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A novel stereoselective synthesis of (−)-quinic acid starting from the naturally abundant (−)-shikimic acid

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ABSTRACT

A new stereoselective synthesis of (−)-quinic acid from the naturally abundant (−)-shikimic acid is described. Ethyl shikimate **2** was first prepared in 97% yield via esterification of (−)-shikimic acid according to a previous report. Ester **2** was then transformed into an epimeric mixture of 3,4-*O*-benzylidene shikimate **3**, which was directly converted into compound **4** in 90% yield (over 2 steps from ester **2**) via an NBS-mediated acetal ring-opening reaction. Acetylization of the hydroxyl group at the C-5 position of compound **4** gave compound **5** in 98% yield. Compound **5** was transformed into compound **6** in 91% yield via a highly stereoselective Ru-catalyzed dihydroxylation. Subsequently, compound **6** was converted into epoxide **7** in 82% yield via an intramolecular S_N2 type substitution. A regioselective epoxide-opening of compound **7** by PPh_3–I_2 complex furnished an iodo compound **8** in 79% yield. Removal of the iodine atom in compound **8** by Pd/C-catalyzed hydrogenation produced compound **9** in 92% yield. Methanolysis of compound **9** gave methyl quinate **10** in 92% yield. Finally, hydrolysis of compound **10** afforded the targeted compound (−)-quinic acid **1** in 90% yield. The title compound (−)-quinic acid **1** was stereoselectively synthesized through 10 steps starting from (−)-shikimic acid in 38% overall yield.

1. Introduction

(−)-Quinic acid **1** (Scheme 1) is an important natural cyclitol (cyclic polyol). (−)-Quinic acid is ubiquitous in the plant kingdom, and exists in many different plants such as cinchona bark, coffee beans, tobacco leaves, carrot leaves, apples, peaches, pears, plums, vegetables, and so forth.[1] (−)-Quinic acid was first isolated by Hofmann in 1790,[2] and its structure and stereochemistry were established by Fisher and Dangschart in 1932 and 1937.[3] The absolute stereochemistry of (−)-quinic acid was further confirmed by means of X-ray analysis of a single crystal by Allen et al. in 1988.[4] (−)-Quinic acid is known to exhibit antioxidative, anti-inflammatory effects,[5] as well as the ability to chelate transition metals in vitro.[6] Many derivatives of (−)-quinic acid, which exhibit various bioactivities, have also been isolated from natural resources.[7] Moreover, (−)-quinic acid is a versatile chiral synthon in organic synthesis, and it has been widely used as a starting material for the synthesis of natural products and bioactive compounds.[8]

Due to the pharmaceutical importance of (−)-quinic acid and its derivatives as well as the wide utility of (−)-quinic acid in asymmetric synthesis, the ready availability of (−)-quinic acid is highly desirable. Although (−)-quinic acid can be isolated from Nature,[1] synthetic preparations from the inexpensive starting materials are enormously helpful. Several syntheses of racemic (±)-quinic acid and enantiomerically pure (−)-quinic acid have been reported,[9] while the development of a new efficient and practical synthesis of (−)-quinic acid remains considerable interest.

(−)-Shikimic acid (see Scheme 1) can be readily obtained in large quantities by extraction from Chinese star anise or other natural plants,[10] and has been recently used as a starting material for the syntheses of oseltamivir phosphate,[11] (+)-valiolamine,[12] (+)-valienamine,[13] and some chiral building blocks.[14] Due to the wide availability of (−)-shikimic acid, (−)-shikimic acid being less expensive than (−)-quinic acid, and the structural resemblance between (−)-shikimic acid and (−)-quinic acid, (−)-shikimic acid could be accordingly used as an appropriate starting material for the synthesis of (−)-quinic acid. In 1991, Tamm et al.[9e] reported the synthesis of (−)-quinic acid from (−)-shikimic acid; herein we report a new stereoselective synthesis of (−)-quinic acid starting from the naturally abundant (−)-shikimic acid.

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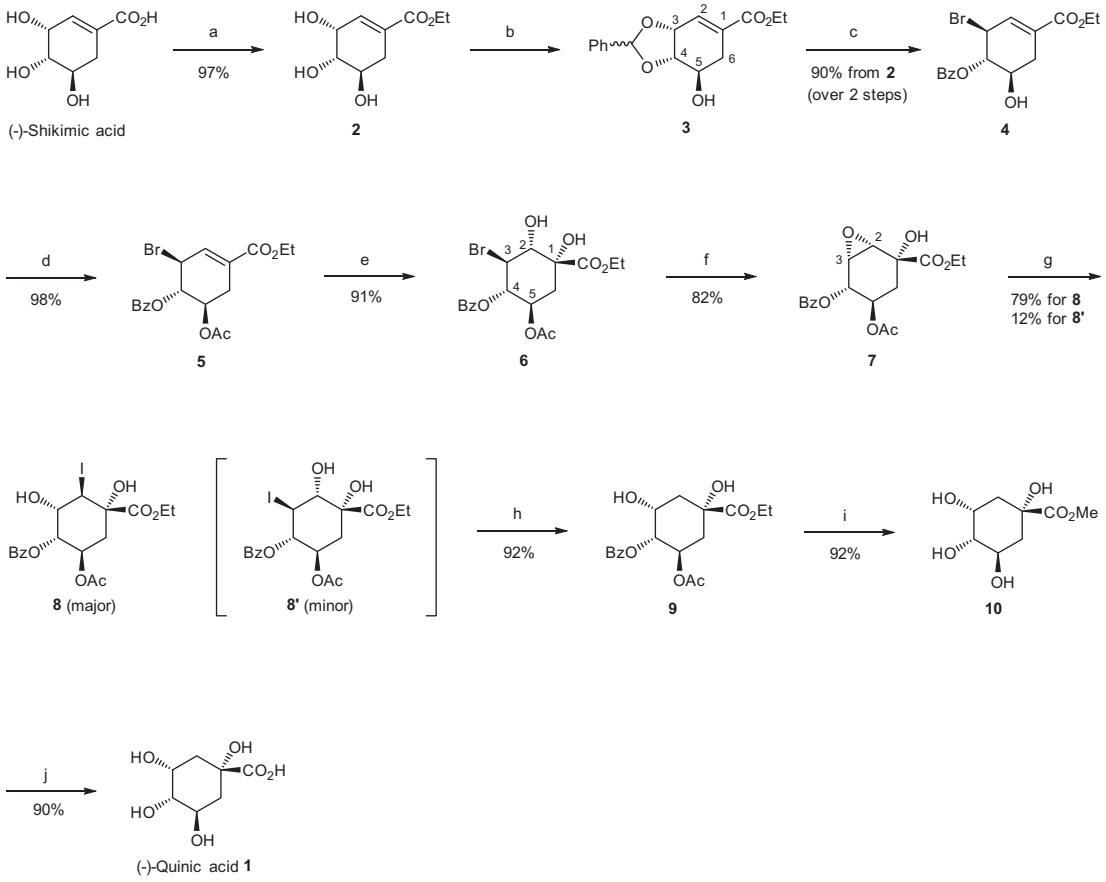

