Chinese Chemical Letters Vol. 15, No. 11, pp 1273-1275, 2004 1273
http://www.imm.ac.cn/journal/ccl.html

A Novel Synthesis of (-)-10-*epi*-α-Cyperone

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Abstract: An alternative route for the synthesis of (-)-10-e*pi*-α-cyperone **1** starting from (+)-dihydrocarvone **2** is described by using an asymmetric Michael addition as a key step. The route features more efficiently and can be performed in large scale.

Keywords: (-)-10-*epi*-α-Cyperone, (+)-dihydrocarvone.

The eudesmane derivative, (-)-10-*epi*-α-cyperone **1**, is widely used as a chiral starting material for the synthesis of other fused-ring sesquiterpenes[1]. The first synthetic work was reported by Howe and co-workers *via* condensation of (+)-dihydrocarvone **2** with 1-diethylaminopentan-3-one methiodide in 32% yield[2]. Previously, our group reported the synthesis of compound **1** by treating ketone **2** with ethyl vinyl ketone (EVK) directly under different conditions[1a], but the yields were not satisfactory (nearly 40%). Soon after that, our laboratory reported an improved route[3], using an asymmetric Michael addition of the corresponding chiral imine, derived from ketone **2** to EVK, and better yield (72%) was obtained with higher diastereomeric excess (>95%). But there still were two problems. One was the need of expensive reagents EVK and S-(-)- phenylethylamine. The other was the bad repetition of the cyclization yield (only nearly 60%). Thus, the preparation in large scale was limited.

In connection with our efforts towards the asymmetric synthesis of dihydro-β-agarofuran and eudesmane type natural products, we found a novel and more efficient way for the synthesis of ketone **1**, involving the Michael addition and dehydroxy as key steps. The result was achieved with higher steroselectivity and comparable total yield. The detailed pathway of synthesis is summarized in **Scheme 1**.

It commenced from the commercially available (+)-dihydrocarvone **2**. In the presence of 2 eq anhydrous K_2CO_3, compound **3** was easily prepared in 85% yield with >95% diastereomeric excess when ketone **2** and methyl acrylate was refluxed in *tetr*-butanol for 24 h. The methyl acrylate attacked from the vertical side in stable conformation of ketone **2**[2]. Then ester **3** was protected with glycol to give compound **4** in 94% yield. Following a DIBAL reduction, aldehyde **5**, a useful intermediate in the synthesis of 4,5-dioxo-*seco*-eduesmane and iphionane, was obtained in 95% yield. We

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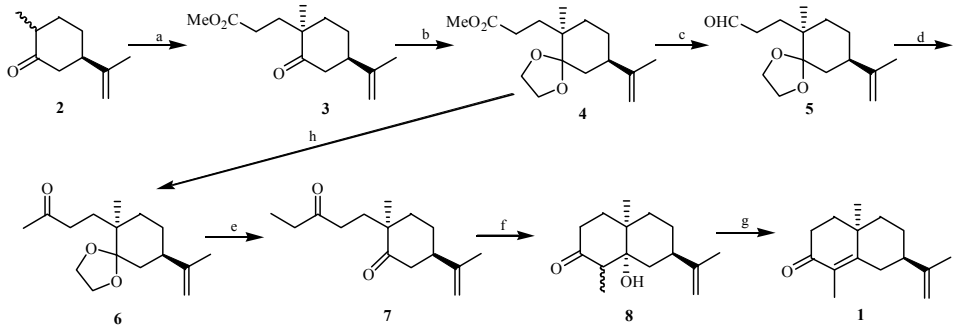
Scheme 1



Reagents and conditions: a) CH_2=CHCOOMe, K_2CO_3, reflux, 12 h, 85%; b) glycol, PPTS, C_6H_6, reflux, 4 h, 94%; c) DIBAL, CH_2Cl_2, -78 ^{0}C, 0.5 h, 95% or $LiAlH_4$, ether, r.t.1 h then PCC, CH_2Cl_2, r.t., 3 h, 86% (two steps); d) i. EtMgBr, Et_2O, r.t., 0.5 h; ii. PCC, CH_2Cl_2, r.t., 7 h, 88%; e) PPTS, acetone, H_2O, reflux, 3 h, 91%; f) MeONa, MeOH, r.t., 3 h, 100%; g) MsCl, Et_3N, CH_2Cl_2, r.t., 12 h, 98%; h) EtMgBr, HMPT, 80^{0}C , 15%.

also afforded compound **5** in 86% yield by reduction with $LiAlH_4$ and oxidation the crude alcohol product with PCC. We attempted to obtain ketone **6** in one step by treating compound **5** with EtMgBr/HMPT, but the yield was very poor (15%) (step h). Thus, we adopted two steps to improve the yield. First, aldehyde **5** was reacted with EtMgBr/Et_2O, then the crude products were oxidized by PCC and ketone **6** was obtained in 88% yield. After deprotection, diketone **7**, the cyclization former, was gained in 91% yield. We successfully improved the cyclization yield *via* two steps. First, former **7** was treated with NaOMe/MeOH at room temperature to afford alcohol **8** in nearly 100% yield, then the product was stirred in the solution of MsCl/Et_3N overnight to afford (-)-10-*epi*-α-cyperone **1** in 98% yield.

In summary, ketone **1**, a popular starting material widely used in the synthesis of eudesmane and agarofuran type sesquiterpenes, was synthesized in seven steps with 59% overall yield. Compared with literature methods, the expensive reagents, EVK and S-(-)-phenylethylamine, were avoided and the large scale preparation became easy work.

Acknowledgment

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

References and Notes

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3. Z. M. Xiong, Y. L. Li, R. N. Liao, Z. M. Li, *J. Chem. Research(s)*, **1996**, 477.

4. Spectral data of **3**: $[\alpha]_D^{26}$ +9 (*c*=2.4, $CHCl_3$); IR (film) λ_v 2928, 1740, 1706, 1439, 1199, 1175, 893 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$, δ ppm): 1.00 (s, 3 H, 10-Me), 1.72 (s, 3 H, $MeC=CH_2$), 3.64 (s, 3H, Me-O), 4.70 (brs,1H,HC=C), 4.76 (brs,1H, HC=C); ^{13}C NMR (75 HMz, $CDCl_3$, δ ppm): 20.63, 21.81, 25.84, 28.75, 32.06, 38.26, 43.36, 46.08, 47.28, 51.66, 109.98, 147.24, 173.74, 214.59; EIMS: *m/z* (%): 238 (M^+, 12), 206(23), 152(17), 151(16), 123(30), 95(67), 81(74), 67(92), 55(87), 41(100). Spectral data of **1**: $[\alpha]_D^{26}$ -198 (*c*=0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.23 (s, 3 H, 10-Me), 1.72 (s, 3 H, 11-Me), 1.81 (s, 3 H, 4-Me), 4.61 (brs, 1 H, 12-H), 4.80 (brs, 1H, 12-H); ^{13}CNMR (75 HMz, $CDCl_3$, δ ppm): 10.95, 22.55, 23.10, 31.10, 33.96, 35.84, 35.89, 37.54, 40.95, 52.53,111.00, 129.17, 147.40, 162.91, 198.71.

Received 9 October, 2003