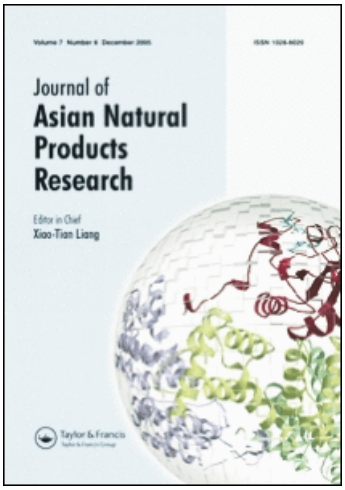


Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

Stereoselective Total Synthesis of Chrysanthemol

Li-Yuan Mou[a]; Li-Ya Zhu; Zi-Yun Lin[a]; Xiao-Tian Liang[a]
[a] Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking, Union Medical College, Beijing, China

To cite this Article Mou, Li-Yuan , Zhu, Li-Ya , Lin, Zi-Yun and Liang, Xiao-Tian(2001) 'Stereoselective Total Synthesis of Chrysanthemol', Journal of Asian Natural Products Research, 3: 2, 103 — 116
To link to this Article: DOI: 10.1080/10286020108041377
URL: http://dx.doi.org/10.1080/10286020108041377

JANPR, Vol. 3, pp. 103–116
Reprints available directly from the publisher
Photocopying permitted by license only

STEREOSELECTIVE TOTAL SYNTHESIS OF CHRYSANTHEMOL

LI-YUAN MOU, LI-YA ZHU*, ZI-YUN LIN
and XIAO-TIAN LIANG

Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

(Received 20 April 2000; In final form 10 May 2000)

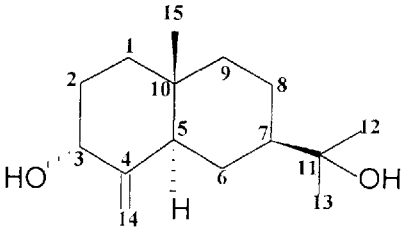
Chrysanthemol (**1**), a trans-eudesmane type sesquiterpene from *Chrysanthemum indicum* L., possesses certain anti-inflammatory activity. Its total synthesis was approached from two alternative routes and finally accomplished in ten steps from R-(+)-carvone *via* α-eudesmol (**10**) as the key intermediate. The overall yield is 2.4% and the spectral data of the synthetic target compound were identical with that of natural chrysanthemol (**1**). Seven intermediary compounds were tested for inhibitory effects on the carragenan-induced swelling of mouse paw but demonstrated no obvious activities.

Keywords: Chrysanthemol (**1**); Total synthesis; Anti-inflammatory activity

INTRODUCTION

Chrysanthemum indicum L., a traditional Chinese medicinal herb, is commonly used for antipyretic, antidote and antihypertension purposes. Pharmacological study shows that it has good antibiotic activity, resists bacteriums, controls blood platelet aggregation [1], expands coronary arteries, and reduces blood pressure. Its components are mainly terpenes [2]. Chrysanthemol (**1**) is a trans-eudesmane type sesquiterpene, isolated by Yu and Xie [3] from the polar lypophilic extracts of the flower of *Chrysanthemum indicum* L. and possesses significant anti-inflammatory activity. Its structure and absolute stereochemistry is elucidated on the basis of spectral and chemical evidence.

*Corresponding author. Tel.: 8610 63165254, Fax: 63017757, e-mail: zhuliya@imm.ac.cn



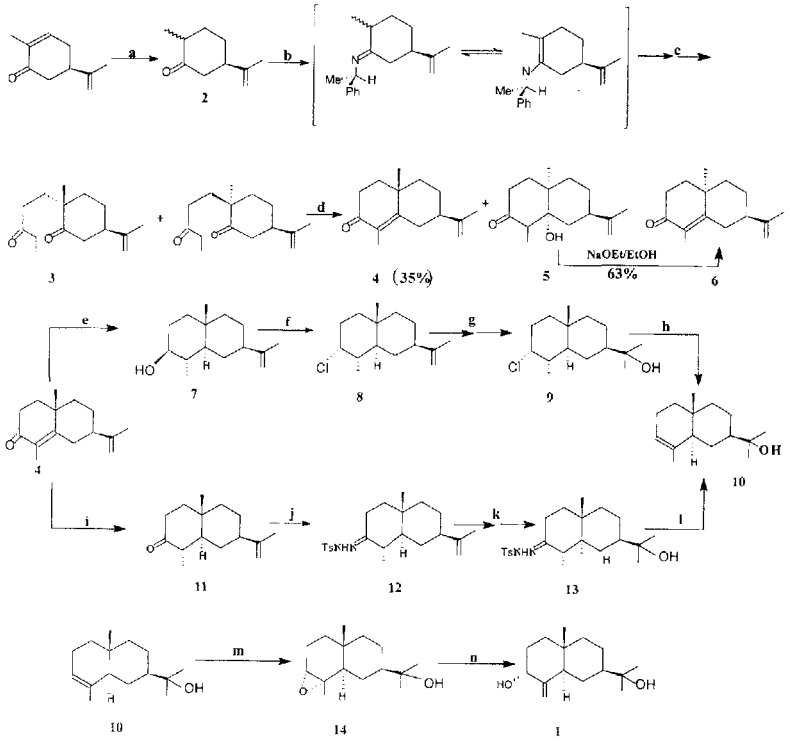
Chrysanthemol (**1**)

