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Dicaffeoyl- or Digalloyl Pyrrolidine and Furan Derivatives as HIV Integrase Inhibitors

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Abstract—Human immunodeficiency virus (HIV) integrase (IN) catalyzes the integration of HIV DNA copy into the host cell DNA. Such integration is essential for the production of progeny viruses, and therefore therapeutic agents that can inhibit this process should be effective anti-HIV agents. We have previously reported the inhibitory activity of dicaffeoylglucosides against HIV IN. In the present study, we have synthesized and tested dicaffeoyl or digalloyl compounds joined through a five-membered heterocyclic ring as HIV IN inhibitors to explore the SARs of this family of compounds. The starting heterocyclic diols were prepared from L-tartaric acid, diethyl L-tartarate or D-(+)-ribonic γ-lactone. We found that the HIV IN inhibitory activities of dicaffeoyl derivatives were comparable to that of L-chicoric acid (IC_{50} = 24.9 μM). On the other hand, digalloyl derivatives were more potent than L-chicoric acid with IC_{50} values of 4.7–15.6 μM.

Introduction

Human immunodeficiency virus (HIV-1) is the probable causative agent of acquired immune deficiency syndrome (AIDS), which is one of the world's most serious health problems. HIV integrase (IN) catalyzes the integration of HIV DNA copy into the host cell DNA. Such integration is essential for the production of progeny viruses, and therefore therapeutic agents that can inhibit this process should be effective anti-HIV agents.[1–3]

Recent studies showed that L-chicoric acid (**1**) and dicaffeoylquinic acids (DCQAs, for example, compound (**2**) display potent activity against HIV IN and can inhibit HIV replication with moderate anti-HIV activity (Fig. 1).[4–9] Extensive efforts have therefore been made to develop caffeoyl-based HIV IN inhibitors. The common structural features of reported synthetic analogues are caffeic acid esters separated by aliphatic, alicyclic, or aromatic linker.[10,11] We also recently reported a new type of caffeoyl-based HIV IN inhibitors (**4**), which have a glucose ring as a basic skeleton.[12] However, there was no report on the synthesis of caffeic acid esters separated by a five-membered ring linker for HIV IN inhibitors. In the present study, we have synthesized and tested dicaffeoyl or digalloyl compounds (**III**) joined through a functionalized pyrrolidine or furan ring linker to explore the structure and HIV IN inhibitory activity relationships (Scheme 1). Since the use of conformationally restricted molecules as a means to better understand or improve the activity of the parent molecule is a common theme in medicinal chemistry, we selected five-membered ring, more rigid linker as a central linker. Additionally, the linkers were designed to functionalized five-membered rings which have hydrogen bond accepting or donating groups in place of carboxylic acid moiety in L-tartaric acid.

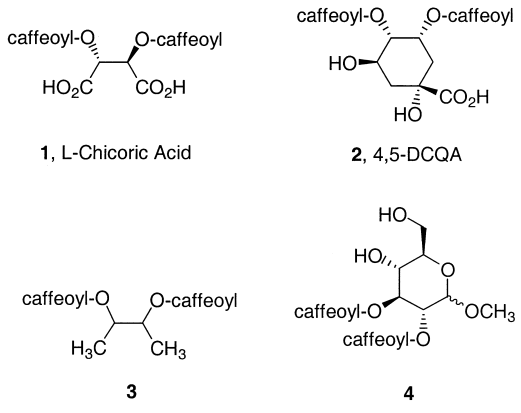

Figure 1.

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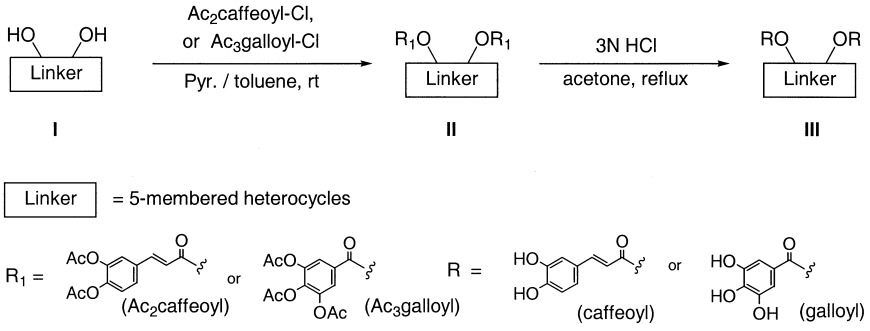
Results and Discussion

The starting five-membered ring diols (**I-a–e**) were prepared from L-tartaric acid as depicted in Scheme 2. *N*-Methyl-3,4-dihydroxysuccinimide (**I-a**) was synthesized by treatment of diacetylated compound **5**, which was derived from L-tartaric acid,[13] with acetyl chloride in ethanol (equation 1). 3,4-Dihydroxysuccinimide (**I-b**) was also synthesized by the similar procedure from compound **8** (eq (2)). *N*-Methyl-3,4-dihydroxypyrrolidone (**I-c**) was prepared from acetoxylactam **6** by reduction with triethylsilane followed by deprotection of acetyl groups.[14] The compound **6** was derived from diacetoxysuccinimide **5** through $NaBH_4$ reduction and acetylation of the resulting hydroxyl group. 3,4-Dihydroxypyrrolidone (**I-d**) was again synthesized similarly from the compound **I-b** except for using TBS protecting groups instead of acetyl groups. The TBS protecting groups could also be removed in the final step by using acetyl chloride in ethanol. 3,4-Dihydroxyfuranone (**I-e**) was synthesized by the reduction of intermediary ring-opened aldehydo-amide, which equilibrate with hydroxylactam **7**, and ring closure of the resulting hydroxyamide to form a lactone ring by using aqueous HCl in 1,4-dioxane.[15] The TBS protecting groups were removed concomitantly during the lactone ring formation stage.

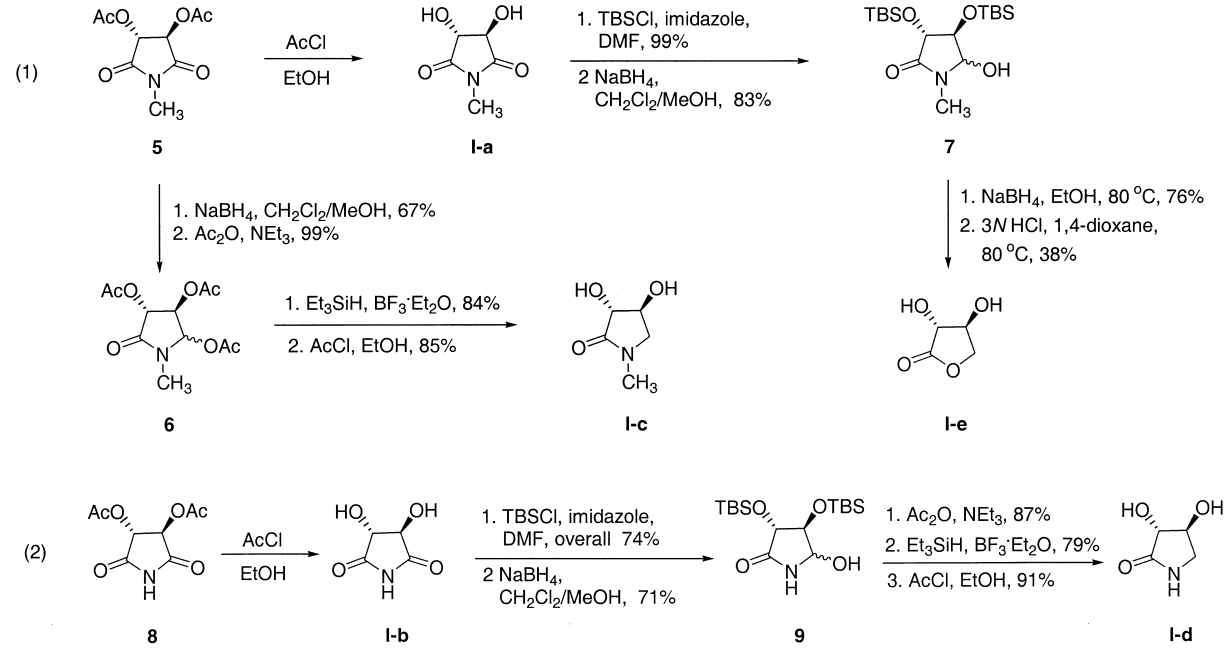
The furan diol **I-f** was synthesized from diethyl L-tartarate as previously reported.[16] The trihydroxyfuranone **I-g** was prepared in 43% yield from commercially available D-(+)-ribonic γ-lactone by selective mono-silylation of primary alcohol.

