Chinese Chemical Letters Vol. 16, No. 5, pp 569-571, 2005
http://www.imm.ac.cn/journal/ccl.html

Total Synthesis of Two 4, 5-Dioxo-*seco*-eudesmane Sesquiterpenes

Li Jing FANG, Chen Xi ZHANG, Jin Chun CHEN, Guo Jun ZHENG, Yu Lin LI*

State Key Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry,
Lanzhou University, Lanzhou 730000

Abstract: A facile synthetic route to two *seco*-eudesmane, 4, 5-dioxo-10-*epi*-4, 5-*seco*-γ-eudesmane (**1**) and 4, 5-dioxo-10-*epi*-4, 5-*seco*-γ-eudesmol (**2**) from (+)-dihydrocarvone has been described. Avoiding expensive reagents, this highly economic method especially suits for the synthesis of 4, 5-*seco*-eudesman-type and ophianon-type sesquiterpenes with a double bond at position 11 and 12.

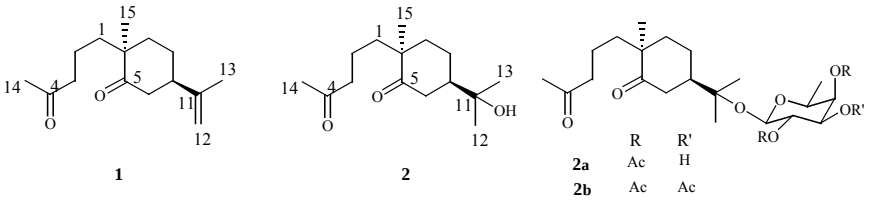
Keywords: (+)-Dihydrocarvone, 4, 5-dioxo-*seco*-eudesmane, sesquiterpenes.

In recent years, 4, 5-dioxo-*seco*-eudesman-type and iphionan-type sesquiterpenes have been found in natural sources that used as folk medicines in many countries[1-5]. For example, *Cyperous rotundus* is a traditional plant used for the treatment of stomach and bowel disorders in Japan. In 1998, 4, 5-dioxo-10-*epi*-4, 5-*seco*-γ-eudesmane (**1**) and its 10-epimer were isolated by Ohira *et al.* from the root of this kind of plant[1]. *Phonus arborescens* is another medical plant found widely in the Spanish South-East and North Africa from which 4, 5-dioxo-10-*epi*-4, 5-*seco*-γ-eudesmol 2′-*O*-acetyl- β -D- fucopyranoside (**2a, b**) were isolated and identified by Barrero *et al.* in 1997 [2].

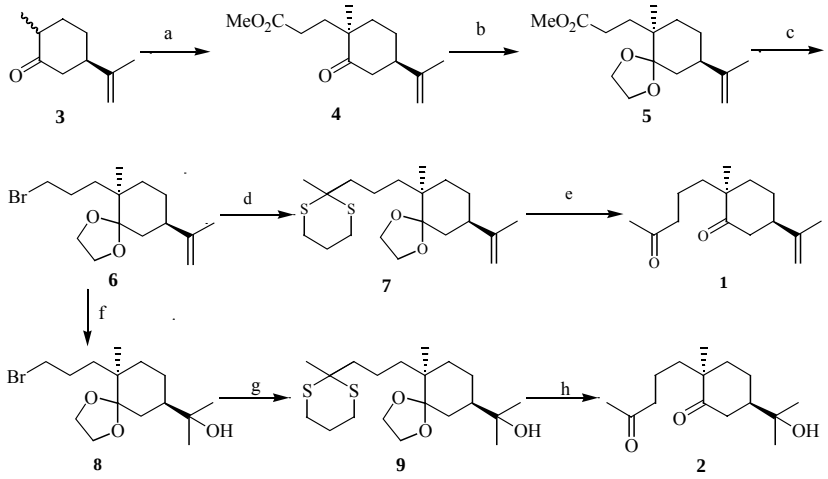
To our best knowledge, the study on the total synthesis of this type of sesquiterpenes was limited to two methods. One was *via* condensation of (+)-dihydrocarvone with 2-(3-iodopropyl)-2-methyl-1, 3-dioxolane in low yield (<10%)[1]. The other generated the 4, 5-dioxo founctional group by ozonolysis of the double bond in (+)-γ-eudesmol with high overall yield [6-8]. However, this method need the expensive reagents EVK and chiral phenylethylamine. And it is also limited to the synthesis of a *seco*-sesquiterpene or iphionane with the 11, 12-double bond, which should be destroyed in ozonolysis step.

In connection with our efforts towards the asymmetric synthesis of biologically active sesquiterpenes, we now introduce a novel and efficient approach to 4, 5-dioxo-*seco*-eudesmane, involving the asymmetric Michael addition and the coupling of alkyl bromide with 2-lithio-1, 3-dithiane as key steps. Avoiding EVK and *S*-(-)-phenylethylamine, the compound **1,** a natural *seco*-eudesmane with a 11, 12-double bond, together with aglycone **2** were synthesized in five and six steps with excellent overall yields.

* E-mail: liyl@lzu.edu.cn



Scheme 1



Reagents and conditions: a) methyl acrylate, K_2CO_3, *t*-BuOH, reflux, 12 h, 85%; b) glycol, PPTS, C_6H_6, reflux, 4 h, 94%; c) $LiAlH_4$, ether, r.t., 1 h then CBr_4, Ph_3P, CH_2Cl_2, r.t., 0.5 h, 96%; d) 2-methyl-1, 3-dithiane, *n*-butyllithium, THF, -40^{0}C, 2 h, then bromide **6**, -20^{0}C, 14 h, 84%; e) DDQ, CH_3CN/H_2O (9:1), 10 h, 91%; f) *m*CPBA, CH_2Cl_2, r.t., 24 h then $LiAlH_4$, ether, r.t., 10 h, 72% ; g) same as step d (81%); h) same as step e (92%).

