



# Novel synthesis of (*d,l*)-*cis*-chrysanthemic acid involving $\alpha,\alpha'$ -dibromination of 2,2,5,5-tetramethylcyclohexane-1,3-dione: application to the enantioselective synthesis of (1*R*)-*cis*-chrysanthemic acid

Alain Krief\*, Willy Dumont<sup>✉</sup>, Adrian Kremer

Laboratoire de Chimie Organique de Synthèse, Facultés Universitaires N.-D. de la Paix, 61 rue de Bruxelles, Namur B-5000, Belgium

## ARTICLE INFO

### Article history:

Received 23 January 2009

Revised 20 February 2009

Accepted 2 March 2009

Available online 5 March 2009

Dedicated to Professor Heinz Viehe at the occasion of its 80th birthday

### Keywords:

Pyrethroids  
Ketone halogenation  
Carbocyclization  
Br–M exchange  
H–M exchange  
Isomerization

## ABSTRACT

*cis*-Chrysanthemic acid has been prepared in a few steps from dimethyldimedone via dibromination at  $\alpha$  positions of each carbonyl carbons. The *trans*-dibromide which is almost exclusively formed has been isomerized to its *cis*-stereoisomer by highly chemoselective tandem H/K–K/H exchanges involving potassium bases at low temperature ( $<-40^\circ\text{C}$ ). Carbocyclization of the potassium enolate intermediate takes place at around  $-30^\circ\text{C}$  and provide the bicyclo[3.1.0]-hexane skeleton. Lithiated bases behave differently and mainly lead to Br/M rather than to H/M exchange. We have been unsuccessful in using state of the art enantioselective metallation reactions to achieve the enantioselective synthesis of (1*R*)-*cis*-chrysanthemic acid using the disclosed strategy. This therefore still remains challenge.

© 2009 Elsevier Ltd. All rights reserved.

We report a new synthetic route to *cis*-chrysanthemic **1** which takes advantage of the efficient transformation of dimethyldimedone **2** to the corresponding *trans*- $\alpha,\alpha'$ -dibromide **3<sub>trans</sub>** on reaction with 2 equiv of bromine (2 mol equiv Br<sub>2</sub>, CCl<sub>4</sub>, 0 °C, 1 h, 93% yield, Scheme 1).<sup>1,2</sup>

Easy cyclization of **3<sub>trans</sub>** to the bicyclic-diketone **4** bearing a bromine atom at a bridgehead was achieved by potassium hydroxide (1.3 equiv solid KOH, THF, 20 °C, 4 h).<sup>3</sup> Regio- and diastereoselective reduction using sodium borohydride and cerium trichloride is reminiscent to the reduction of a related compound bearing a trimethylsilyl group instead of bromine at bridgehead.<sup>4</sup> It selectively occurs on the carbonyl away from the bromine atom and by the concave face leading to **5** possessing an *exo*-hydroxyl group.<sup>5</sup>

The Br/H exchange at bridgehead of **5** is not, as we expected, as easy as for other  $\alpha$ -bromo-ketones and the presence of the aldol functional group adds to the difficulties. For example, Zn in acetic acid which usually reduces  $\alpha$ -halogeno-ketones to ketones<sup>6,7</sup> reacts with **5** but leads to an intractable mixture of unidentified compounds. Tributyltin hydride<sup>8</sup> however reduces **5** to **6** very efficiently (1.1 equiv Bu<sub>3</sub>SnH, 0.1 equiv AIBN, benzene, reflux, 4 h,

71% yield) and achieves the formal synthesis of (*d,l*)-*cis*-chrysanthemic acid **1** (Scheme 1).<sup>4,9</sup>

This approach offers the advantage over the former one<sup>4,9a</sup> which also produces **6**, to avoid the use of mono-brominated dimethyldimedone **9** which cannot be achieved selectively from **2** and requires tedious separation from the mixture of unreacted dimethyldimedone **2** and its dibrominated homolog **3**.<sup>9</sup> It also offers the possibility to reach scalemic (1*R*)-*cis*-chrysanthemic acid by, for example, promoting the enantioselective carbocyclization of **3** to scalemic **4**.

