Tetrahedron Vol. 49, No 15, pp 3075-3080, 1993
Printed in Great Britain

0040-4020/93 $6 00+00

SYNTHESIS OF (±) – 9 – OXOEUDESMA – 4, 11 (13) – DIENE – 7αH – 12 – OIC ACID METHYL ESTER

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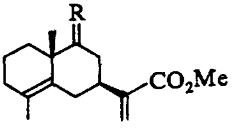
(*Received in Japan* 20 *January* 1993)

Key Words (±) – 9 –oxoeudesma – 4, 11 (13) – diene– 7αH – 12 – oic acid methyl ester, synthesis, Ene–type chlorination

Abstract: *The first synthesis of (±) – 9 – oxoeudesma – 4, 11 (13) – diene – 7αH – 12– oic acid methyl ester (**1**) has been described, employing the Ene–type chlorination with hydrogen peroxide / Vilsmeier reagent system as the key step*

In recent years, a large number of eudesmane acids and eudesmane lactones have been isolated from natural sources [2] These natural products have aroused much interest on account of their wide spectrum of biological properties, particularly antifeedant, cell growth inhibitory and plant growth regulating activities [2,3]

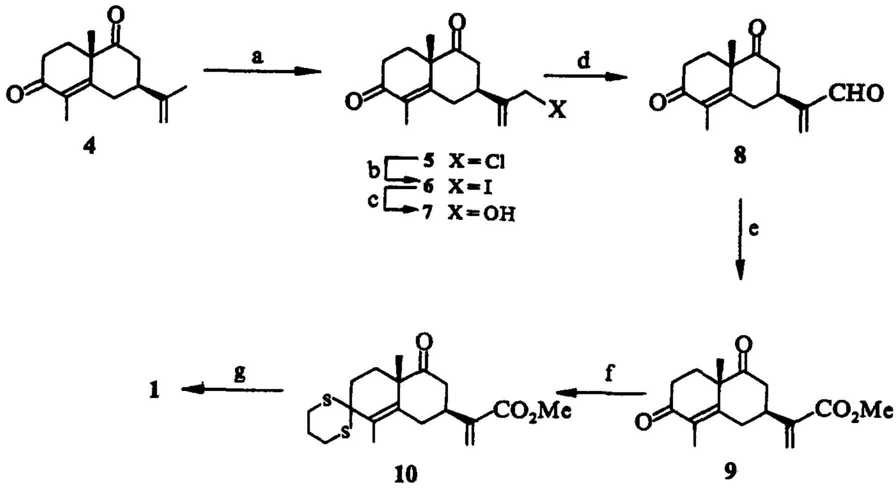
(–)–9–Oxoeudesma–4,11(13)–diene–7αH–12–oic acid, (+)–9β–hydroxyeudesma– 4,11(13)–diene–7αH–12–oic acid and (+)–9β–acetoxyeudesma–4,11(13)–diene–7αH– 12–oic acid have been isolated as the corresponding methyl esters **1**, **2** and **3** from *Artemisia tournefortiana* [4] The transformation of **1** to **2** and **3** has also been reported by Sanz *et al* [4] Herein we describe the first synthesis of **1** in racemic form (**Scheme 1**) The key step of this synthetic route is the Ene–type chlorination with hydrogen peroxide / Vilsmeier reagent system



1 R=O
2 R=H, βOH
3 R=H, βOAc

Eudesma–4,11(13)–diene–7αH– 3,9–dione (**4**) was prepared easily from (–)–carvone in three steps [5] After all attempts were made unsuccessfully to obtain directly allylic alcohol **7** (or allylic aldehyde **8**) by allylic oxidation (SeO_2, CrO_3, PDC, PCC) of **4**, we turned our attention to the Ene–type chlorination [6] Employing hydrogen peroxide / Vilsmeier reagent system, **4** was converted to allylic chloride **5** in 64% yield Compound **5** was transformed (NaI, Me_2CO) to reactive iodide **6**, which without purification was hydrolyzed (Cu_2O, DMSO, H_2O) to allylic alcohol **7**

