Synthesis of a Glycosidic Precursor of Isomeric Marmelo Oxides, Volatile Components of Quince Fruit, *Cydonia oblonga*

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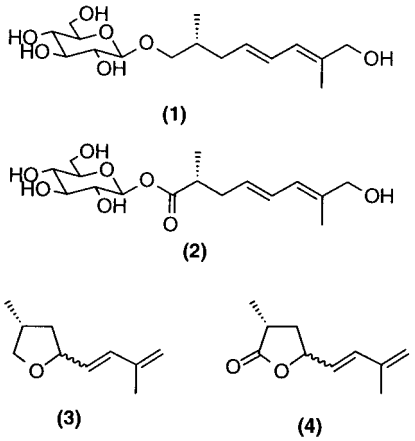
Synthesis of (*R*)-8-hydroxy-2,7-dimethyl-(4*E*,6*E*)-octadienyl β-D-glucopyranoside (**1**), a glycosidic precursor of marmelo oxides, the volatile components of quince fruit, *Cydonia oblonga* Mill., was achieved starting from (*S*)-3-hydroxy-2-methylpropanoate (**5**). The conjugated diene moiety was constructed in one step by a Horner reaction, and the final glycosidation was executed via the chloroimidate method.

In the past ten years an explosion of research activities in the study of the glycosidic precursors of flavor substances has produced a number of publications concerning the structures of these glycosides, their occurrence, and their role in the plant kingdom. Glycosides of more than 200 different aglycons, including structurally diverse terpenoids and nonterpenoids, have been characterized.[1−4] To have enough of these glycosides in essential-oil plants, to study their role they must be obtained in adequate amounts, and it is, thus, necessary to provide these amounts by chemical synthesis.

In 1991, Schreier and co-workers isolated glycosidic precursors **1**[5] and **2**[6] of marmelo oxides (**3**) and marmelo lactones (**4**), the key flavor of the quince fruit, *Cydonia oblonga* Mill. (Rosaceae)[7] (Scheme 1). At almost the same time, Näf and Velluz identified several acyclic precursors of these flavors in the hydrolyzate of the MeOH extract from the quince fruit.[8] In the case of the precursor **1** and marmelo oxide (**3**), the amount of natural product was rather small and prompted us to synthesize **1** in optically active form. We report herein the synthesis of (*R*)-8-hydroxy-2,7-dimethyl-(4*E*,6*E*)-octadienyl β-D-glucopyranoside (**1**) starting from readily available methyl (*S*)-3-hydroxy-2-methylpropanoate (**5**).[9]

The ester **5** was converted to a siloxyalcohol (**6**) in two steps, according to a known procedure.[10] Tosylation of **6** was followed by treatment with NaCN to give the nitrile **7** (85%). DIBAL reduction of **7** afforded the know aldehyde **8** (78%).[11] To introduce the conjugated diene moiety in one step, we decided to use a Horner-type reaction with the phosphonate **9**, which we had prepared for the synthesis of sirenin.[12] As it happened, reaction of the aldehyde **8** with the sodium salt of **9** in THF smoothly gave the product **10** as an (*E*/*Z*) mixture in a 2.5:1 ratio (85%). The ratio was improved to 10:1, however, by using lithiophosphonate (*n*-BuLi−THF) (53% yield). Finally, we achieved the ratio 8:1 and 98% yield by using lithium diisopropylamide in THF. Separation of the desired *trans*-isomer from the *cis*-isomer was much easier at the next step. DIBAL reduction of **10** at −78 °C and simple chromatography furnished pure dienol aglycon (**11**). Acetylation of **11** gave the acetate **12**, which was treated with tetrabutylammonium fluoride (TBAF) to give the diol monoacetate **13** the substrate for glycosylation.

