An Enantiospecific Route to (+)-(1*R*,3*S*)-*cis*-Chrysanthemic Acid from (–)-D-Pantolactone[1]

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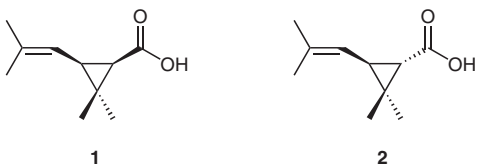
Abstract: In this paper, a novel route for the synthesis of (+)-(1*R*,3*S*)-*cis*-chrysanthemic acid is described. The use of readily available (–)-D-pantolactone as a starting point, application of ring-closing metathesis to form the cyclopentene intermediate, and Haller–Bauer/Grob-type fragmentation to form the target compound are the highlights of the present synthesis.

Key words: ring closure, stereoselective synthesis, Wittig reaction, alkenes, metathesis

Chrysanthemic acids and their analogues/derivatives are important starting materials for the preparation of a variety of pyrethroid insecticides.[2] The high insecticidal activity of the pyrethroids coupled with their low mammalian toxicity and biodegradability made them an attractive class of compounds. Due to their high importance in human life, several syntheses of both *cis*- **1** and *trans*-chrysanthemic acids **2** in racemic and enantiopure form have been documented in the literature (Figure 1).[3] The pioneering and continued work by Krief's group needs special mention in this regard. The creation of new and efficient synthetic routes to important molecules like **1** and **2** is always exciting and rewarding. We have attempted an enantiospecific route for the synthesis of **1** starting from commercially available (–)-D-pantolactone and the results are disclosed in this paper.[4] It is noteworthy to mention that majority of efforts have been focused on the synthesis of *trans*-chrysanthemic acid despite the importance of both compounds. In fact, the most important insecticides of this class are deltamethrin and cypermethrin which have a *cis* relationship.[5]



1 2

Figure 1 Structures of *cis*- and *trans*-chrysanthemic acids

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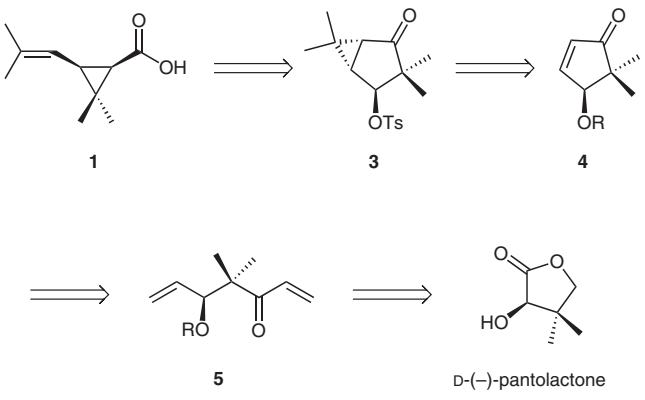
Retrosynthetically, the target compound (+)-(1*R*,3*S*)-*cis*-chrysanthemic acid (**1**) could be prepared from Krief's intermediate **3** using Haller–Bauer/Grob-type fragmentation. The cyclopentene intermediate **4** could be transformed to **3** via cyclopropanation of the double bond and conversion of hydroxy handle into a leaving group like tosylate. It was proposed that ring-closing metathesis (RCM) could generate the key cyclopentenone intermediate **4** from its acyclic precursor **5**, which in turn could be prepared from commercially available (–)-D-pantolactone using routine functional group transformations (Scheme 1).

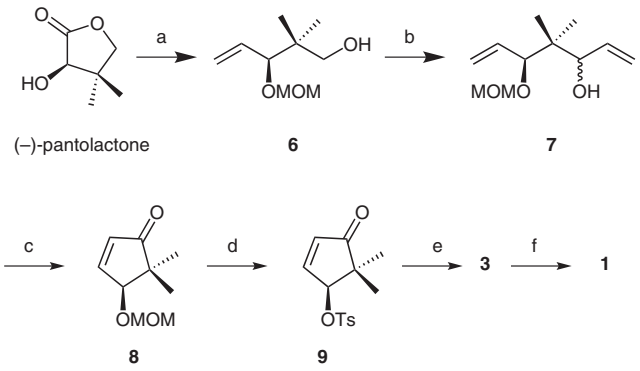


1 3 4 5 D-(–)-pantolactone

Scheme 1

The details of this synthesis are outlined in Scheme 2. Our synthesis began with the construction of the known acyclic precursor **6** following analogous procedures reported in the literature from our group and others.[4,6] Dess–Martin oxidation and vinyl Grignard addition to the resulting aldehyde produced a diastereomeric mixture of alcohols **7** in excellent yields. Stereoselectivity at the newly formed center is not important as it will be transformed into a carbonyl group. Having key acyclic precursor **7** in hand, we subjected it to RCM using Grubbs' second-generation catalyst {[1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene](benzylidene)dichloro(tricyclohexylphosphine)ruthenium} to give a hydroxycyclopentene derivative, which upon Dess–Martin oxidation with DMP provided cyclopentenone **8**. Deprotection of the methoxymethyl protecting group with aqueous sulfuric acid resulted in an

