Synthesis of (*E*)-9,10,13-Trihydroxy-11-octadecenoic Acids

Tadahiro KATO,* Toshihumi HIRUKAWA, and Masakuni YANO
Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo 162
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Our previous research concerning anti-rice blast fungus substances from the rice plants has led to the isolation of various types of oxygenated fatty acids as exemplified by 9,12,13-trihydroxy C-18 fatty acid. The fatty acids play an important role in the defense of the rice plants against this fungus. For evaluation of biological activity, we needed the isomeric trihydroxy fatty acids. This paper describes the synthesis of four stereoisomers of 9,10,13-trihydroxy fatty acid.

Our previous research concerning anti-rice blast fungus materials from the rice plants has led to the isolation of various types of oxygenated unsaturated fatty acids,[1] which play an important role in the defense of the rice plants against rice blast fungus.[2] Among the fatty acids isolated as defense substances were highly oxygenated ones as exemplified by 9,12,13-trihydroxy C-18 fatty acid (**1a**).[3] During the isolation work, the existence of the regioisomeric 9,10,13-trihydroxy acid (**2**) was not completely ruled out in the crude extracts of rice plants. In addition, some other biological activity was attributed to the trihydroxy acid **1** or **2** isolated from other origins although structure elucidation remained equivocal due to the limitted amounts of the materials.[4] It is, therefore, needed to evaluate the physiological properties including anti-rice blast fungus activity of the trihydroxy acid **2**. The paper concerns with the preparation of four stereoisomers of 9,10,13-trihydroxy acids **2a**—**2d** (Chart 1).

The easily available methyl (*dl*,*Z*)-9,10-epoxy-12-octadecenoate (**3**) was chosen as our starting material, which was prepared from methyl linoleate [methyl (9*Z*, 12*Z*)-9,12-octadecadienoate] by epoxidation with *m*-chloroperbenzoic acid and purifying by normal column chromatography. The epoxide **3** was subjected to epoxide ring opening with potassium pivalate in pivalic acid at 120 °C, leading to a 1 : 1 mixture of hydroxy pivaloyloxy derivatives **4** and **5** (Scheme 1). Trans opening of the epoxide ring under the conditions employed is well precedented in related system.[5] Without separating each isomer, the mixture was treated with Sharpless reagent, the hydroxy directed epoxidation of **5** thereby taking place smoothly to deliver the epoxy derivative **6**, while the isomeric **4** remained unaffected under these conditions. Oxidation of the hydroxy epoxide **6** with Collins reagent furnished an epoxy ketone, which isomerized easily to a hydroxy enone **7** when contacted by silica-gel at room temperature. The hydroxy enone **7** was quantitatively converted to an acetoxy enone **8**. The *trans* geometry of the newly introduced double bond at 11, 12-positions was assigned by the coupling constant of $J_{11,12}$=15.6 Hz, while the relative configuration at 9 and 13 positions is evident from the established stereochemistry of the Sharpless epoxidation.[6]

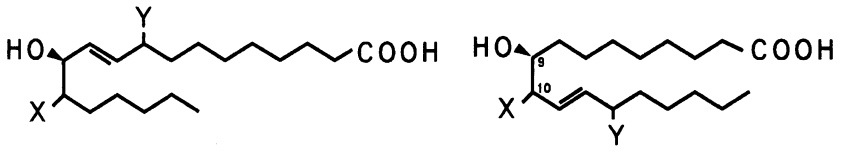
Face selective reduction of the carbonyl group of **8** was achieved by the action of dimethylphenylsilane and hexamethylphosphoric triamide (HMPA) in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF).[7] This reaction favored the formation of the *threo* alcohol over the *erythro* isomer by up to 5 : 1. Since separation was quite difficult at this stage, the dimethylphenylsilyl and acyl groups were removed by sequential reactions with hydrochloric acid and then with lithium hydroxide solution to give crude trihydroxy carboxylic esters after esterifying with diazomethane. Treatment of the crude trihydroxy esters with 2,2-dimethoxypropane followed by purification by HPLC provided pure isopropylidenedioxy derivatives **9** and **10**. The *threo* and *erythro* configuration was estimated by comparison of chemical shifts in the NMR spectra of **9** and **10**. The chemical shifts of two methyl groups on the [1,3]-dioxolane ring are almost equivalent in both ^{1}H and ^{13}C NMR spectra of *threo* derivatives **9** and **11** while those of *erythro* isomers **10** and **12** are completely different. These phenomena were also observed in the NMR spectra of isopropylidenedioxy derivatives obtained from analogous compounds **1a**—**1d**.[3,8]