Scheme 1



Initially we attempted modified Königs−Knorr-type glycosylation of **13** with 2,3,4,6-tetra-*O*-acetylglucosyl bromide in the presence of mercuric cyanide,[13] but the reaction product was a complex mixture, and we were unable to isolate the desired glycoside (**14**). It was postulated that the conjugated diene was destroyed under the procedure using mercuric ion. This result prompted us to employ Schmidt's glycosylation with trichloroacetimidate (**15**).[14] Treatment of the aglycon **13** with **15** in the presence of TMSOTf at low temperature afforded the expected glycoside **14** in 52% yield. Spectral data (^{1}H NMR, ^{13}C NMR) of synthetic **14** were entirely superimposable with those reported.[5] Finally transesterification of **14** with a catalytic amount of NaOMe in MeOH yielded the target glycoside **1** in 77% yield (Scheme 2).

In conclusion, the synthesis of (*R*)-8-hydroxy-2,7-dimethyl-(4*E*,6*E*)-octadienyl β-D-glucopyranoside (**1**), a glycosidic precursor of marmelo oxides, was completed in 13% overall yield through 11 steps from methyl (*R*)-2-hydroxypropanoate. As a substantial amount of the synthetic glycoside (**1**) is now available, we plan to study the chemical and physiological properties of **1**. The results of these studies will be reported in due course.

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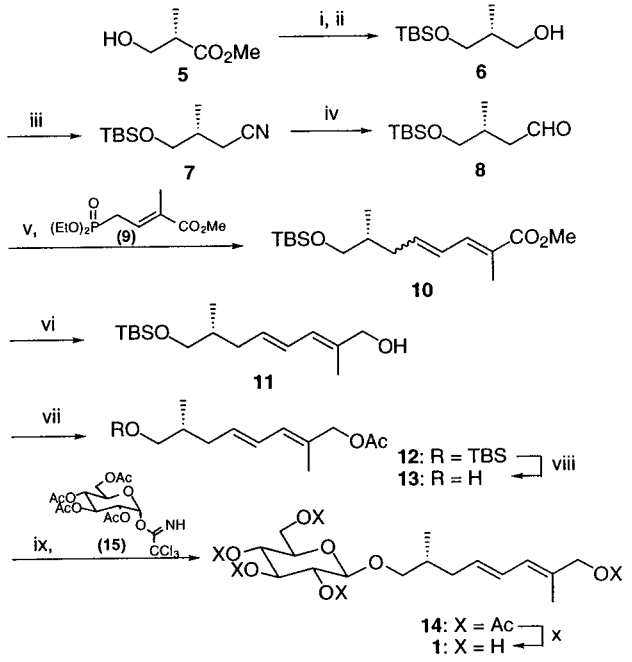
Scheme 2[a]



[a] Key: (i) TBSCl, $(i\text{-Pr})_2$NEt, CH_2Cl_2, rt; (ii) DIBAL, $PhCH_3$ 0 °C; (iii) TsCl, Py, 4 °C then NaCN, DMSO, rt; (iv) DIBAL, CH_2Cl_2, −30 °C; (v) **9**, LDA, THF; rt; (vi) DIBAL, $PhCH_3$ −78 °C then chromatography; (vii) Ac_2O, Py; (viii) TBAF, THF; (ix) **15**, TMSOTf, CH_2Cl_2, −78 °C; (x) NaOMe, MeOH.

Experimental Section

General Experimental Procedures. NMR spectra were recorded at 90 MHz on JEOL JMN-EX90 in $CDCl_3$ and 300 MHz on Bruker AC-300 in $CDCl_3$ or MeOH-d_4. IR spectra were measured as films on a JASCO A-102 spectrometer. HRMS measurements were performed on a JEOL JMS-SX102/SX102. Optical rotations were measured on a JASCO DIP 371 polarimeter. Merck Kieselgel 60 (Art. no. 7734) was used for column chromatography.