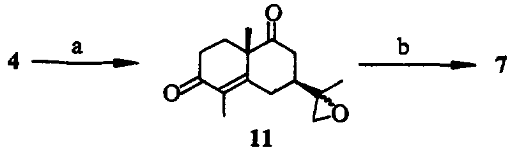
Scheme 1



Reagents and conditions a) Vilsmeier reagent, 30% H_2O_2, CH_2Cl_2, -20°C, 20 min, b) NaI, Me_2CO, rt, 3h, c) Cu_2O, DMSO, H_2O, 60°C, 2h, d) Jones reagent, Me_2CO, rt, 10 min, e) MnO_2, NaCN, AcOH, MeOH, rt, 14h, f) 1, 3-propanedithiol, 8% $FeCl_3$ on silica gel, CH_2Cl_2, rt, 30 min, g) W-2 Raney Ni, EtOH, rt, 1h

An alternative procedure for preparation of **7** was also investigated (**Scheme 2**) epoxidation of **4** quantitatively afforded epoxide **11** and rearrangement of the latter with LDA[7] gave **7** in 24% yield This route was rejected due to the very poor yield of the rearrangement

Scheme 2



a) *m*-CPBA, $CHCl_3$, rt, 20h, b) LDA, ether, rt, 6h

Oxidation of **7** with Jones reagent generated allylic aldehyde **8** The overall yield of three steps from **5** to **8** was 81% The conversion of **8** to methyl ester **9** was carried out by Corey method,[8] which involved treatment of **8** with active manganese dioxide, sodium cyanide and acetic acid in dry methanol at room temperature for 14h

The final phase of the synthesis (**Scheme 1**) was concerned with reduction of the α,β–unsaturated ketone **9** to the corresponding olefin On treatment with an equivalent amount of 1, 3–propanedithiol in the presence of 8% anhydrous ferric chloride dispersed on silica gel,[9] the unsaturated carbonyl group of **9** was thioketalized quickly to afford thioketal **10** Desulfurization of **10** with freshly prepared W–2 Raney nickel in ethanol at room temperature furnished the title compound **1** in a yield of 72%, whose spectral properties were identical with the reported data [4]

The formation of allylic chloride **5** indicates that the Ene–type chlorination of keto–olefins with hydrogen peroxide / Vilsmeier reagent system may provide an efficient synthetic procedure to other natural eudesmane acids (esters)

The conversion of **1** to the related eudesmane lactones[4] is in progress

EXPERIMENTAL

For column chromatography, 200–300 mesh silica gel and 60–90℃ petroleum ether (PE) were used Elemental analyses were performed on an Italian 1106 analyzer IR spectra were recorded on a Nicolet FT–170SX as liquid films ^{1}H NMR spectra were measured on a Varian FT–80A and a Bruker AM–400 spectrometers (TMS, $CDCl_3$) Mass spectra were determined on a V G ZAB–HS spectrometer(EI, 70 ev)

12–Chloroeudesma–4, 11(13)–diene–7αH–3,9–dione (5)

To a well–stirred mixture of **4** (2 0 g, 8 6 mmol) and 30% H_2O_2 (56 mL) was added dropwise the Vilsmeier reagent[6] (86 mmol) in CH_2Cl_2(30 mL) in 15 min at −20℃ under argon, and the mixture was further stirred at the same temperature for 20 min The two–phase reaction solution was separated, and the aqueous phase was extracted with CH_2Cl_2(2 × 30 mL) The combined organic fractions were washed with H_2O (2 × 20 mL), 10% aq Na_2SO_3(20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$ The crude products were purified by silica gel chromatography eluting with PE ether (3 1) to afford **5** (1 46g, 64% yield) as a light–yellow oil v_{max} 1707, 1663 (C=O) cm^{-1}, δ_H(80 MHz) 1 43 (s, 3H, C_{10}–CH_3), 1 87 (s, 3H, C_4–CH_3), 4 13 (br s, 2H, 12–H), 5 15, 5 34 (2 br s, 2H, 13–H), *m / z* (%) 268(M^++2,12), 266(M^+,36),253(12),231(20), 226(46), 175(100) Anal Calcd for $C_{15}H_{19}O_2Cl$ C, 67 54, H, 7 18% Found C,67 07, H, 7 60%

