

An Efficient Asymmetric Route To Eudesmane Acids. Total Synthesis Of (+)-12-Hydroxy- α -cyperone, (+)-12-Oxo- α -cyperone And (+)-3-Oxo-eudesma-4,11(13)-dien-12-oic Acid

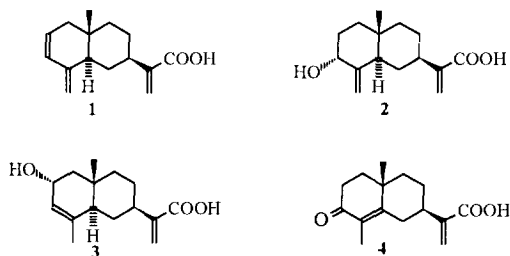
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Abstract: An efficient asymmetric synthesis of (+)-3-oxoeudesma-4,11(13)-dien-12-oic acid **4**, (+)-12-hydroxy- α -cyperone **6** and (+)-12-oxo- α -cyperone **7** from (+)-dihydrocarvone **5** is described, which involves a novel diastereoselective preparation of (+)- α -cyperone **8**. Copyright © 1996 Published by Elsevier Science Ltd

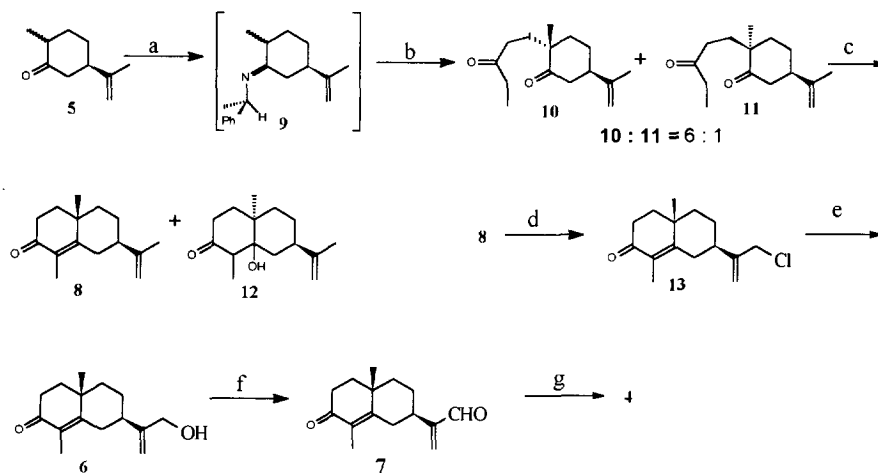
Sesquiterpenes constitute a group of natural compounds widely distributed in the plant kingdom¹. These kinds of compounds exhibit considerable biological activities such as antiinflammatory², ichthyotoxic and cytotoxic³, seed germination inhibitory⁴ and molluscicidal activities^{4,5} and consequently efficient syntheses of these compounds are a synthetic challenge that has received much attention in the past decades⁶.

In recent years a number of eudesmane acids have been isolated from natural sources⁷. However the synthesis of this particular kind of compound have received little attention. In association with our synthesis work on eudesmane-type sesquiterpenes, we have been interested in studying the synthetic approaches to this kind of compound, in particular the synthesis of compounds with structure as shown in **1**^{7a}, **2**^{7d}, **3**^{7d} and **4**^{7f}. Herein, we report the asymmetric synthesis of (+)-3-oxoeudesma-4,11(13)-dien-12-oic acid **4**, which was isolated from Mexican genus *Eupatorium*^{7f} and *X. pungens*^{7g}, starting from (+)-dihydrocarvone **5**⁸. (+)-12-hydroxy- α -cyperone **6** and (+)-12-oxo- α -cyperone **7** are two new 12-oxyfunctionized eudesmane derivatives, isolated from *Artemisia afra*^{7b} and the roots of *C. uncatu* Cunn. ex DC^{7c}, respectively. As a part of our work, compounds **6** and **7** have been obtained as intermediates and their syntheses are also reported.



Our synthetic strategy can be divided into two sections: first to construct the eudesmane skeleton with the correct configuration at C-7 and C-10 positions [(+)- α -cyperone **8** and its derivatives are the ideal compounds] and then to convert it to eudesmane acid by introduction of a hydroxyl group to its C-12 position and further oxidation of the hydroxyl group. Hence, in our synthesis works on these compounds, (+)- α -cyperone **8** is needed as a key intermediate.