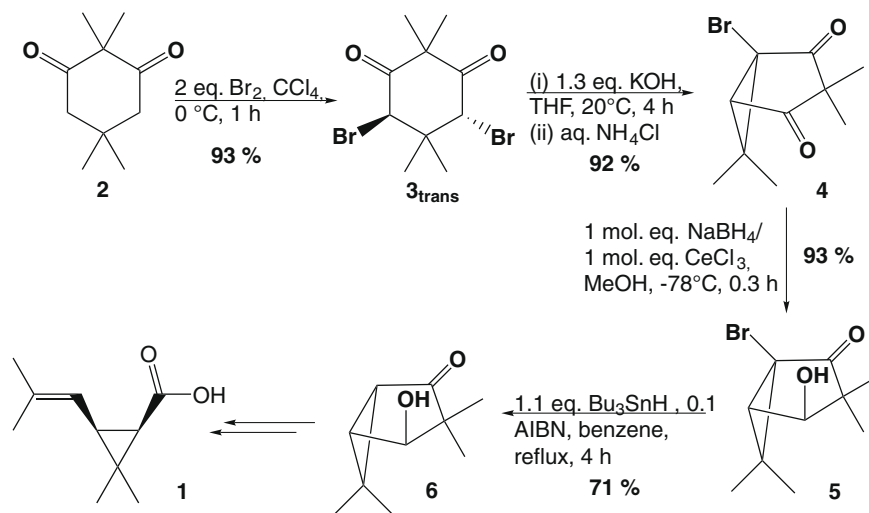
For that purpose we carefully studied the reactivity of **3<sub>trans</sub>** toward bases including chiral ones. The behavior of **3<sub>trans</sub>** toward bases was almost unknown when we started this work.<sup>10</sup> We have found that metallation occurs efficiently in THF (Scheme 2) with bases containing sodium and potassium counter ions including hydroxides (Table 1, entries 2,3), alkoxides (Table 1, entry 6), and amides (Table 1, entries 5,7,8). Potassium carbonate suspended in hot THF however is not strong enough to achieve metallation (Table 1, entry 1).

The reaction already takes place at  $-78^\circ\text{C}$  with sodium and potassium hexamethyldisilazide (NaHMDS or KHMDS) or potassium *t*-butoxide (*t*-BuOK) but cyclization of **3<sub>trans</sub>** to **4** does not occur even after standing for 2 hours at that temperature since the reaction leads after acidification to the isomerized *cis*-dibromodiketone **3<sub>cis</sub>**

\* Corresponding author. Tel.: +32 0 81 72 45 39; fax: +32 0 81 72 45 36.

E-mail address: [alain.krief@fundp.ac.be](mailto:alain.krief@fundp.ac.be) (A. Krief).

<sup>✉</sup> Deceased on the 17th September 2008.



Scheme 1.

in almost quantitative yield and extremely high diastereoisomeric ratio (Scheme 2, Table 1, entries 5,6).<sup>11</sup>

Raising the temperature to 20 °C before acidification leads to the bicyclic-diketone **4** bearing a bromine atom at bridgehead in very good yield (Scheme 2, Table 1, entry 7). Cyclization also occurs by reacting at room temperature **3trans** dissolved in THF with sodium hexamethyldisilazide or potassium or sodium hydroxide.

Lithium reagents especially lithium hydroxide and lithium diisopropylamide (LDA) behave differently. Thus lithium hexamethyl disilazide (LiHMDS) in THF does not metallate **3trans**, even at room temperature, as efficiently as its potassium analog (compare remaining **3trans**, Table 1, entries 7,9) under these conditions, cyclization of the enolate **7Li** is not taking place to a reasonable extent (compare amount of **4** produced, Table 1, entries 7,9).

