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An Efficient Synthetic Method of 11,12-Dihydroxyl Eudesmanolide Sesquiterpenoid from α-Santonin

Wu Jiong XIA[1], De Run LI[1] , Yong Qiang TU[1]*, Ao Cheng CAO[2]

[1]Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000
[2]Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100094

Abstract: A short and efficient procedure for introduction of tertiary hydroxyl to C-11 of eudesmanolide based on the rearrangement-oxidation of the exocylic double bond has been developed, which is synthetically valuable for a series of natural eudesmanolide sesquiterpenoids containing the 11,12-diol.

Keywords: Introduction, tertiary hydroxyl, rearrangement-oxidation.

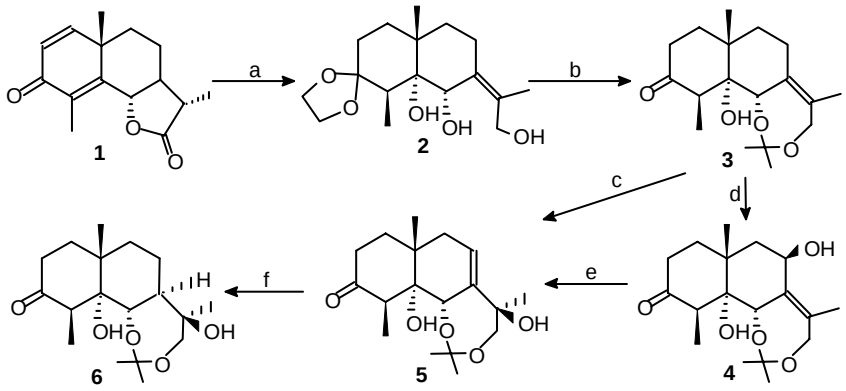
The 11,12-dioxygenated eudesmanolide sesquiterpenoid is a large kind of naturally occuring sesquiterpenoids isolated from the medicinal plants, such as *J. glutinosa*[1] and *Flourensia heterolepsis* [2]. In constrast to much investigation of their isolation and structure characterization, the less about their synthesis have been reported. One of the reason may be the difficult hydroxylation at C-11. For example, the synthesis of a simple natural product, kudtriol[3], required thirteen steps of reactions for introduction such hydroxyl group. In our recent research, we have designed and developed a short and efficient procedure based on the rearrangement-oxidation of the intermediate containing allylic exocylic double bond with $SeO_2/{}^tBuO_2H/CH_2Cl_2$ system[4].

Our approach began with the cheap and abundant material, α-santonin **1**(as shown in **scheme 1**). One of the strategic consideration is the introduction of substable exocyclic 11,12-double bond, which is expected to rearrange to be endocylic one under some condition. Thus the key intermediate **2** was synthesized in our reported procedure[5-7].

Initially, a directive oxidation of **2** with $SeO_2/{}^tBuO_2H/CH_2Cl_2$ could not provide the right product , but complicated mixture unidentified. So compound **2** was protected with acetone to get the acetonide **3**[8]. Upon treatment with $SeO_2/{}^tBuO_2H/CH_2Cl_2$, compound **3** was converted into single product **5** in 92% (based on the recovery of the starting material). Interestingly, when compound **3** was oxidized with $SeO_2/{}^tBuO_2H$ using

dioxane as solvent, a C_8-hydroxylated product **4** was got in high yield (95%). Furthermore, the only product **5** was obtained from the rearrangement of **4** with aqueous KOH. Stereoslective hydrogenation of **5** catalyzed by 10% Pd/C led to the compound **6** in 98%[9]. The stereochemistry of C_7 and C_{11} of the compound **6** was determined by 2D-Noesy technique, which was identified with those existing in the natural products.

Scheme 1



Reagents and conditions:
a) ref. 5; b) acetone, PTS; c) SeO_2, $^tBuO_2H$, CH_2Cl_2; d) SeO_2, $^tBuO_2H$, dioxane; e) 30% KOH; f) 10%Pd/C, H_2.

