Regio- and Chemoselective Alkylation of L-Ascorbic Acid under Mitsunobu Conditions

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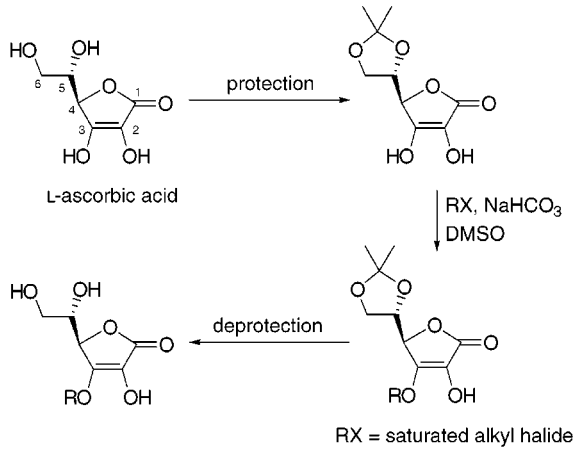
There has been a great deal of interest in the chemistry of L-ascorbic acid (vitamin C) with the aim of preparing pharmacologically active analogues with optimum activity.[1,2] To this end, the development of selective methodologies for the synthesis of *C*- and *O*-alkyl derivatives of ascorbic acid has been the focus of many investigations. Jackson and Jones[3] were the first to report alkylation of sodium ascorbate with benzyl chloride to afford a mixture of C-2 and O-3 benzylated products. Poss and Belter[4] obtained C-2 allylated derivatives by treating potassium ascorbate with various allylic bromides. Reaction of ascorbic acid with various Michael acceptors has been extensively studied[5a−h] as a means of generating C-2 alkylated analogues, with α,*β*-unsaturated carbonyl compounds undergoing conjugate addition and 1,4-dialdehydes and 4-keto aldehydes giving aldol-derived products. Addition of ascorbate anion to protonated quinone methides, generated from *p*-hydroxybenzyl alcohols, was elegantly employed to synthesize a number of sugar-derived natural products.[6] Moreno-Manas and co-workers[7] developed a palladium-catalyzed methodology for the C-2 allylation of 5,6-*O*-isopropylidene-L-ascorbic acid.

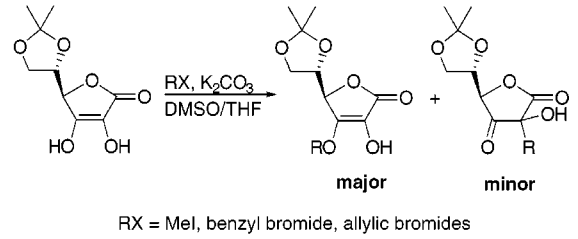
As for selective O-alkylation of ascorbic acid, there are few reports in the literature. Szarek and Kim[8] obtained only 3-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-L-ascorbic acid, though in very low yield, by treating ascorbate anion with the corresponding glycosyl bromide. In an attempt to develop clinically useful scavengers of active oxygen species, Nihro and co-workers[2b] prepared a series of 3-*O*-alkyl analogues by regioselective alkylation of 5,6-*O*-isopropylidene-L-ascorbic acid, as summarized in Scheme 1. Recently, 5,6-*O*-isopropylidene-L-ascorbic acid was also alkylated using various alkyl halides and bases to give both 3-O and 2-C substituted products[9] (Scheme 2). In light of the medicinal importance of 3-*O*-alkyl analogues, we decided to investigate a shorter and more general route to these derivatives. In this paper, we report a Mitsunobu reaction[10]-based methodology that delivers a wide range of 3-O substituted analogues in good yields and with complete regio- and chemoselectivity[11] (Scheme 3).

Scheme 1[a]



[a] See ref 2b.

Scheme 2[a]



[a] See ref 9a.

Our one-step protocol offers a number of advantages over the existing methods. First, one does not need to protect[2b,9] OH-5 and OH-6, thereby eliminating two steps. The procedure employs readily available alcohols as alkylating agents, as opposed to alkyl halides[2b,9] that may not be commercially available. Finally, the reaction proceeds under mild, essentially neutral conditions.