The target compounds as typified by general structure **III** were prepared by acylation of diols **I** with diacetylcaffeoyl chloride (Ac_2-caffeoyl-Cl) followed by removal of acetyl protecting groups in refluxing acetone containing aqueous HCl (Scheme 1).[11] The yields and structures of compounds at each step, and HIV IN inhibitory activities of dicaffeoyl compounds were shown in Table 1.[17]

The inhibitory activity of L-chicoric acid was included for comparison. In general, all compounds **III-a–f** showed moderate HIV IN inhibitory activities with IC_{50} values in the range of 22.4–47.4 μM. Their inhibitory activities were comparable or somewhat inferior to

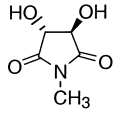
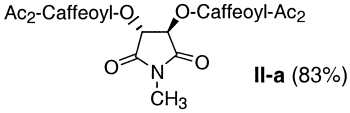
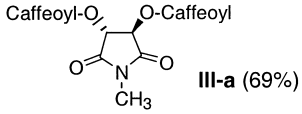
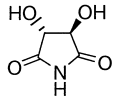
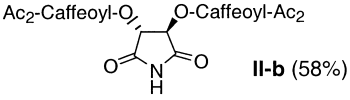
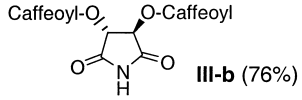
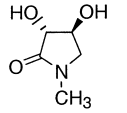
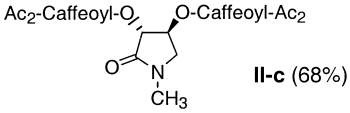
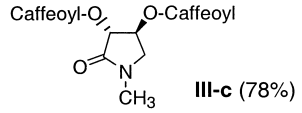
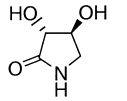
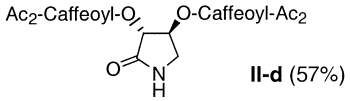
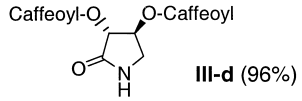
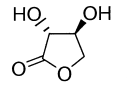
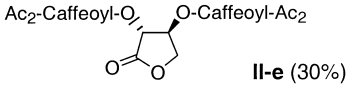
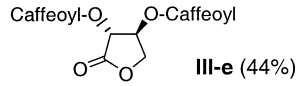
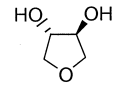
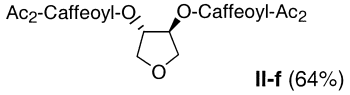
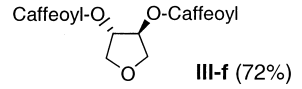
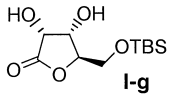
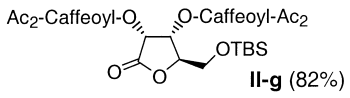
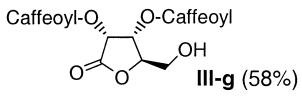


Scheme 1.



Scheme 2.

Table 1. Structures, yields, and HIV IN inhibitory activities of dicaffeoyl compounds (**III-a–g**)

Entry	Starting diols, **I**	Structure of **II** (yields from **I**)	Structure of **III** (yields from **II**)	$IC_{50}(\mu M)$[a] of **III**
1	 **I-a**	 **II-a** (83%)	 **III-a** (69%)	39.2
2	 **I-b**	 **II-b** (58%)	 **III-b** (76%)	25.2
3	 **I-c**	 **II-c** (68%)	 **III-c** (78%)	27.9
4	 **I-d**	 **II-d** (57%)	 **III-d** (96%)	33.8
5	 **I-e**	 **II-e** (30%)	 **III-e** (44%)	32.3
6	 **I-f**	 **II-f** (64%)	 **III-f** (72%)	47.4
7	 **I-g**	 **II-g** (82%)	 **III-g** (58%)	22.4
8	—	—	L-Chicoric acid (**3**)[b]	24.9

[a]All values are averages of at least two runs.
[b]L-Chicoric acid was prepared by known method.[10]

L-chicoric acid. The nature of five-membered heterocyclic ring linker did not markedly influence the inhibitory activity. Among synthesized, compound **III-g**, which contains a ribonolactone ring as a linker showed the best inhibitory activity.

Digalloyl compounds (**III-h–k**) were also synthesized from selected diols by using triacetylgalloyl chloride (Ac_3-galloyl-Cl) in a similar procedure as above since digalloyl-substituted tartaric acid derivatives were found to be potent inhibitors of HIV IN.[11,12] The yields and structures of compounds at each step, and HIV IN inhibitory activities of digalloyl compounds were shown in Table 2.

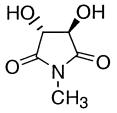
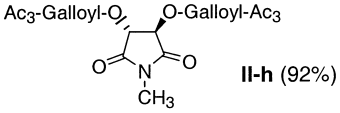
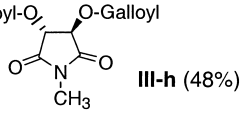
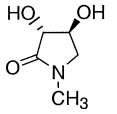
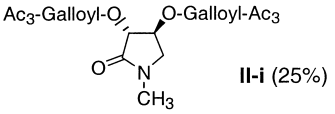
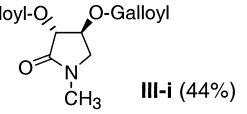
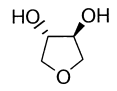
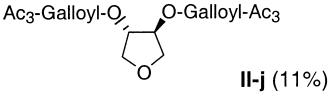
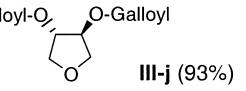
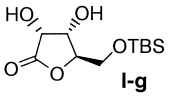
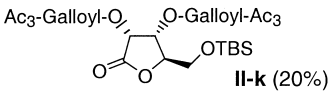
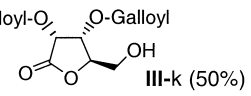
As was previously observed, upon substitution of digalloyl groups at five-membered heterocyclic ring instead of caffeoyl groups, the inhibitory activities were remarkably increased. Digalloyl compounds (**III-h–k**) were 2 to 5-times more potent than L-chicoric acid against HIV IN. In case of galloyl series, the inhibitory activities of compounds **III-j** and **III-k** were more potent than those of **III-h** and **III-i** indicating that furan ring is better than pyrrolidine ring in enhancing HIV IN inhibitory activity. Although the digalloyl compounds exhibited good inhibition against isolated HIV IN, none of the dicaffeoyl and digalloyl compounds synthesized in this study could inhibit the replication of HIV in cell bases assay at nontoxic concentration (data not shown)[18] implicating the important role of carboxylic acid in L-chicoric acid.

In conclusion, we have synthesized and tested the inhibitory activities of a new type of HIV IN inhibitors, which have a pyrrolidine or furan ring as a basic skeleton. This work is the first example on the synthesis of caffeic or gallic acid esters separated by a functionalized five-membered heterocyclic ring as a central linker for the development of HIV integrase inhibitors. We are undergoing synthesis of furan ring-based digalloyl compounds containing carboxylic acid functionality for HIV IN inhibitors.