Conversion of stereochemistry at 13-hydroxyl group of isopropylidenedioxy compounds **9** and **10** was achieved by modified Mitunobu conditions employing chloroacetic acid[9] to give methyl (9*SR*, 10*SR*,13*RS*)-(**11**) and (9*SR*,10*RS*,13*RS*)-(**12**)-(*E*)-13-hydroxy-9,10-isopropylidenedioxy-11-octadecenoates. Use of benzoic acid or acetic acid was unsuccessful in the Mitunobu inversion reaction. Deprotection of the [1,3]-dioxolan ring followed by alkaline hydrolysis of the ester group afforded the corresponding pure trihydroxy acids **2a**—**2d**.

Studies on biological activity of the trihydroxy acids are now in progress.

Experimental

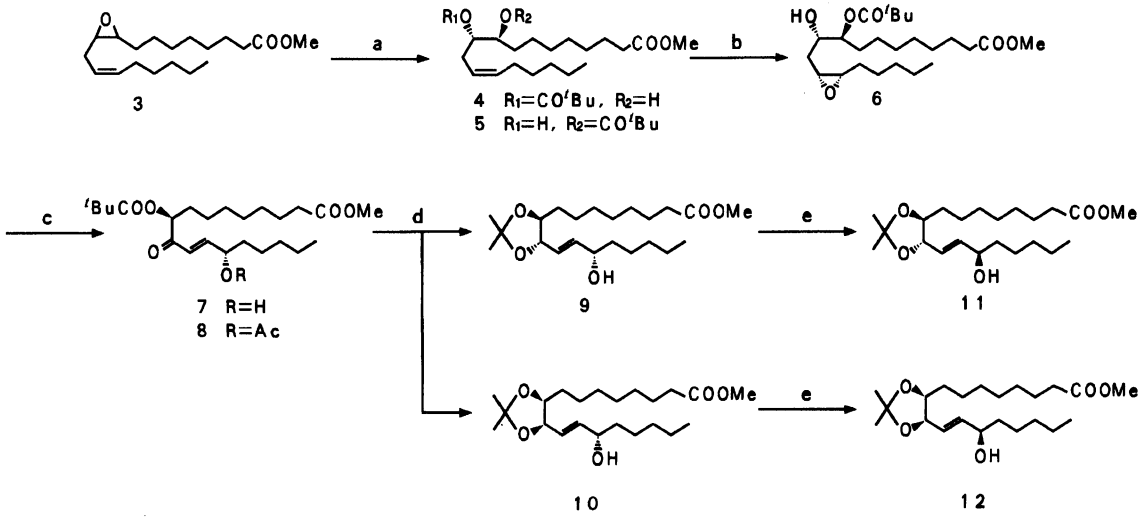
General Procedure and Instrumentation. Column chromatographic purifications were carried out on Kieselgel 60, Art 7734 (70—230 mesh) using solvent as indicated. Unless otherwise stated, all the spectroscopic data were determined on pure samples obtained by column chromatography, checking the purity by TLC or HPLC analyses. The IR spectra were determined on a Hitachi 270-30 spectrophotometer. The NMR spectra were recorded with JEOL spectrometers (FX-90Q or GSX-500) with tetramethylsilane as an internal standard. The mass spectra were measured with a Hitachi



1 a X=α-OH ; Y=β-OH
b X=Y=α-OH
c X=Y=β-OH
d X=β-OH ; Y=α-OH

2 a X=Y=α-OH
b X=β-OH ; Y=α-OH
c X=α-OH ; Y=β-OH
d X=Y=β-OH

Chart 1.



