SHORT PAPER

J. Chem. Research (S), 2000, 174–175

A synthesis of the C-11 epimer of the sesquiterpenoid 5-epi-kudtriol†

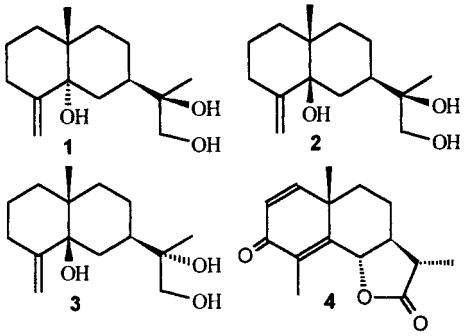
Gang Zhou, Xiaolei Gao, Zhe Zhang and Yulin Li*

National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R. China

The C-11 isomer of natural trihydroxyl sesquiterpene 5-epi-kudtriol **3** has been synthesized starting from (+)-dihydrocarvone *via* asymmetric dihydroxylation as a key step.

Eudesmane derivatives contain a number of naturally occurring compounds including some which possess interesting biological properties.[1,2]

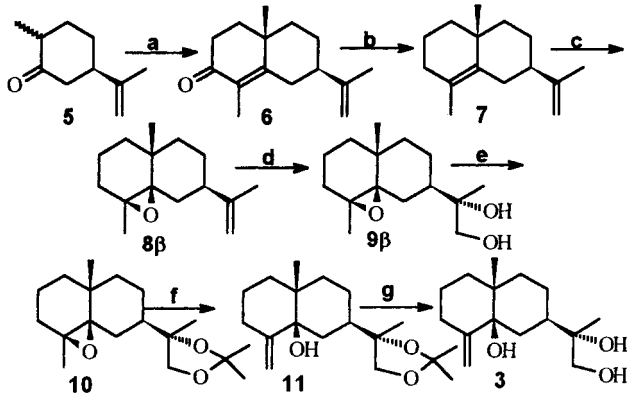
Kudtriol **1** and 5-epi-kudtriol **2** were first isolated from the aerial parts of *Jasania glutinosa* by Tereasa *et al*,[3] and their structures were determined as (-)-[11*R*]-eudesm-4(14)-en-5α,11,12-triol and (+)-[11*R*]-eudesm-4(14)-en-5β,11,12-triol respectively by spectroscopic methods.



Although a previous paper reported the synthesis of **2** from α-santonin **4** in 11 steps,[4] an efficient and flexible synthetic route leading to these compounds is still required in order to clarify the absolute configuration. Herein, we report a new, general approach to the synthesis of the C-11 isomer **3** of **1** from (+)-dihydrocarvone **5** in eight steps by the use of the Sharpless asymmetric dihydroxylation as key reaction.

As shown in Scheme 1, (+)-α-cyperone **6** was easily prepared from (+)-dihydrocarvone in two steps.[5] According to published work,[6] deoxygenation[7] of **6** with $AlCl_2H$ afforded diene **7** which was converted to the inseparable epoxides **8**α and **8**β by regioselective epoxidation[8] with 0.9eq. *m*CPBA. The mixture of epoxides was treated with commercially available AD-mix-α[9] in *t*-BuOH-H_2O to afford diols **9**α in 64% yield and **9**β in 34% yield. These were carefully separated by chromatography on silica gel. The diastereoselectivity was determined by analysis of the ^{1}H NMR (400 MHz) data. The rearrangement of oxirane ring in these epoxides was unsuccessful using LDA, $Al(OPr^i)_3$[10] or $Ti(OPr^i)_4$[11]. We assumed that the glycol on the side chain was responsible for these results. After protection as the acetonide **10** according to Ikekawa's procedure in 80% yield[12], **9**β was converted to the allylic alcohol **11** smoothly with 5eq LDA in ether. Removal of the protecting group in **11** in 1NHCl gave the title compound **3** in 90% yield. The spectroscopic data of ^{1}HNMR, IR, MS are consistent with the structure of synthetic product.

In summary, we present here a convenient method for the preparation of kudtriol compounds.



Scheme 1 *Reagents and conditions:* a, ref 5; b, $AlCl_2H$, ether, rt, 3h; c, *m*CPBA (0.9 eq), CH_2Cl_2, 0°C, 2h; d AD-mix-α, 0°C, 24h; e, p-TsOH, acetone, rt, 10min; f, LDA, ether, rt; g, 1NCHl, THF, reflux, 3h.