alcohol,[7] which was further transformed (TsCl, py) to its tosyl ester **9**. The tosylate **9** reacted smoothly with isopropylidenediphenylsulfurane ($Ph_2S{=}CMe_2$) generated in situ to produce the bicyclo[3.1.0] derivative **3**.[3c,8] By following the protocol (KOH, DMSO, H_2O) described by Krief et al.,[3d,e] we were able to convert **3** into the target molecule (+)-(1*R*,3*S*)-*cis*-chrysanthemic acid (**1**) in 56% yield. The spectral data of our compound **1** was compared to the reported data and found to be identical, $[\alpha]_D^{22.0}$ +82.0 (*c* 0.1, $CHCl_3$) {Lit.[3c] $[\alpha]_D^{20}$ +83.0 (*c* 1.75, $CHCl_3$)}.[3c] Thus, we have completed the synthesis of **1** in an enantiospecific manner.



Scheme 2 *Reaction conditions:* (a) (i) DIPEA, MOMCl, CH_2Cl_2, 0 °C to r.t. 48 h, 90%; (ii) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, 91%; (iii) Ph_3PCH_3Br, BuLi, THF, 0 °C to r.t., 20 h, 81%; (b) (i) DMP, CH_2Cl_2, 0 °C 1 h, 90%; (ii) $H_2C{=}CHMgBr$, THF, 0 °C, 1 h, 81%; (c) (i) Grubb's catalyst, CH_2Cl_2, r.t., 1 h, 83%; (ii) DMP, CH_2Cl_2, 0 °C, 1 h, 86%; (d) (i) 10% aq H_2SO_4, THF, reflux, 3 h, 80%; (ii) TsCl, py, 0 °C to r.t., 15 h, 77%; (e) $Ph_2SCHMe_2{\cdot}BH_4$, LDA, CH_2Cl_2, DME, –78 °C, 30 min, 93%; (f) KOH, DMSO, H_2O, 70 °C, 4 h, 56%.

In summary, we have utilized the chiral pool compound (–)-D-pantolactone for the enantiospecific synthesis of (+)-(1*R*,3*S*)-*cis*-chrysanthemic acid (**1**). In addition to the use of a readily available chiral starting material, the application of RCM to form a cyclopentene intermediate and Krief's Haller–Bauer/Grob-type fragmentation to form the final compound are the highlights of the present synthesis.

All reactions were carried out in oven-dried glassware under a positive pressure of argon or N_2 unless otherwise mentioned with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents (including anhyd solvents) were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by TLC with 0.25 mm (E. Merck) pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, or by immersion in phosphomolybdic acid, or $KMnO_4$ solns followed by heating on a heat gun for ~15 s. Column chromatography was performed on silica gel (60–120 mesh). Deuterated solvents (Cambridge Isotope Laboratories) for NMR spectroscopic analyses were used as received. All ^1H and ^{13}C NMR spectra were obtained using a Varian 400 MHz (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer. All chemical shifts use the residual solvent peak as a reference standard. Optical rotation was recorded on Rudolph Autopol-V digital polarimeter at 589 nm (Na D-line) and optical rotation data was reported with *c* in g/100 mL. Mass spectra were measured with ESI ionization using Agilent MSD/VL spectrometer. HRMS data was recorded on MALDI-TOF using 2,5-dihydroxybenzoic acid as the solid matrix. IR spectra were recorded on a Perkin-Elmer 100 FT-IR spectrophotometer.

(*S*)-5-(Methoxymethoxy)-4,4-dimethylhepta-1,6-dien-3-ol (7)

To a stirred soln of (*S*)-3-(methoxymethoxy)-2,2-dimethylpent-4-en-1-ol[6] (**6**, 2.00 g, 11.48 mmol) in CH_2Cl_2 (25 mL) was added DMP (7.31 g, 17.22 mmol) at 0 °C. After stirring for 1 h, the mixture was diluted with CH_2Cl_2 (~30 mL) and filtered through a Celite bed. The filtrate was washed with aq K_2CO_3 soln (20 mL), aq sat. $Na_2S_2O_3$ soln (20 mL), and brine (20 mL), dried (anhyd Na_2SO_4), and concentrated to give (*S*)-3-(methoxymethoxy)-2,2-dimethylpent-4-enal (1.97 g, 90%) as a colorless oil. The crude aldehyde was used as such for further conversion.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 3 H), 1.10 (s, 3 H), 3.34 (s, 3 H), 4.14 (d, *J* = 8.4 Hz, 1 H), 4.47 (d, *J* = 6.8 Hz, 1 H), 4.69 (d, *J* = 7.2 Hz, 1 H), 5.31 (d, *J* = 17.6 Hz, 1 H), 5.38 (d, *J* = 10.4 Hz, 1 H), 5.63–5.72 (m, 1 H), 9.60 (s, 1 H).

