Syntheses of Racemic and Scalemic *cis*-Chrysanthemic Acid from *β,γ*-Unsaturated Cyclohexanol

by **Alain Krief**[a]), **Stéphane Jeanmart**[a])[b]), **Humaira Y. Gondal**[a])[c]), and **Adrian Kremer***[a])[d])

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

[b]) *Syngenta Crop Protection Münchwilen AG*, Schaffhauserstrasse CH-4332 Stein

[c]) Chemistry Department, University of Sargodha, Pakistan

[d]) Laboratoire de Chimie Organique et des Matériaux Supramoléculaires, Facultés Universitaires N.-D. de la Paix, 61 rue de Bruxelles, B-5000 Namur

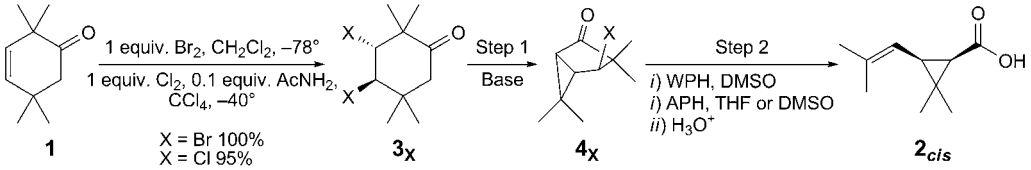
(phone: +32-81-725415; e-mail: adrian.kremer@fundp.ac.be)

Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

2,2,5,5-Tetramethylcyclohexane-1,3-dione is a valuable starting-material precursor of *cis*-chrysanthemic acid. The (1*S*)-stereoisomer is a precursor of pyrethrin I, the most active natural insecticide from *Chrysanthemum cinerariifolium*, whereas the (1*R*)-stereoisomer is efficiently transformed to deltamethrin, the most active commercially available pyrethroid insecticide. Several intermediates have been identified and used with variable success for that purpose.

Introduction. – 2,2,5,5-Tetramethylcyclohex-3-en-1-one (**1**) possesses a C_{10} skeleton, as chrysanthemic acid, a CO group, and two C-atoms each bearing geminal Me groups in suitable position to generate, after proper reactions, *cis*-chrysanthemic acid (**2**$_{cis}$) possessing the above mentioned CO group as part of its carboxy group and geminal Me groups located at its vinylic C-atom and on its cyclopropane ring (*Scheme 1*). *cis*-Chrysanthemic acid (**2**$_{cis}$) is in turn an efficient precursor of deltamethrin, the most powerful commercially available pyrethroid insecticides [1].

Scheme 1. *Synthesis of* **2**$_{cis}$ via *Addition of* X_2 *to C=C Bond of* **1**



We have reported, in the recent past, preliminary work involving the transformation of **1** for that purpose [2], but the experimental part was missing in most of the related papers [2a–2c], which also provided fragmentary information about the topic. We disclose in this article *i*) an integrated view on the whole topic and *ii*) scope and limitation of each of the transformations, and provide, any time it has not yet been done, experimental details.

Thus, the transformation of tetramethyl-cyclohexenone **1** to *cis*-chrysanthemic acid (**2**$_{cis}$) requires three distinct steps *i*) halogenation of its C=C bond leading to 3,4-dihalogeno-2,2,5,5-tetramethylcyclohexanones **3**$_{X}$ (X = Br: 1 equiv. Br_2, CH_2Cl_2, $-78°$; quant. yield, or 1 equiv. Br_2, 0.1 equiv. $AcNH_2$, CCl_4, 0°, 1 h, 98% yield; X = Cl: 1 equiv. Cl_2, 0.1 equiv. $AcNH_2$, CCl_4, $-40°$, titration; 92% yield) [3] (*Scheme 1*). *ii*) Reaction of the resulting **3**$_{X}$ with a base, producing an enolate which, after subsequent elimination of the halogen atom located three C-atom away, generates the cyclopropane ring, part of 4-halogeno-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-ones **4**$_{X}$ (X = Br or Cl, *Scheme 1*) [3]. *iii*) Reaction of **4**$_{X}$ with an appropriate source of HO^- ion, acting as a nucleophile on its CO group and subsequent fragmentation which releases the halide ion and produces the desired vinyl cyclopropane carboxylate precursor of *cis*-chrysanthemic acid (**2**$_{cis}$) after acid hydrolysis (*Scheme 1*) [3].