Scheme 1. A new stereoselective synthesis of (−)-quinic acid **1** starting from (−)-shikimic acid. Reagents and conditions: (a) see Ref. 15. (b) 1.1 equiv of PhCHO, 0.01 equiv of TsOH, reflux for 6 h in CH_3CN. (c) 1.1 equiv of NBS, 0 °C for 1 h in CH_3CN. (d) 1.2 equiv of Ac_2O, 1.2 equiv of Et_3N, 0.1 equiv of DMAP, 0 °C–rt for 2 h in CH_2Cl_2. (e) 1.5 equiv of $NaIO_4$, 1.0 equiv of H_2SO_4, 0.002 equiv of $RuCl_3$, 0 °C to 5 °C for 8 h in a mixed solvent ($EtOAc/CH_3CN/H_2O$ = 3:3:1). (f) 1.5 equiv of NaH, 15–25 °C for 0.5 h in $PhCH_3$/DMSO (2:1). (g) 1.05 equiv of $Ph_3P–I_2$ (1:1), 1.1 equiv of DIPEA, −10 °C for 3 h in CH_2Cl_2. (h) Pd/C, 1.0 equiv of Et_3N, H_2 (1.01 atm.), reflux for 3 h in EtOAc. (i) 10 equiv of Et_3N, reflux for 12 h in MeOH. (j) 2.0 equiv of NaOH, rt for 5 h in a mixed solvent of THF/H_2O (1:1); then 2.0 equiv of HCl.

2. Results and discussion

Our synthetic route for the new stereoselective synthesis of (−)-quinic acid **1** starting from (−)-shikimic acid is depicted in Scheme 1. Ethyl shikimate **2** was first prepared in 97% yield according to a known procedure.[15] Compound **2** was then treated with 1.1 equiv of benzaldehyde at reflux in acetonitrile in the presence of a catalytic amount of *para*-toluenesulfonic acid (TsOH) to furnish an epimeric mixture of ethyl 3,4-*O*-benzylidene shikimate **3**, which was used as such for being exposed to 1.1 equiv of *N*-bromosuccinimide (NBS) at 0 °C in acetonitrile to afford compound **4** in 90% yield over two steps from **2**. A plausible mechanism for the cascade benzylic oxidation and allylic bromination is proposed in Figure 1 according to Hanessian et al.[16] As can be seen from Figure 1, acetal **3** first underwent benzylic bromination to form an unstable intermediate **I-A**, which quickly transformed into intermediate **I-B** via cleavage of C–Br bond. The bromide anion then attacked the C-3 position to form compound **4**. Since the allylic C-3 position is much more reactive than the non-allylic C-4 position, the regioselectivity of the above reaction is exclusive.

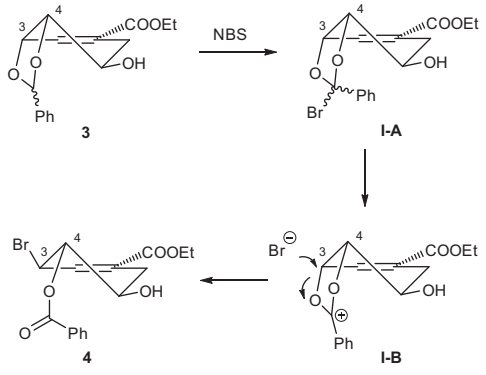

Figure 1. A plausible mechanism for the conversion of **3** into **4**.

Compound **4** was treated with 1.2 equiv of acetic anhydride, 1.2 equiv of trimethylamine and a catalytic amount of 4-*N*, *N*-dimethylaminopyridine (DMAP) in dichloromethane at 0 °C to room temperature to produce compound **5** in an almost quantitative yield. Compound **5** was transformed into compound **6** via a highly stereoselective Ru-catalyzed dihydroxylation.[17] When compound **5** was treated with 0.002 equiv of ruthenium trichloride, 1.5 equiv of sodium periodate and 1.0 equiv of sulfuric acid at 0–5 °C in a mixed solvent of ethyl acetate, acetonitrile, and water ($EtOAc/CH_3CN/H_2O$ = 3:3:1), a highly stereoselective dihydroxylation smoothly took place to afford dihydroxy compound **6** in 91% yield. The bulkiness of the bromine atom at the C-3 position rendered the ruthenium catalyst to approach the double bond from the opposite side of the bromine atom during the stereoselective dihydroxylation, thus the two hydroxyl groups at the C-1 and C-2 positions of compound **6** have the orientation *trans* to the bromine atom at the C-3 position, meaning that the two stereogenic

centers at the C-1 and C-2 positions should have (*R*,*R*) absolute configurations. The stereoselectivity of the dihydroxylation was very high; almost none of other diastereomer was detected by careful TLC and ^{1}H NMR monitoring of crude product.

Subsequently, compound **6** was converted into epoxide **7** via an intramolecular S_N2 type substitution. When compound **6** was treated with 1.5 equiv of sodium hydride in a mixed solvent of toluene and dimethyl sulfoxide ($PhCH_3$/DMSO = 2:1) at 15–25 °C, compound **7** was obtained in 82% yield. The formation of epoxide **7** proved the *trans* relationship between the vicinal bromine atom and the hydroxy group on the six-membered ring.