As shown in Scheme 3, the method consists of treating the preformed adduct[12] of Ph_3P and diethyl azodicarboxylate (DEAD) in THF, at −78 °C, with a solution of ascorbic acid in DMF to give presumably the phosphonium intermediate **1**, which was then reacted with an alcohol to provide the 3-*O*-alkyl derivative **2** as the only product[13] (63−77% isolated yield). Five different alcohols,

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(12) Preformation of the Ph_3P−DEAD adduct is essential for the success of this reaction. The standard sequence of reagent additions led to a number of products.

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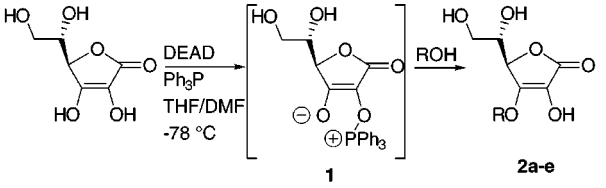
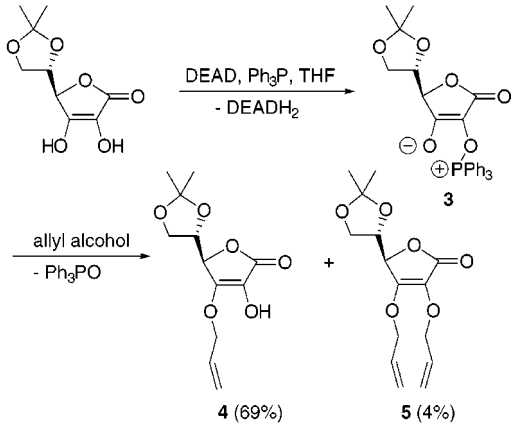
Scheme 3



R	Yield
Me (**2a**)	77%
propyl (**2b**)	63
octyl (**2c**)	72
allyl (**2d**)	72
benzyl (**2e**)	64

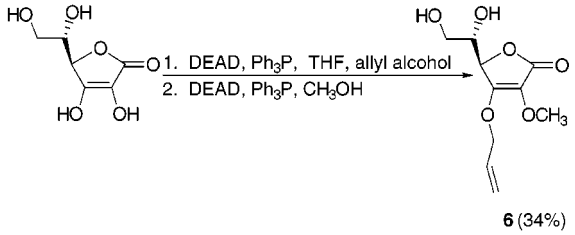
Scheme 4



namely, methyl alcohol, propyl alcohol, octyl alcohol, allyl alcohol, and benzyl alcohol, were employed as alkylating agents. In all of the cases, we saw only one spot on TLC, besides a light spot at the baseline (most probably for the unreacted ascorbic acid). While 3-*O*-methyl-L-ascorbic acid (**2a**) was characterized by comparing its melting point, specific rotation, IR, UV, and ^{1}H and ^{13}C NMR spectral data with the literature values,[14,15] the structures of products **2b**−**e** (R = propyl, octyl, allyl, benzyl) were assigned on the basis of their ^{1}H and ^{13}C NMR spectra. We hypothesized the intermediacy of the phosphonium species **1** in the above reaction in analogy with the intermediate **3** (see below).

Reaction of 5,6-*O*-isopropylidene-L-ascorbic acid[16] with 1 equiv of the Ph_3P−DEAD adduct (also called the Mitsunobu betaine) led to an intermediate which was, in this case, stable enough to be observed on TLC. Subsequent addition of allyl alcohol to the reaction mixture gave the monoallyl derivative **4** in 69% yield, along with the disubstituted product **5** (4%) (Scheme 4). Using a slight excess of the betaine (1.25 equiv), we were able to obtain **4** in 79% yield. The intermediate formed above was isolated by simply removing the solvent under anhydrous conditions and is proposed to have the structure **3** on the basis of its ^{1}H, ^{31}P, and ^{13}C NMR data. The

