulted in retained anti-HIV activity, whereas a large substituent (over three carbons) at these positions significantly decreased activity against non-drug-resistant HIV in H9 lymphocytes, and substitution at the 6-position is not favorable.

Against the HIV-1 RTMDR1 strain, compound **8** (C-2 ethyl) showed the most promising anti-HIV activity (EC_{50} 0.06 μM, TI 718), while **9** and **10** (C-2 propyl and isopropyl, respectively) were slightly less potent (EC_{50} 0.14 μM). Compounds **7** and **12** showed almost identical activity, with EC_{50} values of 0.19 and 0.17 μM and TI values of 63 and 71, respectively, and compound **13** had an EC_{50} value of 0.31 μM. Compound **14**, with 6-*tert*-butyl and 2-ethyl substitution, had an EC_{50} value of only 7.36 μM, an analogous result to the SAR of DCK analogues, where 6-substitution is not favorable. The data also showed that substitution on the DCP 3-position is not favorable against the resistant strain. Compound **5** (3-methyl), although quite active against the non-drug-resistant strain, had an EC_{50} value of only 1.28 μM against the drug-resistant strain, and compound **6** (3-phenyl) was inactive at the testing concentration. In addition, the unsubstituted parent compound **4** lost potency against the resistant strain, as did **1** (DCK) and **2** (4-methyl DCK). On the basis of these data, a hydrophobic moiety, either aliphatic or phenyl, on the 2-position is crucial for anti-HIV activity against the multi-drug-resistant HIV strain and may increase binding of these compounds to a putative hydrophobic cleft. The extremely high anti-HIV activity of **8** indicated that a C-2 ethyl group probably fits well into the putative hydrophobic cleft on the active surface of the target, greatly increasing the affinity of the agent and the desired pharmacological response. Furthermore, from comparison of EC_{50} and IC_{50} values for compounds **5** (3-methyl) and **7** (2-methyl), substitution on the 2-position appears to increase the activity against the multi-RT inhibitor-resistant strain and also decrease the cytotoxicity.

Several DCP derivatives (**15**−**21**) with different acyl substituents on the 3′-position were synthesized and evaluated in both assays (Table 2). Against the non-drug-resistant strain in H9 lymphocytes, compound **15** (3′-acetyl) showed only slight activity (EC_{50} 2.29 μM, TI 22), **16** (3′-isobutyryl) exhibited moderate activity (EC_{50} 0.88 μM, TI 46), and **17** (3′-isovaleryl) was most potent (EC_{50} 0.0057 μM, TI > 5600). From this rank order, an isovaleryl on the 3′-position appears essential for high anti-HIV potency in H9 lymphocytes, as **17** (3′-isovaleryl) showed similar potency to **2** and **7** (in both latter compounds, an isovaleryl moiety is contained within the 3′-camphanoyl group). In addition, all three 3′-isobutyryl compounds, **16**, **18**, and **19**, showed weaker activity than their parent compounds **7**, **8**, and **11** against the non-drug-resistant strain. The 2-phenyl, 3′-acetyl, and 3′-

isobutyryl analogues (**20** and **21**) showed weak activity, comparable to **15**.

Against the HIV-1 RTMDR1 strain, 3′-isobutyryl- or -isovaleryl-substituted compounds exhibited comparable or slightly weaker potency than the corresponding 3′-camphanoyl compounds. Accordingly, **16** and **17** (EC_{50} 0.30 and 0.59 μM, respectively) had slightly weaker potency than **7** (EC_{50} 0.19 μM), while **18** (EC_{50} 0.28 μM) was less active than **8** (EC_{50} 0.06 μM), and **19** (EC_{50} 1.09 μM) was less active than **11** (EC_{50} 0.37 μM). 3′-Isobutyryl-2-phenyl DCK (**21**) was inactive at the testing concentration. As in the nonresistant strain, acetyl substitution was not favorable at the 3′-position; **15** and **20** had EC_{50} values of only 2.2 μM and 4.46 μM, respectively.

In conclusion, this study provided the following results. (1) DCP analogues are more promising than DCK analogues, as most DCP analogues are active against the multiple RT inhibitor-resistant strain. Although the structurally similar DCK derivatives exhibit potent anti-HIV activity against the non-drug-resistant strain, they are generally ineffective against the multiple RT inhibitor-resistant HIV-1 strain. (2) An appropriate alkyl substituent at position 2 is critical for the anti-HIV activity of DCP analogues against both non-drug-resistant and multi-RT-resistant viral strains. In addition, most 2-substituted DCP analogues are less toxic to the cells compared with DCP. (3) DCP analogues showed different SAR in non-drug-resistant and multi-RT inhibitor-resistant viral strains. 2- and 3-Substitutions are favorable for activity against the non-drug-resistant strain, but only 2-substituted DCP analogues show high activity against a multi-RT inhibitor-resistant strain.

Experimental Section

Melting points were measured with a Fisher Johns melting apparatus without correction. The proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a 300 MHz Varian Gemini 2000 spectrometer using TMS as internal standard. The solvent used was $CDCl_3$ unless indicated. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. All target compounds were analyzed for C, H and gave values within ±0.4% of the theoretical values. Optical rotations were measured with a Jasco Dip-1000 digital polarimeter at 25 °C at the sodium D line. The diastereoisomeric excess percentages were determined from intensity of protons at the 3′-position in the ^{1}H NMR spectra. Thin-layer chromatography (TLC) was performed on PLC silica gel 60 F_{254} plates (0.5 mm, Merck). Biotage Flash+ and Isco Companion systems were used as medium-pressure column chromatography. Silica gel (200−400 mesh) from Aldrich, Inc., was used for column chromatography. All other chemicals were obtained from Aldrich, Inc.

7-Hydroxychromone (24a).[10] 70% Perchloric acid (0.66 mL) was slowly added into a suspension of 2,4-dihydroxyacetophenone (**22**, 1 g, 6.7 mmol) in triethyl orthoformate (6 mL) with stirring. The mixture was stirred continuously until it cooled to room temperature. Anhydrous diethyl ether (18 mL) was added to precipitate the intermediate oxonium perchlorate salt, which was subsequently hydrolyzed in 30 mL of hot water to provide 7-hydroxychromone (**24a**) as a dark brown solid: 60% yield; mp 190−193 °C; MS (ESI+) *m*/*z* (%) 163 ($M^+ + 1$, 100); ^{1}H NMR δ 10.76 (1H, s, OH-7), 8.14 (1H, d, J = 6.3 Hz, H-2), 7.87 (1H, d, J = 8.6 Hz, H-5), 6.89 (1H, dd, J = 8.6, 2.1 Hz, H-6), 6.83 (1H, d, J = 2.1 Hz, H-8), 6.20 (1H, d, J = 6.3 Hz, H-3).

7-Hydroxy-3-methylchromone (24b).[10] The procedure was identical to that used for the preparation of **24a**: 68% yield (starting with 3.33 g of **23**); mp 155−157 °C; MS-ESI+ (*m*/*z*, %): 199 ($M^+ + Na$, 10), 198 ($M^+ + Na - 1$, 100), 176 (M^+, 53); ^{1}H NMR δ 10.72 (1H, s, OH-7), 8.11 (1H, s, H-2), 7.88 (1H, d, J = 9.0 Hz, H-5), 6.89 (1H, dd, J = 9.0, 2.4 Hz, H-6), 6.80 (1H, d, J = 2.4 Hz, H-8), 1.87 (3H, s, CH_3-3).

7-Hydroxy-3-phenylchromone (24c).[11] The phenol **25** (840 mg, 3.7 mmol) in dry DMF (8 mL) was heated to 50 °C, and a solution of methanesulfonyl chloride (0.9 mL) in dry DMF (1 mL) was added slowly. Then the mixture was reacted at 60−70 °C for 6 h. After cooling, the reaction mixture was poured into a large volume of ice-cold aq NaOAc (12 g/100 mL). The crude product **24c** was filtered off and purified on a silica gel column (hexane−EtOAc 10:1): 67% yield; mp 155−157 °C; MS-ESI+ (*m*/*z*, %): 239 ($M^+ + 1$, 100); ^{1}H NMR δ (acetone-d_6): 9.62 (1H, s, OH-7), 8.23 (1H, s, H-2), 8.08 (1H, d, J = 8.7 Hz, H-5), 7.61∼7.64 (2H, m, H-2′, 6′-phenyl), 7.36∼7.43 (3H, m, H-3′,4′,5′-phenyl), 7.01 (1H, dd, J = 8.7, 2.4 Hz, H-6), 6.93 (1H, d, J = 2.4 Hz, H-8).