Experimental

Melting points were determined with a Thomas-Hoover capillary apparatus and uncorrected. IR spectra were

Table 2. Structures, yields, and HIV IN inhibitory activities of digalloyl compounds (**III-h–k**)

Entry	Starting diols, **I**	Structure of **II** (yields from **I**)	Structure of **III** (yields from **II**)	IC_{50} (μM)[a] of **III**
1	 **I-a**	 **II-h** (92%)	 **III-h** (48%)	12.4
2	 **I-c**	 **II-i** (25%)	 **III-i** (44%)	15.6
3	 **I-f**	 **II-j** (11%)	 **III-j** (93%)	7.4
4	 **I-g**	 **II-k** (20%)	 **III-k** (50%)	4.7
5			L-Chicoric acid (**3**)[b]	24.9

[a]All values are averages of at least two runs.
[b]L-Chicoric acid was prepared by known method.[10]

obtained on a Perkin Elmer 16F PC FT-IR spectrometer. The NMR spectra were recorded on Varian Gemini 300 FT or Brucker Avance 300 spectrometers at 300 MHz (for ^{1}H NMR) and 75 MHz (for ^{13}C NMR). The chemical shifts are reported in ppm downfield relative to tetramethylsilane. High-resolution FABMS (positive ion mode) were obtained on a Jeol JMS-AX 505WA mass spectrometer, and glycerol was used as a matrix. Optical rotations were measured on an AUTOPOL III automatic polarimeter and all concentrations are given in g/mL. All starting materials were obtained from commercial supplies, and used without further purification. Analytical thin layer chromatography was carried out on pre-coated silica gel (Merck Kiesegel 60 F_{254} layer thickness 0.25 mm). Flash column chromatography was carried out using Kiesegel 60 (230–400 mesh, Merck).

(3*R*,4*R*)-3,4-Dihydroxy-1-methylpyrrolidine-2,5-dione (I-a). To a solution of (3*R*,4*R*)-3,4-diacetoxy-1-methylpyrrolidine-2,5-dione[13] (**5**, 3 g, 13.1 mmol) in EtOH (50 mL) was added dropwise acetyl chloride (2.8 mL, 38.3 mmol) at 0 °C and further stirred at rt for 3 h. After removing solvent under reduced pressure the resulting solid was recrystallized from EtOAc–hexane to give **I-a** (1.79 g, 94%) as a white solid. Mp 175–179 °C; IR (KBr, cm^{-1}) 3434, 2926, 2894, 1718, 1454, 1278, 1146, 1078; ^{1}H NMR (CD_3OD) δ 4.39 (s, 2H), 2.95 (s, 3H).

(3*R*,4*R*)-3,4-Dihydroxy-pyrrolidine-2,5-dione (I-b). To a solution of (3*R*,4*R*)-3,4-diacetoxy-pyrrolidine-2,5-dione (**8**, 770 mg, 3.58 mmol) in EtOH (20 mL) was added dropwise acetyl chloride (1 mL, 13.7 mmol) at 0 °C and further stirred at rt for 2 h. The reaction mixture was concentrated and purified by flash column chromatography (EtOAc/MeOH = 20:1) to give **I-b** (390 mg, 83%) as a white solid. Mp 208 °C (dec.); IR (KBr, cm^{-1}) 3448, 3372, 3234, 2926, 1728, 1400, 1338, 1160, 1094; ^{1}H NMR (CD_3OD) δ 5.05 (s, 2H); ^{13}C NMR (CD_3OD) δ 175.36, 75.56.

(3*R*,4*R*)-3,4,5-Triacetoxy-1-methyl-pyrrolidin-2-one (6). To a solution of **5** (1.06 g, 46.3 mmol) in CH_2Cl_2 (20 mL) and CH_3OH (20 mL) was added $NaBH_4$ (227 mg, 60.1 mmol) at −78 °C. The reaction mixture was stirred at −10 °C for 3 h and then quenched by slow addition of ice-water (ca. 0.5 mL). After evaporation of solvents, insoluble solid was filtered through Celite and washed with EtOAc (40 mL). The filtrate was dried ($MgSO_4$) and purified by flash column chromatography (EtOAc/hexane = 1:1) to afford (3*R*,4*R*)-3,4-diacetoxy-5-hydroxy-1-methyl-pyrrolidin-2-one (716 mg, 67%) as a white solid. Mp 85–87 °C; IR (KBr, cm^{-1}) 3288, 2938, 1748, 1716, 1440, 1372, 1242, 1048; ^{1}H NMR ($CDCl_3$) δ 5.05 (m, 1H), 4.92 (m, 2H), 2.96 & 2.97 (two s, 3H), 2.14–2.20 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 171.23, 170.95, 167.53, 86.17, 79.49, 75.02, 27.30, 21.13, 21.04.

To a solution of above compound (500 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (0.6 mL, 4.3 mmol) and acetic anhydride (0.41 mL, 4.3 mmol) at rt. After stirring for 1 h, the reaction mixture was concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:3) to give acetoxylactam **6** as a yellow oil (590 mg, quantitative). IR (KBr, cm^{-1}) 3622, 3505, 2944, 1738, 1440, 1372, 1216, 1060, 1018; ^{1}H NMR ($CDCl_3$) δ 6.07 (m, 1H), 5.31 (m, 1H), 5.17 (m, 1H), 2.87 & 2.88 (two s, 3H), 2.12–2.16 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 170.37, 170.03, 169.96, 168.15, 85.34, 76.29, 73.42, 28.08, 21.14, 20.99, 20.94.

(3*R*,4*S*)-3,4-Dihydroxy-1-methyl-pyrrolidin-2-one (I-c). To a solution of **6** (400 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}Et_2O$ (0.36 mL, 2.9 mmol) at

−78 °C and stirred for 10 min under N_2 atmosphere. The reaction mixture was treated with triethylsilane (1.17 mL, 7.3 mmol) and the temperature was gradually raised to rt over 3 h. After stirring for 18 h, the mixture was poured into ice water containing excess Na_2CO_3. The mixture was extracted with CH_2Cl_2 and the combined organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:1) to give (3*R*,4*R*)-3,4-diacetoxy-1-methyl-pyrrolidin-2-one as a colorless oil (308 mg, 97%). $[\alpha]_D^{23}$ +118.0° (*c* 0.28, $CHCl_3$); IR (KBr, cm^{-1}) 2936, 1756, 1712, 1500, 1440, 1370, 1224, 1058; ^1H NMR ($CDCl_3$) δ 5.41 (d, 1H, *J* = 5.7 Hz), 5.29 (ddd, 1H, *J* = 7.8, 5.7, 5.3 Hz), 3.82 (dd, 1H, *J* = 10.5, 7.8 Hz), 3.26 (dd, 1H, *J* = 10.5, 5.3 Hz), 2.90 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.77, 170.35, 167.59, 74.69, 71.65, 51.80, 30.31, 21.12, 21.08.

To a solution of above compound (250 mg, 1.16 mmol) in ethanol (5 mL) was added dropwise acetyl chloride (2 mL, 27.4 mmol) at 0 °C. After stirring at rt for 4 h, the reaction mixture was concentrated and purified by flash column chromatography (EtOAc/hexane = 3:1) to afford **I-c** as a white solid (138 mg, 92%). Mp 105–109 °C; $[\alpha]_D^{23}$ +106.1° (*c* 0.23, CH_3OH); IR (KBr, cm^{-1}) 3324, 1680, 1470, 1408, 1268, 1082; ^1H NMR (CD_3OD) δ 4.13 (m, 1H), 4.02 (d, 1H, *J* = 6.4 Hz), 3.54 (dd, 1H, *J* = 9.9, 7.3 Hz), 3.12 (dd, 1H, *J* = 9.9, 6.3 Hz), 2.82 (s, 3H); ^{13}C NMR (CD_3OD) δ 173.62, 76.65, 72.58, 52.97, 29.01.