When compound **7** was treated with 1.05 equiv of the complex of triphenylphosphine and iodine (Ph_3P/I_2 = 1:1)[18] in the presence of 1.1 equiv of diisopropylethylamine (DIPEA) in dichloromethane at −10 °C, a regioselective epoxide-opening smoothly took place to afford compound **8** in 79% yield and its regioisomer **8′** (see Fig. 2) in 12% yield. A plausible mechanism for the regioselective epoxide-opening of compound **7** is proposed in Figure 2. As can be seen from Figure 2, epoxide **7** first reacted with PPh_3–I_2 and DIPEA to form a chelate intermediate compound shown in the square parenthesis. The iodide ion then underwent a favorable axial attack at C-2 via path *a* to produce intermediate **I-C**, which was subject to hydrolysis to afford compound **8** as the major product; iodide ion could also undergo a disfavorable equatorial attack at C-3 via path *b* to produce intermediate **I-D**, which was subject to hydrolysis to afford compound **8′** as the minor product. Here, the intermediate compound **I-C** with two six-membered and bridge-linked chair rings is probably more stable than the intermediate compound **I-D** with six-membered and five-membered fused rings.

The iodide atom in compound **8** was removed via Pd-catalyzed hydrogenation under an atmosphere of H_2 (1.01 atm). Hydrogenation of compound **8** was performed at reflux in ethyl acetate with palladium on carbon as the catalyst in the presence of 1.0 equiv of triethylamine under hydrogen gas, compound **9** was thus obtained in 92% yield. Next, compound **9** was treated with 10 equiv of triethylamine at reflux in methanol for 12 h to furnish methyl quinate **10** in 92% yield. During this reaction, both the Bz and Ac groups were removed, and the ethyl ester group at the C-1 position was simultaneously changed to the methyl ester group.

Finally, compound **10** was treated with 2.0 equiv of sodium hydroxide in a mixed solvent of tetrahydrofuran and water (THF/H_2O = 1:1) at room temperature, which allowed hydrolysis of the ester group to take place smoothly. After neutralization with 2.0 equiv of hydrochloric acid, the crude product was purified by chromatography through a column of acidic resin to afford (−)-quinic acid **1** in 90% yield.

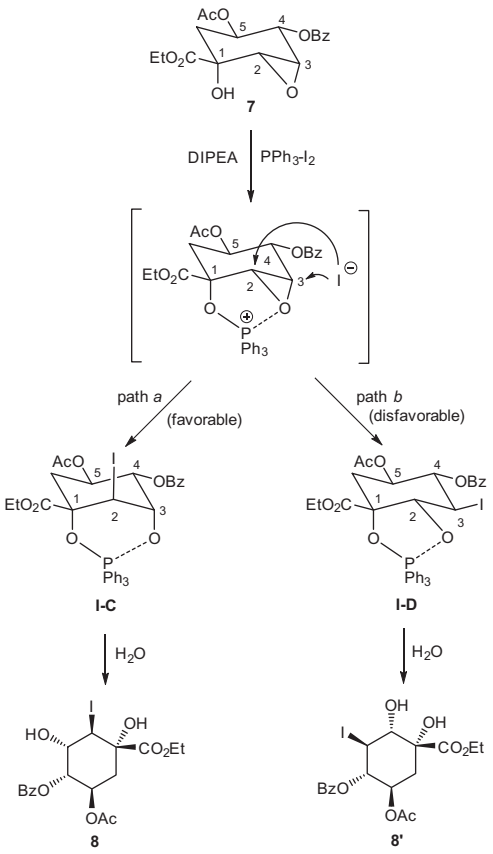

Figure 2. A plausible mechanism for the epoxide-opening of **7**.

3. Conclusion

In conclusion, we have successfully developed a new stereoselective synthesis of (−)-quinic acid **1**. By using the naturally abundant and commercially available (−)-shikimic acid as the starting material, the target compound (−)-quinic acid **1** was synthesized via 10 steps in 38% overall yield. In particular, the overall yield of our synthesis is significantly better than Tamm et al. report[9e] (21–25% overall yield).

Three characteristic reactions in the above-described stereoselective synthesis of (−)-quinic acid **1** are noteworthy. The first one is the NBS-mediated acetal ring-opening reaction[16] of 3,4-*O*-benzylidene shikimate **3**, the exclusive regioselectivity of the reaction is based on the fact that the allylic C-3 position is much more reactive than the non-allylic C-4 position. The second one is the ruthenium-catalyzed highly stereoselective dihydroxylation of compound **5**; the presence of sulfuric acid is crucial for low catalyst-loading (0.002 mol %) for this stereoselective dihydroxylation.[17] The third one is the regioselective epoxide-opening of compound **7**, chelation of the active intermediate rendered the favorable axial attack of iodide ion on C-2 to afford the desired compound **8** as the major product.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM-400 instrument. Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Nicolet Magna IR-550 spectrometer. MS spectra were recorded on a Shimadzu GC–MS 2010 (EI) or a Mariner Mass Spectrum (ESI) equipment. The optical rotations of chiral compounds were measured on WZZ-1S polarimeter at room temperature. Melting points were determined on a Mel-TEMP II melting point apparatus. Column chromatography was performed on silica gel. All chemicals are analytically pure, and were used as received from the chemical suppliers. Ethyl shikimate **2** was prepared via esterification of (−)-shikimic acid according to a previous report.[15]