In the literature, a number of synthetic routes to (+)- α -cyperone **8** have been reported⁹. But these methods have shortcomings: yields of some routes are poor^{9f}, while some routes with good overall yields (20-40%) are too long and tedious^{9a-9e}. In order to make our synthetic routes to eudesmane acids more efficient, we have developed a novel diastereoselective preparation of (+)- α -cyperone starting from (+)-dihydrocarvone **5** with an overall yield of 50% (scheme). The key step involves an asymmetric Michael addition of chiral imine **9** to ethyl



Reagents and conditions: a) R-(+)- α -phenylethylamine, *p*-TsOH, toluene, reflux, 24 h; b) i. EVK, toluene, 40°C, 24 h, ii. 50% aq. AcOH, toluene, 2 h, 77% from **5**; c) KOH, EtOH, 0°C, 3h, 65%; d) Vilsmeier reagent, 30% H_2O_2 , CH_2Cl_2 , -15°C 1h, 61%; e) i. NaI, acetone, r.t., 3h, ii. Cu_2O , DMSO, H_2O , 50-60°C, 4h, 82% from **13**; f) MnO_2 , CH_2Cl_2 , r.t., 6h, 96%; g) AgNO_3 , KOH, EtOH, r.t., 1h, 79%

scheme

vinyl ketone(EVK). The imine **9** was easily prepared from **5** and commercially available R-(+)- α -phenylethylamine by azotropic removal of water in refluxing toluene in the presence of catalytic amount of *p*-toluenesulfonic acid¹⁰. Without isolation, the imine **9** reacted with EVK directly in toluene at 40°C¹¹. After hydrolysis ($\text{AcOH-H}_2\text{O}$), the Michael adduct **10** was obtained in 71% diastereomeric excess. The diastereomeric excess was determined by the integration of 2-methyl protons, which appeared at δ 1.14 ppm for **10** and δ 1.01ppm¹² for **11** in their ^1H NMR spectra, and it can also be determined by the integration of 2-methyl carbons appeared at δ 23.07 ppm for **10** and δ 22.04 ppm¹² for **11** in their ^{13}C NMR spectra. The mixture of **10** and **11** cannot be separated by flash chromatography. So compound **10** (mixture of **10/11**= 6/1)

required careful cyclization and selective dehydration (KOH/EtOH, 0 °C, 3h)¹³ to give enantiomerically pure (+)-**8** and ketol **12**¹⁴, which were easily separated by flash chromatography.

Previously we have reported the introduction of a hydroxyl group to C-12 position of eudesma-4, 11(13)-dien-3, 9-dione has been achieved by an ene-type chlorination as a key step¹⁵. By this method, we successfully introduced a hydroxyl group to the C-12 position of (+)- α -cyperone **8**. On treatment with hydrogen peroxide/Vilsmeier reagent system¹⁶, **8** was converted to allylic chloride **13** in 61% yield. Compound **13** was transformed (NaI, acetone) to reactive iodide, which without purification was hydrolyzed (Cu₂O, DMSO, H₂O) to (+)-12-hydroxy- α -cyperone **6**. Oxidation of **6** with manganese dioxide in methylene dichloride generated (+)-12-oxo- α -cyperone **7** in 96% yield. Following the published procedure¹⁷, allylic aldehyde **7** was oxidized (AgNO₃, KOH, EtOH) at r.t. for one hour to acid **4** in 79% yield. The spectral data of the synthetic products are fully consistent with structures **4**, **6** and **7** and identical with literature data^{7b, c, f} of natural products. Their specific rotations were first determined.

Thus, the title compounds **4**, **6** and **7** were synthesized from dihydrocarvone **5** with overall yields of 25%, 24% and 19%, respectively. The proposed diastereoselective procedure for (+)- α -cyperone **8** and the employment of an ene-type chlorination as a key reaction to introduce a hydroxyl group at C-12 position of eudesmane derivatives are the core of our efficient synthetic route and they may provide an efficient route to other natural eudesmane acids.

The synthesis of **1**, **2** and **3** from (+)- α -cyperone **8** are in progress.

Experimental

Melting point is uncorrected. For column chromatography, 200-300 mesh silica gel and 60-90°C 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. ¹H and ¹³C NMR spectra were measured on a Bruker AM-400 or a Varian FT-80A spectrometer (TMS, CDCl₃). Mass spectra were determined on a V.G.ZAB-HS spectrometer (EI, 70 eV).