The synthesis was commenced with the commercially available (+)-dihydrocarvone (**3**). Compound **4** was easily prepared in 85% yield with >95% diastereomeric excess by refluxing the mixture of methyl acrylate, anhydrous K_2CO_3 and compound **3** in *tert*-butanol for 24 h. The high *de* data was due to the methyl acrylate attacking from the vertical side in the stable conformation of ketone **3**[9]. Following the step of ketone protecting of the ester **4** with glycol, compound **5** was obtained in 94% yield. After a $LiAlH_4$ reduction, the crude product was treated with CBr_4 and PPh_3 to afford bromide **6** in 96% yield. Then underwent the coupling reaction of bromide **6** with 2-lithio-2-methyl-1, 3-dithiane and compound **7** was easily obtained in 84% yield. With prolonged reaction time, the deprotections of the 1, 3-dithiane and 1, 2-dioxolane functional groups could be realized in one step by DDQ in excellent yield (91%). Thus, compound **1**, a *seco*-eudesman-type natural product which has a double bond at position 11 and 12, was synthesized through five steps with 59% overall yield.

Alcohol **8** was easily obtained in 72% yield by epoxidation of bromide **6** with *m*CPBA and reduction of the corresponding crude product with $LiAlH_4$. Because of the additional hydroxy group, two equivalent of 2-lithio-2-methyl-1, 3-dithiane was needed in the coupling step and alcohol **9** was easily obtained in 81% yield. After the same

procedure of deprotection, compound **2**, a *seco*-eudesmane with a hydroxy at position 12 was prepared in 92% yield.

In summary, the enantioselective synthesis of 4, 5-dioxo-10-*epi*-4, 5-*seco*-γ-eudesmane **1** and 4, 5-dioxo-10-*epi*-4, 5-*seco*-γ-eudesmol **2** has been accomplished in five and six steps, respectively. The spectra data of the synthetic compound **1** and **2** are identical with the natural products[1, 2]. The application of the present methodology to the synthesis of more complex biologically active sesquiterpenes will be investigated in due course.

Acknowledgment

This work was financially supported by the National Natural Science Foundation of China (No. 20272021).

References and Notes

1. S. Ohira, T. Hasegawa, K. Hayashi, *et al*., *photochemistry*, **1998**, *47*, 1577.
2. A. F. Barrero, P. Arteaga, J. F. Quilez, I. Rodriguez, M. M. Herrador, *J. Nat. Prod.*, **1997**, *60*, 1026.
3. a) F. Bohlmann, C. Zdero, R. M. King, H. Robinson, *Lieb. Ann. Chem.*, **1983**, 2227; b) G. Appendino, P. Gariboldi, M. Callin, G. Chiari, D. Viterbo, *J. Chem. Soc. Perkin trans. I*, **1983**, 2705.
4. a) M. G. El-Ghazouly, N. A. El-Sebakhy, A. A. S. El-Din, C. Zdero, F. Bohlmann, *Phytochemistry*, **1987**, *26*, 439; b) A. A. Ahmed, A. A. S. El-Din, *J. Nat. Prod.*, **1990**, *53*, 1031.
5. L. V. Castillo, A. M. D. Lanza, R. Faure, *et al*., *Phytochemistry*, **1995**, *40*, 1193.
6. Z. M. Xiong, G. Zhou, X. L. Gao, Y. G. Chen, Y. L. Li, *Chin. Chem. Lett.*, **2000**, *11*, 113.
7. Z. Zhang, Z. M. Xiong, G. J. Zheng,. Y. L. Li, *Tetrahedron: Asymmetry,* **2001**, *12*, 2137.
8. X. L. Gao, Z. M. Xiong, G. Zhou, Y. L. Li, *Synthesis*, **2001**, *1*, 37.
9. Howe and F. J. McQuillin, *J. Chem. Soc.*, **1955**, 2423.
10. Spectral data of **1**: $[\alpha]_D^{26}$ +118 (c 1.1, $CHCl_3$); IR (film) λ_{max} 2932, 2878, 1176, 1129, 1092, 1038, 952, 888 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm) 1.02 (s, 3 H,10-Me), 1.73 (s, 3 H, 11-Me), 2.11 (s, 3 H, 4-Me), 4.71 (br s, 1 H, 12-H), 4.76 (br s, 1 H, 12-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 17.96, 20.60, 21.95, 25.96, 29.90, 36.51, 38.17, 43.39, 43.56, 46.26, 47.97, 109.80, 147.50, 208.31, 215.23; EIMS: *m/z* (%): 236 (M^+),152, 121, 109, 95, 81, 43 (100); Spectral data of **2**: $[\alpha]_D^{26}$ +103 (c 0.6, $CHCl_3$); IR (film) λ_{max} 3416, 2967, 2936, 1703, 1369, 1165, 1123, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 1.01 (s, 3 H, 10-Me), 1.21 (s, 3 H, 11-Me), 1.22 (s, 3 H, 11-Me), 1.86-1.91 (d, 1 H, *J*=10.5 H_Z), 2.11 (s, 3 H, 4-Me), 2.39-2.43 (m, 4 H); ^{13}C NMR (75 HMz, $CDCl_3$, δ ppm) 17.92, 21.52, 21.70, 27.17, 27.44, 29.93, 36.28, 38.28, 39.80, 43.48, 47.80, 71.99, 208.40, 215.93; EIMS: *m/z* (%): 254 (M^+), 239, 221, 203, 196, 178, 170, 152, 135, 112, 111, 95, 81, 71, 59, 43 (100).

Received 26 May, 2004