2-Hydroxy-4-(methoxymethyl)acetophenone (26). Chloromethyl methyl ether (2.25 mL, 25 mmol) was added dropwise into a mixture of **22** (2.0 g, 13 mmol) and potassium carbonate (4.3 g) in anhydrous acetone (12 mL). The reaction mixture was stirred for 12 h at room temperature. After filtration, the filtrate was solved in water and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried in vacuo to provide **26** as a white solid: 89% yield; mp 36−38 °C; MS-ESI− (*m*/*z*, %) 195 ($M^+ - 1$, 100); ^{1}H NMR δ 7.62 (1H, d, J = 8.7 Hz, H-6), 6.56 (1H, d, J = 2.4 Hz, H-3), 6.52 (1H, dd, J = 8.7, 2.4 Hz, H-5), 5.18 (2H, s, O*CH*$_2$OCH$_3$-4), 3.45 (3H, s, OCH$_2$O*CH*$_3$-4), 2.54 (3H, s, CO*CH*$_3$-1).

Synthesis of 2-substituted-7-hydroxychromones.[12] A mixture of **26** (498 mg, 2.5 mmol) and ethyl alkanoate (5.0 mmol) in absolute THF (2 mL) was added slowly to a sodium hydride (320 mg, 8 mmol)/THF (2 mL) suspension under nitrogen. The mixture was warmed to reflux temperature for 2 h, cooled and neutralized with 2N HCl, and extracted with $CHCl_3$ three times. The organic layer was collected and evaporated in vacuo. The residue and Amberlyst 15 resin (0.5 g) were stirred in 2-propanol (10 mL) at reflux temperature to give the target 2-substituted-7-hydroxychromone (**24d** and **24f**) in a total yield of 63−75%.

7-Hydroxy-2-methylchromone (24d). 75% yield (starting with 476 mg of **26**); mp >185 °C sublimed; MS-ESI+ (*m*/*z*, %) 176 (M^+, 100); ^{1}H NMR δ (DMSO-d_6): 10.73 (1H, s, OH-7), 7.83 (1H, d, J = 8.4 Hz, H-5), 6.87 (1H, dd, J = 8.4, 2.1 Hz, H-6), 6.81 (1H, d, J = 2.1 Hz, H-8), 6.10 (1H, s, H-3), 2.33 (3H, s, CH_3-2).

7-Hydroxy-2-propylchromone (24f). 63% yield (starting with 230 mg of **26**); mp 140−142 °C; MS-ESI− (*m*/*z*, %): 204 (M^+, 70), 203 ($M^+ - 1$, 95); ^{1}H NMR δ: 7.92 (1H, d, J = 8.4 Hz, H-5), 6.88 (1H, dd, J = 8.4, 2.1 Hz, H-6), 6.80 (1H, d, J = 2.1 Hz, H-8), 6.10 (1H, s, H-3), 2.62 (2H, t, J = 7.6 Hz, *CH*$_2$CH$_2$CH$_3$-2), 1.75 (2H, m, CH$_2$*CH*$_2$CH$_3$-2), 1.01 (3H, t, J = 7.6 Hz, CH$_2$CH$_2$*CH*$_3$-2).

7-Acetoxy-2,3-dimethylchromone (27).[13] A mixture of **23** (1.66 g, 10.0 mmol), Ac_2O (7 mL), and anhydrous NaOAc (0.83 g, 10 mmol) was heated under reflux for 14 h. After cooling, the reaction mixture was diluted with water and extracted with CH_2Cl_2 three times. The organic layer was evaporated to afford **27** as a yellow solid; 96% yield; mp 99−100 °C; MS-ESI+ (*m*/*z*, %): 233 ($M^+ + 1$, 67); ^{1}H NMR δ 8.19 (1H, d, J = 8.7 Hz, H-5), 7.18 (1H, d, J = 2.1 Hz, H-8), 7.07 (1H, dd, J = 8.7, 2.1 Hz, H-6), 2.39 (3H, s, *CH*$_3$CO-7), 2.33 (3H, s, CH_3-2), 2.04 (3H, s, CH_3-3).

2,3-Dimethyl-7-hydroxychromone (24j).[13] Compound **27** (1.00 g, 4.3 mmol) was stirred in a mixture of MeOH and saturated sodium bicarbonate (v:v = 1:1, 100 mL) for 3 h at room temperature. The reaction mixture was filtered and the solid washed with water to provide pure **24j** as a yellow solid; 76% yield; mp >168 °C sublimed; MS-ESI+ (*m*/*z*, %) 213 ($M^+ + Na$, 100), 191 ($M^+ + 1$, 75); ^{1}H NMR δ (CD_3OD): 7.98 (1H, d, J = 8.7 Hz, H-5), 6.88 (1H, dd, J = 8.7, 2.1 Hz, H-6), 6.78 (1H, d, J = 2.1 Hz, H-8), 2.42 (3H, s, CH_3-2), 2.03 (3H, s, CH_3-3).

6-Acetyl-2,2-dimethyl-5-hydroxy-2*H*-chromene (30). Compound **22** (1 g, 6.6 mmol) was reacted with 4,4-dimethoxyl-2-methyl-2-butanol (1.5 mL) in anhydrous pyridine (2 mL) at 140 °C for 6 h. Another 1 mL 4,4-dimethoxyl-2-methyl-2-butanol was added and the reaction continued for 4 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with 10% aqueous HCl, water, and brine. The organic layer was separated, and solvent was removed in vacuo. The residue was purified by column chromatography with hexane:EtOAc = 25:1 to afford **30** as a yellow solid: 40% yield; mp 90−92 °C; MS-ESI+ (*m*/*z*, %): 241 (M^+ + Na, 100), 219 (M^+ + 1, 78); ^{1}H NMR δ 7.51 (1H, d, J = 8.7 Hz, H-7), 6.70 (1H, d, J = 9.9 Hz, H-4), 6.33 (1H, d, J = 8.7 Hz, H-8), 5.57 (1H, d, J = 9.9 Hz, H-3), 2.53 (3H, CH_3CO-6), 1.44, 1.56 (each 3H, CH_3-2).

5-*tert*-Butyl-2,4-dihydroxyacetophenone (31).[18] *tert*-Butyl alcohol (3.8 mL) was added to a mixture of 2,4-dihydroxyacetophenone (**22**, 760 mg, 5 mmol), H_3PO_4 (60 mL), and P_2O_5 (4.4 g) at 60−70 °C. After the mixture was stirred for 1 h, additional P_2O_5 (4.4 g) and *tert*-butyl alcohol (3.8 mL) were added, and reaction was continued for an additional 1 h at the same temperature. The reaction mixture was cooled to room temperature, poured into 500 mL of ice−water, and filtered to afford crude product, which was purified by column chromatography on Si gel with an eluant of hexane:EtOAc = 10:1 to provide pure **31** as a white solid; 56% yield; mp: 148−150 °C; MS-ESI+ (*m*/*z*, %): 209 (M^+ + 1, 100); ^{1}H NMR δ 7.58 (1H, s, H-6), 6.23 (1H, s, H-3), 2.56 (3H, CH_3CO-1), 1.38 (9H, $(CH_3)_3$C-5).

6-Acetyl-8-*tert*-butyl-2,2-dimethyl-5-hydroxy-2*H*-chromene (32). The procedure was identical to that used for the preparation of **30**: 40% yield (starting with 416 mg of **31**); mp 64−65 °C; MS-ESI+ (*m*/*z*, %): 297 (M^+ + Na, 80), 275 (M^+ + 1, 100); ^{1}H NMR δ 7.48 (1H, s, H-7), 6.72 (1H, d, J = 10.0 Hz, H-4), 5.57 (1H, d, J = 10.0 Hz, H-3), 2.54 (3H, CH_3CO-6), 1.56, 1.55 (each 3H, CH_3-2), 1.36 (9H, $(CH_3)_3$C-8).

Syntheses of Substituted 2′,2′-Dimethylpyrano[2,3-*f*]-chromone from Substituted 7-Hydroxychromone Derivatives. Method 1. A mixture of substituted 7-hydroxychromone (**24**), K_2CO_3 (2.5 equiv), KI (1 equiv), and excess 3-chloro-3-methyl-1-butyne (2∼3 equiv) in dry DMF was heated to 70−80 °C with stirring until the reaction was complete as monitored by TLC. After the solid was filtered, the filtrate was concentrated in vacuo. Without purification, the residue (crude product **28**) was directly heated to reflux in 10 mL of *N*,*N*-diethylaniline for 4−6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with 10% aqueous HCl, water, and brine. The organic layer was separated, and solvent was removed in vacuo. The residue was purified by column chromatography on TLC with an eluant of hexane:EtOAc = 4:1 to afford substituted **29**.