(+)-2-Methyl-2-(3-pentanonyl)-5-isopropenylhexanone **10**

A mixture of (+)-dihydrocarvone **5** (0.94 g), R-(+)- α -phenylethylamine (0.9 g, 1.2 eq.) and *p*-toluenesulfonic acid (10 mg) in toluene (15 mL) was heated at reflux under argon with azeotropic removal of water for 24 h. The solution was then cooled in an ice bath, ethyl vinyl ketone (0.55 g, 1.05 eq.) was added with a syringe under argon and the mixture was stirred and heated at 40°C for 24 h. To the resulted solution, cooled in an ice bath, a 50% aqueous acetic acid (4 mL) was added and the heterogeneous mixture was stirred at room temperature for 2 h. The reaction mixture was poured into brine (15 mL) and extracted with ether (3×20 mL). The organic layer was washed with 10% hydrochloric acid (2×15 mL), water (20 mL), brine (2×15 mL) and dried (Na₂SO₄). After removal of the solvents, the oily residue was chromatographed on silica gel eluting with

PE:ether (15:1) to give the mixture of **10** and **11** in the ratio 6:1 (1.12 g, 77% from **5**) as a light yellow oil. $[\alpha]_D^{22} +56.5$ ($c=1.3$, CHCl_3); IR: $\nu(\text{cm}^{-1})$ 1708, 1457, 1377, 894; $^1\text{H NMR}(400 \text{ MHz})$: $\delta(\text{ppm})$ 1.05(t, 3H, $J=7.4 \text{ Hz}$), 1.14(s, 3H, 2-Me), 1.74(s, 3H, MeC=C), 4.72, 4.79(each brs, 2H, C=CH₂); $^{13}\text{C NMR}(100 \text{ MHz})$: $\delta(\text{ppm})$ 7.79, 20.63, 23.07, 25.79, 31.60, 35.76, 36.58, 37.27, 43.20, 45.62, 46.90, 110.04, 147.21, 211.34, 214.73; EIMS: $m/z(\%)$ 236(M^+ , 22), 207(10), 179(15), 152(90), 137(15), 121(30), 109(90), 57(100).

(+)- α -Cyperone 8

To a solution of **10** (mixture of **10** and **11**, 260 mg) in ethanol (10 mL) was added 5% ethanolic KOH at 0°C, and the mixture was stirred at this temperature for 3 h. The reaction mixture was neutralized with acetic acid. After removal of the solvent, the residue was dissolved in water (10 mL) and extracted with ether (3×20 mL). The organic layer was washed with brine (2×10 mL) and dried (Na_2SO_4). The solvent was removed and the crude products were purified by silica gel chromatography using PE:ether (6:1) as eluent to afford **8** (155 mg, 65%) and ketol **12** (30 mg). **8**: $[\alpha]_D^{22} +112.5$ ($c=0.8$, CHCl_3) [lit.^{9b}, $[\alpha]_D^{14} +111.7$ ($c=1.2$, CHCl_3)]; $^1\text{H NMR}$ (80 MHz): $\delta(\text{ppm})$ 1.23(s, 3H, 10-Me), 1.76(s, 6H, 4-Me and 11-Me); 4.79(brs, 2H, 12-H). **12**: IR: (cm^{-1}) 3515, 3072, 1694; $^1\text{H NMR}(80 \text{ MHz})$: $\delta(\text{ppm})$ 1.02(d, 3H, $J= 6.8 \text{ Hz}$, 4-Me), 1.23(s, 3H, 10-Me), 1.68(s, 3H, 11-Me), 4.66(brs, 2H, 12-H).

(+)-12-Chloro- α -cyperone 13

To a well stirred mixture of **8** (170 mg) and 30% H_2O_2 (5 mL) was added dropwise the Vilsmeier reagent¹⁶ (3 mL) in CH_2Cl_2 (6 mL) in 10 minutes at -15°C under argon, and the mixture was further stirred at this temperature for 50 minutes. The two-phase reaction solution was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic fractions were washed with water (2×10 mL), 10% aqueous Na_2SO_4 (10 mL), brine (2×10 mL) and dried (MgSO_4). After removal of the solvents, the oily residue was chromatographed on silica gel (eluent: PE:ether 6:1) to yield **13** (120 mg, 61%) as a yellow oil. $[\alpha]_D^{22} +96.0$ ($c=1.25$, CHCl_3); IR: (cm^{-1}) 1663, 1611; $^1\text{H NMR}(400 \text{ MHz})$: $\delta(\text{ppm})$ 1.24(s, 3H, 10-Me), 1.77(s, 3H, 4-Me), 4.19(brs, 2H, 12-H), 5.00, 5.13(each brs, 2H, 13-H); EIMS: $m/z(\%)$ 254(M^++2 , 32), 252(M^+ , 95), 237(40), 217(65), 195(40), 175(37), 161(35), 136(100); Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{OCl}$: C, 71.27, H, 8.37. Found: C, 70.94; H, 8.14%.