Experimental

For column chromatography, 200–300 mesh silica gel and 60-69 °C petroleum ether were used. IR spectra were recorded on a Nicolet FT-170SX as liquid films. ^{1}H NMR spectra were measured on Bruker AM-400 spectrometers with Me_4Si as an internal standard and $CDC1_3$ as a solvent. Mass spectra were determined on V.G. ZAB-HS spectrometer (EI, 70eV). Elemental analysis was performed on an Carlo Erba 1106 analyser.

(-)-[11S]-4β, 5β-epoxyeudesm-11,12-diol **9**β: A mixture of AD-mix-α (1.4 g) in tert-butyl alcohol (5 ml) and water (5 ml) was stirred at room temperature until both phases were clear, and then cooled to 0°C. Epoxide mixture **8**α and **8**β (220 mg, 1 mmol) in 50% aq. *t*-BuOH (2 ml) was added dropwise. The resulting mixture was stirred at 0°C for 24 h before it was quenched by addition of Na_2SO_3 (1.5 g) at 0°C. After being stirred for a further 1 h, the reaction mixture was extracted several times with ethyl acetate. The combined organic fractions were washed with 5% KOH (2 × 10 ml), water (2 × 10 ml), brine (2 × 10 ml), and dried ($MgSo_4$). After removal of the solvents, the oily residue was chromatographed on silica gel to afford **9**α (163 mg, 64%) and **9**β (86 mg, 34%) both as colourless oil. **9**β (45% de): Found: C, 71.04; H, 10.01, $C_{15}H_{26}O_3$ requires C, 70.87; H, 10.24%); $[\alpha]_D^9$ –5.3 (c 1.895, $CHCl_3$); ν/ cm^{-1} 3346, 2936, 1458, 1377, 1131, 1096; ^{1}H NMR (400 MHz, $CDCl_3$) : δ_H1.02 (s, 3H, 10-Me), 1.10 (s, 3H, 11-Me), 1.31 (s, 3H, 4-Me), 3.42 and 3.52 (dd, 2H, *J* = 10.8Hz, 12-H); *m/z* 254 (M^+, 1%), 239 (3), 236 (2), 223 (21), 205 (25), 178 (31), 161 (58), 147 (42), 121 (85), 43 (100).

Acetonization of **9**β: The diol **9**β (80 mg) in acetone (3ml) was treated with *p*-toluenesulfonic acid (cat) for 10 min at room temperature. The reaction mixture was diluted with ethyl acetate (20 ml), and the organic layer was washed successively with aq. Na_2CO_3 (2 × 10 ml), water (2 × 10 ml), bring (2 × 10 ml), and dried over $MgSO_4$. Evaporation of the solvent and separation on silica gel gave the acetonide **10** as colourless oil (74 mg, 80%). **10** ν/cm^{-1} 2990, 2929, 2880, 1467, 1376, 887; δ_H 1.05 (s, 3H, 10-Me), 1.25 (s, 3H, 11-Me), 1.34 (s, 3H, 4-Me), 1.38 (s, 3H, acetonide), 1.42 (s, 3H, acetonide), 3.67 and 3.82 (dd, 2 H, *J* 8.5Hz, 12-H); *m/z* 294 (M^+, 2%), 279 (10), 261 (3), 236 (45), 219 (13), 201 (54), 187 (6), 115 (100), 95 (10), 55 (48), 43 (25).