Method 2. The procedure was similar to that used for synthesis of **24d** from **26**. A mixture of **30** and ethyl alkanoate in absolute THF was added slowly to a sodium hydride/THF suspension under nitrogen. The mixture was warmed to reflux temperature for 2−6 h monitored by TLC, followed by neutralization with 2 N HCl, and extraction with $CHCl_3$ three times. The organic layer was collected and evaporated in vacuo. The residue and Amberlyst 15 resin were stirred in 2-propanol at reflux temperature to give 2-substituted dimethylpyranochromone **29**.

2′,2′-Dimethylpyrano[2,3-*f*]chromone (29a). Using method 1, 50% yield (starting with 194 mg of **24a**); mp 93−95 °C; EI-MS (*m*/*z*, %) 228 (M^+, 70), 213 ($M^+ - CH_3$, 100); ^{1}H NMR δ 7.95 (1H, d, J = 8.7 Hz, H-5), 7.78 (1H, d, J = 6.3 Hz, H-2), 6.83 (1H, d, J = 8.7 Hz, H-6), 6.76 (1H, d, J = 10.5 Hz, H-4′), 6.26 (1H, d, J = 6.3 Hz, H-3), 5.69 (1H, d, J = 10.5 Hz, H-3′), 1.48 (6H, s, 2 × CH_3-2′).

3,2′,2′-Trimethylpyrano[2,3-*f*]chromone (29b). Using method 1, 52% yield (starting with 588 mg of **24b**); mp 66−67 °C; MS-ESI+ (*m*/*z*, %) 265 (M^+ + Na, 15), 264 (M^+ + Na − 1, 100), 242 (M^+, 29); ^{1}H NMR δ 7.95 (1H, d, J = 8.8 Hz, H-5), 7.72 (1H, s, H-2), 6.81 (1H, d, J = 8.8 Hz, H-6), 6.75 (1H, d, J = 10.0 Hz, H-4′), 5.68 (1H, d, J = 10.0 Hz, H-3′), 2.00 (3H, s, CH_3-3), 1.46, 1.47 (each 3H, s, CH_3-2′).

2′,2′-Dimethyl-3-phenylpyrano[2,3-*f*]chromone (29c). Using method 1, 66% yield (starting with 119 mg of **24c**); mp 182 °C sublimed; MS-ESI+ (*m*/*z*, %) 305 (M^+ + 1, 100); ^{1}H NMR δ 8.07 (1H, d, J = 8.7 Hz, H-5), 7.96 (1H, s, H-2), 7.52∼7.56 (2H, m, H-2″,6″-phenyl), 7.36∼7.46 (3H, m, H-3″,4″,5″-phenyl), 6.86 (1H, d, J = 8.7 Hz, H-6), 6.81 (1H, d, J = 9.9 Hz, H-4′), 5.72 (1H, d, J = 9.9 Hz, H-3′), 1.50 (6H, s, 2 × CH_3-2′).

2,2′,2′-Trimethylpyrano[2,3-*f*]chromone (29d). Using method 1, 56% yield (starting with 1.3 g of **24d**); mp 123−125 °C; MS-ESI+ (*m*/*z*, %) 243 (M^+ + 1, 100); ^{1}H NMR δ 7.90 (1H, d, J = 8.6 Hz, H-5), 6.78 (1H, d, J = 8.6 Hz, H-6), 6.75 (1H, d, J = 10.2 Hz, H-4′), 6.06 (1H, s, H-3), 5.67 (1H, d, J = 10.2 Hz, H-3′), 2.34 (3H, s, CH_3-2), 1.45 (6H, s, 2×CH_3-2′).

2′,2′-Dimethyl-2-ethylpyrano[2,3-*f*]chromone (29e). Using method 2, 69% yield (starting with 654 mg of **30**); mp 97−98 °C; MS-ESI+ (*m*/*z*, %) 279 (M^+ + Na, 100), 257 (M^+ + 1, 81); ^{1}H NMR δ 7.92 (1H, d, J = 8.7 Hz, H-5), 6.80 (1H, d, J = 8.7 Hz, H-6), 6.77 (1H, d, J = 10.2 Hz, H-4′), 6.10 (1H, s, H-3), 5.69 (1H, d, J = 10.2 Hz, H-3′), 2.65 (2H, q, J = 7.5 Hz, CH_2-CH_3-2), 1.44, 1.48 (each 3H, s, CH_3-2′), 1.30 (3H, t, J = 7.5 Hz, CH_2CH_3-2).

2′,2′-Dimethyl-2-propylpyrano[2,3-*f*]chromone (29f). Using method 1, 41% yield (starting with 500 mg of **24f**); mp 80−81 °C; MS-ESI+ (*m*/*z*, %) 293 (M^+ + Na, 100), 271 (M^+ + 1, 57); ^{1}H NMR δ 7.90 (1H, d, J = 8.7 Hz, H-5), 6.78 (1H, d, J = 8.7 Hz, H-6), 6.75 (1H, d, J = 9.9 Hz, H-4′), 6.08 (1H, s, H-3), 5.67 (1H, d, J = 9.9 Hz, H-3′), 2.57 (2H, t, J = 7.5 Hz, CH_2-CH_2CH_3-2), 1.74 (2H, m, $CH_2CH_2CH_3$-2), 1.46 (6H, s, 2×CH_3-2′), 1.01 (3H, t, J = 7.5 Hz, $CH_2CH_2CH_3$-2).

2′,2′-Dimethyl-2-isopropylpyrano[2,3-*f*]chromone (29g). Using method 2, 50% yield (starting with 218 mg of **30**); mp 84−86 °C; MS-ESI+ (*m*/*z*, %) 293 (M^+ + Na, 100), 271 (M^+ + 1, 60); ^{1}H NMR δ 7.88 (1H, d, J = 8.8 Hz, H-5), 6.75 (1H, d, J = 8.8 Hz, H-6), 6.73 (1H, d, J = 10.0 Hz, H-4′), 6.06 (1H, s, H-3), 5.66 (1H, d, J = 10.0 Hz, H-3′), 2.82 (1H, m, J = 5.1 Hz, $CH(CH_3)_2$-2), 1.43 (6H, s, 2 × CH_3-2′), 1.27 (3H × 2, d, J = 5.1 Hz, $CH(CH_3)_2$-2).

2′,2′-Dimethyl-2-ethoxymethylpyrano[2,3-*f*]-chromone (29h). Using method 2, 31% yield (starting with 109 mg of **30**); yellow oil; MS-ESI+ (*m*/*z*, %) 309 (M^+ + Na, 100), 287 (M^+ + 1, 57); ^{1}H NMR δ 7.91 (1H, d, J = 8.4 Hz, H-5), 6.80 (1H, d, J = 8.4 Hz, H-6), 6.73 (1H, d, J = 10.2 Hz, H-4′), 6.32 (1H, s, H-3), 5.68 (1H, d, J = 10.2 Hz, H-3′), 3.63 (2H, q, J = 6.6 Hz, $CH_2OCH_2CH_3$-2), 3.45 (2H, s, $CH_2OCH_2CH_3$-2), 1.45 (6H, s, 2 × CH_3-2′), 1.27 (3H, t, J = 6.6 Hz, $CH_2OCH_2CH_3$-2).

2′,2′-Dimethyl-2-phenylpyrano[2,3-*f*]chromone (29i). Using method 1, 52% yield (starting with 958 mg of commercially available **24i**); mp 135−137 °C; MS-ESI+ (*m*/*z*, %) 327 (M^+ + Na, 100), 304 (M^+, 25); ^{1}H NMR δ 7.98 (1H, d, J = 8.8 Hz, H-5), 7.89 (2H, m, H-2″,6″-phenyl), 7.53 (3H, m, H-3″, 4″, 5″-phenyl), 6.92 (1H, d, J = 10.0 Hz, H-4′), 6.85 (1H, d, J = 8.8 Hz, H-6), 6.75 (1H, s, H-3), 5.75 (1H, d, J = 10.0 Hz, H-3′), 1.51 (6H, s, 2 × CH_3-2′).

2,3,2′,2′-Tetramethylpyrano[2,3-*f*]chromone (29j). Using method 1, 44% yield (starting with 270 mg of **24j**); mp 148−149 °C; MS-ESI+ (*m*/*z*, %) 257 (M^+ + 1, 100); ^{1}H NMR δ 7.95 (1H, d, J = 8.7 Hz, H-5), 6.79 (1H, d, J = 8.7 Hz, H-6), 6.78 (1H, d, J = 10.2 Hz, H-4′), 5.68 (1H, d, J = 10.2 Hz, H-3′), 2.39 (3H, s, CH_3-2), 2.03 (3H, s, CH_3-3), 1.47 (6H, s, 2 × CH_3-2′).

