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AN EFFICIENT SYNTHESIS OF EUDESMANOLIDE SESQUITERPENOIDS POSSESSING α-METHOXYMETHYL BUTENOLIDE AND BUTADIENOLIDE

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Abstract: A novel procedure for introduction of α-methoxy-methyl butenolide and butadienolide structures to the eudesmanolide have been developed, which is convenient and synthetically valuable for the natural sesquiterpenoids containing the moieties above.

During the past ten more years, a series of sesquiterpenoids possessing the C_{12}–oxygen functionalized butenolide such as **A** (R_1= H, Ac) and butadienolide such as **B** (R_2= H, Me, Et, Ac) have been isolated and identified from natural sources,[1-9] which were

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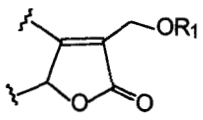
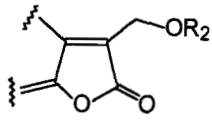
demonstrated to show some important biological behaviors, such as toxicity and borderline activities against P-388 lymphoid leukemia and cytotoxic activities against the 9KB human nasopharynx carcinome cells, and so on.[8-11] Although there was a synthetic method reported for construction of the partial structure A,[12] it needs several steps and the experiment performance seems quite complicated. Therefore, only few successful synthesises of sesquiterpenoids containing moiety **A** have been reported up to present.[13] Furthermore, there is still no successful method reported about the construction of moiety **B**. In our recent research on the synthesis of sesquiterpernoids, one of our attentions was focussed on the construction of structures **A** and **B**, and here we present an efficient approach of both moieties, which was simply based on the repeated epoxidation of the γ,δ-unsaturated γ-lactone intermediate and the successive NaOMe-induced rearrangement of the γ,δ-epoxy of γ-lactone.

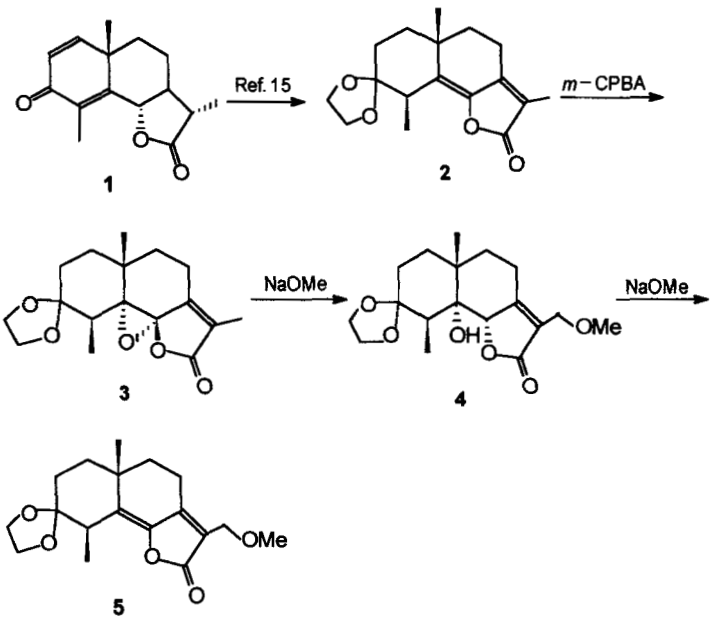


A



B

Our synthesis began with the common eudesmanolide, α-santonin **1**, which possesses the potential versatile funtionals but is easily available from natural sources and has been frequently used as a starting substrate for synthesis of a number of natural products.[14] Thus the santonin **1** was converted into **2** by our previous procedure.[15] Upon treatment with *m*-CPBA, compound **2** was converted to the only epoxide **3** in 66%. The stereochemistry of the epoxy rings of compounds **3** was assigned to α-orentation on the basis of the general facts that the adjacent β-methyl at C-4 and C-10 showed the steric exclusion against the epoxidation process and the *trans*-fused configuration at C-5 and C-10 are generally more favorable.



Treatment of epoxide **3** with excess of NaOMe in MeOH at 0°C directly led to methoxy-functionalization at α-methyl of the butenolide to yield compound **4** in 50% yield, if the reaction was quenched with H_2O upon complete consumption of epoxide **3** on TLC. Furthermore treatment of epoxide **3** with excess of NaOMe in MeOH at room temperature formed rapidly the α-methoxymethyl butadienolide **5** in 76% yield. An attempt to prepare an α-hydroxyl-methyl substituted **4** from the corresponding α-methyl-substituted substance [15] by directly hydroxylation with SeO_2/EtOH, SeO_2/dioxane/H_2O, SeO_2/H_2O_2/THF or SeO_2/$^tBuO_2H$/CH_2Cl_2 systems was not successful, which indicated that the procedure here reported is indeed an efficient method for construction of these key structures **A** and **B**.