Scheme 1. (a) ^{t}BuCOOK, ^{t}BuCOOH, 120 °C; (b) VO (acac)$_2$, ^{t}BuOOH, C_6H_6, r.t., 43% (from **3**); (c) (i) CrO_3·2py; (ii) SiO_2, 91%; (iii) Ac_2O, Et_3N, DMAP, 96%; (d) (i) $PhMe_2SiH$, HMPA, TBAF, 0 °C; (ii) HCl, MeOH; (iii) LiOH, MeOH; (iv) CH_2N_2; (v) $(MeO)_2CMe_2$, PPTS, DMF; (e) (i) $ClCH_2COOH$, PPh_3, DEAD, C_6H_6; (ii) KOH, MeOH, 83% (**9**→**11**), 80% (**10**→**12**).

M-80 mass spectrometer.

Sharpless Epoxidation of Methyl (*Z*)-10-Hydroxy-9-pivaloyloxy-12-octadecenoate (5). A mixture of methyl (*Z*)-9,10-epoxy-12-octadecenoate (**3**) (221 mg, 0.71 mmol)[3] and $^{t}BuCO_2K$ (798 mg, 5.7 mmol) in $^{t}BuCO_2H$ (6.4 ml) was stirred at 120 °C for 5 h. The resulting cooled solution was diluted with ether (100 ml). The ether solution was carefully washed with saturated aq $NaHCO_3$ solution and then brine, dried (Na_2SO_4), and the solvent was removed. The oily crude product was purified by silica-gel (8 g) column chromatography (hexane : AcOEt=10 : 1) to give a 1 : 1 mixture of **4** and **5** (282 mg, 96%). The mixture (1.2 g, 2.91 mmol) was taken into CH_2Cl_2 (40 ml). $NaHCO_3$ (2.44 g, 29.1 mmol), VO(acac)$_2$ (23 mg) and then 70% aq ^{t}BuOOH (520 μl, 2.91 mmol) were successively added to the CH_2Cl_2 solution. The solution was stirred for 4 h at room temperature. The mixture was taken into ether (200 ml) and the ether solution was successively washed with water, aq $Na_2S_2O_3$ solution and then brine, and dried (Na_2SO_4). The ether was removed and the resultant oily residue was purified by silica-gel (40 g) column chromatography (hexane : AcOEt=10 : 1 containing 0.1% of Et_3N) to elute first the unreacted hydroxy pivaloyloxy octadecenoate **4** (0.62 g) and then methyl 12,13-epoxy-10-hydroxy-9-pivaloyloxy octadecanoate (**6**) (0.56 g, 45%).

Methyl 9- Hydroxy- 10- pivaloyloxy- 12- octadecenoate (4) : Colorless oil; IR (CCl_4) 3604 and 1742 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=5.56 (1H, dt, J=11.6 and 6.3 Hz) and 5.27 (1H, dt, J=11.6 and 6.4 Hz) (H-12 and H-13), 4.81 (1H, dt, J=3.9 and 6.4 Hz, H-10), 3.45—3.80 (4H, br, H-9, overlapped with OCH_3 at 3.67), 2.41 (2H, t, J=6.4 Hz, H-11), 2.31 (2H, t, J=7.2 Hz, H-2), 2.00 (br, OH), 1.22 (9H, s, $C(CH_3)\times3$), and 0.87 (3H, t, J=6.2 Hz, H-18); ^{13}C NMR (23 MHz, $CDCl_3$) δ=177.7 (s), 38.8 (s) and 27.2 (q×3) ($^{t}BuCO_2$), 173.7 (s) and 51.0 (q) (CO_2CH_3), 132.7 (d), 124.0 (d), 75.7 (d), 72.1 (d), 33.9 (t), 33.6 (t), 31.4 (t), 29.1 (t×2), 28.9 (t×3), 28.5 (t), 25.4 (t), 24.8 (t), 22.3 (t), and 13.7 (q); EI-MS (70 eV) m/z 394 (M^+-H_2O), 310 ($M^+-{}^{t}BuCO_2H$), 292 ($M^+-{}^{t}BuCO_2H-H_2O$), and 57 (base peak, $(CH_3)_3C$).