6-*tert*-Butyl-2′,2′-dimethyl-2-ethylpyrano[2,3-*f*]-chromone (29k). Using method 2, 56% yield (starting with 135 mg of **32**); mp 86−88 °C; MS-ESI+ (*m*/*z*, %) 335 (M^+ + Na, 75), 313 (M^+ + 1, 82); ^{1}H NMR δ 7.94 (1H, s, H-5), 6.80 (1H, d, J = 10.2 Hz, H-4′), 6.10 (1H, s, H-3), 5.68 (1H, d, J = 10.2 Hz, H-3′), 2.65 (2H, q, J = 7.8 Hz, CH_2CH_3-2), 1.51 (6H, s, 2 × CH_3-2′), 1.40 (9H, $(CH_3)_3$C-6), 1.29 (3H, t, J = 7.8 Hz, CH_2CH_3-2).

Asymmetric dihydroxylation of pyranochromones. A mixture of $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), and $(DHQ)_2$−PYR or $(DHQ)_2$PHAL (2% equiv), and $K_2OsO_2(OH)_4$ (2% equiv)

was dissolved in *t*-BuOH/H_2O (v/v, 1:1) at room temperature. The solution was cooled to 0 °C and methanesulfonamide (1 equiv) added under stirring. When the solution turned from light yellow to orange, the substituted pyranochromone (**29a-k**) was added. The mixture was stirred at 0 °C for 1−2 days, monitored by TLC. At completion, $Na_2S_2O_5$ (excess), water, and $CHCl_3$ were added and stirring continued for 0.5 h at room temperature. The mixture was extracted with $CHCl_3$ three times, the combined organic layer was dried over K_2SO_4, and then solvent was removed. The residue was purified by column chromatography or PTLC with an eluant of hexane: EtOAc = 3:1 to afford the pure substituted (+)-*cis*-3′,4′-dihydroxypyranochromones (**33a-k**).

3′*R*,4′*R*-Dihydroxy-2′,2′-dimethylpyrano[2,3-*f*]chromone (**33a**): 40% yield (starting with 43.7 mg of **29a**); mp 70−71 °C; EI-MS (*m*/*z*, %) 262 (M^+, 45), 244 (M^+ − OH, 15); ^{1}H NMR δ 8.05 (1H, d, J = 8.8 Hz, H-5), 7.84 (1H, d, J = 6.0 Hz, H-2), 6.89 (1H, d, J = 8.8 Hz, H-6), 6.33 (1H, d, J = 6.0 Hz, H-3), 5.18 (1H, d, J = 5.1 Hz, H-4′), 3.87 (1H, d, J = 5.1 Hz, H-3′), 1.43, 1.47 (each 3H, s, CH_3-2′).

3′*R*,4′*R*-Dihydroxy-3,2′,2′-trimethylpyrano[2,3-*f*]chromone (**33b**): 55% yield (starting with 242 mg of **29b**); mp 180−182 °C; MS-ESI+ (*m*/*z*, %) 277 (M^+ + 1, 100); ^{1}H NMR δ 7.98 (1H, d, J = 8.7 Hz, H-5), 7.74 (1H, d, J = 1.0 Hz, H-2), 6.82 (1H, d, J = 8.7 Hz, H-6), 5.15 (1H, dd, J = 5.4, 3.6 Hz, H-4′), 3.85 (1H, dd, J = 5.7, 5.4 Hz, H-3′), 3.43 (1H, d, J = 3.6 Hz, OH-4′), 3.19 (1H, d, J = 5.7 Hz, OH-3′), 1.99 (3H, d, J = 1.0 Hz, CH_3-3), 1.41, 1.42 (each 3H, s, CH_3-2′).

3′*R*,4′*R*-Dihydroxy-2′,2′-dimethyl-3-phenylpyranochromone (**33c**): 55% yield (starting with 194 mg of **29c**); mp > 203 °C sublimed; MS-ESI+ (*m*/*z*, %) 361 (M^+ + Na, 35), 339 (M^+ + 1, 100); ^{1}H NMR δ (CD_3OD) 8.28 (1H, s, H-2), 8.05 (1H, d, J = 9.0 Hz, H-5), 7.53∼7.57 (2H, m, H-2″,6″-phenyl), 7.32∼7.46 (3H, m, H-3”,4”,5”-phenyl), 6.92 (1H, d, J = 9.0 Hz, H-6), 5.15 (1H, d, J = 5.0 Hz, H-4′), 3.81 (1H, d, J = 5.0 Hz, H-3′), 1.46, 1.45 (each 3H, s, CH_3-2′).

3′*R*,4′*R*-Dihydroxy-2,2′,2′-trimethylpyrano[2,3-*f*]chromone (**33d**): 36% yield (starting with 605 mg of **29d**); mp 176−178 °C; MS-ESI+ (*m*/*z*, %) 299 (M^+ + Na, 100), 277 (M^+ + 1, 12); ^{1}H NMR δ (CD_3OD) 7.98 (1H, d, J = 9.0 Hz, H-5), 6.98 (1H, d, J = 9.0 Hz, H-6), 6.17 (1H, s, H-3), 5.12 (1H, d, J = 4.6 Hz, H-4′), 3.81 (1H, d, J = 4.6 Hz, H-3′), 2.46 (3H, s, CH_3-2), 1.46, 1.47 (each 3H, s, CH_3-2′).

3′*R*,4′*R*-Dihydroxy-2′,2′-dimethyl-2-ethylpyrano[2,3-*f*]chromone (**33e**): 54% yield (starting with 512 mg of **29e**); mp 153−155 °C; MS-ESI+ (*m*/*z*, %) 313 (M^+ + Na, 100), 291 (M^+ + 1, 35); ^{1}H NMR δ 8.01 (1H, d, J = 9.0 Hz, H-5), 6.85 (1H, d, J = 9.0 Hz, H-6), 6.14 (1H, s, H-3), 5.20 (1H, dd, J = 4.8, 4.2 Hz, H-4′), 3.87 (1H, dd, J = 6.6, 4.8 Hz, H-3′), 3.08 (1H, d, J = 4.2 Hz, OH-4′), 2.99 (1H, d, J = 6.6 Hz, OH-3′), 2.68 (2H, q, J = 7.5 Hz, CH_2CH_3-2), 1.42, 1.47 (each 3H, s, CH_3-2′), 1.32 (3H, t, J = 7.5 Hz, CH_2CH_3-2).

3′*R*,4′*R*-Dihydroxy-2′,2′-dimethyl-2-propylpyrano[2,3-*f*]chromone (**33f**): 55% yield (starting with 241 mg of **29f**); mp 143−144 °C; MS-ESI+ (*m*/*z*, %) 327 (M^+ + Na, 86), 305 (M^+ + 1, 100); ^{1}H NMR δ 7.95 (1H, d, J = 9.0 Hz, H-5), 6.82 (1H, d, J = 9.0 Hz, H-6), 6.09 (1H, s, H-3), 5.17 (1H, dd, J = 5.0, 3.6 Hz, H-4′), 3.86 (1H, dd, J = 5.8, 5.0 Hz, H-3′), 3.39 (1H, d, J = 3.6 Hz, OH-4′), 3.20 (1H, d, J = 5.8 Hz, OH-3′), 2.59 (2H, t, J = 4.5 Hz, $CH_2CH_2CH_3$-2), 1.75 (2H, m, J = 4.5 Hz, $CH_2CH_2CH_3$-2), 1.48, 1.42 (each 3H, s, CH_3-2′), 1.02 (3H, t, J = 4.5 Hz, $CH_2CH_2CH_3$-2).

3′*R*,4′*R*-Dihydroxy-2′,2′-dimethyl-2-isopropylpyrano[2,3-*f*]chromone (**33g**): 72% yield (starting with 126 mg of **29g**); mp 152 °C sublimed; MS-ESI+ (*m*/*z*, %) 327 (M^+ + Na, 100), 305 (M^+ + 1, 55); ^{1}H NMR δ (CD_3OD) 7.96 (1H, d, J = 8.8 Hz, H-5), 6.88 (1H, d, J = 8.8 Hz, H-6), 6.18 (1H, s, H-3), 5.14 (1H, d, J = 4.6 Hz, H-4′), 3.81 (1H, d, J = 4.6 Hz, H-3′), 2.99 (1H, m, J = 6.6 Hz, $CH(CH_3)_2$-2), 1.48 (6H, s, 2 × CH_3-2′), 1.39 (6H, t, J = 6.6 Hz, $CH(CH_3)_2$-2).