Scheme 5



signal for H-4 which appeared as a doublet of doublets (J = 5.0, 1.0 Hz) at δ 4.03 simplified to a doublet (J = 5.0 Hz) in a ^{31}P-decoupled spectrum. Moreover, ionization of OH-3 was evident from the upfield shift[15] (0.4 ppm) of H-4, relative to the starting 5,6-*O*-isopropylidene-L-ascorbic acid. The ^{31}P NMR spectrum showed a signal at δ 67.35, suggesting a phosphonium species.[17] In addition, there were two small peaks at δ 29.70 and −5.36, which corresponded to Ph_3PO (presumably formed from the hydrolysis of the phosphonium intermediate or betaine) and the unreacted Ph_3P, respectively. Finally, unequivocal support for the assigned structure was provided by its ^{13}C NMR data. Appearance of C-3 at δ 170.8 confirmed the structure as **3** in light of the fact that C-3 of L-ascorbic acid moves downfield with an increase in pH[15] (δ 156.4 at pH 2 → δ 176.2 at pH 7). While C-2 appeared as a doublet ($J_{P,C}$ = 9.8 Hz) at δ 110.4, the doublets for C-1 and C-3 at δ 176.1 and 170.8, respectively, displayed significantly lower coupling constants (1.7 and 1.6 Hz). The presence of a doublet at δ 120.0 (J = 107.0 Hz) corresponding to the aromatic C-1 further established the intermediate **3** to be a triphenylphosphonium derivative. As expected, these signals collapsed to singlets in a ^{31}P-decoupled spectrum.

We also employed this alkylation strategy to prepare 3-*O*-allyl-2-*O*-methyl-L-ascorbic acid (**6**) in one pot. Thus, reaction of ascorbic acid with preformed Mitsunobu betaine and allyl alcohol gave the 3-*O*-allyl derivative, which was then treated with another equivalent of Ph_3P and DEAD in the presence of methanol to afford the disubstituted product **6** in 34% overall yield (Scheme 5). That the alkylation took place at OH-2 and OH-3, not at OH-5 and OH-6, was confirmed by the in situ derivatization of **6** with trichloroacetyl isocyanate. The ^{1}H NMR spectrum recorded in $CDCl_3$ following the addition of trichloroacetyl isocyanate displayed the expected downfield-shifted signals for H-5, H-6a, and H-6b at δ 5.48, 4.61, and 4.53, respectively.

In summary, we have developed a novel methodology for the preparation of 3-*O*-alkyl derivatives of L-ascorbic acid, employing Mitsunobu conditions. This one-step procedure provides access to these biologically important analogues in good yields and with complete regio- and chemoselectivity. Furthermore, this method can be utilized to obtain differentially alkylated 2,3-*O*-disubstituted derivatives in one-pot fashion via two successive Mitsunobu alkylations.

Experimental Section

3-*O*-Methyl-L-ascorbic Acid (2a). To a stirred solution of Ph_3P (590 mg, 2.25 mmol) in dry THF (10 mL) at −78 °C was added dropwise DEAD (0.35 mL, 2.22 mmol). After ∼15 min at −78 °C, a white solid (Mitsunobu betaine) was formed. Stirring was continued at −78 °C for an additional 10 min. Then a solution of L-ascorbic acid (348 mg, 1.98 mmol) in DMF (10 mL + 2 mL for rinsing) was added through a cannula to the above

(13) An attempt to identify specific byproducts from the crude product **2d** (reaction using allyl alcohol) by ^{1}H NMR failed because all species were formed in yields less than 5%.

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mixture at −78 °C. The cooling bath was removed. After all of the solid had dissolved (∼5 min), CH_3OH (0.1 mL, 2.49 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2 h. TLC (10:1 CH_2Cl_2−CH_3OH) showed a single spot. The solvents were removed under reduced pressure. The resulting oil was flash-chromatographed (20:1 and 15:1 CH_2Cl_2−CH_3OH) to give **2a** as a white solid (290 mg, 77%): mp 124−126 °C (lit.[14] 121−122 °C); $[\alpha]_D$ +24.3° (*c* 1.1, water) (lit.[14] +28.9°); IR υ_{max} 3348, 3153, 1742, 1687 cm^{-1}; UV (CH_3OH) λ_{max} 244 nm, ϵ 10 689 (lit.[14] 245 nm, ϵ 13 050); ^1H NMR (360 MHz, CD_3OD) δ 4.76 (d, 1H, J = 2.0 Hz), 4.17 (s, 3H), 3.83 (ddd, 1H, J = 7.5, 6.5, 2.0 Hz), 3.68−3.59 (m, 2H); ^{13}C NMR[15] (75.5 MHz, CD_3OD) δ 173.1, 152.8, 121.0, 76.6, 70.5, 63.4, 59.7. Anal. Calcd for $C_7H_{10}O_6$: C, 44.22; H, 5.3. Found C, 44.17; H, 5.24.