(3*R*,4*R*)-3,4-Bis(*tert*-butyl-dimethyl-silyloxy)-5-hydroxy-pyrrolidin-2-one (9). To a solution of **1-b** (633 mg, 4.83 mmol) and imidazole (987 mg, 14.5 mmol) in DMF (20 mL) was added TBSCl (1.82 g, 12.1 mmol). After stirring at rt for 1 h, the reaction mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was washed with water, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:15) to give (3*R*,4*R*)-3,4-bis(*tert*-butyl-dimethyl-silyloxy)-pyrrolidine-2,5-dione (1.28 g, 74%) as a colorless oil. $[\alpha]_D^{23}$ +132.0° (*c* 1.30, $CHCl_3$); IR (KBr, cm^{-1}) 3518, 3262, 2942, 2862, 1736, 1468, 1324, 1254, 1136, 842; ^1H NMR ($CDCl_3$) δ 9.45 (bs, 1H, CON*H*), 4.46 (s, 2H), 0.88 (m, 18H), 0.16 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 177.69, 81.49, 29.54, 22.17, −1.06, −1.11.

To a solution of above compound (1.15 g, 3.2 mmol) in CH_2Cl_2 (20 mL) and MeOH (10 mL) was added $NaBH_4$ (145 mg, 3.8 mmol) at −78 °C. The mixture was stirred for 1 h and further stirred at 0 °C for 2 h. The reaction mixture was quenched by slow addition of water (ca. 1 mL) and diluted with CH_2Cl_2 (60 mL). The organic layer was washed with water, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:2) to afford hydroxylactam **9** (822 mg, 71%) as a white solid. Mp 87–89 °C; IR (KBr, cm^{-1}) 3274, 2930, 1716, 1474, 1254, 1134, 838; ^1H NMR ($CDCl_3$) δ 6.88 (bs, 1H, CON*H*), 4.82 (dd, 1H, *J* = 10.1, 2.7 Hz), 4.02 (d, 1H, *J* = 4.5 Hz), 3.95 (dd, 1H, *J* = 4.5, 2.7 Hz), 3.80 (d, 1H, O*H*, *J* = 10.1 Hz), 0.83–0.92 (m, 18H), 0.12–0.17 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 174.12, 83.93, 82.46, 77.13, 26.12, 18.57, 18.32, −4.03, −4.12, −4.36, −4.62.

(3*R*,4*S*)-3,4-Dihydroxy-pyrrolidin-2-one (1-d). To a solution of hydroxylactam **9** (700 mg, 1.94 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (1.5 mL, 11.6 mmol) and acetic anhydride (1 mL, 11.6 mmol) at rt. After stirring for 6 h, the reaction mixture was concentrated and purified by flash column chromatography (EtOAc/hexane = 1:4) to give (3*R*,4*R*)-5-acetoxy-3,4-bis-(*tert*-butyl-dimethyl-silyloxy)-pyrrolidin-2-one (680 mg, 87%) as a white solid. Mp 89–91 °C; IR (KBr, cm^{-1}) 3386, 2932, 2858, 1754, 1472, 1386, 1258, 1138, 842; ^1H NMR ($CDCl_3$) δ 6.52 (bs, 1H, CON*H*), 5.81 (dd, 1H, *J* = 5.0, 2.4 Hz), 4.33 (d, 1H, *J* = 7.9 Hz), 4.24 (dd, 1H, *J* = 7.9, 5.0 Hz), 2.06 (s, 3H), 0.88 (m, 18H), 0.21–0.09 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 174.44, 171.43, 77.61, 75.78, 74.22, 26.08, 25.97, 18.62, 18.23, −4.52, −4.57.

To a solution of (3*R*,4*R*)-5-acetoxy-3,4-bis(*tert*-butyl-dimethyl-silyloxy)-pyrrolidin-2-one (618 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) was added dropwise $BF_3.Et_2O$ (0.4 mL, 3.1 mmol) at −78 °C over 10 min under N_2 atmosphere. The mixture was stirred for 20 min and then treated with triethylsilane (0.9 mL, 7.7 mmol). The reaction mixture was stirred for 30 min at −78 °C and further stirred at 0 °C for 3 h. The reaction mixture was poured into ice-water containing Na_2CO_3. The mixture was washed with CH_2Cl_2 and the organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:4) to give (3*R*,4*R*)-3,4-bis(*tert*-butyl-dimethyl-silyloxy)-pyrrolidin-2-one (418 mg, 79%) as a white solid. Mp 40–41 °C; $[\alpha]_D^{23}$ +59.3° (*c* 0.22, $CHCl_3$); IR (KBr, cm^{-1}) 3242, 2942, 1724, 1466, 1254, 1126, 842; ^1H NMR ($CDCl_3$) δ 7.25 (bs, 1H, CON*H*), 4.24 (m, 1H), 4.11 (d, 1H, *J* = 7.1 Hz), 3.43 (m, 1H), 3.01 (dd, 1H, *J* = 9.4, 7.1 Hz), 0.87 & 0.91 (two s, 18H), 0.16–0.06 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 174.62, 77.24, 75.95, 46.29, 25.78, 25.75, 18.32, 17.90, −4.85, −4.92.

To a solution of above compound (201 mg, 0.58 mmol) in ethanol (5 mL) was added dropwise acetyl chloride (1 mL, 14.1 mmol) at 0 °C for 15 min. After stirring at rt for 4 h, the reaction mixture was concentrated and recrystallized from EtOAc to afford **I-d** as a white solid (62.3 mg, 91%). Mp 135 °C (dec.); $[\alpha]_D^{23}$ +86.1° (*c* 0.25, CH_3OH); IR (KBr, cm^{-1}) 3298, 3240, 2888, 1688, 1480, 1356, 1266, 1112; ^1H NMR (CD_3OD) δ 4.18 (m, 1H), 4.02 (d, 1H, *J* = 7.2 Hz), 3.49 (dd, 1H, *J* = 9.7, 7.5 Hz), 3.02 (dd, 1H, *J* = 9.7, 7.1 Hz); ^{13}C NMR (CD_3OD) δ 175.41, 75.25, 73.75, 44.86.

(3*R*,4*R*)-3,4-Bis-(*tert*-butyl-dimethyl-silyloxy)-5-hydroxy-1-methyl-pyrrolidin-2-one (7). To a solution of **1-a** (1.59 g, 10.9 mmol) and imidazole (2.23 g, 32.8 mmol) in DMF (8 mL) was added TBSCl (4.12 g, 27.3 mmol). After stirring at rt for 1 h, the reaction mixture was poured into ice water (100 mL) and extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was washed with water, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:20) to give (3*R*,4*R*)-3,4-bis(*tert*-butyl-dimethyl-

silyloxy)-1-methyl-pyrrolidine-2,5-dione (4.02 g, 99%) as a colorless oil. $[\alpha]_D^{23}$ +141.6° (*c* 0.55, $CHCl_3$); IR (KBr, cm^{-1}) 2944, 2870, 1724, 1454, 1370, 1260, 1086, 838; ^1H NMR ($CDCl_3$) δ 4.45 (s, 2H), 2.95 (s, 3H), 0.92 (s, 18H), 0.15 & 0.2 (two s, 12H); ^{13}C NMR ($CDCl_3$) δ 173.93, 77.43, 26.02, 24.88, 18.59, −4.09, −4.66.

To a solution of above compound (3.84 g, 10.28 mmol) in CH_2Cl_2 (30 mL) and CH_3OH (15 mL) was added $NaBH_4$ (388 mg, 12.3 mmol) at −78 °C. The reaction mixture was stirred at −10 °C for 3 h and then quenched by the slow addition of water. After evaporation of solvents, insoluble solid was filtered out through Celite 545 and washed with EtOAc (100 mL). The filtrate was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:3) to give **7** as a white solid (3.22 g, 83%). Mp 141–143 °C; IR (KBr, cm^{-1}) 3374, 2946, 1682, 1470, 1396, 1254, 1138, 1066, 844; ^1H NMR ($CDCl_3$) δ 4.45 (dd, 1H, *J* = 10.9, 2.2 Hz), 3.78 (d, 1H, *J* = 3.3 Hz), 3.69 (dd, 1H, *J* = 3.3, 2.2 Hz), 2.71 (s, 3H), 2.43 (d, 1H, O*H*, *J* = 10.9 Hz), 0.69–0.76 (m, 18H), −0.30–0.04 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 171.81, 89.23, 80.25, 77.15, 27.05, 26.12, 18.54, 18.36, −4.02, −4.20, −4.34, −4.65.