3′*R*,4′*R*-Dihydroxy-2′,2′-dimethyl-2-ethoxymethylpyrano[2,3-*f*]chromone (**33h**): 54% yield (starting with 57 mg of **29h**); yellow oil; MS-ESI+ (*m*/*z*, %) 321 (M^+ + 1, 100); ^{1}H NMR δ 8.01 (1H, d, J = 9.1 Hz, H-5), 6.87 (1H, d, J = 9.1 Hz, H-6), 6.31 (1H, s, H-3), 5.20 (1H, dd, J = 5.1, 3.9 Hz, H-4′), 4.47, 4.35 (1H each, d, J = 14.1 Hz, $CH_2OCH_2CH_3$-2), 3.87 (1H, t, J = 5.1 Hz, H-3′), 3.71 (1H, d, J = 3.9 Hz, OH-4′), 3.63 (2H, q, J = 7.2 Hz, $CH_2OCH_2CH_3$-2), 3.08 (1H, d, J = 5.1 Hz, OH-3′), 1.48, 1.40 (each 3H, s, CH_3-2′), 1.27 (3H, t, J = 7.2 Hz, $CH_2OCH_2CH_3$-2).

3′*R*,4′*R*-Dihydroxy-2′,2′-dimethyl-2-phenylpyrano[2,3-*f*]chromone (**33i**): 79% yield (starting with 128 mg of **29i**); mp 238−241 °C; MS-ESI+ (*m*/*z*, %) 361 (M^+ + Na, 100), 338 (M^+, 28); MS-ESI− (*m*/*z*, %) 337 (M^+ − 1, 100); ^{1}H NMR δ 7.97 (1H, d, J = 8.7 Hz, H-5), 7.81∼7.88 (2H, m, H-2″,6″-phenyl), 7.42∼7.53 (3H, m, H-3″,4″,5″-phenyl), 6.82 (1H, d, J = 8.7 Hz, H-6), 6.63 (1H, s, H-3), 5.28 (1H, d, J = 5.0 Hz, H-4′), 3.89 (1H, d, J = 5.0 Hz, H-3′), 1.51, 1.46 (each 3H, s, CH_3-2′).

3′*R*,4′*R*-Dihydroxy-2,2,2′,2′-tetramethylpyrano[2,3-*f*]chromone (**33j**): 52% yield (starting with 150 mg of **29j**); mp >280 °C; MS-ESI+ (*m*/*z*, %) 291 (M^+ + 1, 100); ^{1}H NMR δ 8.02 (1H, d, J = 8.8 Hz, H-5), 6.83 (1H, d, J = 8.8 Hz, H-6), 5.19 (1H, t, J = 5.1 Hz, H-4′), 3.87 (1H, dd, J = 6.3, 5.1 Hz, H-3′), 3.10 (1H, d, J = 5.1, OH-4′), 2.99 (1H, d, J = 6.3 Hz, OH-3′), 2.42 (3H, s, CH_3-2), 2.03 (3H, s, CH_3-3), 1.46, 1.41 (each 3H, s, CH_3-2′).

6-*tert*-Butyl-3′*R*,4′*R*-dihydroxy-2′,2′-dimethyl-2-ethylpyrano[2,3-*f*]chromone (**33k**): 35% yield (starting with 75.3 mg of **29k**); mp >260 °C sublimed; MS-ESI+ (*m*/*z*, %) 347 (M^+ + 1, 100); ^{1}H NMR δ (CD_3OD) 7.97 (1H, s, H-5), 6.18 (1H, s, H-3), 5.15 (1H, d, J = 4.6 Hz, H-4′), 3.79 (1H, d, J = 4.6 Hz, H-3′), 2.77 (2H, q, J = 7.5 Hz, CH_2CH_3-2), 1.54, 1.49 (each 3H, s, CH_3-2′), 1.42 (9H, s, $(CH_3)_3$C-6), 1.35 (3H, t, J = 7.5 Hz, CH_2CH_3-2).

Syntheses of Substituted DCP Derivatives. The substituted 3′*R*,4′*R*-dihydroxypyranochromones (**33a**−**k**), (*S*)-(−)-camphanic chloride (3 equiv), and DMAP (3 equiv) were stirred in CH_2Cl_2 for 1−2 days at room temperature, monitored by TLC. At completion, the mixture was concentrated and the residue was purified by PTLC with an eluant of hexane/EtOAc = 3:1 to afford the appropriately substituted 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]-chromones (**4**−**14**) and 3′*R*-hydroxy-4′*R*-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromones (**34b**−**e**, **34h**, and **34i**).

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP, 4): 71% yield (starting with 15 mg of **33a**); mp 90−92 °C; MS-ESI+ (*m*/*z*, %) 645 (M^+ + Na, 100); ^{1}H NMR δ 8.15 (1H, d, J = 9.0 Hz, H-5), 7.69 (1H, d, J = 6.3 Hz, H-2), 6.94 (1H, d, J = 9.0 Hz, H-6), 6.72 (1H, d, J = 4.8 Hz, H-4′), 6.32 (1H, d, J = 6.3 Hz, H-3), 5.37 (1H, d, J = 4.8 Hz, H-3′), 2.46, 2.20, 1.90, 1.74 (each 2H, m, camphanoyl CH_2), 1.52, 1.47 (each 3H, s, CH_3-2′), 1.11, 1.10, 1.08, 1.02, 0.99, 0.89 (each 3H, s, camphanoyl CH_3); 93% de. $[\alpha]_D$ −95.3° (c = 0.17, $CHCl_3$). Anal. ($C_{34}H_{38}O_{11}\cdot 1^1/_2H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-3,2′,2′-trimethyldihydropyrano[2,3-*f*]chromone (5): 43% yield (starting with 83 mg of **33b**); mp 233−235 °C; MS-ESI+ (*m*/*z*, %) 659 (M^+ + Na, 100); ^{1}H NMR δ 8.16 (1H, d, J = 9.0 Hz, H-5), 7.61 (1H, s, H-2), 6.91 (1H, d, J = 9.0 Hz, H-6), 6.70 (1H, d, J = 4.8 Hz, H-4′), 5.36 (1H, d, J = 4.8 Hz, H-3′), 2.56, 2.32, 2.24, 1.85 (each 2H, m, camphanoyl CH_2), 2.12 (3H, s, CH_3-3), 1.64, 1.59 (each 3H, s, CH_3-2′), 1.32, 1.24, 1.22, 1.12, 1.10, 1.00 (each 3H, s, camphanoyl CH_3); 90% de. $[\alpha]_D$ −36.2° (c = 0.23, $CHCl_3$). Anal. ($C_{35}H_{40}O_{11}\cdot {}^1/_4H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyl-3-phenyldihydropyrano[2,3-*f*]chromone (6): 55% yield (starting with 17 mg of **33c**); mp 103−105 °C; MS-ESI+ (*m*/*z*, %) 699 (M^+ + 1, 100); ^{1}H NMR δ 8.25 (1H, d, J = 9.0 Hz, H-5), 7.84 (1H, s, H-2), 7.38∼7.51 (5H, m, phenyl), 6.97 (1H, d, J = 9.0 Hz, H-6), 6.76 (1H, d, J = 4.6 Hz, H-4′), 5.39 (1H, d, J = 4.6 Hz, H-3′), 2.50, 2.20, 1.91, 1.73 (each 2H, m, camphanoyl CH_2), 1.57 (6H, s, 2 × CH_3-2′), 1.24, 1.18, 1.09, 1.02, 0.98, 0.92 (each 3H, s, camphanoyl CH_3); 60% de. $[\alpha]_D$ −279.5° (c = 0.15, $CHCl_3$). Anal. ($C_{40}H_{42}O_{11}\cdot H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2,2′,2′-trimethyldihydropyrano[2,3-*f*]chromone (7): 35% yield (starting with 206 mg of **33d**); mp 146−148 °C; MS-ESI+ (*m*/*z*, %) 659 (M^+ + Na,

