First Total Synthesis of (+)-Chrysanthemol

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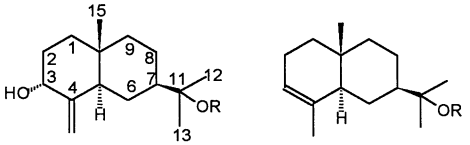
The first total synthesis of (+)-chrysanthemol (**1**) has been described starting from (+)-dihydrocarvone (**4**). The features of our synthesis are the high yield introduction of C_3-C_4 double bond into eudesmane skeleton and rearrangement of epoxide to allylic alcohol promoted by BF_3•OEt_2-Bu_4NI reagent. In our synthesis, (+)-α-eudesmol (**5**) has been used as a key intermediate.

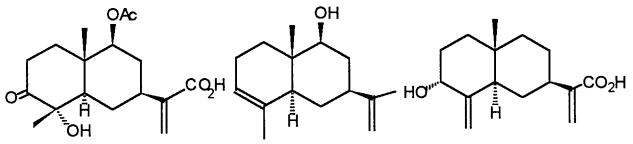
Chrysanthemum indicum L. is a traditional Chinese medicine in common use.[1] It has functions of antipyretion, detoxification and reducing blood pressure as known before. In recent years, clinic indicates that the preparation of *Chrysanthemum indicum L.* has fairly good effects on chronic pelvic carity inflammation, pelvic carity tuberculosis and prostrate gland inflammation. The pharmacodynamics study demonstrates that it can resist bacteriums, control blood platelet aggregation, expand coronary, and reduce blood pressure.

In 1987, Yu and Xie[1] isolated (+)-chrysanthemol (**1**) from the flower of *Chrysanthemum indicum L.* and elucidated its structure on the basis of spectral and chemical evidence. Chrysanthemol showed strong antiinflammatory activity. At the same time, El-Ghazouly *et al*[2] isolated sesquiterpene α-xylopyranosides **2** and **3** from the aerial parts of *Iphiona scarbra*.. Herein we report the first total synthesis of **1** from (+)- dihydrocarvone **4**. In our synthesis, (+)-α-eudesmol **5**[3] has been obtained as a key intermediate.



1 R = H
2 R = oxyl

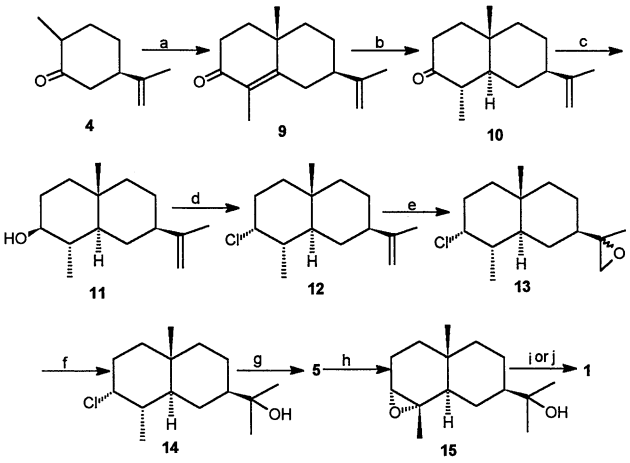
5 R = H
3 R = oxyl



6 **7** **8**

Our synthetic design is to employ (+)-α-eudesmol **5** as a key intermediate (Scheme 1). We think that the difficulty in the synthesis of (+)-α-eudesmol is to introduce a double bond at the C_3-C_4 position efficiently. Of eudesmane derivatives, many are functionalized at the C-3 and C-4 positions (for example, **6**,[4] **7**,[5] and **8**[6]) and there are many attempts for introduction of C_3-C_4 double bond.[7] But these reported methods have shortcomings. By some of them, an olefin mixture was obtained with low yields.[7a,b,c,e] By the others, only racemic products were obtained.[7d,f,g,h] Several of these attempts[7b,d,e,g] have been utilized in the synthesis of α-eudesmol. Herein we report an efficient synthetic route to (+)-α-eudesmol through elimination of halide to introduce C_3-C_4 double bond..