RESULTS AND DISCUSSION

The novel structure of chrysanthemol (**1**), compared with other anti-inflammatory drugs, makes its total synthesis worthwhile. Its stereoselective total synthesis was from **4** to **10**, two alternatives routes were taken as shown in Scheme 1 accomplished in ten steps from (R)-(+)-carvone *via* (+)-α-eudesmol (**10**) as the key intermediate.

The overall yield of ten steps in the first route was 2.4%, during which the key intermediate **10** was obtained from (+)-α-cyperone (**4**) *via* reduction by Na/propanol, chlorination by NCS/PPh_3, mercuration/reduction and elimination. The overall yield in the second route was 1.0% and the transformation from **4** to **10** was carried out through reduction by Li/NH_3, conversion to tosylhydrazone, oxymercuration/reduction and Bamford-Stevens reaction. The Bamford-Stevens reaction gave a poor yield which affected the overall yield.

Treatment of (R)-(+)-carvone with Zn in the presence of KOH furnished (R)-dihydrocarvone (**2**) in 80% yield. Enantiomerically pure **4**, an important building block for the synthesis of homochiral sesquiterpenes, was obtained by an improved Robinson annulation in which the key step involves an asymmeteric Michael addition. According to the method of Tenius [4], we synthesized **4** from **2**, using R-(+)-1-phenethylamine as the chiral auxiliary. Its simple procedure and mild reaction conditions made it suitable for the reaction with unstable ethyl vinyl ketone (EVK). (R)-dihydrocarvone (**2**), R-(+)-phenethylamine and catalytic amount of p-TSA were refluxed in toluene for 24 hr with a Dean-Stark trap, leading to the formation of the chiral imine derivative. We tried to use potassium carbonate instead of p-TSA as catalyst, but only recovered most of the starting materials. We also added some 4A molecular sieves as dehydrating agent, but there was no improvement. Without separation, the chiral Schiff base was directly treated with ethyl vinyl ketone (EVK) to carry out Michael addition [5]. The product **3** is a mixture of 10β-CH_3 and 10α-CH_3 isomers with the same R_f

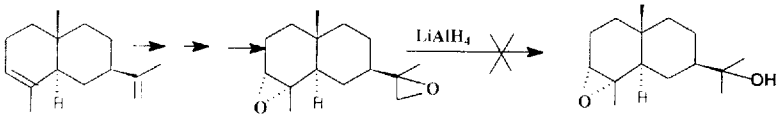


SCHEME 1 The total synthesis of chrysanthemol (**1**). Reagent and conditions: (a) Zn, KOH, 95% EtOH, reflux, 12 hr, 80%; (b) R-(+)phenylethylamine, p-TsOH, toluene, reflux, 24 hr; (c) (i) ethyl vinyl ketone (EVK), toluene, 40°C, 24 hr; (ii) 50% aq. AcOH, 2 hr; (d) KOH, EtOH, 0°C, 3 hr; (e) Na, propanol, 50°C, 6 hr; 62.7%; (f) NCS/pph_3, r.t., 12 hr, 68.1%; (g) $Hg(Oac)_2$, $NaBH_4$, r.t., 75%; (h) $LiBr/Li_2CO_3$/DMF, 140°C, 3 hr; 66.7%; (i) Li, NH_3, 70%; (j) T_sNHNH_2; (k) $Hg(Oac)_2$, $NaBH_4$, r.t., 55.1%; (l) Na, EG, 36.4%; (m) m-CPBA/$NaCO_3$ Li_2CO_3, CH_2Cl_2, r.t., 3.5 hr, 84%; (n) diisopropylamine, BuLi, Et_2O, r.t., 12 hr, 45.5%.

value and could not be separated by chromatography. The ^{1}HNMR spectra showed the ratio of the mixture as 10β-CH_3 : 10α-$CH_3 = 5:1$ where the chemical shift of angular CH_3 is δ 1.12 in 10β- and δ 1.02 in 10α-. According to the reaction mechanism, the key factor affecting stereoselectivity was the steric effect while the electronic effect also played a role. The electronically favoured axial attack was blocked by the bulky phenyl ring with the major 10β-isomer being formed from the disfavoured equatorial approach. The minor 10α isomer arose from an axial attack on the sterically favoured conformer with the phenyl group lying in the plane of the enamine. We tried two methods to achieve the cyclization of compound **3**, NaOEt/EtOH and KOH/EtOH. The former condition was too drastic and both 10β- and 10α-isomers were cyclized and further dehydrated, forming two diastereomers **4** and 10-epi-α-cyperone (**6**), which had the same R_f and could not be

separated through column chromatography. With KOH as cyclizing base, the 10β-isomer was cyclized and further dehydrated to give **4** ($R_f = 0.45$) while the 10α-isomer was only cyclized to form alcohol **5** ($R_f = 0.15$). Thus pure **4** was easily obtained from the mixture of **4** and **5**. Alcohol **5** afforded **6** through dehydration by NaOEt, which was needed for the less vulnerable equatorially disposed for using a hydroxyl group.