(3*R*,4*S*)-3,4-Dihydroxy-dihydrofuran-2-one (I-e). To a solution of **7** (1.32 g, 3.5 mmol) in EtOH (50 mL) was added $NaBH_4$ (1.32 g, 35.5 mmol) at 0 °C. The temperature was raised to 80 °C and then stirred for 4 h at that temperature. The reaction mixture was cooled to rt and quenched by dropwise addition of water (ca. 1 mL) until disappearing of gas evolution. The mixture was filtered through Celite 545 and the filtrate was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:3) to afford (2*R*,3*R*)-2,3-bis(*tert*-butyl-dimethyl-silyloxy)-4-hydroxy-*N*-methyl-butyramide (1.01 g, 76%) as a white solid. Mp 53–55 °C; $[\alpha]_D^{23}$ +43.6° (*c* 0.66, $CHCl_3$); IR (KBr, cm^{-1}) 3276, 2928, 1646, 1544, 1252, 1078, 836; ^1H NMR ($CDCl_3$) δ 6.86 (bs,1H, CON*H*), 4.26 (td, 1H, *J* = 6.9, 5.8 Hz), 4.12 (d, 1H, *J* = 6.9 Hz), 3.63 (d, 2H, *J* = 5.8 Hz), 3.43 (bs, 1H, O*H*), 2.81 & 2.82 (two s, 3H), 0.88–0.86 (m, 18H), 0.07–0.02 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 177.72, 76.95, 76.86, 69.21, 30.45, 30.25, 22.85, 22.54, −0.67, −0.66.

To a solution of above compound (2.01 g, 5.3 mmol) in 1,4-dioxane (10 mL) was added 3*N* HCl (3 mL) and the temperature was raised to 80 °C for 2 h. After cooling to rt, solvent was removed under reduced pressure and the residue of solvent was eliminated with toluene and CCl_4. The residue was purified by flash column chromatography (EtOAc/hexane = 3:1) to give **I-e** (236 mg, 38%) as a white solid. Mp 62–64 °C; $[\alpha]_D^{23}$ +44.2° (*c* 0.63, CH_3OH); IR (KBr, cm^{-1}) 3384, 2916, 1778, 1636, 1344, 1186, 1144, 1089, 1010, 904; ^1H NMR (CD_3OD) δ 4.41 (dd, 1H, *J* = 8.6, 6.6 Hz), 4.30 (ddd, 1H, *J* = 7.4, 7.1, 6.6 Hz), 4.22 (d, 1H, *J* = 7.4 Hz), 3.75 (dd, 1H, *J* = 8.6, 7.1 Hz); ^{13}C NMR (CD_3OD) δ 177.90, 75.18, 74.48, 71.50.

(3*R*,4*R*,5*S*)-5-(*tert*-Butyl-dimethyl-silyloxymethyl)-3,4-dihydroxy-dihydrofuran-2-one (I-g). To a solution of D-(+)-ribonic γ-lactone (0.5 g, 3.38 mmol), 4-dimethylaminopyridine (20.6 mg, 0.17 mmol), and triethylamine (0.94 mL, 6.75 mmol) in DMF (5 mL) was added TBSCl (0.56 g, 3.71 mmol) at 0 °C and stirred at rt for 16 h. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layer was washed with water, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane = 1:2) to give **I-g** (0.23 g, 43%) as a white solid. Mp 89–91 °C; $[\alpha]_D^{23}$ +35.9° (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.60 (t, 1H, *J* = 4.4 Hz), 4.46 (m, 1H), 4.37 (d, 1H, *J* = 5.5 Hz), 3.85 (m, 2H), 3.12 (bs, 1H, O*H*), 2.96 (bs, 1H, O*H*), 0.80 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 177.67, 86.14, 70.65, 69.85, 63.06, 26.14, 26.02, 18.54, −5.32, −5.35.

General procedure for the preparation of acetyl protected dicaffeoyl and digalloyl compounds (II-a–k). A solution of diols (0.25 mmol, **I-a**–**g**) in pyridine (1 mL) was treated with a solution of 3,4-diacetylcaffeoyl chloride (1.25 mmol) or 3,4,5-triacetylgalloyl chloride (1.5 mmol) in toluene (3 mL) at rt and stirred overnight. After removal of solvents, the residue was purified by column chromatography (EtOAc/hexane = 3:1 or CH_2Cl_2/CH_3OH = 40:1) to give **II–a**∼**II–k**.

General Procedure for Preparation of Dicaffeoyl and Digalloyl Compounds (III–a∼III–k). To a solution of above compounds (0.18 mmol, **II-a**∼**II–k**) in acetone (6 mL) was added 3*N* HCl (2 mL). The reaction mixture was refluxed for 3∼5 h. After cooling to rt, the solution was diluted with EtOAc (50 mL), washed with brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane/AcOH = 3:1:0.002) to give **III-a**–**k**.

(3*R*,4*R*)-Bis(3,4-diacetoxy-phenyl-acryloyloxy)-1-methyl-pyrrolidine-2,5-dione (II-a). Yield 83%; Mp 83–85 °C; $[\alpha]_D^{23}$ +207.7° (*c* 0.20, $CHCl_3$); IR (KBr, cm^{-1}) 2927, 1778, 1726, 1442, 1377, 1198, 913; ^1H NMR ($CDCl_3$) δ 7.73 (d, 2H, *J* = 16.0 Hz), 7.43–7.22 (m, 6H), 6.44 (d, 2H, *J* = 16.0 Hz) 5.70 (s, 2H), 3.15 (s, 3H), 2.30 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 169.48, 167.83, 167.72, 166.30, 145.74, 144.13, 142.61, 132.63, 126.63, 124.05, 123.10, 116.88, 73.22, 25.4, 20.58.

(3*R*,4*R*)-Bis(3,4-dihydroxy-phenyl-acryloyloxy)-1-methyl-pyrrolidine-2,5-dione (III-a). Yield 69%; Mp 127–129 °C; $[\alpha]_D^{23}$ +381.4° (*c* 0.27, CH_3OH); IR (KBr, cm^{-1}) 3405, 2957, 1726, 1611, 1521, 1447, 1273, 1158, 1058, 809; ^1H NMR (CD_3OD) δ 7.68 (d, 2H, *J* = 15.9 Hz), 7.10–6.81 (m, 6H), 6.40 (d, 2H, *J* = 15.9 Hz), 5.84 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (CD_3OD) δ 172.30, 168.23, 150.54, 149.61, 147.29, 127.84, 123.88, 116.94, 115.78, 113.47, 74.71, 25.76. HRMS(FAB) calcd for $C_{23}H_{19}NO_{10}(M+H^+)$ 470.1087, found 470.1090.

(3*R*,4*R*)-Bis(3,4-diacetoxy-phenyl-acryloyloxy)-pyrrolidine-2,5-dione (II-b). Yield 58%; Mp 98–100 °C; $[\alpha]_D^{23}$ +214.2° (*c* 0.16, $CHCl_3$); IR (KBr, cm^{-1}) 3246, 3100, 2932, 1744, 1636, 1506, 1372, 1208, 1112, 1074, 902, 836; ^1H NMR ($CDCl_3$) δ 7.74 (d, 2H, *J* = 16.0 Hz), 7.41–7.25 (m, 6H), 6.45 (d, 2H, *J* = 16.0 Hz), 5.74 (s, 2H), 2.31 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 169.04, 168.45,

168.34, 165.73, 146.31, 144.45, 142.88, 132.99, 127.18, 124.47, 123.54, 117.07, 74.04, 21.05.

