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A PRACTICAL SYNTHESIS OF A HYDROXYLATED SESQUITERPENE COUMARIN 10'*R*-ACETOXY-11'-HYDROXYUMBELLIPRENIN BY REGIOSELECTIVE DIHYDROXYLATION

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Abstract – A practical synthesis of 10'*R*-acetoxy-11'-hydroxyumbelliprenin was achieved using regioselective Sharpless asymmetric dihydroxylation as a key reaction, in which the regioselectivity was achieved by using $(DHQD)_2AQN$ as a ligand instead of the conventional $(DHQD)_2PHAL$. 10'*R*-Acetoxy-11'-hydroxyumbelliprenin was synthesized by the coupling of a coumarin unit (umbelliferone) and sesquiterpene unit in 11% overall yield through 5 steps.

Sesquiterpene coumarins isolated from *Ferula*, *Heptaptera*, *Heraclum*, *Peucedanum*, *Angelica* (Apiaceae), *Artemisia* (Asteraceae), and *Haplophyllum* (Rutaceae) have attracted attention due to anti-inflammatory, cytotoxic, cancer chemopreventative, and antibacterial activities.[1,2] More than 230 natural products including over 120 sesquiterpene coumarins have been reported from the genus *Ferula*. 10'*R*-Acetoxy-11'-hydroxyumbelliprenin (**1**, Figure 1) is a new sesquiterpene coumarin isolated from a $CHCl_3$-soluble extract of *Ferula assa-foetida* through bioassay-guided fractionation in 2009 by Lee et al.[3] Compound **1** has one acetoxy group at C-10', one hydroxy group at C-11', and two double bonds at C-2' and C-6' of the sesquiterpene part connected to 7-hydroxycoumarin. The absolute configuration of **1** was established as *R* by the derivatization to the MTPA ester combined with specific rotation. In an *in vitro* anti-influenza A viral (H_1N_1) assay, **1** showed a similar potency to the positive control, amantadine;[3] the IC_{50} (μg/mL) of **1** is 0.94±0.07 and that of amantadine is 0.92±0.04. Synthesis of **1** has not been reported

to date, although the related sesquiterpene coumarin, karatavicinol (**2**, Figure 1), was synthesized using an enzymatic resolution by Faber et al.[4] In the course of studying anti-virus agents, we became interested in this class of compounds. Herein we report a practical asymmetric synthesis of **1** using regioselective Sharpless asymmetric dihydroxylation.

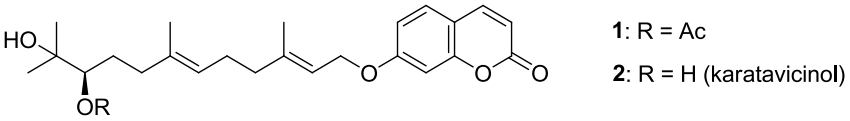
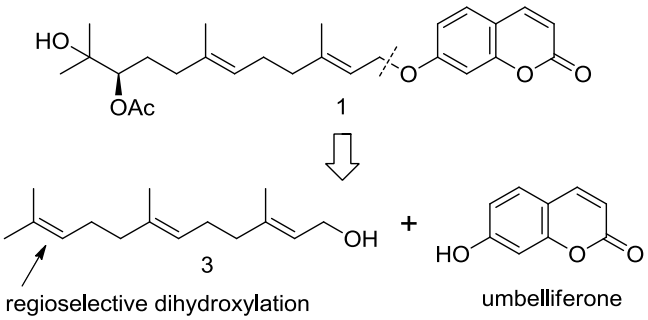