48), 658 ($M^+ + Na - 1$, 100), 636 (M^+, 12); ^{1}H NMR δ 8.11 (1H, d, J = 8.8 Hz, H-5), 6.90 (1H, d, J = 8.8 Hz, H-6), 6.75 (1H, d, J = 4.6 Hz, H-4′), 6.12 (1H, s, H-3), 5.37 (1H, d, J = 4.6 Hz, H-3′), 2.46, 2.12, 1.92, 1.70 (each 2H, m, camphanoyl CH_2), 2.27 (3H, s, CH_3-2), 1.53, 1.46 (each 3H, s, CH_3-2′), 1.11, 1.10, 1.07, 1.00, 0.97, 0.94 (each 3H, s, camphanoyl CH_3); 60% de. $[\alpha]_D$ −69.6° (c = 0.25, $CHCl_3$). Anal. ($C_{35}H_{40}O_{11}\cdot{}^1/_2H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyl-2-ethyldihydropyrano[2,3-*f*]chromone (8): 51% yield (starting with 290 mg of **33e**); mp 137−139 °C; MS-ESI+ (m/z, %) 673 ($M^+ + Na$, 100), 651 ($M^+ + 1$, 16); ^{1}H NMR δ 8.11 (1H, d, J = 9.0 Hz, H-5), 6.90 (1H, d, J = 9.0 Hz, H-6), 6.74 (1H, d, J = 4.8 Hz, H-4′), 6.13 (1H, s, H-3), 5.38 (1H, d, J = 4.8 Hz, H-3′), 2.56 (2H, q, J = 7.2 Hz, CH_2CH_3-2), 2.50, 2.14, 1.94, 1.70 (each 2H, m, camphanoyl CH_2), 1.53, 1.46 (each 3H, s, CH_3-2′), 1.23 (3H, t, J = 7.2 Hz, CH_2CH_3-2), 1.11, 1.10, 1.07, 1.00, 0.97, 0.95 (each 3H, s, camphanoyl CH_3); 95% de. $[\alpha]_D$ −773.3° (c = 0.16, $CHCl_3$). Anal. ($C_{36}H_{42}O_{11}\cdot{}^1/_4H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyl-2-propyldihydropyrano[2,3-*f*]chromone (9): 90% yield (starting with 46 mg of **33f**); mp 113−115 °C; MS-ESI+ (m/z, %) 687 ($M^+ + Na$, 100), 665 ($M^+ + 1$, 78); ^{1}H NMR δ 8.10 (1H, d, J = 8.7 Hz, H-5), 6.89 (1H, d, J = 8.7 Hz, H-6), 6.72 (1H, d, J = 4.8 Hz, H-4′), 6.14 (1H, s, H-3), 5.38 (1H, d, J = 4.8 Hz, H-3′), 2.50 (2H, m, J = 7.2 Hz, $CH_2CH_2CH_3$-2), 2.48, 2.14, 1.94, 1.68 (each 2H, m, camphanoyl CH_2), 1.65 (2H, m, J = 7.2 Hz, $CH_2CH_2CH_3$-2), 1.52, 1.45 (each 3H, s, CH_3-2′), 1.23 (3H, t, J = 7.2 Hz, $CH_2CH_2CH_3$-2), 1.10, 1.09, 1.00, 0.96, 0.95, 0.94 (each 3H, s, camphanoyl CH_3); 60% de. $[\alpha]_D$ −56.0° (c = 0.40, $CHCl_3$). Anal. ($C_{37}H_{44}O_{11}\cdot{}^3/_4H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyl-2-isopropyldihydropyrano[2,3-*f*]chromone (10): 35% yield (starting with 42 mg of **33g**); mp 181−182 °C; MS-ESI+ (m/z, %) 687 ($M^+ + Na$, 100), 665 ($M^+ + 1$, 15); ^{1}H NMR δ 8.10 (1H, d, J = 9.0 Hz, H-5), 6.88 (1H, d, J = 9.0 Hz, H-6), 6.74 (1H, d, J = 4.6 Hz, H-4′), 6.13 (1H, s, H-3), 5.39 (1H, d, J = 4.6 Hz, H-3′), 2.72 (1H, m, J = 7.5 Hz, $CH(CH_3)_2$-2), 2.48, 2.16, 1.94, 1.68 (each 2H, m, camphanoyl CH_2), 1.54, 1.45 (each 3H, s, CH_3-2′), 1.24 (6H, d, J = 7.5 Hz, $CH(CH_3)_2$-2), 1.11, 1.10, 1.06, 1.02, 0.97, 0.96 (each 3H, s, camphanoyl CH_3); 88% de. $[\alpha]_D$ −60.9° (c = 0.22, $CHCl_3$). Anal. ($C_{37}H_{44}O_{11}\cdot{}^1/_2H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyl-2-ethoxymethyldihydropyrano[2,3-*f*]chromone (11): 45% yield (starting with 40 mg of **33h**); mp 105−106 °C; MS-ESI+ (m/z, %): 681 ($M^+ + 1$, 100); ^{1}H NMR δ 8.13 (1H, d, J = 9.0 Hz, H-5), 6.92 (1H, d, J = 9.0 Hz, H-6), 6.72 (1H, d, J = 4.8 Hz, H-4′), 6.41 (1H, s, H-3), 5.37 (1H, d, J = 4.8 Hz, H-3′), 4.28, 4.25 (each 1H, d, J = 15.3 Hz, $CH_2OCH_2CH_3$-2), 3.58 (2H, q, J = 7.0 Hz, $CH_2OCH_2CH_3$-2), 2.50, 2.16, 1.95, 1.65 (each 2H, m, camphanoyl CH_2), 1.53, 1.47 (each 3H, s, CH_3-2′), 1.24 (3H, t, J = 7.0 Hz, $CH_2OCH_2CH_3$-2), 1.12, 1.10, 1.07, 0.99, 0.97, 0.94 (each 3H, s, camphanoyl CH_3); 90% de. $[\alpha]_D$ −66.0° (c = 0.10, $CHCl_3$). Anal. ($C_{37}H_{44}O_{12}\cdot{}^3/_4H_2O$) C, H.

3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyl-2-phenyldihydropyrano[2,3-*f*]chromone (12): 52% yield (starting with 162 mg of **33i**); mp 153−155 °C; MS-ESI+ (m/z, %) 721 ($M^+ + Na$, 100), 699 ($M^+ + 1$, 15); ^{1}H NMR δ 8.18 (1H, d, J = 9.0 Hz, H-5), 7.80 (2H, m, H-2″,6″-phenyl), 7.49 (3H, m, H-3″, 4″, 5″-phenyl), 6.96 (1H, d, J = 9.0 Hz, H-6), 6.92 (1H, d, J = 5.0 Hz, H-4′), 6.82 (1H, s, H-3), 5.46 (1H, d, J = 5.0 Hz, H-3′), 2.54, 2.23, 1.98, 1.78 (each 2H, m, camphanoyl CH_2), 1.55, 1.49 (each 3H, s, CH_3-2′), 1.13, 1.12, 0.99, 0.96, 0.84, 0.64, (each 3H, s, camphanoyl CH_3); 33% de. $[\alpha]_D$ +25.5° (c = 0.13, $CHCl_3$). Anal. ($C_{40}H_{42}O_{11}\cdot{}^1/_4H_2O$) C, H.

3′R,4′R-Di-*O*-(−)-camphanoyl-2,3,2′,2′-tetramethyldihydropyrano[2,3-*f*]chromone (13): 50% yield (starting with 183 mg of **33j**); mp 189−190 °C; MS-ESI+ (m/z, %) 673 ($M^+ +$ Na, 100), 651 ($M^+ + 1$, 35); ^{1}H NMR δ 8.11 (1H, d, J = 8.8 Hz, H-5), 6.86 (1H, d, J = 8.8 Hz, H-6), 6.74 (1H, d, J = 4.6 Hz, H-4′), 5.36 (1H, d, J = 4.6 Hz, H-3′), 2.46, 2.14, 1.92, 1.69 (each 2H, m, camphanoyl CH_2), 2.27 (3H, s, CH_3-2), 1.98 (3H, s, CH_3-3), 1.51, 1.45 (each 3H, s, CH_3-2′), 1.10, 1.08, 1.05, 0.97, 0.96, 0.91 (each 3H, s, camphanoyl CH_3); 92% de. $[\alpha]_D$ −76.5° (c = 0.23, $CHCl_3$). Anal. ($C_{36}H_{42}O_{11}\cdot{}^1/_2H_2O$) C, H.

6-*tert*-Butyl-3′*R*,4′*R*-di-*O*-(−)-camphanoyl-2′,2′-dimethyl-2-ethyldihydropyrano[2,3-*f*]chromone (14): 57% yield (starting with 28 mg of **33k**); mp 253−254 °C; MS-ESI+ (m/z, %) 707 ($M^+ + 1$, 100); ^{1}H NMR δ 8.10 (1H, s, H-5), 6.75 (1H, d, J = 4.8 Hz, H-4′), 6.12 (1H, s, H-3), 5.41 (1H, d, J = 4.8 Hz, H-3′), 2.52 (2H, q, J = 7.5 Hz, CH_2CH_3-2), 2.47, 2.18, 1.92, 1.70 (each 2H, m, camphanoyl CH_2), 1.56, 1.53 (each 3H, s, CH_3-2′), 1.40 (9H, $(CH_3)_3$C-6), 1.22 (3H, t, J = 7.5 Hz, CH_2CH_3-2), 1.12, 1.10, 1.07, 1.01, 0.97, 0.95 (each 3H, s, camphanoyl CH_3); 99% de. $[\alpha]_D$ −64.8° (c = 0.29, $CHCl_3$). Anal. ($C_{40}H_{50}O_{11}$) C, H.