(3*R*,4*R*)-Bis(3,4-dihydroxy-phenyl-acryloyloxy)-pyrrolidine-2,5-dione (III-b). Yield 76%; Mp 144 °C (dec.); $[\alpha]_D^{23}$ +348.2° (*c* 0.27, CH_3OH); IR (KBr, cm^{-1}) 3306, 2947, 1815, 1731, 1606, 1521, 1273, 1123, 978; ^1H NMR (CD_3OD) δ 7.57 (d, 2H, *J* = 15.9 Hz), 6.98–6.69 (m, 6H), 6.25 (d, 2H, *J* = 15.9 Hz), 5.82 (s, 2H); ^{13}C NMR (CD_3OD) δ 172.88, 168.29, 150.49, 149.57, 147.24, 127.87, 123.91, 116.95, 115.80, 113.54, 75.48. HRMS(FAB) calcd for $C_{22}H_{17}NO_{10}(M+H^+)$ 456.0931, found 456.1301.

(3*R*,4*S*)-Bis(3,4-diacetoxy-phenyl-acryloyloxy)-1-methyl-pyrrolidin-2-one (II-c). Yield 68%; Mp 82–84 °C; $[\alpha]_D^{23}$ +231.8° (*c* 0.74, $CHCl_3$); IR (KBr, cm^{-1}) 3535, 2937, 1791, 1711, 1646, 1497, 1222, 1183, 1010, 918; ^1H NMR ($CDCl_3$) δ 7.64 (d, 1H, *J* = 16.0 Hz), 7.62 (d, 1H, *J* = 16.0 Hz), 7.31–7.17 (m, 6H), 6.39 (d, 1H, *J* = 16.0 Hz), 6.34 (d, 1H, *J* = 16.0 Hz), 5.54 (d, 1H, *J* = 5.6 Hz), 5.41 (ddd, 1H, *J* = 7.8, 5.6, 5.1 Hz), 3.86 (dd, 1H, *J* = 10.6, 7.8 Hz), 3.30 (dd, 1H, *J* = 10.6, 5.1 Hz), 2.88 (s, 3H), 2.24 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 168.28, 167.58, 166.19, 165.80, 145.04, 145.00, 144.29, 144.15, 142.90, 142.84, 133.35, 133.17, 126.99, 124.43, 123.37, 118.24, 118.13, 74.98, 72.08, 52.19, 30.41, 21.04 (2C), 21.00 (2C).

(3*R*,4*S*)-Bis(3,4-dihydroxy-phenyl-acryloyloxy)-1-methyl-pyrrolidin-2-one (III-c). Yield 78%; Mp 131–134 °C; $[\alpha]_D^{23}$ +407.3° (*c* 0.15, CH_3OH); IR (KBr, cm^{-1}) 3176, 2927, 1701, 1606, 1517, 1282, 1158, 814; ^1H NMR (CD_3OD) δ 7.63 (d, 1H, *J* = 15.9 Hz), 7.60 (d, 1H, *J* = 15.9 Hz), 7.05–6.77 (m, 6H), 6.32 (d, 1H, *J* = 15.9 Hz), 6.29 (d, 1H, *J* = 15.9 Hz), 5.62 (d, 1H, *J* = 5.9 Hz), 5.48 (ddd, 1H, *J* = 8.0, 5.9, 5.5 Hz), 3.93 (dd, 1H, *J* = 10.4, 8.0 Hz), 3.43 (dd, 1H, *J* = 10.4, 5.5 Hz), 2.91 (s, 3H); ^{13}C NMR (CD_3OD) δ 170.35, 168.64, 168.28, 150.34, 148.62, 147.26, 127.93, 123.71, 116.92, 115.67, 114.31, 114.23, 76.57, 73.16, 47.84, 30.54. HRMS(FAB) calcd for $C_{23}H_{21}NO_9(M+H^+)$ 456.1295, found 456.1307.

(3*R*,4*S*)-Bis(3,4-diacetoxy-phenyl-acryloyloxy)-pyrrolidin-2-one (II-d). Yield 57%; Mp 108 °C (dec.); $[\alpha]_D^{23}$ +85.3° (*c* 0.19, $CHCl_3$); IR (KBr, cm^{-1}) 3346, 2927, 1786, 1726, 1646, 1497, 1372, 1224, 1172, 1112; ^1H NMR ($CDCl_3$) δ 7.73 (d, 1H, *J* = 15.6 Hz), 7.68 (d, 1H, *J* = 15.6 Hz), 7.39–7.22(m, 6H), 6.63 (bs, 1H, N*H*), 6.47 (d, 1H, *J* = 15.6 Hz), 6.41 (d, 1H, *J* = 15.6 Hz), 5.68 (d, 1H, *J* = 5.5 Hz), 5.58 (ddd, 1H, *J* = 8.6, 6.0, 5.5 Hz), 4.00 (dd, 1H, *J* = 10.4, 8.6 Hz), 3.35 (dd, 1H, *J* = 10.4, 6.0 Hz), 2.31 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 169.86, 167.88, 166.67, 166.39, 144.78, 144.64, 143.95, 143.86, 142.58, 142.54, 132.98, 126.54, 124.04, 123.98, 123.02, 117.84, 117.80, 73.67, 73.44, 44.62, 20.65, 20.59, 20.52.

(3*R*,4*S*)-Bis(3,4-dihydroxy-phenyl-acryloyloxy)-pyrrolidin-2-one (III-d). Yield 96%; Mp 132 °C (dec.); $[\alpha]_D^{23}$ +408.8° (*c* 0.16, CH_3OH); IR (KBr, cm^{-1}) 3292, 2924, 1706, 1600, 1516, 1278, 1152, 1100, 974, 810; ^1H NMR (CD_3OD) δ 7.64 (d, 1H, *J* = 15.9 Hz), 7.57 (d, 1H, *J* = 15.9 Hz), 7.06–6.77 (m, 6H), 6.32 (d, 1H, *J* = 15.9 Hz), 6.28 (d, 1H, *J* = 15.9 Hz), 5.64 (d, 1H, *J* = 6.3 Hz), 5.56 (m, 1H), 3.90 (dd, 1H, *J* = 10.4, 7.8 Hz), 3.60 (m, 1H); ^{13}C NMR (CD_3OD) δ 172.50, 168.24, 167.97, 149.87, 148.42, 148.22, 146.84, 127.68, 127.64, 123.30, 116.60, 115.44, 115.39, 114.04, 75.58, 74.68, 45.56. HRMS(FAB) calcd for $C_{22}H_{19}NO_9(M+H^+)$ 442.1138, found 442.1121.

(3*R*,4*S*)-Bis(3,4-diacetoxy-phenyl-acryloyloxy)-dihydrofuran-2-one (II-e). Yield 30%; Mp 93 °C (dec.); $[\alpha]_D^{23}$ +202.6° (*c* 0.04, $CHCl_3$); IR (KBr, cm^{-1}) 2928, 1774, 1722, 1638, 1506, 1372, 1208, 1100, 1012, 902, 836; ^1H NMR ($CDCl_3$) δ 7.74 (d, 1H, *J* = 15.9 Hz), 7.68 (d, 1H, *J* = 15.9 Hz), 7.43–7.26 (m, 6H), 6.45 (d, 1H, *J* = 15.9 Hz), 6.40 (d, 1H, *J* = 15.9 Hz) 5.60–5.67 (m, 2H), 4.89 (dd, 1H, *J* = 9.9, 6.2 Hz), 4.27 (dd, 1H, *J* = 9.9, 4.9 Hz), 2.30 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 169.82, 168.10, 166.78, 166.38, 145.99, 145.54, 144.45, 142.94, 132.34, 126.96, 124.41, 123.41, 117.49, 117.23, 73.10, 72.18, 69.49, 20.91.