Methyl 12,13-Epoxy-10-hydroxy-9-pivaloyloxy Octadecanoate (6): Colorless oil; IR (CCl_4) 3608 and 1742 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ=4.90 (1H, m, H-9), 3.90 (1H, m, H-10), 3.68 (3H, s, OCH_3), 3.13 (1H, m, H-12), 2.91 (1H, m, H-13), 2.46 (1H, br s, OH), 2.31 (2H, t, J=7.2 Hz, H-2), 1.25 (9H, s, $C(CH_3)_3$), and 0.90 (3H, t, J=6.7 Hz, H-18); ^{13}C NMR (23 MHz, $CDCl_3$) δ=177.9 (s), 39.0 (s) and 27.2 (q×3) ($^{t}BuCO_2$), 173.8 (s) and 51.0 (q) (CO_2CH_3), 75.7 (d), 71.3 (d), 56.3 (d), 54.5 (d), 33.9 (t), 31.5 (t), 30.0 (t), 29.1 (t), 28.9 (t×3), 27.8 (t), 26.0 (t), 25.3 (t), 24.8 (t), 22.4 (t), and 13.7 (q). Exact mass: Found: m/z 429.3535. Calcd for $C_{24}H_{45}O_6$: M+1, 429.3219.

Collins Oxidation of Methyl 12-13-Epoxy-10-hydroxy-9-pivaloyloxy Octadecanoate (6). A CH_2Cl_2 (20 ml) solution of epoxy ester **6** (1.28 g, 2.99 mmol) was added to CrO_3·pyridine complex freshly prepared from anhydrous CrO_3 (3.58 g, 35.8 mmol) and pyridine (5.8 ml) in CH_2Cl_2 (110 ml), and the solution was stirred for 2 h at room temperature. The reaction mixture was diluted with ether and the ether solution was filtered through a short SiO_2 column. The silica gel was washed with ether and the combined organic layers were washed with brine and dried ($MgSO_4$). The organic solution was concentrated to about 10 ml. The concentrated solution was poured into silica-gel (60 g) column, and the substrates were adsorbed on the silica gel. After the SiO_2 column had been left to stand for 2 h, the elution was started with hexane : AcOEt = 6 : 1 to give hydroxy enone **7** (1.16 g, 91%). IR (CCl_4) 3520, 1740, and 1636 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=7.00 (1H, dd, J=4.3 and 15.6 Hz, H-12), 6.47 (1H, dd, J=1.9 and 15.6 Hz, H-11), 5.10 (1H, t, J=6.2 Hz, H-9), 4.30 (1H, br, H-13), 3.68 (3H, s, OCH_3), 2.31 (2H, t, J=7.2 Hz, H-2), 2.08 (1H, br, OH), 1.27 (9H, s, $CCH_3\times3$), and 0.87 (3H, t, J=6.7 Hz); ^{13}C NMR (23 MHz, $CDCl_3$) δ=196.2 (s, C-10), 177.7 (s), 38.7 (s), and 27.1 (q×3) ($^tBuCO_2$), 173.9 (s) and 51.2 (q) (CO_2CH_3), 149.9 (d), 123.4 (d), 77.5 (d), 71.2 (d), 36.8 (t), 34.0 (t), 31.7 (t), 30.6 (t), 28.9 (t×3), 25.1 (t), 24.9 (t×2), 22.5 (t), and 13.8 (q). Exact mass: Found: m/z 426.2976. Calcd for $C_{24}H_{42}O_6$: M, 426.2983.