At first, we chose (−)-α-selinene as the key intermediate and tried to get the target chrysanthemol (**1**) through epoxidation, selective reduction and rearrangement of the epoxide **15**. The stratogry is to epoxidize the two double bonds in (−)-α-selinene at the same time and then introduce the side chain OH by selective reduction. But the difference of reactivities between the two epoxides were not significant enough to carry out the regioselective reduction.



(-)-α-selinene 15

After the failure, we decided to introduce the side chain hydroxy group before the epoxidation and rearrangement and chose **10** as the key intermediate. The selective reduction of **4** with Na clippings in *n*-propanol [6] gave an oily compound **7** in 67% yield. Both C_3−OH and C_4−Me in this structure were equatorial. ^{1}HNMR spectra showed that the chemical shift of C_{10}−Me was at δ 0.86 which was typical for the *trans*- isomer because C_{10} Me of *cis*- isomer is normally downfield at δ 0.99. The configuration of C_4 - Me must be α-(equatorial) or it would have 1,3-interaction with 10β-Me. The C_3- H, a triple-doublet at δ 3.00 ($J_1 = 10.8$ Hz, $J_2 = 5.8$ Hz) is typical for α-H combined with *trans*-skeleton and 10β-Me. For those C_3−OH *trans*-eudesmane terpene compounds, 3α-H is near δ 3.00 while 3β-H is downfield at δ 3.90 that further confirmed the structure of compound **7**.

Attempts to chlorinate alcohol **7** with $SOCl_2$, $POCl_3$/pyridine were unsuccessful because they also acted as dehydrating agent and gave rise to alkene mixture as $\Delta^{2,3}$-elimination product [7]; On treatment with NCS/PPh_3 [8] in THF at room temperature, alcohol **7** was converted into 3α-chloro derivative **8** in 68% yield. The reaction mechanism was S_N2 and the stereoselectivity was very high with the configuration totally inverted. ^{1}HNMR spectrum of **8** showed a multiple peak at δ 4.35, integrated as one H, for the equatorial 3β-H. The two-proton singlet at δ 4.70 was $=CH_2$. In the mass spectrum, the base peak is 240 (M^+), with other fragments 197(8), 171(80).

Having obtained halide **8**, we successfully introduced a hydroxy group to the C-11 position through oxymercuration with $Hg(OAc)_2$ followed by *in situ* reduction of the organomercurial with alkaline $NaBH_4$ [9]. The yield of compound **9** was 75%. Elimination of the halide of **9** with Li_2CO_3/LiBr/DMF [10] was influenced by the temperature of heating. When the temperature of the oil bath was controlled below 140°C, the major product was **10** in 66% yield and minor product (−)-α-selinene which resulted from further elimination of C-11 hydroxy group in 11% yield. When the temperature went over 160°C, the product was totally (−)-α-selinene.

The conversion from **4** to **10** was also achieved by another route. **4** was stereoselectively reduced to C_3-one **11** in 70% yield using Li/NH_3 [11], Upon treatment with $BF_3 \cdot Et_2O$ and *p*-toluenesulfonylhydrazide the ketone **11** formed **12** [12] in 61% yield. After oxymercuration with $Hg(OAc)_2$ followed by *in situ* reduction of the organomercurial with alkaline $NaBH_4$, **13** was obtained in 55% yield. The yield was not very good because there were other side reactions and the reaction mixture was dark-brown. Bamford-Stevens reaction [13] was carried out by treating compound **13** with Na/EG at 170°C for 1 h and the yield of **10** was 36% yield.

With the key intermediate **10** in hand, we sought to introduce the epoxide at $C_{3,4}$ position. 10β-Me played an important role in the stereoselectivity of epoxidation of $\Delta^{3,4}$ double bond while the configuration differed by using different epoxidizing reagents [14]. Since the C_3-OH in chrysanthemol is α-, we chose m-CPBA as epoxidizing reagent. The epoxidation of **10** was carried out in $CH_2Cl_2/NaHCO_3$ and epoxide **14** was obtained in 84% yield. **14** should be 3α,4α-epoxide from the epoxidation mechanism of m-CPBA and its ^{1}HNMR showed a broad singlet at δ2.94 ppm which was a typical equatorial H, thus confirming this configuration.