Reactions involving **3trans** and LiOH and LDA are even more puzzling since Br/Li exchange which produces **8** is now favorably competing with H/Li exchange leading to **7** since **9** is produced, in substantial amounts, after acidification besides the epimerized dibromo-diketone **3cis** (Table 1, entries 4,10,11).<sup>12,13</sup> It is interesting to notice that neither **7Li** nor **8Li** is prone to transannular alkylation even under forcing conditions (Table 1, compare entries 11 to 10).

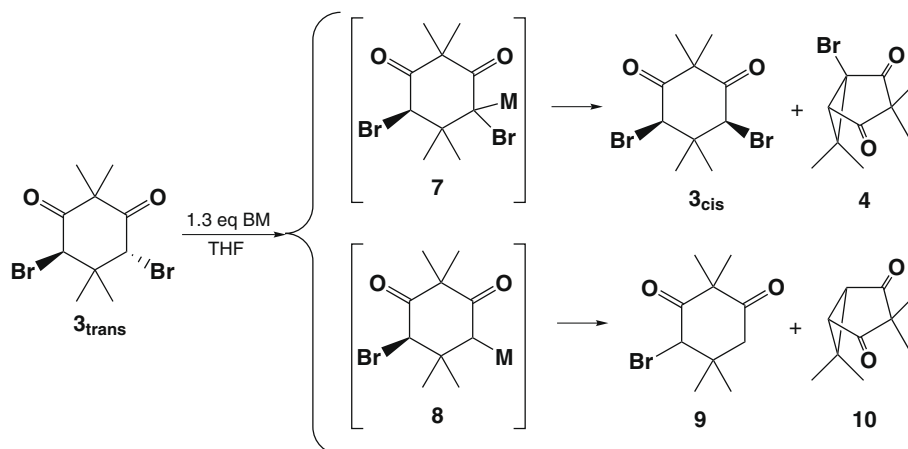
Br/Li exchange is not unexpected since **3trans** possesses in  $\alpha$ - and  $\alpha'$ -position one axial hydrogen and one axial bromine atom well suited to deliver an enolate by constant overlapping of

the orbital during the whole process. In conjunction with this hypothesis we found that **3cis** is less prone to Br/Li exchange when reacted with LDA (**3trans**/**3cis**/9/10: 22/47/27/4, compare to Table 1, entry 11).

Rationalization of these results is highly speculative and, for example, they are not in agreement with Pearson's theory.<sup>14</sup> Furthermore only few reports deal with Br/Li prevailing over H/Li exchange in  $\alpha$ -bromo-ketones, especially when metal hydroxides or metal amides<sup>15</sup> are used. It however prevails with reagents such as metal selenolates and tellurolates possessing a softer reacting species with  $\alpha$ -iodoketones.<sup>16</sup> Furthermore it is surprising that the Br/M exchange observed with LDA and LiOH is not observed when lithium hexamethyldisilazide is used instead.

With these results in hand we performed the reaction of chiral bases possessing potassium or ammonium counterions (Fig. 1) with the prochiral dibromodiketone **3cis** (Scheme 3).

Sodium and potassium (1*S*,2*R*)-2-(dibutylamino)-1-phenylpropan-1-olate **11** (Fig. 1) the Soai base<sup>17</sup> which was also exploited in the Duhamels group<sup>18</sup> effectively reacts with **3cis** and leads to the desired compound **4** in 81% yield but as a racemate (1.3 equiv **11K**, THF, 0 °C, 1 h). Performing the reaction at lower temperature (−40 °C) dramatically lowers the yield but still leads to the racemate (29%, ee 0%).



Scheme 2.