4.2. (3*R*,4*S*,5*R*)-Ethyl 3,4-*O*-benzylidene shikimate 3

Ethyl shikimate **2** (10.00 g, 49.45 mmol) was dissolved in acetonitrile (120 mL). Benzyl aldehyde (5.780 g, 54.46 mmol) and a catalytic amount of *p*-toluenesulfonic acid (86.10 mg, 0.50 mmol) were then added to the solution. The mixture was then stirred and heated at reflux for 6 h with continuous removal of the water by azeotropic distillation. After the reaction was complete (checked by TLC, eluent: CH_2Cl_2/MeOH = 10:1), the solvent was removed

by vacuum distillation. The residue was then partitioned between two phases of ethyl acetate (150 mL) and an aqueous solution of sodium bicarbonate (30 mL, 5% w/w). Two phases were separated, and the organic phase was washed with brine (15 mL). The organic solution was dried over anhydrous $MgSO_4$, and then filtered. Evaporation of solvent under vacuum gave an epimeric mixture of compound **3** as a pale yellow oil, which could be used directly for the next step without separation. Some of the crude oily product was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to give two pure isomers of compound **3** for characterization. The characterization data of the two pure isomers are as follows:

One isomer of **3** (upper spot, R_f = 0.525 on TLC with CH_2Cl_2/MeOH = 15:1 as the eluent): $[\alpha]_D^{25} = -41.7$ (*c* 1.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.51 (m, 2H, aromatic protons in Ph), 7.35–7.43 (m, 3H, aromatic protons in Ph), 6.93 (dd, J_1 = 3.5 Hz, J_2 = 1.2 Hz, 1H, H-2), 5.97 (s, 1H, PhC*H* in the acetal moiety), 4.86 (dd, J_1 = 3.5 Hz, J_2 = 6.4 Hz, 1H, H-3), 4.34 (dd, J_1 = 6.5 Hz, J_2 = 6.4 Hz, 1H, H-4), 4.24 (q, J = 7.1 Hz, 2H, CH_2 in COOEt), 4.07–4.16 (m, 1H, H-5), 3.35 (br s, 1H, O*H*), 2.82 (dd, J_1 = 17.5 Hz, J_2 = 4.5 Hz, 1H, H-6), 2.35 (ddd, 1H, J_1 = 17.5 Hz, J_2 = 4.5 Hz, J_3 = 1.2 Hz, 1H, another H-6), 1.32 (t, J = 7.1 Hz, 3H, CH_3 in COOEt) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 166.21 (*C*OOEt), 137.84 (Ar–C), 133.27 (Ar–C), 131.46 (Ar–C), 129.34 (Ar–C), 128.43 (C-1), 126.36 (C-2), 102.61 (PhCH in the acetal moiety), 77.91 (C-3), 72.56 (CH_2 in COOEt), 67.02 (C-4), 61.21 (C-5), 28.95 (C-6), 14.17 (CH_3 in COOEt) ppm. HRMS (EI) calcd for $C_{16}H_{19}O_5$ $[M+H]^+$: 291.1232; found: 291.1235. IR (neat): ν = 3469, 2911, 1715, 1459, 1402, 1251, 1065, 756 cm^{-1}. The other isomer of **3** (lower spot R_f = 0.510 on TLC with CH_2Cl_2/MeOH = 15:1 as the eluent): $[\alpha]_D^{25} = -127.6$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.49 (m, 2H, aromatic protons in Ph), 7.31–7.41 (m, 3H, aromatic protons in Ph), 6.98 (dd, J_1 = 3.5 Hz, J_2 = 1.2 Hz, 1H, H-2), 5.92 (s, 1H, PhC*H* in the acetal moiety), 4.77 (dd, J_1 = 3.5 Hz, J_2 = 7.4 Hz, 1H, H-3), 4.22 (q, J = 7.1 Hz, 2H, CH_2 in COOEt), 4.15 (dd, J_1 = 7.5 Hz, J_2 = 7.4 Hz, 1H, H-4), 3.83–3.93 (m, 1H, H-5), 3.00 (br s, 1H, O*H*), 2.80 (dd, J_1 = 17.4 Hz, J_2 = 4.7 Hz, 1H, H-6), 2.26 (ddd, J_1 = 17.4 Hz, J_2 = 4.7 Hz, J_3 = 1.2 Hz, 1H, another H-6), 1.29 (t, J = 7.1 Hz, 3H, CH_3 in COOEt) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.02 (*C*OOEt), 136.45 (Ar–C), 132.55 (Ar–C), 131.82 (Ar–C), 129.73 (Ar–C), 128.48 (C-1), 126.87 (C-2), 104.33 (PhCH in the acetal moiety), 78.69 (C-3), 74.09 (CH_2 in COOEt), 68.99 (C-4), 61.21 (C-5), 29.52 (C-6), 14.18 (CH_3 in COOEt) ppm. HRMS (ESI) calcd for $C_{16}H_{19}O_5$ $[M+H]^+$: 291.1232; found: 291.1228. IR (neat): ν = 3468, 2912, 1716, 1459, 1405, 1251, 1065, 758 cm^{-1}.

4.3. (3*S*,4*S*,5*R*)-Ethyl 3-bromo-4-benzoyloxy-5-hydroxyl-cyclohex-1-ene carboxylate 4

The above-obtained epimeric mixture of compound **3** was dissolved in acetonitrile (150 mL), and the resulting solution was cooled to 0 °C by an ice bath. After *N*-bromosuccinimide (9.700 g, 54.50 mmol) was added in portions over 10 min, the mixture was stirred at 0 °C for 1 h, and then the reaction was complete (checked by TLC, eluent: EtOAc/hexane = 1:4). Acetonitrile was removed by vacuum distillation, and the residue was partitioned between two phases of ethyl acetate (180 mL) and an aqueous solution of sodium sulfite (30 mL, 10% w/w). The two phases were separated, and the organic phase was washed with brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, and then filtered. Evaporation of the solvent under vacuum gave a crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to furnish pure compound **4** (16.39 g, 44.51 mmol) as a colorless oil in 90% yield (over 2 steps from **2**). $[\alpha]_D^{25}$ = +58.8 (*c* 1.32, $CHCl_3$). ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.02 (d, J = 7.1 Hz, 2H, *ortho* protons in Ph), 7.55 (t, J = 7.3 Hz, 1H, *para* proton in Ph), 7.41 (dd, J_1 = 7.2 Hz, J_2 = 7.3 Hz, 2H, *meta* protons in Ph), 6.89 (dd, J_1 = 3.0 Hz, J_2 = 1.0 Hz, 1H, H-2), 5.53 (dd, J_1 = 7.4 Hz, J_2 = 7.5 Hz, 1H, H-4), 4.84 (dd, J_1 = 3.0 Hz, J_2 = 7.5 Hz, 1H, H-3), 4.27 (q, J = 7.1 Hz, 2H, CH_2 in COOEt), 3.93–4.03 (m, 1H, H-5), 3.39 (br s, 1H, O*H*), 2.93 (dd, J_1 = 17.9 Hz, J_2 = 5.3 Hz, 1H, H-6), 2.52 (ddd, J_1 = 17.9 Hz, J_2 = 5.3 Hz, J_3 = 1.0 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H, CH_3 in COOEt) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.31 (PhCO), 165.40 (*C*OOEt), 135.90 (Ar–C), 133.48 (Ar–C), 129.91 (Ar–C), 129.70 (Ar–C), 129.29 (C-1), 128.47 (C-2), 78.70 (C-4), 68.45 (CH_2 in COOEt), 61.39 (C-5), 46.14 (C-3), 32.05 (C-6), 14.16 (CH_3 in COOEt) ppm. HRMS (ESI) calcd for $C_{16}H_{18}BrO_5$ $[M+H]^+$: 369.0338; found: 369.0331. IR (neat): ν = 3420, 2982, 1725, 1717, 1271, 1102, 1070, 713 cm^{-1}.