3-*O*-Propyl-L-ascorbic Acid (2b). Ph_3P (687 mg, 2.62 mmol), DEAD (0.4 mL, 2.54 mmol), L-ascorbic acid (352 mg, 2.0 mmol), and propanol (0.2 mL, 2.66 mmol) were reacted as described above (preparation of **2a**). Stirring was continued overnight. Flash chromatography (20:1 CH_2Cl_2−CH_3OH) gave **2b** (273 mg, 63%): ^1H NMR (360 MHz, CD_3OD) δ 4.76 (d, 1H, J = 2.0 Hz), 4.51−4.38 (m, 2H), 3.84 (ddd, 1H, J = 7.5, 6.5, 2.0 Hz), 3.65 (d, 2H, J = 7 Hz), 1.81−1.70 (m, 2H), 0.99 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 173.2, 152.3, 120.4, 76.6, 74.1, 70.6, 63.5, 24.1, 10.3; HRMS calcd for $C_9H_{14}O_6Na$ $(M + Na)^+$ 241.0688, found 241.0691.

3-*O*-Octyl-L-ascorbic Acid (2c). Ph_3P (688 mg, 2.62 mmol), DEAD (0.4 mL, 2.54 mmol), L-ascorbic acid (352 mg, 2.0 mmol), and octanol (0.4 mL, 2.54 mmol) were reacted as described above (preparation of **2a**). Stirring was continued overnight. Flash chromatography (25:1 CH_2Cl_2−CH_3OH) gave **2c** (416 mg, 72%): mp 71−73 °C (lit.[2b] 58−60 °C); ^1H NMR (360 MHz, CD_3OD) δ 4.76 (d, 1H, J = 2.0 Hz), 4.55−4.41 (m, 2H), 3.83 (ddd, 1H, J = 7.5, 6.5, 2.0 Hz), 3.69−3.60 (m, 2H), 1.79−1.69 (m, 2H), 1.47−1.25 (m, 10 H), 0.90 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 173.3, 152.3, 120.5, 76.7, 72.7, 70.6, 63.5, 33.0, 30.9, 30.4, 30.3, 26.6, 23.7, 14.4; HRMS calcd for $C_{14}H_{25}O_6$ $(M + H^+)$ 289.1651, found 289.1640.

3-*O*-Allyl-L-ascorbic Acid (2d). Ph_3P (680 mg, 2.59 mmol), DEAD (0.4 mL, 2.54 mmol), L-ascorbic acid (353 mg, 2.0 mmol), and allyl alcohol (0.2 mL, 2.94 mmol) were reacted as described above (preparation of **2a**). Stirring was continued overnight. Flash chromatography (20:1 CH_2Cl_2−CH_3OH) gave **2d** (312 mg, 72%): ^1H NMR (360 MHz, CD_3OD) δ 6.05 (dddd, 1H, J = 17.0, 10.5, 6.0, 6.0 Hz), 5.40 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.26 (dddd, 1H, J = 10.5, 1.3, 1.3, 1.3 Hz), 5.01 (dddd, 1H, J = 13.0, 6.0, 1.5, 1.5 Hz), 4.94 (dddd, 1H, J = 13.0, 6.0, 1.5, 1.5 Hz), 4.79 (d, 1H, J = 2.0 Hz), 3.85 (ddd, 1H, J = 7.5, 6.5, 2.0 Hz), 3.70−3.60 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 173.0, 151.6, 134.3, 120.9, 118.7, 76.7, 72.9, 70.6, 63.5; HRMS calcd for $C_9H_{12}O_6Na$ $(M + Na^+)$ 239.0532, found 239.0538.