Acetylation of Hydroxy Enone 7. A mixture of hydroxy enone **7** (177 mg, 0.42 mmol), Ac_2O (0.53 ml), 4-dimethylaminopyridine (DMAP) (5 mg), and Et_3N (1.1 ml) in CH_2Cl_2 (5 ml) was kept at room temperature for 3 h. The reaction mixture was then diluted with ether (100 ml) and the ether solution was successively washed with aq NH_4Cl solution and brine, and dried (Na_2SO_4). Evaporation of the volatile materials and subsequent silica-gel (10 g) column chromatography (hexane : AcOEt = 8 : 1) afforded acetoxy enone **8** (186 mg, 96%) as a colorless oil. IR (CCl_4) 1744, 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ=6.87 (1H, dd, J=5.5 and 15.9 Hz, H-12), 6.35 (1H, dd, J=1.9 and 15.9 Hz, H-11), 5.43 (1H, q, J=5.4 Hz, H-13), 5.10 (1H, t, J=7.2 Hz, H-9), 3.68 (3H, s, OCH_3), 2.31 (2H, t, J=7.2 Hz, H-2), 2.10 (3H, s), 1.28 (9H, s), and 0.90 (3H, t, J=5.7 Hz); ^{13}C NMR (23 MHz, $CDCl_3$) δ=195.8 (s, C-10), 177.7 (s), 38.8 (s), and 27.0 (q×3) ($^tBuCO_2$), 173.9 (s) and 51.2 (q) (CO_2CH_3), 169.8 (s) and 20.8 (q) ($OCOCH_3$), 145.0 (d), 124.7 (d), 77.5 (d), 72.8 (d), 34.1 (t), 33.9 (t), 31.5 (t), 30.7 (t), 29.0 (t×3), 25.1 (t), 24.9 (t), 24.6 (t), 22.4 (t), and 13.8 (q). Exact mass: Found: m/z 468.3091. Calcd for $C_{26}H_{44}O_7$: M, 468.3088.

Reduction of Acetoxy Enone 8 with Me_2PhSiH. To an HMPA (0.45 ml) solution of acetoxy enone **8** (94 mg, 0.20 mmol) were added Me_2PhSiH (33 μl) and 1 M THF solution (1 M = 1 mol dm^{-3}) of $^nBu_4NF$ (9 μl), and the mixture was kept at room temperature for 4 h. The mixture was diluted with ether, washed with brine, and dried (Na_2SO_4). After evaporation of the volatile materials, the crude product was taken into MeOH (2 ml) and 2 M HCl–MeOH (0.5 ml) was added. The solution was kept at room temperature for 10 min and then quenched with aq $NaHCO_3$. The reaction mixture was taken into ether, before the ether solution was washed with brine and dried (Na_2SO_4). The volatile materials were removed, and the resulting residue was purified by silica-gel (10 g) column chromatography (hexane : AcOEt = 5 : 1) to give a 5 : 1 mixture of *threo* and *erythro* alcohols (77 mg, 82%). Methyl ester of pivalate of **2a** and **2b**. EI-MS (70 eV): 453 (M^+-H_2O+H), 439 (M^+-OCH_3+H).

The 5 : 1 mixture of resulting alcohols (77 mg) was dissolved in MeOH (2 ml), 1 M LiOH in MeOH (1.6 ml) was added, and the resultant mixture was kept at room temperature overnight. The mixture was diluted with water, acidified by adding oxalic acid to give a pH value near 4, and then extracted with ether. The ether solution was washed with brine, dried over Na_2SO_4 and evaporated. The residue was taken into MeOH, and excess CH_2N_2 in ether was added. Evaporation of the volatile materials and subsequent silica-gel column chromatography (CH_2Cl_2 : MeOH = 20 : 1) gave crude trihydroxy ester (45 mg) as white powder. The crude trihydroxy ester (45 mg), 2,2-dimethoxypropane (0.1 ml), and pyridinium *p*-toluenesulphonate (PPTS) (5 mg) in DMF (0.5 ml) was stirred for 2 h at room temperature. The mixture was diluted with ether (100 ml), washed with brine, dried (Na_2SO_4), and the volatile materials were removed. the resulting residue was purified by SiO_2 (7 g) column chromatography (hexane : AcOEt = 6 : 1) to give pure isopropylidenedioxy compounds **9** (37 mg, 60%) and **10** (8 mg, 13%).