There were many reagents for the rearrangment of epoxide to allylic alcohol of which the most common used one is LDA [15] Cope [15a], Crandal [15b] and Rickborn [15c] made many investigations about the rearrangement reaction of LDA. $R_2AlN(C_2H_5)_2$ was used as rearrangment reagent by Yamamoto [16] but it didnot react with *cis*-epoxide so that it couldnot afford our desired **1**. Much reported dimethyltertbutylsilyl iodide/DBN [17] had poor regioselectivity and the double bond in the product was uncertain. The other reagents such as $NaSeC_6H_5/H_2O_2$ [18a], NaH [18b], $Ti(OC_3H_7-i)_3$ [18c] were only applied in a few cases, often with complicated side reactions. Regioselective rearrangement of 3,4-epoxide **14** with LDA lead to the target allylic alcohol chrysanthemol (**1**) in 45% yield. The analytical data of the synthetic **1** were identical with that of the natural sample (Tabs. I and II).

TABLE 1 The IR, MS, ^{1}HNMR spectral data of synthetic and natural chrysanthemol (**1**)[a]

	m.p./°C	[α]	*IR(KBr) cm*$^{-1}$	*MS*	^{1}*HNMR δppm(CDCl$_3$)*
Synthetic	143.6 – 145.8	$[\alpha]_D^{18} = +5.7$ ($c = 1.0$, $CHCl_3$)	3408(br, OH), 2935, 1649, 1450, 1379, 912	238 (M^+, 2), 220 (8), 203 (20), 187 (10), 180 (18), 162 (35), 147 (50), 105 (24), 59 (100)	0.68 (s, 3H, 10-Me), 1.25 (s, 6H, 11-Me), 1.09 – 2.32 (m, 14H), 4.31 (t, 1H, $J = 3.0$ Hz, 3-H), 4.61 (t, 1H, $J = 1.75$ Hz, $=CH_2$), 4.96 (t, 1H, $J = 1.5$ Hz, $=CH_2$);
Natural	144 – 146	$[\alpha]_D^{20} = +5.8$ ($c = 2.1$, $CHCl_3$)	3500, 3300 (OH), 2940, 1650, 1450, 1380, 910	238 (M^+), 220.1969, 202.1632, 187, 180.1570, 162, 147, 105.0813, 59 (100)	0.68 (s, 3H, 10-Me), 1.25 (s, 6H, 11-Me), 1.2 – 2.2 (m, 14H), 4.30 (m, 1H, 3-H), 4.60 (t, 1H, $=CH_2$), 4.95 (t, 1H, $=CH_2$);

[a]Natural sample [3].

TABLE II The ^{13}CNMR spectral data of synthetic and natural chrysanthemol (1) in $CDCl_3$

	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
Synthetic	29.73	35.77	73.59	152.28	49.40	24.57	43.61	22.37
Natural[a]	29.84	35.70	73.51	152.28	49.46	24.64	43.66	22.42
	C_9	C_{10}	C_{11}	C_{12}[b]	C_{13}[b]	C_{14}	C_{15}	
Synthetic	40.74	35.64	76.99	27.08	27.28	109.02	15.50	
Natural[a]	40.84	35.70	76.98	27.08	27.30	108.72	15.54	

[a] Natural sample [3];
[b] The assignments may be interchanged.

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were determined with a Yanaco micrometer and are uncorrected, NMR spectra were taken on a Varian JEOL.FX-90Q. FX-300 or Bruker-AM-500 spectrometer with TMS as the internal reference. IR spectra were obtained on an Impact 400 FTIR spectrophotometer. Mass spectra were obtained on a ZAB-2F spectrometer (EI). TLC were carried out on silica gel (GF_{254}). VLC were performed on silica gel H and column chromatography were run on silica gel (160–180 mesh) from Qing Dao Ocean Chemicals.

(R)- Dihydrocarvone **(2)** To a 2 L three-necked flask was added KOH (50 g) and water (200 ml), then activated Zn powder (125 g) and 95% ethanol (500 ml). The mixture was vigorously stirred and heated under reflux. To the mixture was added the solution of (R)-(+)-carvone (101 g, 0.67 mol) in 95% ethanol (200 ml) within 6 h. The reaction mixture was further stirred at the same temperature for 6 h. TLC showed that no starting material was left. The reaction mixture was filtered and the filtrate was evaporated to remove ethanol. The residual aqueous solution was extracted with diethyl ether (100 ml × 3). The combined organic phase was dried over Na_2SO_4. After removal of the solvent 78.5 g of crude product was obtained which was distilled *in vacuo* to afford pure (R)- dihydrocarvone **2** (62.8 g), bp: 60–6°C/1 mm. yield: 80%. IR(film.) ν_{max}2931, 2859 (CH), 1709 (C=O), 1645 (C=C), 1452,891 cm^{-1}.

(+)-α-Cyperone **(4)** and compound **5** A solution of **2** (9.12 g, 0.06 mol) and p-TSA (100 mg) in toluene (30 ml) was placed in a 100 ml flask equipped with a Dean-Stark trap. (R)-(+)-1-Phenethylamine (9.00 g, 0.07 mol) was added under nitrogen. The reaction mixture was refluxed for 24 h with azeotropic removal of water. After cooling by ice bath, ethyl vinyl ketone (6.4 ml, 0.07 mol) was added dropwise. The reaction mixture was further stirred at 40°C for 24 h under nitrogen and then a solution of 50% aqueous acetic acid (40 ml) was added under ice-bath. After additional stirring at r.t., for 2 h, the mixture was poured into brine (40 ml). The organic layer was separated and the aqueous phase was extracted with ethyl ether (60 ml × 3). The combined organic phase was washed with 10% HCl (40 ml), water (40 ml), brine (40 ml) and dried over Na_2SO_4 and evaporated to give the diketone **3** (13.5 g). To an ice-cooled solution of 5% KOH (60 ml), was added dropwise a solution of diketone **3** in ethanol (100 ml) under nitrogen.