3-*O*-Benzyl-L-ascorbic Acid (2e). Ph_3P (685 mg, 2.61 mmol), DEAD (0.4 mL, 2.54 mmol), L-ascorbic acid (352 mg, 2.0 mmol), and benzyl alcohol (0.25 mL, 2.42 mmol) were reacted as described above (preparation of **2a**). Stirring was continued overnight. Flash chromatography (20:1 CH_2Cl_2−CH_3OH) gave **2e** (338 mg, 64%): ^1H NMR (360 MHz, CD_3OD) δ 7.46−7.29 (m, 5H), 5.57 (d, 1H, J = 12.0 Hz), 5.47 (d, 1H, J = 12.0 Hz), 4.79 (d, 1H, J = 2.0 Hz), 3.86 (ddd, 1H, J = 7.5, 6.5, 2.0 Hz), 3.69−3.60 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 173.0, 151.7, 137.9, 129.5, 129.4, 129.1, 121.3, 76.8, 74.0, 70.6, 63.5; HRMS calcd for $C_{13}H_{14}O_6Na$ $(M + Na^+)$ 289.0688, found 289.0684.

Phosphonium Intermediate 3. To a stirred solution of Ph_3P (182 mg, 0.694 mmol) in dry THF (2 mL) at room temperature was added dropwise DEAD (0.1 mL, 0.635 mmol). The resulting light yellow solution was stirred for 10 min, and then a solution of 5,6-*O*-isopropylidene-L-ascorbic acid[16] (128 mg, 0.592 mmol) in dry THF (3 mL + 1 mL for rinsing) was added dropwise through a cannula. TLC (10:1 CH_2Cl_2−CH_3OH) after 5 min showed a UV-active spot that also charred with 5% H_2SO_4 (in EtOH). An aliquot (∼1 mL) of the reaction solution was evaporated on vacuum pump. The white foamy solid thus obtained was further dried for 5 h. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00−7.20 (aromatic), 4.40 (d, ∼0.15H, J = 4.5 Hz, starting material's H-4), 4.03 (dd, 1H, J = 5.0, 1.0 Hz, H-4), 4.02−3.87 (m, 3H, H-5, H-6a, H-6b), 1.33 and 1.27 (2 small s, starting material's acetal methyls), 1.22 (6H, acetal methyls) ($DEADH_2$ and THF signals not listed); ^{31}P NMR (162 MHz, $CDCl_3$) δ +67.35 (alkoxyphosphonium[17]), +29.70 (Ph_3PO, formed from the hydrolysis of the phosphonium intermediate or betaine), −5.36 (unreacted Ph_3P); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.1 (C-1, J = 1.7 Hz), 170.8 (C-3, J = 1.6 Hz), 135.6 (aromatic C-4, J = 2.9 Hz), 134.1 (aromatic C-2, J = 11.7 Hz), 129.5 (aromatic C-3, J = 13.7 Hz), 120.0 (aromatic C-1, J = 107.0 Hz), 110.4 (C-2, J = 9.8 Hz), 109.03 (acetal quarternary) 78.4, 75.5 (C-4, C-5), 65.3 (C-6), 26.1, 25.7 (acetal methyls) (signals from Ph_3P, Ph_3PO, $DEADH_2$, and THF not listed). These assignments were made on the basis of ^{13}C APT experiments with and without ^{31}P decoupling.