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

(-)-[11S] 5β - Hydroxyeudesm -4 (14) - en - 11, 12-isopropylidene ketal **11**: To a freshly prepared solution of LDA (0.17 M in THF, 5 ml) was added a solution of **10** (50 mg) in dry THF (4 ml) under argon. The reaction mixture was stirred at room temperature for 24h. Then some water was added to the reaction mixture at 0°C, and stirring was continued for an additional 10 min. The organic layer was separated and aqueous layer was extracted with ether (2 × 20 ml). The combined organic fractions were washed with H_2O (2 × 10 ml), brine (2 × 10 ml), and dried ($MgSO_4$). After removal of the solvents, the crude products were chromatographed on silica gel eluting with petroleum ether-ether (6 : 1) to yield **11** (42 mg, 84%) as colourless oil. **11**: Found: C, 73.22; H, 10.79. $C_{18}H_{30}O_3$ requires C, 73.47; H, 10.20%), $[\alpha]_D^{20}$ - 27.3 (c 0.55, $CHC1_3$), ν/cm^{-1} 3485, 3085, 2982, 2928, 2871, 1637, 1377, 1209, 1067, 1039, 895; δ_H 1.06 (s, 3 H, 10-Me), 1.30 (s, 3 H, 11-Me), 1.40 (s, 3H, acetonide), 1.44 (s, 3H, acetonide), 3.70 and 3.95 (dd, 2 H, *J* 8.3Hz, 12-H), 4.96 (br s, 14-H); *m/z* 294 (M^+, 7%), 279 (23), 276(14), 236 (20), 201 (55), 187 (60), 137 (20), 115 (100), 43 (35).

(-)-[11S]-Eudesm-4(14)-en-5β, 11, 12-triol **3**: Some drops of aqueous HCl (1 N, 0.5 ml) were added dropwise to a solution of **11** (20 mg) in THF (5 ml), and the mixture was refluxed for 3 h. After cooling, the reaction mixture was diluted with ethyl acetate (20 ml). The organic layer was washed with 10% aq. Na_2CO_3 (2 × 10 ml), H_2O (2 × 10 ml), brine (2 × 10 ml), and dried over $MgSO_4$. Evaporation of the solvents afforded the crude product which was chromatographed on silica gel to yield **3** (15 mg, 90%) as colourless oil. **3**: (Found: C, 70.56; H, 10.49. $C_{15}H_{26}O_3$ requires C, 70.87; H, 10.24%), $[\alpha]_D$ –42.3 (c 0.36, $CHCl_3$); ν/cm^{-1} 3400, 2932, 2869, 1641, 1449, 1378, 1281, 1028; ^{1}H NMR (400 MHz, $CDCl_3$); δ_H 1.02 (s, 3H, 10-Me), 1.13 (s, 3H, 11-Me), 3.44 and 3.63 (dd, 2H, AB, *J* 10.8Hz, 12-H), 4.94 (brs, 1H, 14-H), 5.07 (brs, 1H, 14-H); *m/z* 254 (M^+, 3%), 239 (3), 236 (5), 222 (2), 205 (15), 187 (12), 161 (56), 147 (27), 43 (100).

We are grateful for the financial supports from National Natural Science Foundation of China (Grant No. 29732060).

Received 7 December 1999; accepted 29 February 2000
Paper 99/41

References

1 T.A. Van Beek, A. De Groot, *Recl. Trav. Pays-Bas*, 1986, **105**, 573.
2 M. Ando, K. Isogai, H. Azami, N. Hivrata, Y. Yanagi, *J. Nat. Prod*., 1991, **54**, 1017.
3 J.P. Teresa, A.F. Barrero, A.S. Feliciano and M. Medardle; *Phytochemistry*, 1980, **19**, 2155.
4 R.S. Harapanhalli, *J. Chem. Soc. Perkin Trans. I*, 1988, 3149.
5 Z.M. Xiong, J. Yang and Y.L. Li, *Tetrahedron Asymmetry*, 1996, **7**, 2607.
6 Z. Xiong, G. Zhou, Y. Chen and Y. L. Li, *J. Chem. Res*., 1998, **8**, 450.
7 For a review of the deoxygenation of carbonyl compound, see: S. Yamamura, S. Nishiyama, in Comprehensive Organic Synthesis, ed. B.M. Trost and I. Fleming, Pergamon Press, New York, 1991, vol. **8**, P307.
8 For a review of epoxidation of alkenes, see: A.S. Rao, in Comprehensive Organic Synthesis, B.M. Trost and I. Fleming, Ed., Pergamon Press, New York, 1991, vol. **7**, P357.
9 H.C. Kolb, M.S. Vannieuwenhze, K.B. Sharpless, *Chem. Rev*., 1994, **94**, 2483.
10 G. Smith, *Synthesis*, 1984, 629.
11 J.D. White, H. Shin, T.S. Khim and N.S. Cutshall, *J. Am. Chem. Soc*., 1997, **119**, 240.
12 S. Takatsuto, N. Yazawa, M. Ishiguro, M. Morisaki, M. Ikekawa, *J. Chem. Soc. Perkin Trans, I*. 1984, 139.