4.4. (3*S*,4*S*,5*R*)-Ethyl 5-acetoxy-3-bromo-4-benzoyloxy-cyclohex-1-ene carboxylate 5

Compound **4** (10.00 g, 27.16 mmol), triethylamine (3.300 g, 32.61 mmol), and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (330 mg, 2.701 mmol) were dissolved in dichloromethane (150 mL). The resulting solution was cooled to 0 °C by an ice bath, after which acetic anhydride (3.330 g, 32.62 mmol) was added dropwise over 5 min. After the addition was completed, the ice bath was removed, and the mixture was further stirred at room temperature for 2 h. After the reaction was complete (checked by TLC, eluent: EtOAc/hexane = 1:4), the solution was transferred into a separatory funnel. The organic phase was washed successively with aqueous HCl solution (2 M, 30 mL), aqueous K_2CO_3 (2 M, 30 mL) solution and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, and then filtered. Evaporation of the solvent under vacuum gave a crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:4) to furnish pure compound **5** (10.93 g, 26.58 mmol) in 98% yield. $[\alpha]_D^{25}$ = +87.6 (*c* 1.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H, *ortho* protons in Ph), 7.62 (t, J = 7.3 Hz, 1H, *para* proton in Ph), 7.45 (dd, J_1 = 7.2 Hz, J_2 = 7.3 Hz, 2H, *meta* protons in Ph), 6.99 (dd, J_1 = 3.2 Hz, J_2 = 1.2 Hz, 1H, H-2), 5.73 (dd, J_1 = 6.8 Hz, J_2 = 6.4 Hz, 1H, H-4), 5.22–5.29 (m, 1H, H-5), 4.85 (dd, J_1 = 6.8 Hz, J_2 = 3.2 Hz, 1H, H-3), 4.26 (q, J = 7.1 Hz, 2H, CH_2 in COOEt), 2.93 (dd, J_1 = 16.7 Hz, J_2 = 5.4 Hz, 1H, H-6), 2.64 (ddd, J_1 = 16.7 Hz, J_2 = 5.4 Hz, J_3 = 1.0 Hz, 1H, another H-6), 1.96 (s, 3H, CH_3 in Ac), 1.33 (t, J = 7.1 Hz, 3H, CH_3 in COOEt). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.11 (PhCO), 165.18 (*C*OOEt), 165.13 (MeCO), 135.49 (Ar–C), 133.60 (Ar–C), 129.85 (Ar–C), 129.04 (Ar–C), 129.02 (C-1), 128.57 (C-2), 73.77 (C-4), 68.01 (C-5), 61.47 (CH_2 in COOEt), 43.93 (C-3), 28.44 (C-6), 20.85 (CH_3 in Ac), 14.19 (CH_3 in COOEt). HRMS (ESI) calcd for $C_{18}H_{20}BrO_6$ $[M+H]^+$: 411.0443; found: 411.0438. IR (neat): ν = 2982, 1729, 1725, 1711, 1449, 1366, 1246, 1112, 710 cm^{-1}.

4.5. (1*R*,2*R*,3*S*,4*S*,5*R*)-Ethyl 5-acetoxy-4-benzoyloxy-3-bromo-1,2-dihydroxy-cyclohexane carboxylate 6

An aqueous solution of H_2SO_4 (5.0 mL, 1 M, 5.000 mmol) and powdered $NaIO_4$ (1.600 g, 7.480 mmol) were added into a 100-mL round-bottomed flask equipped with a magnetic stirring bar. The mixture was stirred at room temperature for 10 min, and then a dilute aqueous solution of $RuCl_3$ (1.0 mL, 0.01 M, 0.01 mmol) was added. The resulting solution was stirred at room temperature until the color turned bright yellow, after which the temperature was cooled down to 0 °C by an ice-bath. A solution of compound **5** (2.056 g, 5.000 mmol) in a mixed solvent of ethyl acetate (18 mL) and CH_3CN (18 mL) was added at 0 °C. The mixture was then vigorously stirred at 0–5 °C for approximately 8 h. When TLC (eluent: EtOAc/hexane = 1:2)