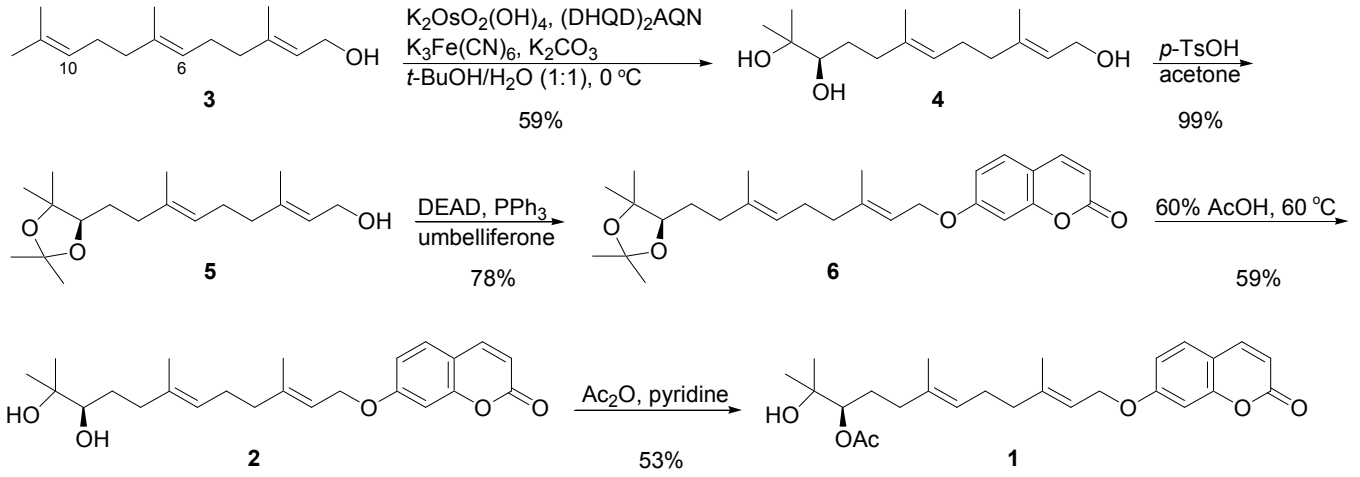
Figure 1. The structure of 10'*R*-acetoxy-11'-hydroxyumbelliprenin (**1**).

Our synthetic plan is outlined in Scheme 1. Compound **1** is constructed by the coupling of a coumarin unit (umbelliferone) and sesquiterpene unit, which is prepared by single step stereoselective dihydroxylation of a commercially available *trans*,*trans*-farnesol (**3**).



Scheme 1. Synthetic route for **1**.

Synthesis of **1** according to the above plan is shown in Scheme 2. The regioselective asymmetric dihydroxylation of *trans*,*trans*-farnesol (**3**), a key step in the synthesis, was examined first.[5] No selectivity was observed resulting in an equal mixture of C-6 and C-10 isomers when the conventional ligand $(DHQD)_2PHAL$ was used in the Sharpless asymmetric dihydroxylation. The ratio of the isomers was estimated from the integration of C-6 and C-10 protons in ^1H NMR. Among the commercially available ligands, $(DHQD)_2AQN$[6] gave the best results; 2:1 ratio of the desired C-10 isomer **4** and undesired C-6 isomer. 1,4-Anthraquinone domain in $(DHQD)_2AQN$ might serve as an effective distance-critical spacer for this specific substrate as does the 1,4-dioxanaphthopyridazine domain in Corey's ligand for farnesyl acetate.[7] Since the separation of the isomer **4** was difficult, the enantiomeric excess of **4** could not be estimated at this stage.



Scheme 2. Synthesis of **1**.

After protection of the 1, 2-diol of **4**, the resulting primary alcohol of **5** was converted to bromide for the coupling to the coumarin unit. However, the product was a complex mixture and separation of the desired product was difficult. The conversion of the hydroxy group of **5** to the corresponding tosyl group gave similar results. Avoiding the separate step of activation, Mitsunobu reaction using the alcohol **5** and umbelliferone gave the desired product **6** with 78% yield. Treatment of **6** with 60% AcOH gave the desired diol **2**, although the deprotection of the acetonide with TFA gave a complex mixture. The crude product was purified by silica gel column chromatography to remove the concomitant C-6 isomer derived from the regioselective asymmetric dihydroxylation.[8] Mono-acetylation at the secondary hydroxy group of **2** with acetic anhydride-pyridine gave the desired product **1** with moderate yield. The spectroscopic data (^{1}H NMR, ^{13}C NMR, and MS) of the synthetic **1** all agreed with those of the natural product.[3] The optical purity of the synthetic **1** was confirmed by the comparison of specific rotation of the synthetic and the natural product; $[\alpha]^{25}_D$ +10.8 (*c* 0.2, $CHCl_3$) for **1** and $[\alpha]^{25}_D$ +11.2 (*c* 0.5, $CHCl_3$) for the natural product.[3] Thus, we have achieved a practical synthesis of 10'*R*-acetoxy-11'-hydroxyumbelliprenin (**1**) in 11% yield through 5 steps using an regioselective asymmetric dihydroxylation employing $(DHQD)_2AQN$ ligand as a key step. Using this straightforward synthetic route, the structure-activity relationship studies are now underway.