Table 1

	BM	Conditions	<b>3<sub>trans</sub></b>	<b>3<sub>cis</sub></b>	<b>4</b>	<b>9</b>
1	K <sub>2</sub> CO <sub>3</sub>	(i) 80 °C, 4 h, (ii) aq HCl	95			
2	KOH	(i) 20 °C, 4 h, (ii) aq NH <sub>4</sub> Cl			92	
3	NaOH	(i) 20 °C, 4 h, (ii) aq NH <sub>4</sub> Cl			88	
4	LiOH	(i) 20 °C, 4 h, (ii) aq NH <sub>4</sub> Cl	22	20	30	28
5	KHMDS	(i) –78 °C, 2 h (ii) aq NH <sub>4</sub> Cl, –78 °C	02	98		
6	<i>t</i> -BuOK	(i) –78 °C, 2 h, (ii) aq NH <sub>4</sub> Cl, –78 °C	02	98		
7	KHMDS	(i) –78 °C, 2 h, (ii) –78 to 20 °C, 2 h, (iii) aq NH <sub>4</sub> Cl	04	04	93	
8	NaHMDS	(i) –78 °C, 2 h, (ii) –78 to 20 °C, 2 h, (iii) aq NH <sub>4</sub> Cl	14	12	74	
9	LiHMDS	(i) –78 °C, 2 h, (ii) –78 to 20 °C, 2 h, (iii) aq NH <sub>4</sub> Cl	53	42	05	
10	LDA	(i) –78 °C, 1 h, (ii) HCl, MeOH, –78 °C	26	22		52
11	LDA	(i) –78 °C, 2 h, (ii) –78 to 20 °C, 2 h, (iii) aq NH <sub>4</sub> Cl	22	16	02	55

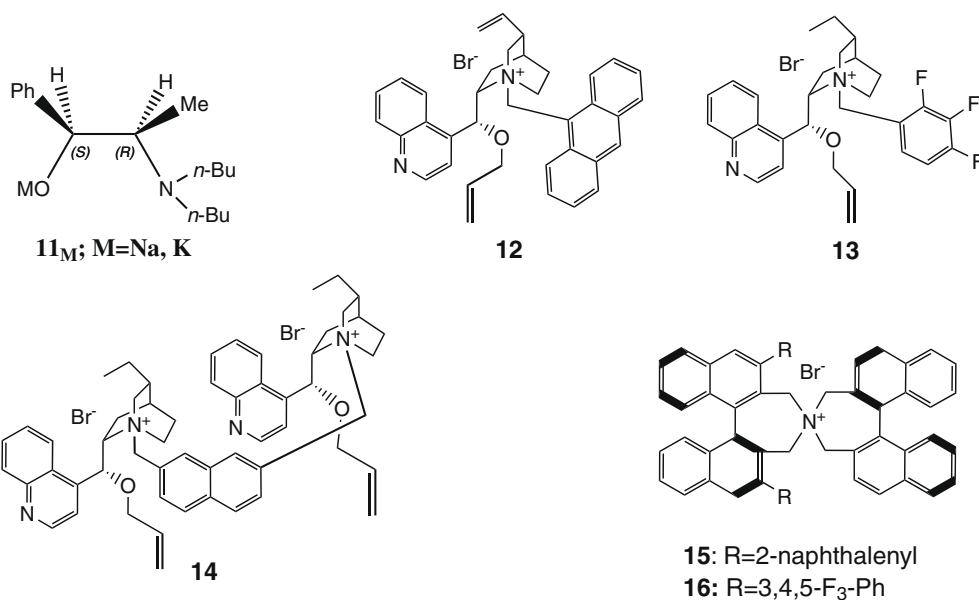
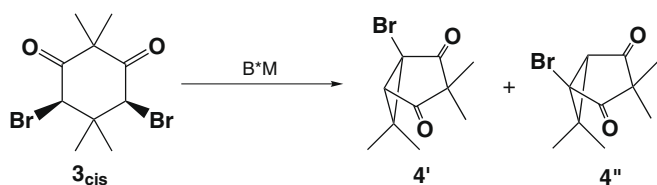


Figure 1.



Scheme 3.