Compound 9: ^1H NMR (500 MHz, $CDCl_3$) δ=5.84 (ddd, J=0.6, 5.8, and 15.6 Hz, H-12), 5.65 (ddd, J=1.2, 7.4, and 15.6 Hz, H-11), 4.16 (q, J=5.8 Hz, H-13), 3.99 (t, J=7.9 Hz, H-10), 3.64—3.68 (m, H-9 overlapped with OCH_3 at 3.67), 2.30 (2H, t, J=7.6 Hz, H-2), 1.413 and 1.405 (each 3H, s, $CH_3\times2$ on 1,3-dioxolane ring), and 0.89 (3H, t, J=7.0 Hz, H-18); ^{13}C NMR (23 MHz, $CDCl_3$) δ=173.6 (s) and 50.9 (q) (CO_2CH_3), 108.1 (s, 1,3-dioxolane ring carbon), 137.4 (d, C-11), 127.2 (d, C-12), 81.6 (d, C-10), 80.7 (d, C-9), 71.4 (d, C-13), 37.1(t), 33.7 (t), 31.5 (t), 29.1 (t), 28.7 (t×2), 25.6 (t), 24.7 (t×2), 22.3 (t), 27.0 (q) and 26.8 (q) ($CH_3\times2$ on 1,3-dioxolane ring), and 13.6 (q, C-18).

Compound 10: ^1H NMR (500 MHz, $CDCl_3$) δ=5.73 (dd, J=6.4 and 15.6 Hz, H-12), 5.63 (ddd, J=0.6, 7.9, and 15.6 Hz, H-11), 4.49 (dd, J=6.1 and 7.9 Hz, H-10), 4.13 (q, J=6.0 Hz, H-13), 4.10—4.12 (m, H-9), 3.67 (3H, s, OCH_3), 2.30 (2H, t, J=7.6 Hz, H-2), 1.48 and 1.36 (each 3H, s, $CH_3\times2$ on 1,3-dioxolane ring), and 0.89 (3H, t, J=7.0 Hz, H-18); ^{13}C NMR (23 MHz, $CDCl_3$) δ=173.8 (s) and 51.1 (q) (CO_2CH_3), 107.9 (s, 1,3-dioxolane ring carbon), 137.2 (d, C-11), 126.8 (d, C-12), 79.0 (d, C-10), 78.4 (d, C-9), 72.1 (d, C-13), 37.3 (t), 34.0 (t), 31.7 (t), 30.5 (t), 29.3 (t), 29.0 (t×2), 26.0 (t), 25.0 (t), 24.9 (t), 22.5 (t), 28.3 (q) and 25.6 (q) ($CH_3\times2$ on 1,3-dioxolane ring), and 13.8 (q, C-18). Exact mass: Found for **9**: m/z 384.2865 and for **10**: m/z 384.2884. Calcd for $C_{22}H_{40}O_5$: M, 384.2877.

Mitsunobu Inversion of Isopropylidenedioxy Compounds 9 and 10. To a mixture of compound **9** (42 mg, 0.11 mmol) and triphenylphosphine (86 mg, 0.33 mmol) in anhydrous benzene (2 ml) was dropped benzene (3 ml) solution of chloroacetic acid (26 mg, 0.27 mmol) and diethyl azodicarboxylate (DEAD) (43 μl, 0.27 mmol) and the mixture was stirred at room temperature for 3 h. The benzene solution was diluted with ether, washed with brine, dried (Na_2SO_4), and the volatile materials were removed. The residue was purified by SiO_2 (7 g) column chromatography (hexane : AcOEt = 10 : 1) to give pale yellow oil (47 mg). To a MeOH (2 ml) solution of the oil was added 2 M KOH in

MeOH (0.3 ml) and the mixture was kept at room temperature for 10 min. Aq oxalic acid solution was added to the mixture to make pH near 4 and then diluted with ether. The ether solution was washed with brine and dried (Na_2SO_4). Evaporation of volatile materials and subsequent SiO_2 (7 g) column chromatography (hexane : AcOEt=6 : 1) afforded isopropylidenedioxy compound **11** (35 mg, 83%). Similarly, compound **10** (40 mg, 0.1 mmol) was converted to the isomer **12** (32 mg, 80%) as a pale yellow oil.