(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutanenitrile (7). To a solution of **6** (2.85 g, 1.88 mmol) in pyridine (12 mL) was added *p*-toluenesulfonyl chloride (4.62 g, 24.5 mmol), and the mixture was stirred for 12 h at 4 °C. The reaction mixture was poured into H_2O and extracted with ether. The organic layer was washed with saturated $CuSO_4$ solution, saturated $NaHCO_3$ solution, and brine; dried ($MgSO_4$), and concentrated *in vacuo*. To a solution of the residue in DMSO (30 mL) was added NaCN (1.84 g, 37.6 mmol), and the mixture was stirred for 3 h. The reaction mixture was poured into ice-cooled H_2O and extracted with ether. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by SiO_2 (20 g) chromatography [*n*-hexane−EtOAc (17:1)] to give 3.40 g (85%) of the nitrile **7** as a colorless oil: $[\alpha]^{19}_D$ +19.1° (*c* 1.04, $CHCl_3$); IR (film) ν_{max} 2956 (s), 2246 (m, −CN), 1471 (s), 1390 (m), 1255 (s), 1101 (s), 1032 (m), 839 (s), 777 (s) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.06 (6H, s, CH_3−Si), 0.90 (9H, s, *t*-Bu−Si), 1.04 (3H, d, J = 6.7 Hz, CH_3-3), 2.03 (1H, m, H-3), 2.29 (1H, dd, J = 6.9, 16.6 Hz, H-2a), 2.41 (1H, dd, J = 5.6, 16.6 Hz, H-2b), 3.37 (1H, dd, J = 7.3, 10.0 Hz, H-4a), 3.55 (1H, dd, J = 4.6, 10.0 Hz); *anal.* C 61.75%, H 10.87%, N 6.61%; calcd for $C_{11}H_{23}ON$, C 61.91%, H 10.86%, N 6.56%.

(*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutan-1-al (8). To a solution of **7** (10.32 g, 1.49 mmol) in CH_2Cl_2 (25 mL) was added dropwise DIBAL (1.01 M in toluene 1.62 mL) at −78 °C under Ar. The mixture was stirred at −30 °C for 4 h. The reaction mixture was quenched with saturated NH_4Cl solution, acidified to pH 3 with 5% H_2SO_4 to hydrolize imine complex, neutralized with saturated $NaHCO_3$ solution, and extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by SiO_2 (8.4 g) chromatography [*n*-hexane−EtOAc (20:1)] to give 0.25 g (77.7%) of the aldehyde **8** as a colorless oil: $[\alpha]^{18}_D$ +10.7° (*c* 2.04, $CHCl_3$); IR (film) ν_{max} 2956 (s), 2713 (m, CHO), 1727 (s, CHO), 1471 (m), 1388 (m), 1255 (s), 1095 (s), 837 (s), 777 (s) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.04 (6H, s, CH_3−Si), 0.88 (9H, s, *t*-Bu−Si), 0.97 (3H, d, J = 6.6, CH_3-3), 2.18 (1H, ddd, J = 2.2, 6.9, 9.6 Hz, H-2a), 2.23 (1H, m, H-3), 2.48 (1H, ddd, J = 2.2, 3.0, 9.6 Hz, H-2b), 3.34 (1H, ddd, J = 7.2, 9.8 Hz, H-4a), 3.53 (1H, dd, J = 4.7, 9.8 Hz, H-4b), 9.75 (1H, t, J = 2.2 Hz, H-1); *anal.* C 60.80%, H 11.09%; calcd for $C_{11}H_{24}O_2$, C 61.06%, H 11.18%.

(*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,7-dimethyl-(2*E*,4*E*)-octandien-1-ol (11). Procedure A: NaH as the base: To a suspension of NaH (60% in mineral oil, 120 mg, 3.0 mmol) in THF (7 mL) was added a solution of **9** (0.578 g, 2.3 mmol) in THF (8 mL) with ice-cooling under Ar. The mixture was further stirred for 2.5 h at room temperature. To this was added a solution of **8** (0.25 g, 1.2 mmol) in THF below −10 °C. The mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with H_2O, and the mixture was extracted with ether. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by SiO_2 (15 g) chromatography [*n*-hexane−EtOAc (20:1)] to give 0.31 g (85%) of (*E*/*Z*) mixture [(E/Z) = 2.5:1].