3-*O*-Allyl-5,6-*O*-isopropylidene-L-ascorbic Acid (4) and 2,3-di-*O*-Allyl-5,6-*O*-isopropylidene-L-ascorbic Acid (5). To a stirred solution of Ph_3P (345 mg, 1.32 mmol) in dry THF (10 mL) at room temperature was added dropwise DEAD (0.2 mL, 1.27 mmol). Then 5,6-*O*-isopropylidene-L-ascorbic acid (269 mg, 1.24 mmol) was added in one portion. After ∼5 min, the mixture was treated with allyl alcohol (0.2 mL, 2.94 mmol) and stirred overnight. TLC (10:1 CH_2Cl_2−CH_3OH) showed two new spots, besides a light spot corresponding to the unreacted starting matrial. The solvents were removed under reduced pressure. The resulting oil was flash-chromatographed (4:1 pentane−EtOAc) to give **5**[9a] (13 mg, 4%): ^1H NMR (360 MHz, $CDCl_3$) δ 6.01−5.89 (m, 2H), 5.39−5.22 (m, 4H), 4.91 (ddd, 2H, J = 5.5, 1.5, 1.5 Hz), 4.62 (dddd, 1H, J = 12.0, 6.0, 1.3, 1.3 Hz)), 4.56 (dddd, 1H, J = 12.0, 6.0, 1.3, 1.3 Hz), 4.51 (d, 1H, J = 3.5 Hz), 4.26 (ddd, 1H, J = 6.5, 6.5, 3.5 Hz), 4.11 (dd, 1H, J = 8.5, 6.5 Hz), 4.01 (dd, 1H, J = 8.5, 6.5 Hz), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.9, 155.8, 132.9, 131.9, 121.5, 119.2, 118.9, 110.4, 74.7, 74.0, 72.6, 72.4, 65.3, 25.9, 25.6.

Further elution with the same solvent system (4:1 pentane−EtOAc) provided **4**[9a] (218 mg, 69%): ^1H NMR (360 MHz, $CDCl_3$) δ 5.98 (dddd, 1H, J = 17.0, 10.5, 5.5, 5.5 Hz), 5.58 (br s, 1H), 5.39 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.29 (dddd, 1H, J = 10.5, 1.3, 1.3, 1.3 Hz), 4.99−4.89 (m, 2H), 4.55 (d, 1H, J = 4.0 Hz), 4.26 (ddd, 1H, J = 6.5, 6.5, 4.0 Hz), 4.12 (dd, 1H, J = 8.5, 6.5 Hz), 4.01 (dd, 1H, J = 8.5, 6.5 Hz), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.4, 148.8, 132.2, 119.4, 119.1, 110.4, 75.7, 74.3, 72.3, 65.3, 25.9, 25.6.

3-*O*-Allyl-2-*O*-methyl-L-ascorbic Acid (6). To a stirred solution of Ph_3P (683 mg, 2.60 mmol) in dry THF (10 mL) at −78 °C was added dropwise DEAD (0.4 mL, 2.54 mmol). After ∼15 min, a white solid (Mitsunobu betaine) was formed. Stirring was continued at −78 °C for an additional 10 min. Then a solution of L-ascorbic acid (353 mg, 2.0 mmol) in dry DMF (8 mL + 2 mL for rinsing) was added through a cannula. The cooling bath was removed. After all of the solid had dissolved (∼5 min), allyl alcohol (0.18 mL, 2.64 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. TLC (10:1 CH_2Cl_2−CH_3OH) showed a single spot corresponding to 3-*O*-allyl-L-ascorbic acid. To this reaction solution was then added Ph_3P (600 mg, 2.28 mmol). The mixture was cooled to −78 °C, and DEAD (0.35 mL, 2.22 mmol) was added dropwise. After 30 min at −78 °C, the reaction solution was treated with CH_3OH (0.2 mL, 4.93 mmol). The cooling bath was removed, and the mixture was stirred overnight at room temperature. TLC (10:1 CH_2Cl_2−CH_3OH) showed one major spot. The solvents were removed under reduced pressure. The resulting oil was flash-chromatographed (30:1 CH_2Cl_2−CH_3OH) to give **6** (158 mg, 34%): ^1H NMR (360 MHz, CD_3OD) δ 6.04 (dddd, 1H, J = 17.0, 11.0, 5.5, 5.5 Hz), 5.42 (dddd, 1H, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.30 (dddd, 1H, J = 11.0, 1.3, 1.3, 1.3 Hz), 5.02−4.90 (m, 2H), 4.85 (d, 1H, J = 1.5 Hz), 3.87 (ddd, 1H, J = 7.5, 6.5, 1.5 Hz), 3.78 (s, 3H), 3.69−3.60 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 172.0, 158.7, 133.6, 123.8, 118.8, 76.5, 73.3, 70.4, 63.2, 60.8; HRMS calcd for $C_{10}H_{14}O_6Na$ $(M + Na^+)$ 253.0688, found 253.0693.

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