EXPERIMENTAL

General

^{1}H and ^{13}C NMR spectra were measured with a Bruker AM-300 FT-NMR spectrometer in $CDCl_3$ at 300 and 75 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hz. Mass spectra were obtained on JMS-SX 102A mass spectrometer. Optical rotations were determined with a HORIBA SEPA-300 polarimeter.

(2*E*,6*E*,10*R*)-3,7,11-Trimethyldodec-2,6-diene-1,10,11-triol (4). To a suspension of **3** (63.9 mg, 0.288 mmol) in *t*-BuOH/H_2O (1:1, 0.5 mL) were added $(DHQD)_2AQN$ (2.49 mg, 0.00291 mmol), $K_2OsO_2(OH)_4$ (0.44 mg, 0.0012 mmol) $K_3Fe(CN)_6$ (284 mg, 0.864 mmol), K_2CO_3 (119 mg, 0.864 mmol) in *t*-BuOH/H_2O (1:1, 0.5 mL) at 0 °C. The mixture was stirred for 12 h at the same temperature, and then the reaction was quenched with aqueous Na_2SO_3. The organic materials were extracted with EtOAc and washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to afford **4** and C-6 isomer (42.9 mg, 0.169 mmol) as a colorless oil. ^{1}H NMR δ: 5.45 (0.34H, dt, *J* = 6.8, 1.2 Hz), 5.37 (0.66H, dt, *J* = 6.7, 1.5 Hz), 5.17-5.09 (1H, m), 4.15-4.12 (2H, m), 3.40-3.33 (1H, m), 3.04 (2H, brs), 2.67 (1H, brs), 2.27, (0.34H, m), 2.20-2.05 (5.66H, m), 1.68 (1H, s), 1.64 (2H, s), 1.62 (1H, s), 1.60 (2H, s), 1.59-1.34 (3H, m), 1.17 (2H, s), 1.14 (2H, s), 1.11 (1H, s); HRFABMS calcd for $C_{15}H_{29}O_3$ $[M+H]^+$ 257.2117, found 257.2113.

(2*E*,6*E*,4'*R*)-(2',2',5'-Trimethyl-1',3'-oxolan-4'-yl)-3,7-dimethylnona-2,6-dien-1-ol (5). Compound **4** (42.9 mg, 0.169 mmol) was treated with acetone (2.0 mL) and catalytic amount of *p*-TsOH. The mixture was stirred for 2 h at room temperature, and then the reaction was quenched with saturated aqueous $NaHCO_3$. The organic materials were extracted with EtOAc and washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to afford **5** and C-6 isomer (49.7 mg, 0.168 mmol) as a colorless oil. ^{1}H NMR δ: 5.48-5.34 (1H, m), 5.17 (0.66H, m), 5.12-5.07 (0.34H, m), 4.17-4.14 (2H, m), 3.73 (0.34H, dd, *J* = 9.6, 2.8 Hz), 3.66 (0.66H, dd, *J* = 9.2, 3.6 Hz), 2.31-1.99 (5H, m), 1.70 (1H, s), 1.68 (2H, s), 1.62 (2H, s), 1.61 (1H, s), 1.67-1.44 (6H, m), 1.43 (1H, s), 1.42 (2H, s), 1.33 (2H, s), 1.24 (1H, s), 1.10 (2H, s), 1.09 (1H, s); HRFABMS calcd for $C_{18}H_{33}O_3$ $[M+H]^+$ 297.2430, found 297.2427.