(3*R*,4*S*)-Bis(3,4-dihydroxy-phenyl-acryloyloxy)-dihydrofuran-2-one (III-e). Yield 44%; Mp 98–100 °C; $[\alpha]_D^{23}$ +121.7° (*c* 0.06, CH_3OH); IR (KBr, cm^{-1}) 3354, 2926, 1774, 1724, 1636, 1506, 1372, 1258, 1178, 1110, 1070, 902, 836; ^1H NMR (acetone-d_6) δ 7.83 (d, 1H, *J* = 14.9 Hz), 7.79 (d, 1H, *J* = 14.9 Hz), 7.71–7.38 (m, 6H), 6.69 (d, 1H, *J* = 14.9 Hz), 6.57 (d, 1H, *J* = 14.9 Hz), 5.87 (d, 1H, *J* = 8.6 Hz), 5.46 (m, 1H), 5.20 (dd, 1H, *J* = 5.3, 2.4 Hz), 3.75 (dd, 1H, *J* = 9.7, 2.4 Hz); ^{13}C NMR (acetone-d_6) δ 169.50, 168.47, 168.36, 145.19, 145.04, 133.81, 133.72, 133.69, 127.43, 124.93, 124.09, 124.04, 118.83, 83.00, 74.97, 71.71.

(3*R*,4*R*)-Bis(3,4-diacetoxy-phenyl-acryloyloxy)-tetrahydrofuran (II-f). Yield 64%; Mp 158–160 °C; $[\alpha]_D^{23}$ +183.1° (*c* 0.20, $CHCl_3$); IR (KBr, cm^{-1}) 1781, 1716, 1646, 1502, 1382, 1207, 1178, 1113, 1018, 903; ^1H NMR ($CDCl_3$) δ 7.65 (d, 2H, *J* = 16.0 Hz), 7.37–7.21(m, 6H), 6.36 (d, 2H, *J* = 16.0 Hz), 5.35 (m, 2H), 4.19 (dd, 2H, *J* = 10.6, 4.5 Hz), 3.87 (dd, 2H, *J* = 10.6, 1.7 Hz), 2.27 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 167.81, 165.47, 144.13, 132.95, 124.00, 122.92, 118.22, 77.66, 72.10, 20.65, 20.60.

(3*R*,4*R*)-Bis(3,4-dihydroxy-phenyl-acryloyloxy)-tetrahydrofuran (III-f). Yield 72%; Mp 76–78 °C; $[\alpha]_D^{23}$ +306.5° (*c* 0.03, CH_3OH); IR (KBr, cm^{-1}) 3284, 2926, 1696, 1602, 1518, 1278, 1156, 1112, 810; ^1H NMR (CD_3OD) δ 7.59 (d, 2H, *J* = 15.8 Hz), 7.05–6.78 (m, 6H), 6.27 (d, 2H, *J* = 15.8 Hz), 5.32 (m, 1H), 4.18 (dd, 2H, *J* = 10.5, 4.4 Hz), 3.85 (d, 2H, *J* = 10.4 Hz); ^{13}C NMR (CD_3OD) δ 168.07, 149.83, 147.93, 146.86, 127.67, 123.17, 116.58, 115.33, 114.40, 78.80, 72.96. HRMS(FAB) calcd for $C_{22}H_{20}O_9(M+H^+)$ 429.1186, found 429.1181.

(3*R*,4*R*,5*S*)-Bis(3,4-diacetoxy-phenyl-acryloyloxy)-5-(*tert*-butyl-dimethyl-silyloxymethyl)-dihydrofuran-2-one (II-g). Yield 82%; Mp 62–64 °C; $[\alpha]_D^{23}$ −65.7° (*c* 0.14, $CHCl_3$); IR (KBr, cm^{-1}) 2957, 1810, 1776, 1735, 1641, 1512, 1377, 1257, 1198, 1168, 1113, 1023, 854; ^1H NMR

($CDCl_3$) δ 7.66 (d, 1H, $J=16.0$ Hz), 7.59 (d, 1H, $J=16.0$ Hz), 7.30–7.15 (m, 6H), 6.39 (d, 1H, $J=16.0$ Hz), 6.36 (d, 1H, $J=16.0$ Hz), 5.97 (d, 1H, $J=6.1$ Hz), 5.65 (d, 1H, $J=6.1$ Hz), 4.64 (m, 1H), 3.97 (m, 2H), 2.25 (m, 12H), 0.91 (s, 9H), 0.12–0.10 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 168.37, 168.22, 155.21, 165.16, 145.48, 145.32, 143.48, 142.86, 132.97, 127.20, 124.48, 123.25, 117.80, 83.92, 77.61, 71.67, 67.88, 26.17, 21.03, 18.61, −5.26.

(3*R*,4*R*,5*S*)-Bis(3,4-dihydroxy-phenyl-acryloyloxy)-5-hydroxymethyl-dihydrofuran-2-one (III-g). Yield 58%; Mp 112–115 °C; $[\alpha]_D^{23}$ −124.3° (*c* 0.23, CH_3OH); IR (KBr, cm^{-1}) 3366, 1782, 1702, 1630, 1598, 1514, 1444, 1372, 1260, 1156, 1112, 976, 810; ^1H NMR (CD_3OD) δ 7.60 (d, 1H, $J=15.9$ Hz), 7.58 (d, 1H, $J=15.9$ Hz), 7.04–6.72 (m, 6H), 6.33 (d, 1H, $J=15.9$ Hz), 6.26 (d, 1H, $J=15.9$ Hz), 6.02 (d, 1H, $J=6.1$ Hz), 5.69 (d, 1H, $J=6.1$ Hz), 4.76 (m, 1H), 3.92 (m, 2H); ^{13}C NMR (CD_3OD) δ 168.09, 167.34, 150.42, 149.26, 149.05, 147.25, 127.79, 127.71, 124.20, 123.96, 116.91, 116.84, 115.56, 115.30, 114.02, 113.41, 86.05, 72.56, 69.05, 62.48. HRMS(FAB) calcd for $C_{23}H_{20}O_{11}$ ($M+H^+$) 473.1084, found 473.1072.

(3*R*,4*R*)-Bis(3,4,5-triacetoxy-benzoyloxy)-1-methyl-pyrrolidine-2,5-dione (II-h). Yield 93%; Mp 95 °C (dec.); $[\alpha]_D^{23}$ +101.9° (*c* 0.10, $CHCl_3$); IR (KBr, cm^{-1}) 2949, 1795, 1741, 1442, 1379, 1330, 1208, 1056; ^1H NMR ($CDCl_3$) δ 7.84 (s, 4H), 5.80 (s, 2H), 3.18 (s, 3H), 2.30 (m, 18H).

(3*R*,4*R*)-Bis(3,4,5-trihydroxy-benzoyloxy)-1-methyl-pyrrolidine-2,5-dione (III-h). Yield 48%; Mp 101 °C (dec.); $[\alpha]_D^{23}$ +171.1° (*c* 0.27, CH_3OH); IR (KBr, cm^{-1}) 3398, 1731, 1624, 1452, 1345, 1208, 1037; ^1H NMR (CD_3OD) δ 7.09 (s, 4H), 5.88 (s, 2H), 3.10 (s, 3H). HRMS(FAB) calcd for $C_{19}H_{15}NO_{12}$ ($M+H^+$) 450.0673, found 450.0663.

(3*R*,4*S*)-Bis(3,4,5-triacetoxy-benzoyloxy)-1-methyl-pyrrolidin-2-one (II-i). Yield 25%; Mp 98 °C (dec.); $[\alpha]_D^{23}$ +90.1° (*c* 0.07, $CHCl_3$); IR (KBr, cm^{-1}) 2949, 1785, 1731, 1506, 1335, 1198, 1601; ^1H NMR ($CDCl_3$) δ 7.83 (s, 2H), 7.81 (s, 2H), 5.76 (d, 1H, $J=5.4$ Hz), 5.58 (td, 1H, $J=7.8$, 5.4 Hz), 4.02 (dd, 1H, $J=10.8$, 7.8 Hz), 3.41 (dd, 1H, $J=10.8$, 5.4 Hz), 2.97 (s, 3H), 2.30–2.29 (m, 18H).