By the published method, (+)-α-cyperone **9** was stereoselectively prepared from (+)-dihydrocarvone **4** in two steps with an over all yield of 50%.[8] Stereospecific lithium-liquid ammonia reduction of **9**, using ammonium chloride as the proton donor, gave the dihydro-α-cyperone **10**.[7a] Utilizing the steric hindrances of 10β-methyl, stereoselective reduction of **10** by tri-t-butoxyaluminium hydride gave alcohol **11** in high yield. In a stereospecific manner, alcohol **11** was converted into its 3α-chloro derivative **12** by PPh_3-NCS in THF under milder condition.[9] The epoxidation of **12** with m-CPBA, followed by $LiAlH_4$ reduction afforded alcohol **14**, *via* an epoxide **13**. (+)-α-Eudesmol **5** can be obtained by elimination of the halide of compound **14** with LiBr-$LiCO_3$/DMF in high yield(90%).[10] Epoxidation of **5** with m-CPBA, in the presence of $NaHCO_3$, stereoselectively gave 3α,4α-epoxide **15.**



Scheme 1.

a. Ref. 8, 50%; b. Li, liq. NH_3, -78°C, 25 min, 86%; c. $LiAl(OBu^t)_3H$, THF, 18 h, 92%; d. PPh_3-NCS, THF, 3 h, 88%; e. m-CPBA, CH_2Cl_2, 40 min, 94%; f. $LiAlH_4$, Et_2O, 10 h, 92%; g. LiBr-Li_2CO_3, DMF, 138-140°C, 5 h, 90%; h. m-CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 30 min, 82%; i. BF_3•OEt_2-Bu_4NI, $CHCl_3$, 0°C, 10 min, 50%; j. $Al(OPr^i)_3$, toluene, reflux, 2.5 h, 48%.

The last step in the synthesis of the title compound **1** was to bring about regioselective rearrangement of epoxide **15** to an allylic alcohol moiety. In our work, we found that BF_3•OEt_2-Bu_4NI reagent can realize the rearrangement.[11] Treatment of **15** with BF_3•OEt_2-Bu_4NI, at 0 °C for 5 min, afforded **1** in 50% yield. The spectral data[12] of the synthetic product are fully consistent with structure **1** and identical with literature[1] data of natural product.

Rearrangement of epoxides to allylic alcohols is an important transformation in organic synthesis. In general, two different strategies have been utilized to effect this conversion.[13] Lithium di-isopropylamide (LDA) and $Al(OPr^i)_3$ are commonly used as the reagents for this rearrangement. But the use of LDA in microscale synthesis is difficult. The conversion of **15** to **1** was also realized by using $Al(OPr^i)_3$ under refluxing condition in 48% yield. It is suggested that BF_3•OEt_2-Bu_4NI may be a good

reagent for the rearrangement of epoxides to allylic alcohols under mild reaction condition. Further studies on using this reagent for rearrangement of epoxides to allylic alchols and on clarifying its mechanism are in progress.

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References and Notes

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11 BF_3 (mostly as the etherate) is widely used as Lewis acid for rearrangement of epoxides.[14] But most conversions of epoxides to unsaturated alcohols were accompanied with skeletal rearrangements.[15] To our knowledge, only Blunt *et al* have reported such conversion without skeletal rearrangement, but in low yield (15%).[16] The use of $BF_3 \bullet Et_2$-Bu_4NI was reported by Mandal *et al* [17] for the cleavage of ethers and conversion of epoxides to α-iodo-alcohols. The use of this reagent for rearrangement of epoxide to allylic alcohol has not been reported.
12 Spectral data of **1**, **5**.
Compound **1** $[\alpha]_D^{23}$ +5.6 (c 0.72, $CHCl_3$), mp 144-146 ^{0}C, (lit[1] $[\alpha]_D^{19}$ +5.8 (c 0.51, $CHCl_3$), mp 146-148 ^{0}C); IR: 3375 (br), 2935, 1649, 1451, 1380, 1049, 903, cm^{-1}; EIMS m/z (%): 238 (M^+, 3), 220 (5), 202 (4), 187 (6), 180 (21), 162 (28), 147 (42), 105 (24), 59 (100); ^{1}H NMR (80 MHz, $CDCl_3$): δ (ppm) 4.95 and 4.61 (brs, 1H each, 14-H), 4.31 (m, 1H, 4-H), 1.21 (s, 6H, 11-Me), 0.69 (s, 3H, 10-Me);
Compound **5** $[\alpha]_D^{23}$ +27 (c 0.59, $CHCl_3$), mp 74-76 ^{0}C, (lit[7b] $[\alpha]_D$ +28.5 (c 1.2), mp 75 ^{0}C); IR: 3302 (br), 2939, 1453, 1376, 1144, 797, cm^{-1}; EIMS m/z (%): 222 (M^+, 9), 204 (34), 149 (57), 107 (21), 93 (24), 91 (24), 59 (100); ^{1}H NMR (80 MHz, $CDCl_3$):δ (ppm) 5.33 (s, 1H, 3-H), 1.62 (s, 3H, 4-Me), 1.21 (s, 6H, 11-Me), 0.77 (s, 3H, 10-Me).
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