Procedure B: *n*-BuLi as the base: To a solution of **9** (3.9 g, 15.6 mmol) in THF (30 mL) was added a solution of *n*-BuLi (1.59 M, 9.28 mL) in THF (70 mL) with ice-cooling under Ar. The mixture was stirred for 3 h at room temperature. To this was added a solution of **8** (1.98 g, 9.25 mmol) in THF (50 mL) below −10 °C. The mixture was stirred at room temperature for 3.5 h. The reaction mixture was poured into H_2O and extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by SiO_2 (150 g) chromatography [*n*-hexane−EtOAc (22:1)] to give 2.29 g (53%) of (*E*/*Z*) mixture [(E/Z) = 10:1].

Procedure C: Lithium diisopropylamide as the base: To a solution of **9** (4.5 g, 18 mmol) in THF (50 mL) was added a solution of lithium diisopropylamide (0.44 M, 38.3 mL) in THF (25 mL) at −78 °C under Ar. The mixture was stirred for 1 h at room temperature. To this was added a solution of **8** (2.8 g, 12.9 mmol) in THF (50 mL) at −78 °C. The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was

purified by SiO_2 (160 g) chromatography [*n*-hexane−EtOAc (22:1)] to give 3.99 g (98%) of (*E*/*Z*) mixture [(E/Z) = 8:1].

To a solution of this (1.72 g, 5.50 mmol) in toluene (70 mL) was added dropwise DIBAL (1.99 mL 1.01 M toluene solution) at −78 °C under Ar. The mixture was stirred at −78 °C for 2 h and quenched with MeOH. After temperature was raised to 0 °C, Rochelle salt solution was added, and the mixture was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by SiO_2 (15 g) chromatography [*n*-hexane−EtOAc (20:1)] to give 1.26 g (80%) of **11** as a colorless oil: $[\alpha]^{27}_D$ +4.58° (*c* 2.30, $CHCl_3$); IR(film) ν_{max} 3324 (br s, OH), 3035 (w), 2955 (s), 1660 (w), 1625 (w), 1471 (m), 1388 (m), 1254 (m), 1097 (s), 1007 (m), 969 (m), 837 (s), 775 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (6H, s, CH_3−Si), 0.88 (3H, d, J = 6.7 Hz, CH_3-7), 0.90 (9H, s, *t*-Bu−Si), 1.32 (1H, t, J = 5.8 Hz, −OH), 1.70 (1H, m, H-7), 1.78 (3H, s, CH_3-2), 1.90 (1H, dt, 7.5, 13.9 Hz, H-6a), 2.23 (1 H, dt, J = 6.5, 13.9 Hz, H-6b), 3.42 (2H, d, J = 6.1 Hz, H-8), 4.05 (2H, d, J = 5.8 Hz, H-1), 5.68 (1H, dt, J = 7.5, 14.9 Hz, H-5), 6.03 (1H, d, J = 10.5 Hz, H-3), 6.25 (1H, dd, J = 10.5, 14.9 Hz, H-4); *anal*. C 67.22%, H 11.30%; calcd for $C_{16}H_{32}O_2Si$, C 67.55%, H 11.34%.