To a stirred soln of above aldehyde (1.71 g, 9.93 mmol) in anhyd THF (15 mL) was added 1.0 M vinylmagnesium bromide in THF (14.89 mL, 14.89 mmol) at 0 °C. After stirring for 1 h, the reaction was quenched by the addition of aq NH_4Cl soln (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (40 mL), dried (anhyd Na_2SO_4), concentrated, and purified by column chromatography (8% EtOAc–hexane) to give **7** (1.61 g, 81%) as a colorless oil and diastereomeric mixture.

IR (neat): 1639, 3459 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 0.87 (s, 3 H), 0.90 (s, 3 H), 3.41 (s, 3 H), 3.98 (d, *J* = 8.0 Hz, 1 H), 4.12 (br s, 1 H), 4.54 (dd, *J* = 7.6, 6.8 Hz, 2 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 5.19–5.35 (m, 4 H), 5.67–5.83 (m, 1 H), 5.87–5.95 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 20.9, 40.9, 56.5, 77.9, 84.8, 94.6, 116.9, 120.3, 134.4, 137.4.

HRMS (MALDI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{20}O_3Na$: 223.1310; found: 223.1328.

(*S*)-4-(Methoxymethoxy)-5,5-dimethylcyclopent-2-enone (8)

To a stirred soln of **7** (1.20 g, 5.99 mmol) in CH_2Cl_2 (15 mL) was added Grubbs II catalyst (127 mg, 0.15 mmol) at r.t. After stirring for 1 h, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography to give (*S*)-4-(methoxymethoxy)-5,5-dimethylcyclopent-2-enol (860 mg, 83%) as an oil.

LCMS: *m*/*z* = 190.0 $[M + H_2O]^+$.

HRMS (MALDI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{16}O_3Na$: 195.0997; found: 195.1013.

To a cooled soln of (*S*)-4-(methoxymethoxy)-5,5-dimethylcyclopent-2-enol (650 mg, 3.77 mmol) in CH_2Cl_2 (10 mL) was added DMP (2.40 g, 5.66 mmol) at 0 °C. After 1 h, the mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a Celite bed. The filtrate was washed with aq K_2CO_3 soln (20 mL), aq sat. $Na_2S_2O_3$ soln (20 mL), and brine (20 mL), dried (anhyd Na_2SO_4), concentrated, and purified by column chromatography (8% EtOAc–hexanes) to give **8** (550 mg, 86%) as a colorless oil.

$[\alpha]_D^{22.5}$ +52.7 (*c* 1.0, $CHCl_3$).

IR (neat): 1718 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 3 H), 1.18 (s, 3 H), 3.44 (s, 3 H), 4.45 (d, *J* = 2.0 Hz, 1 H), 4.78 (s, 2 H), 6.19 (dd, *J* = 6.0, 2.0 Hz, 1 H), 7.48 (dd, *J* = 6.0, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 23.4, 48.3, 56.0, 85.1, 97.1, 132.9, 160.1, 211.6.

LCMS: *m*/*z* = 171.1 $[M + H]^+$.

HRMS (MALDI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{14}O_3Na$: 193.0841; found: 193.0848.

(*S*)-5,5-Dimethyl-4-oxocyclopent-2-enyl 4-Toluenesulfonate (9)

To a stirred soln of **8** (500 mg, 2.94 mmol) in THF (5 mL) was added 10% aq H_2SO_4 (5 mL) at r.t. and the mixture was refluxed for 3 h. The mixture was cooled to 0 °C and basified with aq sat. $NaHCO_3$ soln and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried (anhyd Na_2SO_4), concentrated, and purified by column chromatography (9% EtOAc–hexanes) to give (*S*)-4-hydroxy-5,5-dimethylcyclopent-2-enone (295 mg, 80%).

$[\alpha]_D^{23.0}$ +80.2 (*c* 1.0, MeOH) {Lit.[7] $[\alpha]_D^{23.0}$ +87.2 (*c* 1.31, MeOH)}.

IR (neat): 1700, 3418 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3 H), 1.17 (s, 3 H), 2.07 (d, *J* = 6.8 Hz, 1 H), 4.58–4.60 (m, 1 H), 6.20 (dd, *J* = 6.0, 1.2 Hz, 1 H), 7.46 (dd, *J* = 5.6, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 23.0, 48.7, 79.9, 132.7, 161.8, 212.9.