We also carried out the reaction which involves potassium hydroxide (Scheme 1) in the presence of scalemic ammonium salts derived from chinconidia alkaloids<sup>19–22</sup> such as **12–14** (Fig. 1) or from binaphthyls<sup>22,23</sup> **15** and **16** (Fig. 1).

As expected all those catalysts allow the synthesis of **4** in good yield but we found that under these conditions the enantioselectivity of the reaction is extremely poor [(a) **12** (0.1 equiv, CsOH·H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 6 h, 82% yield, ee: 11%; or –40 °C, under similar conditions, 23% yield, ee: 14%); (b) **13** (0.1 equiv, 50% aq KOH, CHCl<sub>3</sub>–toluene, 0 °C, 6 h, 42% yield, ee: <2%); (c) **14** (0.1 equiv, 50% aq KOH, CHCl<sub>3</sub>–toluene, 0 °C, 6 h, 86% yield, ee: 5%); (d) **15** (0.01 equiv, 0 °C, 6 h, 50% aq KOH, toluene, 60% yield, ee: <1%)].

Best enantioselectivity, although extremely modest according to usual standards, has been however obtained using Binap-derived chiral catalyst **16** (0.01 equiv **16**, 50% aq KOH, toluene, 0 °C, 6 h, 75% yield, ee: 26%).<sup>24</sup>

We have determined that **4'** is the major enantiomer obtained in the above alkylative annelation by transforming it to (1*R*)-*cis*-chrysanthemic acid<sup>25</sup> **1'** using the set of reactions described in Scheme 1 for the racemate.<sup>4</sup>

Since we have observed similar results (yield and ee's) when performing the reaction, under similar conditions, on the *trans*-diastereoisomer **3<sub>trans</sub>**, we suspect that a complex process involving a series of epimerizations is taking place prior annelation leading to **4**.

### Acknowledgment

We thank Professor A. Luxen (ULG, Belgium) for providing us some of the chiral ammonium salts used in this work.

### References and notes

- Theobald, D. W. *Tetrahedron* **1978**, *34*, 1567–1569.
- trans*-4,6-Dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>trans</sub>**. Into a 500 mL round-bottomed two-necked flask, was added dropwise, at 0 °C, a solution of bromine (32.0 g, 0.2 mol) in CCl<sub>4</sub> (150 mL) to a stirred solution of 2,2,5,5-tetramethylcyclohexane-1,3-dione **2** (16.8 g, 0.1 mol) in CCl<sub>4</sub> (200 mL). After 1 h at 0 °C, 20 mL of satd aq K<sub>2</sub>CO<sub>3</sub> and 20 mL of satd aq Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> were added. The organic layer was decanted, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was crystallized from CH<sub>2</sub>Cl<sub>2</sub>–pentane to furnish 30.5 g (93%) of *trans*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>trans</sub>** as a white solid: mp 109 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.99 (s, 2H), 1.53 (s, 6H), 1.23 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 202.7, 60.5, 58.8, 38.6, 26.3, 24.8; IR (KBr): ν (cm<sup>–1</sup>) 2985,