12–Hydroxyeudesma–4, 11(13)–diene–7αH–3, 9–dione (7)

Method A A mixture of **5** (1 35g, 5 1 mmol) in acetone (50 mL) and sodium iodide (0 92g, 6 1 mmol) was stirred at room temperature for 3 h The solvent was removed at reduced pressure, and the residue was dissolved in CH_2Cl_2(30 mL) After filtering, the filtrate was evaporated to give **6** (1 79g, 98%) as an oil which was used in the succeeding step without purification

The crude iodide (1 79g)was dissolved in DMSO (25 mL) and water (50 mL), and to this was added Cu_2O (1 22 g, 8 5 mmol) The suspension was stirred and heated at 60℃ for 2 h After filtering, the solution was extracted with ether (3 × 30 mL), and the etheral extracts were washed with water (2 × 15 mL) and brine (2 × 10 mL), dried ($MgSO_4$),and chromatographed using PE ether (1 1) to produce 7 (1 11 g, 88%) as an almost colorless oil υ_{max} 3416 (br, OH), 1707, 1662 (C=O) cm^{-1}, δ_H(80 MHz) 1 44 (s, 3H, C_{10}–CH_3), 1 86 (s, 3H, C_4–CH_3), 4 20 (br s, 2H, 12–H), 5 04, 5 21 (2 br s, 2H, 13–H), *m / z(%)* 248(M^+, 100), 233(65), 230(82), 183(51) Anal Calcd for $C_{15}H_{20}O_3$ C, 72 55, H, 8 12% Found C, 72 71, H, 8 30%

Method B To a stirred solution of 4 (1 10g, 4 74 mmol) in dry $CHCl_3$(60 mL) was added 75% *m*–CPBA (1 10 g, 4 80 mmol) in one portion The mixture was stirred at room temperature under Ar for 20 h, resulting a yellow solution The solution was washed successively with 10% aq Na_2SO_3(2 × 20 mL), 10% aq NaOH (2 × 20 mL), water (3 × 15 mL) and brine (20 mL), and dried with anhydrous $MgSO_4$ Removal of the solvent gave a mixture of epimeric epoxides **11** (1 14 g) as a yellow oil which was sufficiently pure for the next step reaction υ_{max} 1709, 1663 (C=O) cm^{-1}, δ_H(80 MHz) 1.35(br s, 3H, C_{11}–CH_3), 1 44 (s, 3H, C_{10}–CH_3), 1 85 (s, 3H, C_4–CH_3), *m / z* (%)248(M^+, 87), 233(60), 197(100), 183(63)

To a freshly prepared solution of LDA (23 mmol) in dry ether (30 mL) at 0℃, under Ar, was added dropwise a solution of the crude epoxide mixture **11** (1 14g, about 4 6 mmol) in dry ether (15 mL), and the reaction mixture was stirred at room temperature for 6 h The reaction was quenched by addition of 5% aq HCl (5 mL), and the mixture was stirred for an additional 15 min The organic layer was separated, and the aqueous portion was extracted with ether (3 × 10 mL) The combined organic phases were washed with water (2 × 20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$ Chromatographic purification (PE ether = 1 1) afforded **7** (0 27g, 24%)

Eudesma–4, 11(13)–diene–7αH–3, 9,12–trione (8)

7 (0 95g, 3 83 mmol) was dissolved in permanganate stable acetone (20 mL), and 8N Jones reagent (0 8 mL, 6 4 mmol) was added dropwise with stirring The resulting light–green mixture was stirred at room temperature for 10 min After usual work–up, **8** (0 86g, 92%) was obtained as a colorless oil υ_{max} 1711 (C=O), 1690 (CHO), 1667 (C=O) cm^{-1}, δ_H(80 MHz) 1 46 (s, 3H, C_{10}–CH_3), 1 85 (s, 3H, C_4–CH_3), 6 15, 6 36 (2 br s, 2H, 13–H), 9 60 (s, 1H, CHO), *m / z* (%) 246(M^+, 50), 231(46), 203(60), 189(33), 157(100) Anal Calcd for $C_{15}H_{18}O_3$ C, 73 15, H, 7 37% Found C, 73 28, H, 7 40%