The reaction mixture was stirred at 0°C for 5 h under nitrogen and then treated with 50% aqueous acetic acid (8 ml). The solvent was removed by evaporation and the residue was treated with water (30 ml) which was further extracted with ethyl ether (60 ml × 3). The combined organic phase was dried over Na_2SO_4 and evaporated to give the crude product (12.5 g) which was separated by column chromatography (PE : EE = 9 : 1). (+)-α-cyperone (**4**) (R_f = 0.45, PE : EE = 9 : 1) was obtained as an oil in 35% yield (4.6 g); compound **5** (R_f = 0.15, PE : EE = 9 : 1) was obtained as white solid in 7.0% yield (0.9 g).

(+)-α-cyperone (**4**) $[\alpha]_D^{18} = +103.8$ ($c = 0.4$, $CHCl_3$), lit [4]: $[\alpha]_D^{20} = +107.2$ ($c = 2.1$, $CHCl_3$); IR (film) ν_{max}2927 (CH), 1670 (C=O),1610,889; ^{1}HNMR ($CDCl_3$) δ 1.22 (s, 3H, 10-Me), 1.78 (s, 6H, 4-Me + 11-Me), 4.78 (brs, 2H, $=CH_2$); compound **5**: mp 134–136°C; IR (film) ν_{max} 3382 (OH), 2939 (CH), 1712 (C=O), 1639 (C=C), 1441, 898 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.05 (d, 3H, J = 8.1 Hz, 4-Me), 1.30 (s, 3H, 10-Me), 1.72 (s, 3H, 11-Me), 3.00 (1H, q, J = 7.2 Hz, 4-H), 4.70 (s, 2H, $=CH_2$).

Compound **6** To an ice-cooled solution of sodium ethoxide (from 35 mg of sodium) in dry ethanol (5 ml) was added compound **5** (100 mg). After additional stirring at 0°C for 2 h under nitrogen, 3N HCl was added. The solvent was removed by evaporation and the residue was treated with water which was further extracted with ethyl ether (30 ml × 3). The combined organic phase was dried over Na_2SO_4 and evaporated to give the crude product (90 mg) which was purified by column chromatography (PE : EE = 6 : 1). **6** (R_f = 0.6, PE : EE = 6 : 1) was obtained as an oil in 63% yield (60 mg) IR(film,) ν_{max} 2927 (CH), 1668 (C=O), 1454, 889 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.84 (s, 3H, 10-Me), 1.20 (s, 3H, 4-Me), 1.74 (s, 3H, 11-Me), 4.72 (s, 2H, $=CH_2$).

Compound **7** To the solution of compound **4** (2.2 g, 10 mmol) in *n*-propanol (20 ml) was added in portions sodium clippings (2.3 g, 0.1 mol) while the temperature was controlled at 50°C to keep the reaction mixture gently refluxing. The addition was completed within 0.5 h and the reaction mixture was further stirred for 6 h until all sodium clippings disappeared. The solvent was removed by evaporation and the residue was treated with water (20 ml) which was further extracted with ethyl ether (40 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (2.2 g) which was purified by column chromatography (PE : EE = 6 : 1). **7** (R_f = 0.35, PE : EE = 6 : 1) was obtained as an oil in 67% yield (1.5 g). $[\alpha]_D^{16} = +15.0$ ($c = 0.6$,$CHCl_3$), Lit[11]: $[\alpha]_D^{20} = +8.9$ ($c = 1.0$,$CHCl_3$);IR (film) ν_{max} 3332 (OH),2927 (CH),

1643 (C=C), 1452, 885 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.86 (s, 3H, 10-Me), 0.97 (s, 3H, J=7.2 Hz, 4-Me), 1.74 (s, 3H, 11-Me), 3.10 (td, 1H, J= 10.8, 5.8 Hz, 3-H), 4.70 (s, 2H, =CH_2).

Compound **8** To a solution of NCS (0.8 g, 6 mmol) in dry THF (36 ml) was added dropwise a solution of triphenylphosphine (1.57 g, 6 mmol) in dry THF (10 ml) under nitrogen. During the addition, an exothermol reaction occurred and white solids precipitated out. A solution of **7** (1.33 g, 6 mmol) in dry THF (15 ml) was added slowly to the above mixture within 10 min. The reaction mixture was stirred at r.t., for 12 h under nitrogen until most precipitate redissolved. After staying overnight, the solvent was removed by evaporation and the residue was treated with water (15 ml) which was further extracted with ethyl ether (30 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (1.6 g) which was purified by column chromatography (PE). **8** (R_f=0.80) was obtained as an oil in 68% yield (0.98 g). $[\alpha]_D^{20}$ = −24.9 (c = 1.4, $CHCl_3$) · IR (film, cm^{-1}) ν_{max}2933 (CH), 1643 (C=C), 1452, 887; ^{1}HNMR δ 0.85 (s, 3H, 10-Me), 0.95 (3H, J=6.7 Hz, 4-Me), 1.73 (s, 3H, 11-Me), 4.35 (m, 1H, 3-H), 4.70 (s, 2H, CH_2); EI MS m/z $[MH]^+$ 240 (3), 225 (1), 197 (8), 171 (80).