(+)-12-Hydroxy- α -cyperone 6

A mixture of **13** (80 mg) in acetone (5 mL) and NaI (70 mg) was stirred at room temperature for 3 h. After removal of the solvent, CH_2Cl_2 (10 mL) was added to the residue and the resulted suspension was filtered. The filtrate was evaporated to give allylic iodide as a yellow oil. Without purification, the crude iodide was dissolved in DMSO (3 mL) and water (5 mL), and to this solution was added Cu_2O (80 mg). The suspension was stirred

and heated at 50-60°C for 4 h. After filtering, the solution was extracted with ether (3×15 mL) and the organic phase was washed with water (2×10 mL), brine (2×10 mL) and dried (MgSO₄). The crude product was purified by silica gel chromatography using PE:ether (5:1) as eluent to afford **6** (60 mg, 82% from **13**) as a colourless oil. $[\alpha]_D^{22} +84.0$ (c=1.1, CHCl₃); IR: $\nu(\text{cm}^{-1})$: 3398(OH), 1659, 1607; ¹HNMR (400 MHz): $\delta(\text{ppm})$ 1.24(s, 3H, 10-Me) 1.77(s, 3H, 4-Me), 4.19(brs, 2H, 12-H), 5.00, 5.13(each brs, 2H, 13-H); EIMS: m/z(%) 234(M⁺, 15), 216(83), 201(100), 187(37), 173(40), 159(68), 145(50), 105(55), 91(80).

(+)-12-Oxo- α -cyperone **7**

To a solution of **6** (40 mg) in CH₂Cl₂ (5 mL) was added MnO₂ (0.5 g) and the mixture was stirred at room temperature for 6 h. After filtering, the filtrate was concentrated and oily residue was chromatographed on silica gel eluting with PE:ether (5:1) to give **7** (38 mg, 96%) as a yellow oil. $[\alpha]_D^{22} +109.1$ (c=1.1, CHCl₃); IR: $\nu(\text{cm}^{-1})$ 1691, 1662, 1610; ¹HNMR (400 MHz): $\delta(\text{ppm})$ 1.25(s, 3H, 10-Me), 1.77(s, 3H, 4-Me), 6.07, 6.35 (each brs, 2H, 13-H), 9.57(s, 1H, 12-H); EIMS: m/z(%) 232(M⁺, 28), 217(27), 203(20), 177(100), 161(30), 135(36), 105(48), 91(68).

(+)-3-Oxo-eudesma-4,11(13)-dien-12-oic acid **4**

To a stirred solution of AgNO₃ (40 mg) in distilled water (2 mL) was added a solution of **7** (18 mg) in ethanol (1 mL). Then 0.4 mL of aqueous KOH (2.1 g KOH dissolved in 35 mL of distilled water) was added dropwise to the mixture, giving immediately a black suspension. After stirring at room temperature for 1 h, the reaction mixture was filtered and the black silver precipitate was washed with water (5 mL). The filtrate was acidified (to pH=1) with 10% chlorhydric acid and extracted with CH₂Cl₂ (3×10 mL). The organic layer was washed with brine (10 mL) and dried (Na₂SO₄). Silica gel chromatographic purification eluting with PE: ether: HOAc (6:1:0.05) yielded **4** (15 mg, 79%) as a colourless crystal. $[\alpha]_D^{22} +73.9$ (c=0.44, CHCl₃); mp 152-153°C; IR: $\nu(\text{cm}^{-1})$ 3066(br), 1703, 1664, 1623, 1602; ¹HNMR (400 MHz, C₆D₆): $\delta(\text{ppm})$ 0.77(s, 3H, 10-Me), 1.89(s, 3H, 4-Me), 5.26, 6.32(each brs, 2H, 13-H). EIMS: m/z(%) 248(M⁺, 95), 233(100), 215(28), 191(35), 137(51), 111(40), 91(65). Anal. Calcd for C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.29; H, 8.02%.

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REFERENCES AND NOTES:

1. Roberts, J. S.; Bryson, I., *Nat. Prod. Rep.* **1984**, *1*, 105. Fraga, B. M. *Nat. Prod. Rep.* **1985**, *2*, 147; **1986**, *3*, 273; **1987**, *4*, 473; **1988**, *5*, 497; **1990**, *7*, 515; **1992**, *9*, 217; **1992**, *9*, 515; **1993**, *10*, 397; **1994**, *11*, 533.
2. Endo, K.; Taguchi, T.; Taguchi, F.; Hikino, H.; Yamahara, J.; Fujimura, H., *Chem. Pharm. Bull.* **1979**, *27*, 2954.