(*R*)-2,7-Dimethyl-8-[(*tert*-butyldimethylsilyl)oxy]-(2*E*,4*E*)-octadienyl Acetate (12). To a solution of **11** (0.14 g, 0.492 mmol) in pyridine (3 mL) was added dropwise Ac_2O (2 mL) with ice cooling. After stirring for 3 h at room temperature, the reaction mixture was poured into cold H_2O and extracted with ether. The combined organic layer was washed with saturated $CuSO_4$ solution, saturated $NaHCO_3$ solution, and brine; dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (5 g) [*n*-hexane−EtOAc (17:1)] to give 0.161 g (quant.) of the acetate **12** as a colorless oil: $[\alpha]^{19}_D$ +4.3° (*c* 0.50, $CHCl_3$; IR-(film) ν_{max} 2955 (s), 1744 (s, acetate), 1660 (w), 1623 (w), 1471 (m), 1374 (m), 1227 (s), 1095 (s), 1021 (m), 967 (m), 837 (s), 776 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (6H, s, CH_3−Si), 0.87 (3H, d, J = 6.7 Hz, CH_3-7), 0.90 (9H, s, *t*-Bu−Si), 1.68 (1H, m, H-7), 1.70 (3H, s, CH_3-2), 1.91 (1H, dt, J = 7.5, 13.9 Hz, H-6a), 2.08 (3H, s, acetyl), 2.25 (1H, dt, J = 6.8, 13.9 Hz, H-6b), 3.51 (2H, d, J = 6.0 Hz, H-8), 4.50 (2H, s, H-1), 5.71 (1H, dt, J = 8.3, 12.7 Hz, H-5), 6.04 (1H, d, J = 10.9 Hz, H-3), 6.23 (1H, dd, J = 10.9, 12.7 Hz, H-4); *anal*. C 66.05%, H 10.40%; calcd for $C_{18}H_{34}O_3Si$, C 66.21%, H 10.49%.

(*R*)-8-Hydroxy-2,7-dimethyl-(2*E*,4*E*)-octadienyl Acetate (13). To a solution of **12** (0.604 g, 1.85 mmol) in THF (5 mL) was added a solution of TBAF (1.34 mL, d = 0.903 THF solution, 4.63 mmol) below 0 °C. After warming to room temperature, the mixture was poured into H_2O and extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (6.7 g) [*n*-hexane−EtOAc (10:1)] to give 0.391 g (quant.) of **13** as a colorless oil: $[\alpha]^{21}_D$ +3.9° (*c* 2.05, $CHCl_3$); IR (film) ν_{max} 3419 (br s, OH), 3035 (w), 3025 (m), 2958 (s), 1739 (s, acetate), 1455 (m), 1375 (m), 1236 (s), 1024 (s), 970 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, d, J = 6.9 Hz, CH_3-7), 1.73 (1H, m, H-7), 1.77 (3H, s, CH_3-2), 2.00 (1H, dt, J = 7.3, 14.1 Hz, H-6a), 2.08 (3H, s, CH_3−acetyl), 2.25 (1H, dt, J = 7.0, 14.1 Hz, H-6b), 3.49 (2H, qui, J = 5.3 Hz, H-8), 4.50 (2H, s, H-1), 5.73 (1H, dt, J = 7.5, 15.0 Hz, H-5), 6.04 (1H, d, J = 10.9 Hz, H-3), 6.27 (1H, dd, J = 10.9, 15.0 Hz, H-4); *anal*. C 67.89%, H 9.50%; calcd for $C_{12}H_{20}O_3$, C 67.78%, H 9.47%.