4′*R*-*O*-(−)-Camphanoyl-3′*R*-hydroxy-3,2′,2′-trimethyldihydropyrano[2,3-*f*]chromone (34b): 21% yield (starting with 83 mg of **33b**); mp 222−224 °C; MS-ESI+ (m/z, %) 457 ($M^+ + 1$, 80), 456 (M^+, 100); ^{1}H NMR δ 8.13 (1H, d, J = 8.8 Hz, H-5), 7.64 (1H, s, H-2), 6.88 (1H, d, J = 8.8 Hz, H-6), 6.54 (1H, d, J = 5.0 Hz, H-4′), 4.13 (1H, d, J = 5.0 Hz, H-3′), 2.50, 2.08, 1.90, 1.72 (each 1H, m, camphanoyl CH_2), 1.98 (3H, s, CH_3-3), 1.52, 1.39 (each 3H, s, CH_3-2′), 1.09, 1.00, 0.94 (each 3H, s, camphanoyl CH_3).

4′*R*-*O*-(−)-Camphanoyl-3′*R*-hydroxy-2′,2′-dimethyl-3-phenyldihydropyrano[2,3-*f*]chromone (34c): 50% yield (starting with 17 mg of **33c**); mp 225−227 °C; MS-ESI+ (m/z, %) 519 ($M^+ + 1$, 100); ^{1}H NMR δ 8.19 (1H, d, J = 9.0 Hz, H-5), 7.87 (1H, s, H-2), 7.52 (2H, m, H-2”, 6”-phenyl), 7.38−7.43 (3H, m, H-3”, 4”, 5”-phenyl), 6.92 (1H, d, J = 9.0 Hz, H-6), 6.58 (1H, d, J = 5.1 Hz, H-4′), 4.12 (1H, d, J = 5.1 Hz, H-3′), 2.46, 2.26, 1.85, 1.65 (each 1H, m, camphanoyl CH_2), 1.53, 1.41 (each 3H, s, CH_3-2′), 1.09, 1.02, 0.97, (each 3H, s, camphanoyl CH_3).

4′*R*-*O*-(−)-Camphanoyl-3′*R*-hydroxy-2,2′,2′-trimethyldihydropyrano[2,3-*f*]chromone (34d): 60% yield (starting with 206 mg of **33d**); mp 223−225 °C; MS-ESI+ (m/z, %) 457 ($M^+ + 1$, 100); ^{1}H NMR δ 8.02 (1H, d, J = 8.8 Hz, H-5), 6.84 (1H, d, J = 8.8 Hz, H-6), 6.59 (1H, d, J = 4.8 Hz, H-4′), 6.10 (1H, s, H-3), 4.11 (1H, d, J = 4.8 Hz, H-3′), 2.48, 2.02, 1.90, 1.67 (each 1H, m, camphanoyl CH_2), 2.26 (3H, s, CH_3-2), 1.51, 1.38 (each 3H, s, CH_3-2′), 1.07, 0.98, 0.97 (each 3H, s, camphanoyl CH_3).

4′*R*-*O*-(−)-Camphanoyl-3′*R*-hydroxy-2′,2′-trimethyl-2-ethyldihydropyrano[2,3-*f*]chromone (34e): 35% yield (starting with 290 mg of **33e**); mp 186−188 °C; MS-ESI+ (m/z, %) 493 ($M^+ + Na$, 62), 471 ($M^+ + 1$, 20); ^{1}H NMR δ 8.06 (1H, d, J = 9.0 Hz, H-5), 6.86 (1H, d, J = 9.0 Hz, H-6), 6.61 (1H, d, J = 4.6 Hz, H-4′), 6.12 (1H, s, H-3), 4.11 (1H, d, J = 4.6 Hz, H-3′), 2.52 (2H, q, J = 7.2 Hz, CH_2CH_3-2), 2.45, 2.02, 1.92, 1.68 (each 1H, m, camphanoyl CH_2), 1.53, 1.40 (each 3H, s, CH_3-2′), 1.23 (3H, t, J = 7.2 Hz, CH_2CH_3-2), 1.09, 1.01, 0.99 (each 3H, s, camphanoyl CH_3).

4′*R*-*O*-(−)-Camphanoyl-3′*R*-hydroxy-2′,2′-dimethyl-2-ethoxymethyldihydropyrano[2,3-*f*]chromone (34h): 21% yield (starting with 40 mg of **33h**); mp 161−163 °C; MS-ESI+ (m/z, %) 523 ($M^+ + Na$, 100); ^{1}H NMR δ 8.06 (1H, d, J = 8.8 Hz, H-5), 6.87 (1H, d, J = 8.8 Hz, H-6), 6.56 (1H, d, J = 4.8 Hz, H-4′), 6.38 (1H, s, H-3), 4.29, 4.24 (each 1H, d, J = 15.3 Hz, $CH_2OCH_2CH_3$-2), 4.11 (1H, d, J = 4.8 Hz, H-3′), 3.58 (2H, q, J = 7.0 Hz, $CH_2OCH_2CH_3$-2), 2.47, 2.06, 1.92, 1.67 (each 1H, m, camphanoyl CH_2), 1.52, 1.39 (each 3H, s, CH_3-2′), 1.34 (3H, t, J = 7.0 Hz, $CH_2OCH_2CH_3$-2), 1.08, 1.00, 0.98 (each 3H, s, camphanoyl CH_3).

4′*R*-*O*-(−)-Camphanoyl-3′*R*-hydroxy-2′,2′-dimethyl-2-phenyldihydropyrano[2,3-*f*]chromone (34i): 45% yield (starting with 162 mg of **33i**); mp 163−165 °C; MS-ESI+ (m/z, %) 541 ($M^+ + Na$, 100), 519 ($M^+ + 1$, 22); ^{1}H NMR δ 8.14 (1H, d, J = 8.5 Hz, H-5), 7.79 (2H, m, H-2″,6″-phenyl), 7.47−7.52 (3H, m, H-3″, 4″, 5″-phenyl), 6.92 (1H, d, J = 8.5 Hz, H-6), 6.79 (1H, d, J = 5.0 Hz, H-4′), 6.77 (1H, s, H-3), 4.20 (1H, d, J = 5.0 Hz, H-3′), 2.48, 2.20, 1.77, 1.62 (each 1H, m, camphanoyl CH_2), 1.56, 1.42 (each 3H, s, CH_3-2′), 1.00, 0.92, 0.77, (each 3H, s, camphanoyl CH_3).

Syntheses of 3′-*O*-Acyl-4′-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromones (15−21). The 4′-camphanoyl-3′-hydroxy-substituted compounds (**34d**, **34e**, **34h**,

and **34i**) were dissolved in DMAP/CH_2Cl_2 and reacted with acetic anhydride or an acyl chloride (1.5 equiv) for 1−2 days at room temperature, monitored by TLC. The reaction mixture was concentrated and purified by PTLC (eluant: hexane/EtOAc = 7:3) and afforded the appropriately substituted 3′-*O*-acyl-4′-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromones (**15-21**).

3′*R*-*O*-Acetyl-4′*R*-*O*-(−)-camphanoyl-2,2′,2′-trimethyldihydropyrano[2,3-*f*]chromone (15): 81% yield (starting with 70 mg of **34d**); mp 229−230 °C; MS-ESI+ (*m*/*z*, %) 521 (M^+ + Na, 95), 499 (M^+ + 1, 100); ^{1}H NMR δ 8.07 (1H, d, J = 9.1 Hz, H-5), 6.87 (1H, d, J = 9.1 Hz, H-6), 6.69 (1H, d, J = 4.6 Hz, H-4′), 6.11 (1H, s, H-3), 5.29 (1H, d, J = 4.6 Hz, H-3′), 2.38, 1.94, 1.88, 1.66 (each 1H, m, camphanoyl CH_2), 2.28 (3H, s, CH_3-2), 2.10 (1H, s, CH_3CO-3′), 1.49, 1.44 (each 3H, s, CH_3-2′), 1.08, 0.99, 0.94 (each 3H, s, camphanoyl CH_3); 20% de. $[\alpha]_D$ +20.0° (c = 0.20, $CHCl_3$). Anal. ($C_{27}H_{30}O_9 \cdot {}^1/_4H_2O$) C, H.

4′*R*-*O*-(−)-Camphanoyl-3′*R*-*O*-isobutyryl-2,2′,2′-trimethyldihydropyrano[2,3-*f*]chromone (16): 53% yield (starting with 30 mg of **34d**); mp 160−162 °C; MS-ESI+ (*m*/*z*, %) 549 (M^+ + Na, 48), 527 (M^+ + 1, 30); ^{1}H NMR δ 8.09 (1H, d, J = 8.8 Hz, H-5), 6.88 (1H, d, J = 8.8 Hz, H-6), 6.73 (1H, d, J = 4.6 Hz, H-4′), 6.11 (1H, s, H-3), 5.31 (1H, d, J = 4.6 Hz, H-3′), 2.56 (1H, m, J = 6.3 Hz, $CH(CH_3)_2$-3′), 2.43, 2.01, 1.90, 1.68 (each 1H, m, camphanoyl CH_2), 2.26 (3H, s, CH_3-2), 1.49, 1.44 (each 3H, s, CH_3-2′), 1.23, 1.22 (3H each, d, J = 6.3 Hz, $CH(CH_3)_2$-3′), 1.09, 0.98, 0.96 (each 3H, s, camphanoyl CH_3); >98% de. $[\alpha]_D$ −92.0° (c = 0.10, $CHCl_3$). Anal. ($C_{29}H_{34}O_9 \cdot H_2O$) C, H.