3. Iguchi, K.; Mori, K.; Suzuki, M.; Takahashi, H.; Yamada, Y., *Chem. Letters* **1986**, 1789.
4. Kubo, I.; Ying, B. P.; Castillo, M.; Brinen, L. S.; Clardy, J., *Phytochemistry* **1992**, *31*, 1545.
5. Delgado, G.; Garcia, P. E.; Bye, R. A.; Linares, E., *Phytochemistry* **1991**, *30*, 1761.
6. (a) Heathcock, C. H., In *The Total Synthesis of Natural Products*; Apsimon, J., Ed., John Wiley & Sons: New York, 1973; Vol. 2, Chapter 2. (b) Roberts, J. S., *Nat. Prod. Rep.* **1985**, *2*, 97.
7. For examples, see: (a) Barbetti, P.; Chiappini, I.; Fardella, G. and Menghini, A., *Planta Med.*, **1985**, 471. (b) Jakupovic, J.; Klemeyer, H.; Bohlmann, F. and Graven, E. H., *Phytochemistry*, **1988**, *27*, 1129. (c) Zdero, C.; Bohlmann, F.; Anderberg, A. and King, R. M., *ibid*, **1991**, *30*, 2643. (d) Ceccherelli, P.; Curini, M.; Marcotullio, M. C. and Menghini, A., *ibid*, **1985**, *24*, 2987. (e) Jakupovic, J.; Lehmann, L.; Bohlmann, F.; King, R. M. and Robinson, H., *ibid*, **1988**, *27*, 2831. (f) Bohlmann, F.; Jakupovic, J. and Lonitz, M., *Chem. Ber.*, **1977**, *110*, 301. (g) Ahmed, A. A.; Jakupovic, J.; Bohlmann, F.; Regaila, H. A. and Ahmed, A. M., *Phytochemistry*, **1990**, *29*, 2211.
8. Chen, X.; Shao, S. C.; Li, T. S. and Li, Y. L., *Synthesis*, **1992**, 1061.
9. For representative examples, see: (a) Agami, C.; Kadouri-Puchot, C. and Le Guen, V., *Tetrahedron: Asymmetry*, **1993**, *4*, 641. (b) Li, Y. L.; Chen, X.; Shao, S. C. and Li, T. S., *Synth. Commun.*, **1993**, *23*, 2457. (c) Haaksma, A. A.; Jansen, B. J. M. and de Groot, A., *Tetrahedron*, **1992**, *48*, 3121. (d) Murai, A.; Abiko, A.; Ono, M. and Masamune, T., *Bull. Chem. Soc. Jpn.*, **1982**, *55*, 1191. (e) Caine, D. and Gupton, J. T., *J. Org. Chem.*, **1974**, *39*, 2654. (f) Howe, R. and McQuillin, F. J., *J. Chem. Soc.*, **1955**, 2423.
10. (a) Pfau, M.; Revial, G.; Guingant, A. and D'Angelo, J., *J. Am. Chem. Soc.*, **1985**, *107*, 273; (b) D'Angelo, J.; Desmaele, D. and Guingant, A., *Tetrahedron: Asymmetry*, **1992**, *3*, 459.
11. Revial, G. and Pfau, M., *Organic Synthesis*, **1992**, *70*, 35.
12. Enantiomerically pure **11** has been synthesized in our previous work, see: Xiong, Z. M.; Yang, J.; Li, Y. L.; Liao, R. A. and Li, Z. M., *Chin. Chem. Lett.* **1996**, in press.
13. Tenius, B. S. M.; de Oliveira, E. R., *Tetrahedron: Asymmetry*, **1993**, *4*, 633.
14. Nan, F. J.; Chen, X.; Xiong, Z. M.; Li, T. S. and Li, Y. L., *Synth. Commun.*, **1994**, *24*, 2319.
15. Chen, X.; Li, T. S.; Nan, F. J.; Shao, S. C. and Li, Y. L., *Tetrahedron*, **1993**, *49*, 3075.
16. Rodriguez, J. and Dulcere, J. P., *Synlett*, **1991**, 477.
17. Shamma, M. and Rodriguez, H. R., *Tetrahedron*, **1968**, *24*, 6583.

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