To a stirred soln of (*S*)-4-hydroxy-5,5-dimethylcyclopent-2-enone (250 mg, 1.98 mmol) in pyridine (5 mL) was added TsCl (567 mg, 2.97 mmol) at 0 °C. After stirring at r.t. for 15 h, pyridine was evaporated under reduced pressure. The resulting residue was taken in EtOAc (10 mL) and washed with 1.0 M HCl (10 mL), H_2O (10 mL), and brine (10 mL), dried (anhyd Na_2SO_4), concentrated, and purified by column chromatography (5% EtOAc–hexanes) to give **9** (425 mg, 77%) as a white solid; mp 71–72 °C.

$[\alpha]_D^{21.7}$ +59.3 (*c* 1.0, $CHCl_3$).

IR (neat): 1366, 1723 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 3 H), 1.04 (s, 3 H), 2.48 (s, 3 H), 5.19 (t, *J* = 1.6 Hz, 1 H), 6.27 (dd, *J* = 6.0, 1.2 Hz, 1 H), 7.28 (dd, *J* = 6.0, 2.4 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.85 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 21.9, 22.4, 47.4, 86.3, 128.0, 130.2, 133.3, 135.0, 145.6, 155.7, 208.7.

Spectra were compared with those of racemic **9** known in the literature[9] and found to be identical.

(1*S*,2*S*,5*R*)-3,3,6,6-Tetramethyl-4-oxobicyclo[3.1.0]hexan-2-yl 4-Toluenesulfonate (3)

A soln of isopropyldiphenylsulfonium tetrafluoroborate[8] (182 mg, 0.57 mmol) and CH_2Cl_2 (42 mg, 0.03 mL, 0.49 mmol) in anhyd DME (6 mL) was cooled to –78 °C and treated with LDA [prepared freshly by the addition of 1.6 M BuLi in hexane (0.31 mL, 0.49 mmol) to *i*-Pr_2NH (0.07 mL, 0.49 mmol) in DME (1 mL) at 0 °C]. After 45 min, a soln of **9** (107 mg, 0.38 mmol) in DME (1 mL) was added and the mixture was stirred for 30 min. The reaction was quenched by the addition of H_2O (5 mL). The aqueous layer was separated and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anhyd Na_2SO_4), concentrated, and purified by column chromatography (4% EtOAc–hexanes) to give **3** (115 mg, 93%) as a white solid; mp 103–104 °C (Lit.[3h] 106 °C).

$[\alpha]_D^{22.0}$ +77.9 (*c* 0.8, $CHCl_3$).

IR (neat): 1728 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.07 (s, 3 H), 1.72 (d, *J* = 5.2 Hz, 1 H), 1.90 (d, *J* = 5.2 Hz, 1 H), 2.47 (s, 3 H), 4.50 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.84 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0, 19.0, 21.8, 22.1, 24.2, 26.8, 34.6, 38.6, 55.5, 83.7, 128.0, 130.1, 133.6, 145.3, 212.8.

LCMS: *m*/*z* = 323.2 $[M + H]^+$.

(1*R*,3*S*)-2,2-Dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic Acid (1)

To a cooled soln of KOH (52 mg, 0.93 mmol) in DMSO–H_2O (4:1, 1 mL) was added tosylate **3** (50 mg, 0.15 mmol) at r.t. After stirring at 70 °C for 4 h, the mixture was cooled to r.t. and acidified with 10% HCl (pH ~2). This was extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried (anhyd Na_2SO_4), concentrated, and purified by column chromatography to give **1** (14.5 mg, 56%) as a solid.

$[\alpha]_D^{22.0}$ +82.0 (*c* 0.1, $CHCl_3$) {Lit.[3c] $[\alpha]_D^{20}$ +83.0 (*c* 1.75, $CHCl_3$)}.

IR (neat): 1697, 3018 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3 H), 1.25 (s, 3 H), 1.65 (d, *J* = 8.8 Hz, 1 H), 1.70 (s, 3 H), 1.75 (s, 3 H), 1.96 (dd, *J* = 8.8, 8.4 Hz, 1 H), 5.35 (dt, *J* = 8.8, 1.2 Hz, 1 H), 10.74 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 18.7, 26.3, 27.8, 29.2, 31.3, 33.5, 118.2, 135.5, 177.2.

LCMS: *m*/*z* = 169.1 $[M + H]^+$.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of ^{1}H and ^{13}C NMR spectra of important intermediates **9**, **8**, **7**, **6**, **3**, and synthesized *cis*-chrysanthemic acid **1**.

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