- 2937, 1731, 1703, 1461, 1386, 1295, 1214, 1096, 1045, 1001, 914, 821, 727, 671, 635; EIMS  $m/z$  247, 245, 177, 175, 149, 147, 137, 125, 122, 107.
3. 1-Bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexane-2,4-dione **4**. Into a 100 mL round-bottomed two-necked flask under Ar, was added solid KOH (730 mg, 13 mmol) to a stirred solution of *trans*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>trans</sub>** (3.26 g, 10 mmol) in dry THF (50 mL) and the reaction mixture was stirred at rt. After 4 h, the reaction mixture was quenched with satd aq NH<sub>4</sub>Cl (20 mL) and extracted with ether (4 × 30 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 90:10) to furnish 2.25 g (92%) of 1-bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexane-2,4-dione **4** as a colorless liquid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.50 (s, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.15 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 207.9, 206.8, 55.5, 47.4, 46.4, 33.2, 26.6, 25.2, 18.8, 15.7; IR (film): ν (cm<sup>-1</sup>) 2976, 2934, 2873, 1762, 1726, 1462, 1382, 1288, 1110, 1073, 863, 833, 759; EIMS  $m/z$  246, 244, 203, 201, 176, 174, 161, 159, 109, 95, 70, 67, 55, 51, 42. Anal. Calcd for C<sub>10</sub>H<sub>13</sub>BrO<sub>2</sub>: C, 49.00; H, 5.35. Found: C, 48.82; H, 5.50.
  4. Krief, A.; Kremer, A. *Synlett* **2007**, 607–610.
  5. 1-Bromo-4-*exo*-hydroxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one **5**. Into a 50 mL round-bottomed two-necked flask under Ar, was added CeCl<sub>3</sub>·7H<sub>2</sub>O (1.12 g, 3 mmol) to a stirred solution of 1-bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexane-2,4-dione **4** (735 mg, 3 mmol) in MeOH (20 mL). After complete dissolution of cerium salt, the solution was cooled to –78 °C before NaBH<sub>4</sub> (114 mg, 3 mmol) was added in one portion. After 0.3 h at –78 °C, the reaction mixture was quenched with aq HCl (10%, 15 mL), allowed to warm to room temperature, and extracted with ether (4 × 25 mL). The combined organic extracts were washed with water (2 × 5 mL) and brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 60:40) to furnish 689 mg (93%) of 1-bromo-4-*exo*-hydroxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one **5** as a colorless liquid: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.89 (s, 1H), 1.93 (br, 1H), 1.82 (s, 1H), 1.38 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 0.99 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 211.2, 74.4, 54.8, 47.8, 43.4, 27.9, 26.7, 21.6, 19.6, 17.0; IR (film): ν (cm<sup>-1</sup>) 3359, 2970, 2931, 1739, 1456, 1381, 1356, 1241, 1135, 1108, 1048, 963, 843, 808, 663; EIMS  $m/z$  248, 246, 205, 203, 176, 174, 167, 159, 121, 107, 95, 67, 57, 41. Anal. Calcd for C<sub>10</sub>H<sub>15</sub>BrO<sub>2</sub>: C, 48.60; H, 6.12. Found: C, 48.36; H, 6.15.
  6. Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1943**, 26, 705–715.
  7. Bertrand, M.; Gil, G.; Junino, A.; Maurin, R. *Tetrahedron* **1985**, 41, 2759–2764.
  8. Ng, W.; Wege, D. *Tetrahedron Lett.* **1996**, 37, 6797–6798.
  9. (a) Krief, A.; Surleraux, D.; Frauenrath, H. *Tetrahedron Lett.* **1988**, 29, 6157–6160; (b) Nozaki, H.; Okada, T. *Bull. Chem. Soc. Jpn.* **1970**, 43, 2908–2911.
  10. Theobald reported<sup>1</sup> 30 years ago that the *trans*-dibromide **3<sub>trans</sub>** resulting from the dibromination of **2** by bromine in acetic acid containing trace of hydrobromic acid, produces after being refluxed in pyridine for 3 h, the *cis*-stereoisomer **3<sub>cis</sub>** in 10–15% yield.