(2'*E*,6'*E*,4''*R*)-7-(2'',2'',5''-Trimethyl-1'',3''-oxolan-4''-yl)-3',7'-dimethylnona-2',6'-dienyloxy)-chromen-2-one (6). DEAD (40% in toluene, 0.31 mL, 0.67 mmol) was added dropwise to a solution of **5** (49.7 mg, 0.168 mmol) umbeliferone (109 mg, 0.672 mmol), and triphenylphosphine (176 mg, 0.672 mmol) in toluene (3.0 mL) at 0 °C. The mixture was stirred for 16 h at room temperature, and then the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3:1) to afford **7** and C-6 isomer (58.2 mg, 0.132 mmol) as a colorless oil. ^{1}H NMR δ: 7.63 (1H, d, *J* = 9.6 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 6.86-6.80 (2H, m), 6.24 (1H, d, *J* = 9.6 Hz), 5.53-5.46 (1H, m), 5.17 (0.66H, t, *J* = 6.6 Hz), 5.11-5.08 (0.34H, m), 4.62-4.60 (2H, m), 3.73 (0.34H, dd, *J* = 9.8, 2.6 Hz), 3.66 (0.66H, dd, *J* = 9.4, 3.4 Hz), 2.34 (0.34H, m), 2.24-1.99 (4.66H, m), 1.79 (1H, s), 1.77 (2H, s), 1.68 (1H, s), 1.63 (2H, s), 1.61 (1H, s), 1.73-1.44 (3H, m), 1.42 (3H, s), 1.33 (1H, s), 1.30-1.26 (2H, m), 1.24 (2H, s),

1.10 (3H, s); HRFABMS calcd for $C_{27}H_{37}O_5$ $[M+H]^+$ 441.2641, found 441.2637.

Karatavicinol (2). Compound **6** (58.2 mg, 0.132 mmol) was treated with 60% AcOH (5.0 mL). The mixture was stirred for 2 h at 60 °C, and then the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (hexane/chloroform/MeOH = 10:50:1) to afford **2** (31.3 mg, 0.0781 mmol) as a colorless oil. $[\alpha]^{25}_D$ +14.8 (*c* 0.3, $CHCl_3$). ^{1}H NMR δ: 7.64 (1H, d, *J* = 9.6 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 6.85 (1H, dd, *J* = 8.4, 2.4 Hz), 6.82 (1H, d, *J* = 2.4 Hz), 6.25 (1H, d, *J* = 9.2 Hz), 5.46 (1H, t, *J* = 6.6 Hz), 5.18 (1H, m), 4.61 (2H, d, *J* = 6.4 Hz), 3.35 (1H, d, *J* = 10.4 Hz), 2.38 (1H, brs), 2.28-2.03 (7H, m), 1.76 (3H, s), 1.62 (3H, s), 1.63-1.55 (1H, m), 1.46-1.36 (1H, m), 1.20 (3H, s), 1.16 (3H, s); ^{13}C NMR δ: 162.1, 161.3, 155.8, 143.5, 142.0, 135.4, 128.7, 124.2, 118.6, 113.3, 112.9, 112.4, 101.5, 78.1, 72.9, 65.5, 39.3, 36.7, 29.6, 26.4, 25.9, 23.3, 16.7, 15.9; HRFABMS calcd for $C_{24}H_{33}O_5$ $[M+H]^+$ 401.2328, found 401.2324.