showed the reaction was complete, a saturated aqueous $Na_2S_2O_3$ solution (35 mL) and a saturated aqueous $NaHCO_3$ solution (25 mL) were added and the mixture was vigorously stirred for 15 min. The mixture was then transferred into a separatory funnel and extracted three times with ethyl acetate (3 × 30 mL). The combined organic extracts were then washed with brine (20 mL), dried over anhydrous $MgSO_4$ and filtered. Concentration of the filtrate under vacuum gave a crude product which was purified by flash chromatography (eluent: EtOAc/CH_2Cl_2/hexane = 1:2:4) to afford compound **6** (2.026 g, 4.550 mmol, 91%) as white crystals, mp 149–150 °C. $[\alpha]_D^{25} = -11.6$ (*c* 2.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H, *ortho* protons in Ph), 7.59 (t, J = 7.4 Hz, 1H, *para* protons in Ph), 7.46 (dd, J_1 = 7.6 Hz, J_2 = 7.4 Hz, 2H, *meta* protons in Ph), 5.60 (dd, J_1 = 7.8 Hz, J_2 = 7.9 Hz, 1H, H-4), 5.37 (ddd, J_1 = 7.9 Hz, J_2 = 6.9 Hz, J_3 = 5.0 Hz, 1H, H-5), 4.32 (q, J = 7.1 Hz, 2H, C*H*$_2$ in COOEt), 4.30 (d, J = 6.5 Hz, 1H, H-2), 4.17 (dd, J_1 = 7.8 Hz, J_2 = 6.5 Hz, 1H, H-3), 3.76 (br s, 1H, O*H*), 2.73 (br s, 1H, O*H*), 2.30 (dd, J_1 = 13.4 Hz, J_2 = 5.0 Hz, 1H, H-6), 2.06 (dd, J_1 = 13.4 Hz, J_2 = 6.9 Hz, 1H, another H-6), 1.89 (s, 3H, C*H*$_3$ in Ac), 1.34 (t, J = 7.1 Hz, 3H, C*H*$_3$ in COOEt). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.38 (Ph*C*O), 169.86 (Me*C*O), 165.42 (*C*OOEt), 133.49 (Ar–C), 129.94 (Ar–C), 129.16 (Ar–C), 128.53 (Ar–C), 75.55 (C-4), 75.51 (C-5) 74.72 (*C*H$_2$ in COOEt), 69.25 (C-1), 63.13 (C-2), 54.54 (C-3), 35.31 (C-6), 20.78 (*C*H$_3$ in Ac), 14.12 (*C*H$_3$ in COOEt). HRMS (ESI) calcd for $C_{18}H_{21}BrO_8Na$ $[M+Na]^+$: 467.0317; found: 467.0327. IR (neat): ν = 3485, 2984, 1730 (br), 1367, 1271, 1240, 1117, 710 cm^{-1}.

4.6. (1*R*,2*S*,3*S*,4*S*,5*R*)-Ethyl 5-acetoxy-4-benzoyloxy-2,3-epoxy-1-hydroxy-cyclohexane carboxylate 7

Compound **6** (2.000 g, 4.492 mmol) was dissolved in a mixed solvent of toluene (20 mL) and dimethyl sulfoxide (10 mL). The resulting solution was cooled to 15 °C by a cooled-water bath. A dispersion of sodium hydride (0.270 g, 60% w/w, 6.751 mmol) in mineral oil was added in portions over 10 min. After the addition was finished, the mixture was stirred at 15–25 °C for 0.5 h. After the reaction was completed (checked by TLC, eluent: acetone/hexane = 1:3), the mixture was diluted by ethyl acetate (50 mL). A dilute aqueous solution of HCl (1 M, 15 mL) was then added dropwise, after which the mixture was transferred into a separatory funnel. Two phases were separated, and the aqueous phase was extracted once more with ethyl acetate (20 mL). The organic extracts were combined and washed with brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, and then filtered. Concentration of the filtrate under vacuum gave a crude product which was purified by flash chromatography (eluent: acetone/CH_2Cl_2/hexane = 1:2:5) to afford compound **7** (1.345 g, 3.692 mmol) in 82% yield, mp 89–90 °C. $[\alpha]_D^{25} = -125$ (*c* 1.62, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 2H, *ortho* protons in Ph), 7.61 (t, J = 7.8 Hz, 1H, *para* protons in Ph), 7.47 (dd, J_1 = 7.6 Hz, J_2 = 7.8 Hz, 2H, *meta* protons in Ph), 5.45–5.55 (m, 2H, H-4 and H-5), 4.35 (q, J = 7.1 Hz, 2H, C*H*$_2$ in COOEt), 3.74 (dd, J_1 = 3.8 Hz, J_2 = 1.2 Hz, 1H, H-3), 3.53 (d, J = 3.8 Hz, 1H, H-2), 2.17 (dd, J_1 = 13.2 Hz, J_2 = 3.6 Hz, 1H, H-6), 2.09 (dd, J_1 = 13.2 Hz, J_2 = 5.1 Hz, 1H, another H-6), 1.96 (s, 3H, C*H*$_3$ in Ac), 1.38 (t, J = 7.1 Hz, 3H, C*H*$_3$ in COOEt). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.45 (Ph*C*O), 169.81 (Me*C*O), 166.21 (*C*OOEt), 133.50 (Ar–C), 129.94 (Ar–C), 129.22 (Ar–C), 128.54 (Ar–C), 72.70 (C-4), 72.37 (C-5), 66.56 (*C*H$_2$ in COOEt), 62.83 (C-1), 57.05 (C-2), 55.44 (C-3), 38.83 (C-6), 20.83 (*C*H$_3$ in Ac), 14.13 (*C*H$_3$ in COOEt). HRMS (ESI) calcd for $C_{18}H_{20}O_8Na$ $[M+Na]^+$: 387.1056; found: 387.1048. IR (KBr film): ν = 3448, 2918, 1729 (br), 1702, 1367, 1256, 1237, 1122, 710 cm^{-1}.

4.7. (1*S*,2*R*,3*S*,4*R*,5*R*)-Ethyl 5-acetoxy-4-benzoyloxy-1,3-dihydroxy-2-iodo-cyclohexane carboxylate 8

Triphenylphosphine (0.795 g, 3.031 mmol) and iodine (0.769 g, 3.030 mmol) were dissolved in dichloromethane (15 mL), the mixture was stirred at room temperature for 0.5 h to give a clear solution, which was immediately used in the following procedure.