(*R*)-8-Acetoxy-2,7-dimethyl-(4*E*,6*E*)-octadienyl 2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranoside (14). To a solution of **13** (0.1 g, 0.471 mmol) and *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)trichloroacetoimidate (**15**) (0.8 g, 1.602 mmol) with molecular sieves AW 300 (0.5 g), in CH_2Cl_2 (9 mL) was added dropwise TMSOTf (16.5 μL, d = 1.23, 4.51 mmol) at −78 °C under Ar. After 3 h stirring at −78 °C, triethylamine was added, and the mixture was allowed to stand at ambient temperature. The reaction mixture was filtered. The filtrate was diluted with H_2O and extracted with ether. The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (40 g) [*n*-hexane−ether (6:1)] to give 0.135 g (53%, 0.289 mmol) of **14** as a viscous, colorless oil: $[\alpha]^{23}_D$ −6.6° (*c* 1.15, $CHCl_3$); IR (film) ν_{max} 3030 (w), 2959 (m), 1757 (s, acetate), 1434 (w), 1372 (m), 1227 (s), 1173 (m), 1039 (s), 980 (w), 906 (w), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 6.7 Hz), 1.61 (3 H, s, CH_3-7), 1.77−2.24 (18H, H-2, H-3, and 5 acetates), 3.28 (1H, dd, J = 7.0, 9.5 Hz, H-1a), 3.69 (1H, ddd, J = 2.3, 4.6, 12.2 Hz, H-5′), 3.72 (1H, dd, J = 5.9, 9.5 Hz, H-1b), 4.14 (1H, dd, J = 2.3, 12.2 Hz, H-6′a), 4.26 (1H, dd, J = 4.6, 12.2 Hz, H-6′b), 4.46 (1H, d, J = 8.0 Hz, H-1′), 4.50 (2H, s, H-8), 4.98−5.23 (3H, H-2′, H-3′, and H-4′), 5.68 (1H, dt, J = 7.3, 14.9 Hz, H-4), 6.03 (1H, d, J = 10.7 Hz, H-6), 6.23 (1H, dd, J = 10.7, 14.9 Hz, H-5); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.3, 16.1, 20.5−20.8, 33.4, 36.4, 61.9, 68.4, 69.8, 71.3, 71.7, 72.7, 74.5, 101.0, 127.4, 128.1, 130.0, 133.13, 169.1, 169.6, 170.0, 170.5, 171.0; *anal*. C 57.56%, H 7.06%; calcd for $C_{26}H_{38}O_{12}$, C 57.42%, H 7.06%.

(*R*)-8-Hydroxy-2,7-dimethyl-(4*E*,6*E*)-octadienyl β-D-Glucopyranoside (1). To a solution of **16** (0.0152 g, 0.028 mmol) in MeOH (0.5 mL) was added sodium methoxide (0.45 mg, 0.008 mmol) with ice-cooling. After stirring 17 h, Amberlyst (0.06 g) was added and filtered. The residue was concentrated *in vacuo* to give 0.0072 g (77.4% 0.0217 mmol) of **1** as a highly viscous and slightly yellow oil: $[\alpha]^{21}_D$ −15.5° (*c* 0.31, CH_3OH); IR (film) ν_{max} 3390 (br s, OH), 2875 (s), 1633 (m), 1454 (m), 1379 (m), 1260 (m), 1165 (m), 1032 (s), 893 (m) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.81 (3H, d, J = 6.7 Hz, CH_3-2), 1.17 (1H, −OH), 1.64 (3H, s, CH_3-7), 1.75 (1H, m, H-2), 1.91 (1H, dt, J = 7.3, 15.4 Hz, H-3a), 2.20 (1H, dt, J = 7.3, 13.4 Hz, H-3b), 3.04−3.29 (4H, H-1a, H-5′, H-6′), 3.54−3.62 (3H, H-2′, H-3′, and H-4′), 3.74 (1H, dd, J = 1.6, 12.3 Hz, H-1b), 3.85 (2H, s, H-8), 4.11 (1H, d, J = 7.7 Hz, H-1′), 5.58 (1H, dt, J = 7.3, 14.7 Hz, H-4), 5.90 (1H, d, J= 10.8 Hz, H-6), 6.20 (1H, dd, J = 10.8, 14.7 Hz, H-5); ^{13}C NMR (300 MHz, CD_3OD) δ 14.2, 17.0, 35.1, 37.9, 62.8, 71.7, 75.2, 75.7, 77.9, 78.1, 104.7, 126.1, 129.0, 133.2, 136.1; HRFABMS *m*/*z* 332.1807 [M^+] (calcd for $C_{16}H_{28}O_7$, 332.1835).

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