Isopropylidenedioxy Compound 11: ^{1}H NMR (90 MHz, $CDCl_3$) δ=5.84 (dd, J=5.5 and 15.4 Hz, H-12), 5.60 (dd, J=6.4 and 15.4 Hz, H-11), 3.84—4.22 (2H, m, H-10 and H-13), 3.48—3.80 (br, H-9 overlapped with OCH_3 at 3.68), 2.30 (2H, t, J=7.6 Hz, H-2), 1.43 (6H, s, CH_3×2 on 1,3-dioxolane ring), and 0.89 (3H, m, H-18); ^{13}C NMR (23 MHz, $CDCl_3$) δ=173.8 (s, C-1) and 51.0 (q) (CO_2CH_3), 108.4 (s, 1,3-dioxolane ring carbon), 137.5 (d, C-11), 127.7 (d, C-12), 81.8 (d, C-10), 80.9 (d, C-9), 71.9 (d, C-13), 37.3 (t), 34.0 (t), 31.9 (t), 31.7 (t), 29.4 (t), 29.0 (t×2), 25.8 (t), 24.9 (t×2), 22.5 (t), 27.2 (q) and 27.0 (q) (CH_3×2 on 1,3-dioxolane ring), and 13.8 (q, C-18).

Isopropylidenedioxy Compound 12: ^{1}H NMR (90 MHz, $CDCl_3$) δ=5.60—5.80 (2H, m, H-11 and H-12), 4.52 (t, J=7.7 Hz, H-10), 3.96—4.28 (2H, br, H-9 and H-13), 3.68 (3H, s, OCH_3), 2.30 (2H, t, J=7.6 Hz, H-2), 1.48 and 1.36 (each 3H, s, CH_3×2 on 1,3-dioxolane ring), and 0.89 (3H, t, J=7.0 Hz, H-18); ^{13}C NMR (23 MHz, $CDCl_3$) δ=174.1 (s, C-1) and 51.2 (q) (CO_2CH_3), 108.1 (s, 1,3-dioxolane ring carbon), 137.2 (d, C-11), 126.8 (d, C-12), 79.1 (d, C-10), 78.6 (d, C-9), 72.1 (d, C-13), 37.5 (t), 34.2 (t), 31.9 (t), 30.7 (t), 29.4 (t), 29.2 (t×2), 26.2 (t), 25.1 (t×2), 22.7 (t), 28.4 (q) and 25.7 (q) (CH_3×2 on 1,3-dioxolane ring), and 13.9 (q, 18-C). Exact mass: Found for **11**: m/z 384.2868 and for **12**: m/z 384.2883. Calcd for $C_{22}H_{40}O_5$: M, 384.2877.

Trihydroxy Esters. A mixture of isopropylidenedioxy compound **9** (56 mg, 0.15 mmol) and *p*-TsOH (5 mg) in MeOH (2 ml) was stirred for 2 h at room temperature and then diluted with ether (100 ml). The ether solution was washed with brine and dried (Na_2SO_4). Evaporation of volatile materials and subsequent SiO_2 (7 g) column chromatography (CH_2Cl_2 : MeOH=30 : 1) afforded methyl ester of trihydroxy carboxylic acid **2a** (48 mg, 96%) as colorless powder. Similarly, isopropylidenedioxy compounds **10** (47 mg, 0.12 mmol), **11** (90 mg, 0.23 mmol), and **12** (45 mg, 0.12 mmol) furnished the corresponding methyl esters of trihydroxy carboxylic acids **2b** (41 mg, 97%), **2c** (76 mg, 96%), and **2d** (35 mg, 87%) as colorless powder.

Trihydroxy Acids 2a—2d. A mixture of methyl ester of trihydroxy carboxylic acid **2a** (48 mg) in 1.5 M methanolic KOH (7 ml) was kept at room temperature overnight. Aq oxalic acid solution was added to make pH near 4 and then extracted with CH_2Cl_2 : MeOH=10 : 1. The organic layer was washed with brine, dried (Na_2SO_4), and then evaporated. The resulting residue was purified by SiO_2 (7 g) column chromatography (CH_2Cl_2 : MeOH=10 : 1) to obtain trihydroxy carboxylic acid **2a** (46 mg) as colorles powder. Similarly, methyl esters of trihydroxy carboxylic acid **2b** (41 mg), **2c** (76 mg), and **2d** (35 mg) were hydrolyzed to give the corresponding trihydroxy carboxylic acids **2b** (37 mg), **2c** (68 mg), and **2d** (30 mg) as colorless powder.

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