Experimental

*Preparation of 11-hydroxyl acetonide **5**:*

190 mg (0.61mmol) of **3** in 1 ml dichloromethane was added 45 mg SeO_2 followed by 0.19 ml $^tBuO_2H$ (75%) at 0 ^oC. Then the ice-water bath was removed and the mixture was stirred at r.t. for 10hrs., extracted with 2×15 ml CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated in vacuum.The residue was chromatographed (petroleum ether / AcOEt: 2/1) to afford 162 mg of **5** (93%, recovery of 25 mg starting material). Spectral data of **5**: ^{1}HNMR:1.17 (3H, s), 1.24 (3H, s), 1.29 (3H, d, J 7.7Hz), 1.37 (3H, s), 1.45 (3H, s), 1.5-2.4 (6H, m), 2.8-2.9 (1H, m), 3.34 (1H, d, J 12Hz), 3.63 (1H, d, J 12Hz), 4.79 (1H, brs), 5.91 (1H, d, J 6.3Hz). ^{13}CNMR: 15.9, 20.6, 22.8, 25.1, 25.8, 33.8, 35.8, 37.9, 39.7, 53.6, 66.3, 70.3, 72.1, 78.9, 101.7, 123.4, 139.4, 213.1. EIMS, *m/z*(%): 306 (M^+-18, 0.4), 248 (5.0), 218 (63.2), 203 (28.7), 175 (20), 160 (37.8), 111 (22.7), 109

(23.7), 59 (25.9), 55 (24.9), 43 (100). FAB-HRMS: found 325.2012, Cacld for [$C_{18}H_{29}O_5$+H]: 325.2101.

*Preparation of 8-hydroxyl acetonide **4**:*

100 mg (0.32mmol) of 3 in 1 ml dioxane was added 25 mg SeO_2 followed by 0.11 ml $^tBuO_2H$ (75%) at 0 ^oC. Then the ice-water bath was removed and the mixture was stirred at r.t. for 10hrs., extracted with 2×15 ml EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The residue was chromatographed (petroleum ether / AcOEt: 2/1) to afford 84 mg of 4 (95%, recovery of 16 mg starting material). Spectral data of compound **4**: ^{1}HNMR: 1.26 (3H, d, J 8.oHz), 1.39 (3H, s), 1.47 (3H, s), 1.53 (3H, s), 1.72 (3H, s), 1.89~2.88 (7H, m), 3.63 (1H, d, J 15.6Hz), 4.64 (1H, d, J 15.6Hz), 4.85 (1H,m), 5.08 (1H, s). ^{13}CNMR: 15.1, 17.6, 23.3, 24.5, 24.8, 33.8, 35.6, 37.3, 43.4, 52.9, 65.4, 66.9, 70.6, 81.0, 101.5, 134.6, 135.6, 215.0. EIMS, *m/z*(%): 325 (M^+,3), 249 (100), 231 (23), 203 (13), 133 (14), 109 (24), 91 (18); FAB-HRMS: found 325.2004, Cacld for [$C_{18}H_{29}O_5$+H]: 325.2014.

*11,12-dihydroxyl eudesmanolide sesquiterpenoid **6**:*

A suspension of 25 mg(0.077 mmol) of **5** and 10 mg of 10% palladium on carbon in 1 ml methanol was hydrogenated for 24 hours at r.t. and then filtered. The filtrate was evaporated in vacuum and chromatographed on silicon column (petroleum ether / AcOEt: 3/1) to get 24.6 mg of **5** (98%). Spectral data of **6**: $[\alpha]_D$= +58. ^{1}HNMR: 1.18 (3H, s), 1.25 (3H, d, J 8.0Hz), 1.34 (3H, s), 1.37 (3H, s), 1.45 (3H, s), 1.55-2.66 (10H, m), 3.80 (1H, d, J 10Hz), 3.83 (1H, s, OH), 4.10 (1H, d, J 10Hz), 4.67 (1H, brs). ^{13}CNMR: 14.8, 20.0, 20.9, 22.1, 26.5, 27.7, 34.3, 34.8, 35.7, 36.5, 46.7, 53.2, 68.6, 75.1, 78.3, 84.7, 110.2, 215.3. EIMS, *m/z* (%): 326 (M^+, 2.6), 268 (2.0), 250 (28.8), 233 (10.5), 165 (12.1), 140 (21.6), 126 (13.6), 115 (100), 109 (11.5), 97 (15). FAB-HRMS: found 327.2101, Cacld for [$C_{18}H_{29}O_5$+H]: 327.2259.

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