(*3R*,*4S*)-Bis(3,4,5-trihydroxy-benzoyloxy)-1-methyl-pyrrolidin-2-one (III–i). Yield 44%; Mp 98 °C (dec.); $[\alpha]_D^{23}$ +154.0° (*c* 0.05, CH_3OH); IR (KBr, cm^{-1}) 3320, 2939, 1707, 1619, 1457, 1335, 1213, 1037; ^1H NMR (CD_3OD) δ 7.11 (s, 2H), 7.09 (s, 2H), 5.74 (d, 1H, $J=5.6$ Hz), 5.58 (m, 1H), 4.04 (dd, 1H, $J=10.6$, 8.0 Hz), 3.52 (dd, 1H, $J=10.6$, 5.4 Hz), 2.96 (s, 3H). HRMS(FAB) calcd for $C_{19}H_{17}NO_{11}$($M+H^+$) 436.0880, found 436.0886.

(3*R*,4*R*)-Bis(3,4,5-triacetoxy-benzoyloxy)-tetrahydrofuran (II-j). Yield 11%; Mp 57–60 °C; $[\alpha]_D^{23}$ +76.6° (*c* 0.14, $CHCl_3$); IR (KBr, cm^{-1}) 2968, 1790, 1741, 1613, 1506, 1443, 1384, 1340, 1198, 1056; ^1H NMR ($CDCl_3$) δ 7.80 (s, 2H), 5.53 (d, 2H, $J=2.0$ Hz), 4.29 (dd, 2H, $J=10.7$, 4.5 Hz), 3.97 (dd, 2H, $J=10.7$, 2.0 Hz), 2.31 (s, 18H).

(3*R*,4*R*)-Bis(3,4,5-trihydroxy-benzoyloxy)-tetrahydrofuran (III-j). Yield 93%; Mp 131 °C (dec.); $[\alpha]_D^{23}$ +107.2° (*c* 0.07, CH_3OH); IR (KBr, cm^{-1}) 3349, 2929, 1721, 1619, 1618, 1531, 1457, 1374, 1218; ^1H NMR (CD_3OD) δ 6.97 (s, 2H), 5.33 (d, 2H, $J=2.3$ Hz), 4.14 (dd, 1H, $J=10.5$, 4.3 Hz), 3.84 (d, 1H, $J=10.5$ Hz). HRMS(FAB) calcd for $C_{18}H_{16}O_{11}$ ($M+H^+$) 409.0771, found 409.0766.

(3*R*,4*R*,5*S*)-Bis(3,4,5-triacetoxy-benzoyloxy)-5-(*tert*-butyl-dimethyl-silyloxymethyl)-dihydrofuran-2-one (II-k). Yield 20%; Mp 94–96 °C; $[\alpha]_D^{23}$ −42.8° (*c* 0.84, $CHCl_3$); IR (KBr, cm^{-1}) 2958, 1780, 1741, 1438, 1384, 1330, 1193, 1046; ^1H NMR ($CDCl_3$) δ 7.74 (s, 2H), 7.72 (s, 2H), 6.13 (d, 1H, $J=6.1$ Hz), 5.81(d, 1H, $J=6.1$ Hz), 4.71 (m, 1H), 4.01 (m, 2H), 2.28–2.25 (m, 18H), 0.94 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H).

(3*R*,4*R*,5*S*)-Bis(3,4,5-trihydroxy-benzoyloxy)-5-hydroxymethyl-dihydrofuran-2-one (III-k). Yield 50%; Mp 115 °C (dec.); $[\alpha]_D^{23}$ −157.9° (*c* 0.02, CH_3OH); IR (KBr, cm^{-1}) 3330, 2968, 1795, 1746, 1614, 1335, 1198, 1056; ^1H NMR (CD_3OD) δ 6.81 (s, 2H), 6.80 (s, 2H), 5.90 (d, 1H, $J=6.1$ Hz), 5.56 (d, 1H, $J=6.1$ Hz), 4.57 (d, 1H, $J=2.2$ Hz), 3.73 (d, 2H, $J=2.2$ Hz). HRMS(FAB) calcd for $C_{19}H_{16}O_{13}$ ($M+H^+$) 453.0669, found 453.0654.

HIV integrase assay[17]

Recombinant human immunodeficiency virus type 1 (HIV-1) integrase was expressed in *Escherichia coli* and purified using nickel-chelated column in a one-step manner. Aliquots of HIV-1 integrase of 0.5 mg/mL as stock solutions were stored at −70 °C until used.

Oligonucleotide substrates

Two 20-mer oligonucleotides whose sequences resemble the end of U5-LTR were obtained from Korea Biotech. Inc.: K16 (U5-LTR, +strand), 5′-TGTGGAAAATC-TCTAGCAGT-3′; K17 (U5-LTR, -strand), 5′-ACT-GCTAGA-GATTTTCCACA-3′. The oligonucleotides were purified by 20% polyacrylamide gel before use. In order to construct oligonucleotide substrate, oligonucleotide K16 of 30 pmol was labeled at the 5′ end using [γ-^{32}P]-ATP of 250 μCi (3,000 Ci/mmol; 1 Ci = 37 GBq; Amersham) and T4 polynucleotide kinase (T4 PNK, New England Biolabs) of 10 units in 40 μL of reaction buffer (70 mM Tris–HCl [pH 7.6], 10 mM $MgCl_2$, 5 mM dithiothreitol) at 37 °C for 15 min. The labeling reaction was subjected to 10 mM EDTA, and heated to 85 °C for 15 min to inactivate T4 PNK. After addition of complementary oligonucleotide K17 of 30 pmol, the reaction mixture was boiled for 3 min and cooled down slowly. Labeled substrate was separated from unincorporated nucleotide by passage through a Biospin 6 (Bio-Rad).

HIV-1 integrase reaction

A standard reaction assay of the endonucleolytic activity was carried out in the presence of potential inhibitor containing 0.1 pmol of duplex oligonucleotide substrate and 15 pmol of HIV-1 integrase in 15 mM Tris–HCl

(pH 7.4), 100 mM NaCl, 1 mM $MnCl_2$, 2 mM 2-mercaptoethanol, 2.5 mM CHAPS, 0.1 mM EDTA, 0.1 mM PMSF, 1% glycerol, and 10 mM imidazole in a total volume of 10 μL. Inhibitors or drugs were dissolved in 100% DMSO and added to the reaction to be 5% DMSO in the final volume. Reaction mixtures were incubated at 33 °C for 90 min and stopped by addition of 4 μL of 95% formamide, 20 mM EDTA, 0.05% bromophenol blue, 0.05% xylene cyanol FF. The reactions were heated to 90 °C for 3 min and electrophoresed on a 20% denaturing polyacrylamide gel. Reaction products were visualized by autoradiography of the wet gel. IC_{50} was calculated by scanning bands on Kodak-5 film (Image Master VDS, Pharmacia Biotech.).

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18. *Anti-HIV and cytotoxicity assay procedures*. Standard virus-induced cytopathic effect (CPE) inhibition assay which employed 3-(4,5-dimethyl thiazoly-2)-2,5-diphenyltetrazolium bromide (MTT) to measure inhibition of virus-mediated cell death (R4) was used with slight modification. MT-4 cells on log phase were pelleted and infected with virus at an M.O.I. (multiplicity of infection) of 100 $CCID_{50}$ (50% cell culture inhibitory dose) per well. The cells were immediately re-suspended with RPMI 1640/10% FBS at the concentration of 1.2×10^5 cells/mL. 100 μL of the re-suspended cells were dropped to the wells of 96 well plate containing 100 μL of 2× concentrated compounds in duplicate. After 5 days incubation at 37 °C, the cells were observed microscopically and quantified by using MTT assay. The liquid was aspirated until 50 μL of liquid and all cells remained and 20 μL of 7.5 mg/mL MTT solution was added. The plates were further incubated for 1 h, and 100 μL of acidified isopropanol was added and shook on a microplate shaker until the formazan form completely dissolved. The absorbance at 540 nm by using 690 nm as reference wavelength was measured with a microplate reader (V_{max}, Molecular Devices). The antiviral effective concentration was expressed as the EC_{50} or concentration of the compound required to inhibit virus-induced CPE by 50%. To measure the effect of compounds on host cell growth, mock-infected cells were applied to the compound containing wells of the same plates in duplicate. The cytotoxic concentration was expressed as the CC_{50} or concentration of the compound required to inhibit cell growth by 50%.