Experimental

^{1}HNMR and ^{13}CNMR spectrum were recorded in acetone-d_6 on a Brucker Am-400 spectrometer with TMS as internal standard (chemical shift in δ , ppm). EIMS and FAB-

HRMS were determined on a Aufostec-3000 spectrometer (energy of ionizing electrons 70ev). For column chromatography, silica gel (200-300 mesh) and petroleum ether (bp.60-90℃) were used.

3,3-Ethylenedioxy- 5α,6α- epoxy-4α-eudesm-7(11)-en-6,13-olide (**3**). A solution of **2** (360 mg, 1.24 mmol, prepared in literature[15]) in CH_2Cl_2 (11.7 mL) was treated with *m*-CPBA (380 mg, 1.4 mmol) for one week at room temperature in dark. The solution was diluted with CH_2Cl_2, washed with aqueous Na_2CO_3 solution and then brine, dried over Na_2SO_4, concentrated in vacuum, and chromatographed on silicon column (petroleum ether/EtOAc: 9/1) to give 250 mg of **3** (66% yield) as a white solid. Spectral data of **3**. –^{1}HNMR: 3.9-3.8(m, 4H), 2.6-2.5(m, 2H), 2.1-2.0(m, 1H), 1.8-1.7(m, 2H), 1.81(s, 3H), 1.6-1.5(m, 1H), 1.43(ddd, J 13.2, 3.3, 3.3 Hz, 1H), 1.18(ddd, J 13.4, 5.8, 2.3 Hz, 1H), 1.12(s, 3H), 1.10(d, J 8.1 Hz, 3H). –^{13}CNMR: 171.5(s), 155.2(s), 126.2(s), 110.7(s), 90.4(s), 72.9(s), 64.9(t), 64.7(t), 41.9(d), 35.1(s), 33.8(t), 33.3(t), 27.5(t), 21.3(q), 19.5(t), 14.6(q), 8.6(q). -EIMS, m/z(%): 306(5)[M$^+$], 291(3), 167(21), 153(7), 99(100), 86(22), 55(11).-FAB-HRMS: found 307.1489, calculated for [$C_{17}H_{23}O_5$+H] 307.1545.

3, 3-Ethylenedioxy- 12- methoxy- 5β- hydroxyeudesm- 7(11)- en- 6, 13- olide (4). A solution of **3** (45 mg, 0.16 mmol) in 5 mL MeOH was treated with 1.3 M NaOMe in MeOH(6 mL, 8 mmol) under ice-water bath. The mixture was stirred at 0°C for 0.5 h. Then the mixture was poured into ice-water, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The residue was chromatographed (petroleum ether/EtOAc: 3.5/1) to afford 25 mg of **4** as a white solid (50%). Spectral data of **7**. –^{1}HNMR: 5.23(s, 1H), 4.07(s, 2H), 4.0-3.9(m, 4H), 3.23(s, 3H), 2.88(dd, J 14.8, 5.2 Hz, 1H), 2.5- 1.2(m, 7H), 1.31(s, 3H), 1.20(d, J 5.7 Hz, 3H). –^{13}CNMR: 167.4(s), 125.7(s), 121.9(s), 112.0(s), 80.7(d), 79.2(s), 65.0(t), 64.7(t), 63.7(t), 57.6(q), 43.8(d), 39.2(s), 38.2(t), 33.4(t), 27.8(t), 22.8(t), 20.9(q), 13.6(q). –EIMS, m/z(100%): 338(11)[M]$^+$, 323(5), 306(62), 184(72), 99(100), 87(44), 55(47). –FAB-HRMS: found 339.1790, calculated for [$C_{18}H_{26}O_6$+H] 339.1808.

3, 3- Ethylenedioxy- 12- methoxy- 4α-eudesm- 5(6), 7(11)-dien- 6,13- olide (**5**). A solution of **3** (75 mg, 0.24 mmol) in 8 mL MeOH was treated with 1.5 M NaOMe in MeOH (12.2 mmol, 8 mL) at room temperature. The mixture was stirred at room temperature for 5 h. Then the mixture was poured into ice-water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated in vacuum and chromatographed (petroleum ether/EtOAc: 3/1) to afford 60 mg of **5** (76%) as a white solid. –Spectral data of **5**. –^{1}HNMR: 4.15(s, 2H), 4.0- 3.8(m, 4H), 3.29(s, 3H), 3.1- 2.8(m, 3H), 2.1- 2.0(m, 1H), 1.8- 1.5(m, 5H), 1.30(s, 3H), 1.18(d, J 7.4 Hz, 3H). –^{13}CNMR: 170.0(s), 152.5(s), 145.4(s), 134.2(s), 119.7(s), 110.8(s), 65.1(t), 64.7(t), 64.3(t), 58.4(q), 40.2(t), 38.8(d), 38.1(t), 34.9(s), 27.1(t), 25.4(q), 20.2(t), 18.1(q). –FAB-HRMS: found 321.1614, calculated for [$C_{18}H_{24}O_5$+H] 321.1701.

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