4′*R*-*O*-(−)-Camphanoyl-3′*R*-*O*-isovaleryl-2,2′,2′-trimethyldihydropyrano[2,3-*f*]chromone (17): 60% yield (starting with 36 mg of **34d**); mp 135−137 °C; MS-ESI+ (*m*/*z*, %) 563 (M^+ + Na, 62), 541 (M^+ + 1, 100); ^{1}H NMR δ 8.08 (1H, d, J = 9.0 Hz, H-5), 6.88 (1H, d, J = 9.0 Hz, H-6), 6.70 (1H, d, J = 4.8 Hz, H-4′), 6.10 (1H, s, H-3), 5.33 (1H, d, J = 4.8 Hz, H-3′), 2.44 (1H, m, $CH_2CH(CH_3)_2$-3′), 2.26 (3H, s, CH_3-2), 2.24 (2H, d, J = 6.0 Hz, $CH_2CH(CH_3)_2$-3′), 2.16, 2.00, 1.90, 1.70 (each 1H, m, camphanoyl CH_2), 1.48, 1.44 (each 3H, s, CH_3-2′), 1.10, 0.99, 0.97 (each 3H, s, camphanoyl CH_3), 1.00 (6H, d, J = 6.0 Hz, $CH_2CH(CH_3)_2$-3′); >95% de. $[\alpha]_D$ −110.0° (c = 0.16, $CHCl_3$). Anal. ($C_{30}H_{36}O_9$) C, H.

4′*R*-*O*-(−)-Camphanoyl-3′*R*-*O*-isovaleryl-2′,2′-dimethyl-2-ethyldihydropyrano[2,3-*f*]chromone (18): 34% yield (starting with 30 mg of **34e**); mp 214−216 °C; MS-ESI+ (*m*/*z*, %): 541 (M^+ + 1, 82); ^{1}H NMR δ 8.09 (1H, d, J = 9.0 Hz, H-5), 6.88 (1H, d, J = 9.0 Hz, H-6), 6.73 (1H, d, J = 4.6 Hz, H-4′), 6.13 (1H, s, H-3), 5.32 (1H, d, J = 4.6 Hz, H-3′), 2.53 (1H, m, $CH(CH_3)_2$-3′), 2.53 (2H, m, CH_2CH_3-2), 2.43, 2.01, 1.92, 1.69 (each 1H, m, camphanoyl CH_2), 1.50, 1.43 (each 3H, s, CH_3-2′), 1.24 (3H, t, J = 7.2 Hz, CH_2CH_3-2), 1.22, 1.21 (3H each, d, J = 6.9 Hz, $CH(CH_3)_2$-3′), 1.09, 0.98, 0.97 (each 3H, s, camphanoyl CH_3); >98% de. $[\alpha]_D$ −80.9° (c = 0.66, $CHCl_3$). Anal. ($C_{30}H_{36}O_9 \cdot {}^1/_4H_2O$), C, H.

4′*R*-*O*-(−)-Camphanoyl-3′*R*-*O*-isovaleryl-2′,2′-dimethyl-2-ethoxymethyldihydropyrano[2,3-*f*]chromone (19): 34% yield (starting with 13 mg of **34h**); mp 113−115 °C; MS-ESI+ (*m*/*z*, %) 571 (M^+ + 1, 100); ^{1}H NMR δ 8.11 (1H, d, J = 8.8 Hz, H-5), 6.90 (1H, d, J = 8.8 Hz, H-6), 6.70 (1H, d, J = 4.5 Hz, H-4′), 6.40 (1H, s, H-3), 5.31 (1H, d, J = 4.5 Hz, H-3′), 4.29, 4.24 (each 1H, dd, J = 15.0, 1.0 Hz, $CH_2OCH_2CH_3$-2), 3.58 (2H, q, J = 7.2 Hz, $CH_2OCH_2CH_3$-2), 2.56 (1H, m, $CH(CH_3)_2$-3′), 2.42, 2.00, 1.90, 1.68 (each 1H, m, camphanoyl CH_2), 1.50, 1.44 (each 3H, s, CH_3-2′), 1.24 (3H, m, $CH_2OCH_2CH_3$-2), 1.22 (6H, m, $CH(CH_3)_2$-3′), 1.09, 0.97, 0.96 (each 3H, s, camphanoyl CH_3); 90% de. $[\alpha]_D$ −58.6° (c = 0.44, $CHCl_3$). Anal. ($C_{31}H_{38}O_{10}$), C, H.

3′*R*-*O*-Acetyl-4′*R*-*O*-(−)-camphanoyl-2′,2′-dimethyl-2-phenyldihydropyrano[2,3-*f*]chromone (20): 40% yield (starting with 20 mg of **34i**); mp 154−156 °C; MS-ESI+ (*m*/*z*, %) 561 (M^+ + 1, 100); ^{1}H NMR δ 8.16 (1H, d, J = 8.8 Hz, H-5), 7.78 (2H, m, H-2″,6″-phenyl), 7.48 (3H, m, H-3″, 4″, 5″-phenyl), 6.94 (1H, d, J = 8.8 Hz, H-6), 6.87 (1H, d, J = 4.8 Hz, H-4′), 6.77 (1H, s, H-3), 5.38 (1H, d, J = 4.8 Hz, H-3′), 2.15 (1H, s, CH_3CO-3′), 2.38, 2.23, 1.90, 1.60 (each 1H, m, camphanoyl CH_2), 1.49, 1.48 (each 3H, s, CH_3-2′), 1.00, 0.89, 0.77, (each 3H, s, camphanoyl CH_3); 70% de. $[\alpha]_D$ +4.4° (c = 0.54, $CHCl_3$). Anal. ($C_{32}H_{32}O_9$) C, H.

4′*R*-*O*-(−)-Camphanoyl-3′*R*-*O*-isobutyryl-2′,2′-dimethyl-2-phenyldihydropyrano[2,3-*f*]chromone (21): 27% yield (starting with 47 mg of **34i**); mp 108−110 °C; MS-ESI+ (*m*/*z*, %) 589 (M^+ + 1, 100); ^{1}H NMR δ 8.16 (1H, d, J = 8.8 Hz, H-5), 7.79 (2H, m, H-2″,6″-phenyl), 7.48 (3H, m, H-3″, 4″, 5″-phenyl), 6.95 (1H, d, J = 8.8 Hz, H-6), 6.88 (1H, d, J = 4.5 Hz, H-4′), 6.78 (1H, s, H-3), 5.40 (1H, d, J = 4.5 Hz, H-3′), 2.59 (1H, m, $CH(CH_3)_2$-3′), 2.10, 1.60 (each 2H, m, camphanoyl CH_2), 1.51, 1.46 (each 3H, s, CH_3-2′), 1.25, 1.24 (each 3H, d, J = 6.9 Hz, $CH(CH_3)_2$-3′), 0.98, 0.82, 0.68, (each 3H, s, camphanoyl CH_3); 70% de. $[\alpha]_D$ +8.5° (c = 0.40, $CHCl_3$). Anal. ($C_{34}H_{36}O_9 \cdot {}^1/_4H_2O$) C, H.

HIV-1 Infectivity Assay in Non-Drug-Resistant Strain in H9 Lymphocytes. This assay was performed by Panacos, Inc. The general procedure was described previously.[8]

HIV-1 Infectivity Assay in HIV-1 RTMDR1 Strain in MT-4 Cell Lines. A diluted drug-resistant HIV-1 stock, HIV-1 RTMDR1/MT2, at a multiplicity of infection (MOI) of 0.001 $TCID_{50}$/cell was used to infect MT4 cells. Twenty microliters of the virus and 20 μL of compounds at various concentrations in RPMI 1640 containing 10% fetal bovine serum were added to 20 μL of MT4 cells at 6×10^5 cells/mL in a 96-well microtiter plate. The cell/virus compound mixture was then incubated at 37 °C in a humidified CO_2 incubator. Fresh medium (180 μL) containing an appropriate concentration of the compound was added to each well of the cultures on day 2. On day 4 postinfection, supernatant samples were harvested and assayed for P24 using an ELISA kit from ZeptoMetrix Corporation, Buffalo, NY.

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Supporting Information Available: Elemental analyses data. This material is available free of charge via the Internet at http://pubs.acs.org.

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