Compound **9** To a solution of $Hg(OAc)_2$ (1.33 g, 4 mmol) in water (6 ml) was added THF (8 ml) and yellow solids precipitated out. A solution of **8** (0.96 g, 4 mmol) in THF (4 ml) was added slowly at 0°C and the reaction mixture became clear during addition. TLC showed no starting material left after additional stirring for 1.5 h. 3 N NaOH (4 ml) was slowly added to the above mixture at 0°C while yellow solids precipitated out, followed by a solution of $NaBH_4$ (0.1 g) in 3N NaOH (4 ml) while grey solids precipitated out. The reaction mixture was further stirred at 0°C for 20 min and then allowed to stand until Hg precipitated out. After filtration, the organic layer of filtrate was separated and the aqueous layer was extracted with ethyl ether (30 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (1.0 g), which was recrystallized by PE to give greyish white solids. **9** in 75% yield (0.81 g) Mp 133.6–134.7°C. $[\alpha]_D^{16}$ = −25.0 (c = 0.1, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3292 (OH), 2970, 2939 (CH), 1379, 1145, 912; ^{1}HNMR($CDCl_3$) δ 0.83 (s, 3H, 10-Me), 0.96 (d, 3H, J=7.0 Hz, 4-Me), 1.20 (s, 3H, 11-Me), 1.22 (s, 3H, 11-Me), 4.33 (brd, 1H, J=2.4 Hz, 3-H) EI MS m/z $[MH]^+$ 256 (3), 225 (6), 202 (100), 199 (56), 59 (72).

Compound **10** A mixture of **9** (0.77 g, 3 mmol), Li_2CO_3 (0.88 g, 12 mmol), LiBr (0.77 g, 9 mmol) in dry DMF (20 ml) was heated to 140°C and stirred at this temperature for 3 h. After cooling to r.t., saturated

aqueous NH_4Cl (10 ml) was added and then to the reaction mixture was extracted with EtOAc (20 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (1.2 g) which was purified by column chromatography (PE: EE = 1 : 1). **10** (R_f = 0.42) was obtained as white solid in 66% yield (0.44 g). mp : 74 – 75°C, IR (KBr, cm^{-1}) ν_{max} 3298 (OH), 2972 (CH), 2842, 1651 (C=C), 1452, 1377, 1143, 914; ^{1}HNMR($CDCl_3$) δ 0.77 (s, 3H, 10-Me), 1.21(s, 3H, 11-Me), 1.22 (s, 3H, 11-Me), 1.6 (s, 3H, 4-Me), 5.31 (brs, 1H, 3-H); EI MS m/z $[MH]^+$ 222 (3), 204 (13), 189 (12), 149 (100), 59 (78).

Compound **11** To a cooled (– 70°C) solution of Li (0.3 g) in liquid NH_3 (300 ml) was added a solution of **4** (1.5 g, 7 mmol) in dry ethyl ether (50 ml). During the addition, the deep blue color of the reaction mixture disappeared so more Li (0.35 g) was added to keep the colour deep blue until the completion of the addition of **4**. The reaction mixture was further stirred at – 70°C for 20 min and solid NH_4Cl was added until the blue colour disappeared and allowed to stand until all NH_3 evaporated. To the residue was treated with water (20 ml) which was further extracted with ethyl ether (20 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (1.5 g) which was purified by column chromatography (PE : EE = 8 : 1). **11** (R_f = 0.50) was obtained as an oil in 70% yield (1.05 g). $[\alpha]_D^{16} = -19.5$ (c = 1.8, $CHCl_3$), Lit[12] : $[\alpha]_D^{20} = -15.1$ (c = 1.8, $CHCl_3$); IR (film) ν_{max} 2929 (CH), 2856, 1712 (C=O), 1643 (C=C), 1452, 887 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.96 (s, 3H, 10-Me), 1.07 (d, 3H, J = 7.5 Hz, 4-Me), 1.75 (s, 3H, 11-Me), 4.72 (s, 2H, $=CH_2$).