Compound **7** (1.050 g, 2.882 mmol) and *N*,*N*-diisopropyl ethylamine (0.410 g, 3.172 mmol) were dissolved in dichloromethane (15 mL). The resulting solution was cooled to −10 °C by a salt-ice bath. The above-prepared solution of Ph_3P–I_2 was then added dropwise over 5 min. After the addition was finished, the mixture was stirred at −10 °C for approximately 3 h, and the reaction was monitored by TLC (eluent: EtOAc/hexane = 1:3). When the reaction was complete, an aqueous solution of sodium sulfite (2 M, 10 mL) was added, and the mixture was vigorously stirred for 5 min. The mixture was then transferred into a separatory funnel, and two phases were separated. The organic phase was dried over anhydrous $MgSO_4$, and then filtered. Concentration of the filtrate under vacuum gave a crude product which was purified by flash chromatography (eluent: EtOAc/CH_2Cl_2/hexane = 1:2:6) to afford compound **8** (1.121 g, 2.277 mmol) as a colorless oil in 79% yield and compound **8′** (0.170 g, 0.345 mmol) as white crystals in 12% yield. Characterization data for compound **8** are as follows: $[\alpha]_D^{25} = -19.6$ (*c* 1.72, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8 Hz, 2H, *ortho* protons in Ph), 7.58 (t, J = 7.6 Hz, 1H, *para* proton in Ph), 7.46 (dd, J_1 = 7.8 Hz, J_2 = 7.6 Hz, 2H, *meta* protons in Ph), 5.81 (dd, J_1 = 9.7 Hz, J_2 = 3.6 Hz, 1H, H-4), 5.73–5.58 (m, 1H, H-5), 4.63 (dd, J_1 = 3.6 Hz, J_2 = 3.8 Hz, 1H, H-3), 4.56 (dd, J_1 = 3.8 Hz, J_2 = 1.6 Hz, 1H, H-2), 4.29 (q, J = 7.1 Hz, 2H, C*H*$_2$ in COOEt), 2.67 (dd, J_1 = 14.2 Hz, J_2 = 10.7 Hz, 1H, H-6), 2.50 (ddd, J_1 = 14.2 Hz, J_2 = 5.3 Hz, J_3 = 1.6 Hz, 1H, another H-6), 2.00 (s, 3H, C*H*$_3$ in Ac), 1.36 (t, J = 7.1 Hz, 3H, C*H*$_3$ in COOEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.39 (Ph*C*O), 169.95 (Me*C*O), 165.37 (*C*OOEt), 133.50 (Ar–C), 129.96 (Ar–C), 129.21 (Ar–C), 128.54 (Ar–C), 78.86 (C-4), 74.76 (C-5), 71.99 (*C*H$_2$ in COOEt), 67.30 (C-1), 62.52 (C-3), 35.36 (C-2), 33.86 (C-6), 20.81 (*C*H$_3$ in Ac), 14.11 (*C*H$_3$ in COOEt). HRMS (ESI) calcd for $C_{18}H_{21}IO_8Na$ $[M+Na]^+$: 515.0179; found: 515.0173. IR (neat): ν = 3376, 2985, 1744 (br), 1722, 1365, 1297, 1110, 1094, 712 cm^{-1}. Characterization data for compound **8′** are as follows: mp 164–165 °C. $[\alpha]_D^{25} = -6.52$ (*c* 1.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 2H, *ortho* protons in Ph), 7.60 (t, J = 7.4 Hz, 1H, *para* proton in Ph), 7.47 (dd, J_1 = 7.6 Hz, J_2 = 7.4 Hz, 2H, *meta* protons in Ph), 5.61 (dd, J_1 = 10.8 Hz, J_2 = 9.6 Hz, 1H, H-4), 5.33 (ddd, J_1 = 10.8 Hz, J_2 = 9.1 Hz, J_3 = 5.0 Hz, 1H, H-5), 4.39 (d, J = 11.0 Hz, 1H, H-2), 4.32 (q, J = 7.1 Hz, 2H, C*H*$_2$ in COOEt), 4.18 (dd, J_1 = 11.0 Hz, J_2 = 9.6 Hz, 1H, H-3), 3.67 (s, 1H, O*H*), 2.52 (s, 1H, O*H*), 2.28 (dd, J_1 = 14.4 Hz, J_2 = 5.0 Hz, 1H, H-6), 2.06 (dd, J_1 = 14.4 Hz, J_2 = 9.1 Hz, 1H, another H-6), 1.88 (s, 3H, C*H*$_3$ in Ac), 1.35 (t, J = 7.1 Hz, 3H, C*H*$_3$ in COOEt). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.39 (Ph*C*O), 169.95 (Me*C*O), 165.37 (*C*OOEt), 133.50 (Ar–C), 129.96 (Ar–C), 129.21 (Ar–C), 128.54 (Ar–C), 76.10 (C-4), 75.37 (C-5), 75.20 (*C*H$_2$ in COOEt), 68.90 (C-1), 63.11 (C-2), 35.36 (C-3), 33.45 (C-6), 20.81 (*C*H$_3$ in Ac), 14.11 (*C*H$_3$ in COOEt). HRMS (ESI) calcd for $C_{18}H_{21}IO_8Na$ $[M+Na]^+$: 515.0179; found: 515.0174. IR (KBr film): ν = 3489, 2987, 1726 (br), 1705, 1367, 1269, 1242, 1092, 708 cm^{-1}.

4.8. (1*S*,3*R*,4*R*,5*R*)-Ethyl 5-acetoxy-4-benzoyloxy-1,3-dihydroxy-cyclohexane carboxylate 9