  11. *cis*-4,6-Dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>cis</sub>**. KHMDS (0.5 M in toluene, 44 mL, 22 mmol) is added to a stirred solution of *trans*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>trans</sub>** (6.52 g, 20 mmol) in dry THF (75 mL) maintained at –78 °C. After 2 h at –78 °C, and usual work-up, the crude product is crystallized from CH<sub>2</sub>Cl<sub>2</sub>–pentane to furnish 6.13 g (94%) of *cis*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>cis</sub>** as a white solid: mp 147 °C; <sup>1</sup>H NMR, <sup>13</sup>C NMR, and EIMS agree with the published ones.<sup>1</sup>
  12. Reaction of *cis*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>cis</sub>** with LDA at –78 °C. LDA (0.5 M in dry THF, 2.6 mL, 1.3 mmol) is added dropwise to a stirred solution of *cis*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>cis</sub>** (326 mg, 1 mmol) in dry THF (5 mL) maintained at –78 °C. The solution is stirred at –78 °C for an additional hour. After usual work-up we obtained 284 mg (100%) of a mixture of *trans*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>trans</sub>**, *cis*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>cis</sub>**, and 4-bromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **9** in a 26:22:52 ratio, respectively. Spectral properties (<sup>1</sup>H NMR, <sup>13</sup>C NMR, and EIMS) of the two dibromides **3<sub>trans</sub>** and **3<sub>cis</sub>** and **9** (mp 117 °C) agree with the published ones.<sup>1,9</sup>
  13. The different products resulting from the reaction of dibromides **3<sub>trans</sub>** or **3<sub>cis</sub>** with bases were quantified by <sup>1</sup>H NMR.
  14. (a) Pearson, R. G. *J. Chem. Edu.* **1987**, 64, 561–567; (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, 85, 3533–3539.
  15. Dubois, J. E.; Lion, C.; Dugast, J. Y. *Tetrahedron Lett.* **1983**, 24, 4207–4208.
  16. Sheshadri, R.; Pegg, W. J.; Israel, M. *J. Org. Chem.* **1981**, 46, 2596–2598.
  17. Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690–1691.
  18. (a) Vadeкард, J.; Plaquevent, J.-C.; Duhamel, L.; Duhamel, P.; Toupet, L. *J. Org. Chem.* **1994**, 59, 2285–2286; (b) Vadeкард, J.; Plaquevent, J.-C.; Duhamel, L.; Duhamel, P. *J. Chem. Soc., Chem. Commun.* **1987**, 116–117.
  19. O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, 111, 2353–2355.
  20. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, 119, 12414–12415.
  21. (a) Jew, S.-S.; Yoo, M.-S.; Jeong, B.-S.; Park II, Y.; Park, H.-G. *Org. Lett.* **2002**, 4, 4245–4248; (b) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-S. *Angew. Chem., Int. Ed.* **2002**, 41, 3036–3038.
  22. Lemaire, C.; Gillet, S.; Guillaouet, S.; Plenevaux, A.; Aerts, J.; Luxen, A. *Eur. J. Org. Chem.* **2004**, 2899–2904.
  23. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, 121, 6519–6520; (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, 122, 5228–5229; (c) Maruoka, K. *J. Fluorine Chem.* **2001**, 112, 95–99.
  24. Enantioselective cyclization of *cis*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>cis</sub>**. KOH (50%, aq solution, 2 mL) is added to a stirred toluene solution (6 mL) of (*S,S*)-3,4,5-trifluorophenyl-NAS bromide **16** (9.1 mg, 0.01 mmol) and *cis*-4,6-dibromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **3<sub>cis</sub>** (326 mg, 1 mmol) maintained at 0 °C. This solution is further stirred for an additional 6 h. The crude product, obtained after usual work-up is purified by column chromatography (pentane/ether: 90:10) to furnish 184 mg (75%) of **4**. The **4**/**4'** ratio is determined by chiral HPLC ([column: DAICEL CHIRALPAK OD-H; solvent: hexane/*i*-propanol = 99.5/0.5; flow rate: 0.8 mL/min; detection: 217 nm]. We observe two distinct peaks on the chromatogram at 22.8 and 25.3 min in a 62:36 ratio. Structural assignment relies on the observation that the major (*S,S*)-enantiomer **4'** leads to the major (1*R*)-*cis* enantiomer of chrysanthemic acid **1'**.
  25.  $[\alpha]_D^{20}$  +21.7 (c 1.75, CHCl<sub>3</sub>); for (1*R*)-*cis*-chrysanthemic acid **1'**: lit.<sup>4</sup>:  $[\alpha]_D^{20}$  +83.0 (c 1.75, CHCl<sub>3</sub>).