Compound **12** To a solution of **11** (0.73 g, 3.3 mmol) in dry THF (25 ml) was added p-toluenesulfonylhydrazide (0.93 g, 5 mmol) and 4 drops of $BF_3 \cdot Et_2O$. The reaction mixture was stirred at rt. overnight. After the removal of solvent by evaporation, the oil residue was crystallized with PE and EE, giving white needle crystals **12** in 61% yield (0.8 g); mp 139 – 141°C; IR (KBr) ν_{max} 3240, 2927 (CH), 1643 (C=C), 1597, 1330, 885, 812 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 0.83 (d, 3H, J = 6.0 Hz, 4-Me), 0.88 (s, 3H, 10-Me), 1.67 (s, 3H, 11-Me), 2.31 (s, 3H, Ar-CH_3), 4.64 (s, 1H, $=CH_2$), 4.67 (s, 1H, $=CH_2$), 7.31 (d, 2H, J = 8.1 Hz, $ArH_{aa'}$), 7.71 (d, 2H, J = 8.1 Hz, $ArH_{bb'}$).

Compound **13** To a solution of $Hg(OAc)_2$ (0.16 g, 0.5 mmol) in water (1 ml) was added THF (1 ml) and yellow solids precipitated out. A solution of **12** (0.19 g, 0.5 mmol) in THF (1 ml) was added slowly at 0°C and the reaction mixture became clear during addition. TLC still showed starting material after additional stirring for 1.5 h. and more $Hg(OAc)_2$ (0.16 g, 0.5 mmol) was added. After additional stirred for 0.5 h, 3 N NaOH (1 ml)

was slowly added at 0°C while the mixture turned into black colour, followed by a solution of $NaBH_4$ (25 mg) in 3N NaOH (1ml) while grey solids precipitated out. The reaction mixture was further stirred at 0°C for 10 min and then allowed to stand until Hg precipitated out. After filtration, the organic layer was separated and the aqueous layer was extracted with ethyl ether (10 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (0.22 g), which was purified by column chromatography (DCM : MeOH = 50 : 1). The main spot was separated as an oil which was crystallized by DCM to give cream-white solids.**13** in 55% yield (0.11g), mp: 142 – 143°C (Lit[19]: 143 – 144°C); IR (KBr) ν_{max} 3450 (OH), 2970, 2929 (CH), 1705, 1598, 1167, 910 cm^{-1}; ^{1}HNMR (DMSO-d_6): δ 0.96 (d, 3H, J = 9.0 Hz, 4-Me), 1.01 (s, 3H, 10-Me), 1.19 (s, 3H, 11-Me), 1.20 (s, 3H, 11-Me), 2.44 (s, 3H, Ar-CH_3), 7.32 (d, 2H, J = 8.1 Hz, $ArH_{aa'}$), 7.86 (d, 2H, J = 8.1 Hz, $ArH_{bb'}$). EI MS m/z $[MH]^+$ 406 (5), 391 (4), 251 (35), 233 (28).

The Bamford-Stevens reaction of compound **13**: To a solution of sodium clippings (0.23 g) in ethylene glycol (10 ml) under nitrogen was added a solution of **13** (0.2 g, 0.5 mmol) in ethylene glycol (5 ml). The mixture was heated to 170°C and stirred at this temperature for 1 h. After cooling, the reaction mixture was poured into ice water, titrated with HCl to pH = 7 and then extracted with ethyl ether (10 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (0.22 g), which was purified by column chromatography (PE : EE = 1 : 1). **10** was obtained as white solids in 36% yield (50 mg), mp 74 – 75°C.

Compound **14** To a solution of **10** (0.33 g, 1.5 mmol) in DCM (20 ml) and aqueous $NaHCO_3$ (0.5 M, 5 ml) was added m-CPBA (85%, 0.34 g) in portions. The mixture was stirred at r.t., for 3.5 h. The organic layer was separated and the aqueous layer was extracted with DCM (10 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (0.35 g) which was purified by column chromatography (PE : EE = 1 : 1). The main spot (R_f = 0.52) was obtained as oil which solidified on cooling. **14** was obtained as white crystals in 84% yield (0.30 g) mp 60 – 62°C, $[\alpha]_D^{20}$ = +30.4(c = 1.2, $CHCl_3$); IR (KBr) ν_{max} 3442 (OH), 2968, 2931 (CH), 1452, 1381, 881 cm^{-1}; ^{1}HNMR $CDCl_3$) δ 0.78 (3H, 10-Me), 1.21 (s, 6H, 11-Me), 1.25 (s, 3H, 4-Me), 2.94 (brs, 1H, 3-H); EI MS m/z $[MH]^+$ 238 (3), 223 (10), 220 (22), 218 (25), 205 (40).

Chrysanthemol (**1**) To an ice-cooled solution of diisopropylamine (0.15 ml, 1.84 mmol) in dry ethyl ether (15 ml) was added a solution of BuLi in hexane (1.25 ml, C = 0.95 M) under nitrogen. The mixture was stirred at