A solution of compound **8** (0.700 g, 1.422 mmol) in ethyl acetate (20 mL) was transferred into a three-necked round bottom flask, which was equipped with a magnetic stirrer bar, an inlet and an outlet of hydrogen gas. Palladium on carbon (100 mg, 10% w/w) and trimethylamine (0.144 g, 1.424 mmol) were added. The flask

was purged several times with hydrogen gas. The suspension was heated at reflux, and was stirred at reflux for approximately 3 h under an atmosphere of hydrogen gas (1.01 atm.). After the reaction was complete (checked by TLC, eluent: EtOAc/hexane = 1:2), the mixture was passed through a thin layer of Celite to remove the catalyst. Evaporation of the solvent gave a crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:2) to furnish pure compound **9** (0.480 g, 1.310 mmol) as a colorless oil in 92% yield. $[\alpha]_D^{25} = -93.6$ (*c* 1.51, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J = 7.3$ Hz, 2H, *ortho* protons in Ph), 7.57 (t, $J = 7.5$ Hz, 1H, *para* proton in Ph), 7.45 (dd, $J_1 = 7.3$ Hz, $J_2 = 7.5$ Hz, 2H, *meta* protons in Ph), 5.77 (ddd, $J_1 = 10.4$ Hz, $J_2 = 9.2$ Hz, $J_3 = 4.9$ Hz, 1H, H-5), 5.14 (dd, $J_1 = 10.4$ Hz, $J_2 = 4.2$ Hz, 1H, H-4), 4.41–4.49 (m, 1H, H-3), 4.29 (q, $J = 7.1$ Hz, 2H, CH_2 in COOEt), 2.35 (dd, $J_1 = 13.2$ Hz, $J_2 = 4.6$ Hz, 1H, H-6), 2.14–2.27 (m, 2H, two H-2 protons), 2.06 (dd, $J_1 = 13.2$ Hz, $J_2 = 9.6$ Hz, 1H, another H-6), 1.95 (s, 3H, CH_3 in Ac), 1.33 (t, $J = 7.1$ Hz, 3H, CH_3 in COOEt). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.90 (PhCO), 170.28 (MeCO), 166.10 (*C*OOEt), 133.33 (Ar–C), 129.88 (Ar–C), 129.65 (Ar–C), 128.50 (Ar–C), 75.88 (C-4), 75.41 (C-5), 68.78 (CH_2 in COOEt), 66.87 (C-1), 62.73 (C-3), 39.10 (C-6), 37.27 (C-2), 20.96 (CH_3 in Ac), 14.12 (CH_3 in COOEt). HRMS (ESI) calcd for $C_{18}H_{22}O_8Na$ $[M+Na]^+$: 389.1212; found: 389.1214. IR (neat): $\nu = 3449, 2959, 2921, 1731$ (br), 1724, 1451, 1367, 1275, 1233, 1114, 1040, 715 cm^{-1}.

4.9. (1*S*,3*R*,4*S*,5*R*)-Methyl 1,3,4,5-tetrahydroxycyclohexane carboxylate 10

Compound **9** (0.440 g, 1.200 mmol) and trimethylamine (1.220 g, 12.05 mmol) were dissolved in anhydrous methanol (15 mL). The mixture was heated at reflux, and was stirred at reflux for 12 h. Methanol was removed by vacuum distillation, and the residue was purified by flash chromatography (eluent: CH_2Cl_2/CH_3OH = 5:1) to furnish pure compound **10** (0.228 g, 1.106 mmol) as white crystals in 92% yield, mp 125–126 °C (lit.[19] 126–127 °C). $[\alpha]_D^{25} = -31.2$ (*c* 1.60, CH_3OH) {lit. [19] $[\alpha]_D^{19} = -30.9$ (*c* 1.86, CH_3OH); lit.[9g] $[\alpha]_D^{30} = -31.6$ (*c* 1.45, CH_3OH)}. ^1H NMR (400 MHz, CD_3OD) δ 4.07 (dd, $J_1 = 6.6$ Hz, $J_2 = 5.4$ Hz, 1H, H-4), 3.92–4.02 (m, 1H, H-5), 3.73 (s, 3H, OCH_3), 3.38–3.46 (m, 1H, H-3), 1.95–2.12 (m, 3H, two H-6 and one H-2), 1.87 (dd, $J_1 = 13.2$ Hz, $J_2 = 9.2$ Hz, 1H, H-2). ^{13}C NMR (100 MHz, CD_3OD) δ 175.92 (*C*OOMe), 76.81 (C-1), 76.50 (C-4), 71.38 (C-5), 68.22 (C-3), 52.90 (CH_3 in COOMe), 41.94 (C-6), 38.31 (C-2). HRMS (ESI) calcd for $C_7H_{12}O_6Na$ $[M+Na]^+$: 215.0532; found: 215.0528. IR (KBr film): $\nu = 3426, 2958, 1721, 1648, 1437, 1323, 1266, 1112, 1085, 710$ cm^{-1}.

4.10. (−)-Quinic acid 1

Compound **10** (0.220 g, 1.066 mmol) was dissolved in a mixed solvent of tetrahydrofuran (2 mL) and water (2 mL). Powdered sodium hydroxide (0.086 g, 2.150 mmol) was then added, and the mixture was stirred at room temperature for 5 h. An aqueous solution of HCl (2.000 M, 1.1 mL, 2.200 mmol) was then added. The mixture was passed through a column of acidic resin (10 cm) with a mixed solvent of methanol and water (1:1) as the eluent. Evaporation of the solvents under vacuum afforded (−)-quinic acid **1** (0.184 g, 0.958 mmol) as white crystals in 90% yield, mp 166–167 °C (lit.[9g] 167–168 °C). $[\alpha]_D^{25} = -43.2$ (*c* 1.80, H_2O) {lit.[9g] $[\alpha]_D^{30} = -43.6$ (*c* 2.03, H_2O)}. ^1H NMR (400 MHz, CD_3OD) δ 4.09 (dd, $J_1 = 6.5$ Hz, $J_2 = 5.2$ Hz, 1H, H-4), 3.95–4.05 (m, 1H, H-5), 3.35–3.42 (m, 1H, H-3), 2.00–2.15 (m, 3H, two H-6 and one H-2), 1.86 (dd, $J_1 = 13.4$ Hz, $J_2 = 9.8$ Hz, 1H, H-2). ^{13}C NMR (100 MHz, CD_3OD) δ 177.64 (*C*OOH), 77.11 (C-1), 76.90 (C-4), 71.99 (C-5), 68.06 (C-3), 42.44 (C-6), 38.45 (C-2). HRMS (ESI) calcd for $C_8H_{14}O_6Na$ $[M+Na]^+$: 229.0688; found: 229.0481. IR (KBr film): $\nu = 3408, 2965, 1726, 1646, 1440, 1267, 1085, 709$ cm^{-1}.

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