3,9–Dioxoeudesma–4,11(13)–diene–7αH–12–oic acid methyl ester (9)

A mixture of **8** (0 78 g, 3 2 mmol) in dry MeOH (80 mL) and active MnO_2(3 4 g, 39 mmol) and NaCN (0 49 g, 10 mmol) in the presence of dry acetic acid (0 2 mL) was stirred at room temperature for 14 h After filtering through celite, the filtrate was evaporated to dryness, and the residue was dissolved in CH_2Cl_2(60 mL), washed with water (2 × 15 mL) and brine (2 × 10 mL), and dried (Na_2SO_4) Chromatography using PE ether (5 1) as eluent gave **9** (0 61 g, 70%) as a viscous oil v_{max} 1714 (CO_2Me), 1710, 1668 (C = O) cm^{-1}, δ_H(80 MHz) 1 45 (s, 3H, C_{10}–CH_3), 1 86 (s, 3H, C_4–CH_3), 3 80 (s, 3H, CO_2Me), 5 68, 6 33 (2 br s, 2H,13–H), *m / z(%)* 276(M^+, 100), 261(29), 244(46), 234(41), 187(37) Anal Calcd for $C_{16}H_{20}O_4$ C, 69 55, H, 7 29% Found C, 69 30, H, 7 35%

3, 3–Trimethylenedithio– 9 –oxoeudesma – 4, 11(13) –diene –7αH –12 –oic acid methyl ester (10)

To a stirred solution of **9** (0 5g, 1 8 mmol) in dry CH_2Cl_2(20 mL) and 1,3–propanedithiol (0 21g, 1 9 mmol) was added 8% $FeCl_3$ dispersed on silica gel (0 5g, 0 24 mmol $FeCl_3$) in one portion The resulting brown suspension was stirred at room temperature for 30 min, and the reaction was quenched by addition of 10% aq NaOH (1 mL) After filtering through celite, the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2(2 × 10 mL) After drying (Na_2SO_4), the crude products were purified on silica gel chromatography eluting with PE ether (6 1) to afford **10** (0 49g, 75%) as a viscous oil v_{max} 1712 (CO_2Me), 1709 (C = O) cm^{-1}, δ_H(400 MHz) 1 34 (s, 3H, C_{10}–CH_3), 2 04 (s, 3H, C_4–CH_3), 3 79 (s, 3H, CO_2Me), 5 63, 6 27 (2 br s, 2H, 13–H), *m / z*(%) 366 (M^+, 72), 351(100), 292(40), 259(62), 229(60) Anal Calcd for $C_{19}H_{26}O_3S_2$ C, 62 26, H, 7 15% Found C, 62 40, H, 7 19%

(±)– 9 – Oxoeudesma – 4, 11(13)–diene–7αH–12–oic acid methyl ester (1)

10 (0 2g, 0 55 mmol) was hydrogenated over freshly prepared W–2 Raney nickel (0 5g) in absolute EtOH (6 mL) at room temperature for 1 h Removal of the catalyst and solvent followed by chromatography using PE ether (8 1) gave **1** (0 1g, 72%) as a viscous oil v_{max} 1736 (CO_2Me), 1706 (C = O) cm^{-1}, δ_H(400 MHz) 1 30 (s, 3H, C_{10}–CH_3), 1 71 (br s, 3H, C_4–CH_3), 3 81 (s, 3H, CO_2Me), 5 67, 6 27 (2 br s, 2H, 13–H), *m / z*(%) 262 (M^+, 41), 247(55), 229(100), 220(38), 133(88)

Acknowledgement: This project was supported by the National Natural Science Foundation of China

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