10'*R*-Acetoxy-11'-hydroxyumbelliprenin (1). To a solution of **2** (31.3 mg, 0.0781 mmol) and pyridine (0.025 mL, 0.31 mmol) in CH_2Cl_2 (1.0 mL) was added acetic anhydrous (0.016 mL, 0.16 mmol) at 0 °C. The mixture was stirred for 12 h at room temperature, and then the reaction was quenched with saturated aqueous NH_4Cl. The organic materials were extracted with AcOEt and washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/chloroform/MeOH = 10:50:1) to afford **2** (18.3 mg, 0.0414 mmol) as a colorless oil. $[\alpha]^{25}_D$ +10.8 (*c* 0.2, $CHCl_3$) {lit.[3] $[\alpha]^{25}_D$ +11.2 (*c* 0.5, $CHCl_3$)}. ^{1}H NMR δ: 7.65 (1H, d, *J* = 9.2 Hz), 7.37 (1H, d, *J* = 8.8 Hz), 6.85 (1H, dd, *J* = 8.4, 2.4 Hz), 6.82 (1H, d, *J* = 2.4 Hz), 6.25 (1H, d, *J* = 9.2 Hz), 5.47 (1H, dd, *J* = 6.6, 1.3 Hz), 5.11 (1H, m), 4.79 (1H, dd, *J* = 10.0, 2.8 Hz), 4.61 (2H, d, *J* = 6.4 Hz), 2.16-2.02 (4H, m), 2.11 (3H, s), 1.99-1.82 (2H, m), 1.74 (3H, s), 1.73-1.62 (3H, m), 1.60 (3H, s), 1.20 (3H, s), 1.19 (3H, s); ^{13}C NMR δ: 172.2, 162.1, 161.3, 155.8, 143.4, 142.2, 134.6, 128.7, 124.2, 118.5, 113.2, 112.9, 112.4, 101.5, 79.6, 72.5, 65.5, 39.4, 36.1, 27.8, 26.1, 24.9, 21.1, 16.8, 16.0; HRFABMS calcd for $C_{26}H_{35}O_6$ $[M+H]^+$ 443.2434, found 443.2440.

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REFERENCES AND NOTES

1. Z. E. Nazari and M. Iranshahi, *Phytother. Res.*, 2011, **25**, 315.
2. A. Gliszczynska and P. E. Brodelius, *Phytochem. Rev.*, 2012, **11**, 77.
3. C.-L. Lee, L.-C. Chiang, L.-H. Cheng, C.-C. Liaw, M. H. A. EI-Razek, F.-R. Chang, and Y.-C. Wu, *J.*

Nat. Prod., 2009, **72**, 1568.

4. K. Eddeger, S. F. Mayer, A. Steinreiber, and K. Faber, *Tetrahedron*, 2004, **60**, 589.
5. For regioselective Sharpless asymmetric aminohydroxylation using $(DHQD)_2AQN$ as a ligand: (a) J. A. Bodkin, G. B. Bacskay, and M. D. McLeod, *Org. Biomol. Chem.*, 2008, **6**, 2544; (b) A. J. Morgan, C. E. Masse, and J. S. Panek, *Org. Lett.*, 1999, **1**, 1949.
6. H. Becker and K. B. Sharpless, *Angew. Chem.*, 1996, **108**, 447; *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 448.
7. E. J. Corey and J. Zhang, *Org. Lett.*, 2001, **3**, 3211.
8. Data for C-6 isomer of **5**: $[\alpha]^{25}_D$ +35.3 (*c* 0.1, $CHCl_3$). ^{1}H NMR δ: 7.64 (1H, d, *J* = 9.6 Hz), 7.36 (1H, d, *J* = 8.8 Hz), 6.85 (1H, dd, *J* = 8.6, 2.6 Hz), 6.82 (1H, d, *J* = 2.4 Hz), 6.25 (1H, d, *J* = 9.6 Hz), 5.52 (1H, dt, *J* = 6.5, 1.3 Hz), 5.14-5.10 (1H, m), 4.60 (2H, d, *J* = 6.8 Hz), 3.41 (1H, dd, *J* = 10.4, 2.0 Hz), 2.38 (1H, ddd, *J* = 14.4, 9.4, 5.0 Hz), 2.28 (1H, brs), 2.20-2.06 (4H, m), 1.98 (1H, brs), 1.78 (3H, s), 1.69 (3H, s), 1.63 (3H, s), 1.76-1.42 (3H, m), 1.34-1.19 (1H, m), 1.13 (3H, s); ^{13}C NMR δ: 162.1, 161.3, 155.8, 143.4, 142.2, 132.2, 128.7, 124.2, 118.9, 113.2, 113.0, 112.5, 101.6, 77.2, 75.0, 65.4, 38.7, 36.5, 29.2, 25.6, 22.0, 20.9, 17.7, 16.8; HRFABMS calcd for $C_{24}H_{33}O_5$ $[M+H]^+$ 401.2328, found 401.2322.