r.t., for 20 min. The formed LDA solution was cooled to 0°C and a solution of **14** (77 mg, 0.3 mmol) in dry ethyl ether (1 ml) was added. The reaction mixture was further stirred at r.t., for 12 h. It was quenched with water (3 ml) and then extracted with ethyl ether (8 ml × 3). The combined organic phase was washed with water, brine, dried over Na_2SO_4 and evaporated to give the crude product (0.10 g), which was purified by column chromatography (PE : EE = 3 : 2). The main spot (R_f = 0.3) was obtained as oil which solidified on cooling. After recrystallization chrysanthemol **1** was obtained as white crystals in 45% yield (35 mg). mp 143.6 – 145.8°C; $[\alpha]_D^{18} = +5.7$ ($c = 1.0$, $CHCl_3$) [Lit 144 – 146°C, $[\alpha]_D^{20} = +5.8$($c = 2.1$, $CHCl_3$)]; IR (KBr) ν_{max} 3408 (brs, OH), 2935 (CH), 1649 (C=C), 1379, 912 cm^{-1}; ^{1}HNMR ($CDCl_3$, 500 MHz)δ 0.68 (s, 3H, 10-Me), 1.25(s, 6H, 11-Me), 1.09 – 2.32 (m, 14H), 4.31 (t, 1H, J = 3.0 Hz, 3-H), 4.61 (t, 1H, J = 1.75 Hz, =CH_2), 4.96 (t, 1H, J = 1.5 Hz, CH_2): ^{13}CNMR($CDCl_3$, 500 MHz): 29.73(C_1), 35.77(C_2), 73.59(C_3), 152.28(C_4), 49.40(C_5), 24.57(C_6), 43.61(C_7), 22.37(C_8), 40.74(C_9), 35.64(C_{10}), 76.99(C_{11}), 27.08(C_{12}), 27.28(C_{13}), 109.02(C_{14}), 15.50(C_{15}); EI MS m/z $[MH]^+$ 238 (M^+, 2), 220 ($M^+ - 18$, 8), 203 (20), 180 (18), 162 (35), 147 (50), 105 (24), 59 (100).

Acknowledgements

We are grateful to Professor Dequan Yu and Fengzhi Xie in our Institute for the generous supply of natural chrysanthemol(**1**).

References

[1] Liu, W. F. (1982). *Chinse Pharm. Bull.*, **17**, 24 – 27.
[2] Chen, Z. X., Chien, M. K. and Tseng, K. F. (1962). *Acta Pharm. Sin.*, **9**, 370 – 374.
[3] Yu, D. Q. and Xie, F. Z. (1987). *Acta Pharm. Sin.*, **22**, 837 – 840.
[4] Tenius, B. S. M., Rohde, A. R. and Victor, M. M. (1996). *Synth. Comm.*, **26**(1), 197 – 203.
[5] Belfield, K. D. and Seo, J. (1995). *Synth. Comm.*, **25**(4), 461 – 466.
[6] Dauben, W. E. and Blanz, E. J. Jr. (1956). *J. Am. Chem. Soc.*, **78**, 3752 – 3755.
[7] Mckenna, J. and Norymberski, J. K. (1959). *J. Chem. Soc.*, pp. 2502 – 2509.
[8] Bose, A. K. and Lal, B. (1973). *Tetrahedron Letters*, **40**, 3937 – 3940.
[9] (a) Brown, H. C. and Geoghegan, P. J. Jr. (1970). *J. Org. Chem.*, **35**, 1844 – 1850; (b) Brown, H. C. and Geoghegan, P. J. Jr. (1972). *J. Org. Chem.*, **37**(12), 1937 – 47.
[10] Blay, G. and Cardona, L. (1992). *Tetrahedron*, **48**(25), 5265 – 5272.
[11] Howe, R. and McQuillin, F. J. (1956). *J. Chem. Soc.*, pp. 2670 – 2675.
[12] (a) Harapanhalli, R. (1988). *Indian Chem.*, **27B**, 884 – 886; (b) Liu, L., Xiong , Z. M. and Nan, F. J. (1995). *Synth. Comm.*, **25**, 1971 – 1979.
[13] Shapiro, R. H., Bamford Stevens Reaction, *Organic. Reactions*, **23**, 405 – 507.
[14] Miller, R. B. and Behare, E. S. (1974). *J. Am. Chem. Soc.*, **96**, 8102 – 8106.
[15] (a) Cope, A. C. and Heeren, J. K. (1965). *J. Am. Chem. Soc.*, **87**, 3125 – 3129; (b) Crandall, J. K. and Crawley, L. C. (1973). *Org. Synth.*, **53**, 17 – 21; (c) Rickborn, B. and Thmmel, R. P. (1969). *J. Org. Chem.*, **34**, 3583 – 3586.

[16] Yamamoto, H. and Nozaki, H. (1974). *J. Am. Chem. Soc.*, **96**, 6513–6514.
[17] Detty, M. R. and Seidler, M. D. (1981). *J. Org. Chem.*, **46**, 1283–1292.
[18] (a) Sharpless, K. B. and Laue, R. F. (1973). *J. Am. Chem. Soc.*, **95**, 2697–2699; (b) Caubere, P. and Moreau, J. (1971). *Bull. Soc. Chim. Fr.*, pp. 3276–3282; (c) Morgans, D. J. Jr. and Sharpless, K. N. (1981). *J. Am. Chem. Soc.*, **103**, 462–464.
[19] Humber, D. C. and Pinder, A. R. (1967). *J. Org. Chem.*, **32**, 2335–2340.