The synthesis of 4-halogeno-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-ones **4**$_{X}$ (X = Br or Cl) has been efficiently achieved at low temperature using stoichiometric amounts of $^{i}Pr_2NLi$ (LDA) in THF (*Table 1*, *Entries a* and *d*; *Conditions 1*) or ^{t}BuOK in THF (*Table 1*, *Entries b* and *e*; *Conditions 1*) acting as a base [3]. The same transformation carried out on **3**$_{Br}$ required excess of MeOLi in MeOH and led to bicyclic derivative **4**$_{Br}$ at higher temperature and in lower yield (*Table 1*, *Entry c*; *Conditions 1*). Therefore, the sub-stoichiometric amount of reagent used does not promote under such drastic conditions the *Grob* fragmentation [4] which would have led instead to methyl chrysanthemate [5].

Table 1. *Synthesis of* cis-*Chrysanthemic Acid* (**2**$_{cis}$) *Involving 3,4-Dihalogeno-2,2,5,5-tetramethylcyclohexanones* **3**$_{X}$. WPH = Aq. KOH in DMSO; APH = ^{t}BuOK/H_2O.

Entry	X	Base	*Conditions 1* for **3** → **4**	Yield of **4** [%]	*Conditions 2* for **4** → **1**	Yield of **2**$_{cis}$ [%]
a	Br	1 equiv. LDA	THF, $-78°$, 1 h	86	WPH, DMSO, 70°, 0.8 h	87
b	Br	1.2 equiv. ^{t}BuOK	THF, -78 to 20°, 1 h	94	APH, THF, 20°, 0.5 h	94
c	Br	6 equiv. MeOLi	MeOH, 65°, 48 h	49	APH, DMSO, 20°, 0.3 h	53
d	Cl	1 equiv. LDA	THF, $-78°$, 1 h	88	WPH, DMSO, 70°, 0.8 h	75
e	Cl	1.2 equiv. ^{t}BuOK	THF, -78 to 20°, 1 h	89	APH, THF, 20°, 0.5 h	91

The synthesis of *cis*-chrysanthemic acid (**2**$_{cis}$) from **4**$_{X}$ (X = Br or Cl) has been achieved at 70° using WPH (*i.e.*, KOH in aqueous DMSO (DMSO/H_2O 4:1); *Table 1*, *Entries a* and *d*; *Conditions 2*) or better at 20° using *Swan–Gassman* reagent [6], generated *in situ* from ^{t}BuOK and H_2O (^{t}BuOK/H_2O 3:1 (APH); *Table 1*, *Entries b*, *c*, and *e*; *Conditions 2*). We have found that, whereas **4**$_{Cl}$ is less reactive than **4**$_{Br}$ towards WPH, they react both very fast, when APH is used, and provide chrysanthemic acid **2**$_{cis}$ in very high yield especially if the reactions are carried out in THF (*Table 1*, *cf. Entries b*, *c*, *e*; *Conditions 2*) [7].

It was tempting to perform both the cyclization and fragmentation steps in the same pot using KOH acting sequentially as a base first then as a nucleophile. This has been successfully achieved from **3** whatever the conditions used (WHP-DMSO [3], APH-THF, or APH-DMSO [8]; *Scheme 2* and *Table 2*). APH in THF, however, is preferred since it generates **2**$_{cis}$ under more reliable and milder conditions than those involving

Scheme 2. *'One-Pot' Cyclization–Fragmentation of* $\mathbf{3_X}$

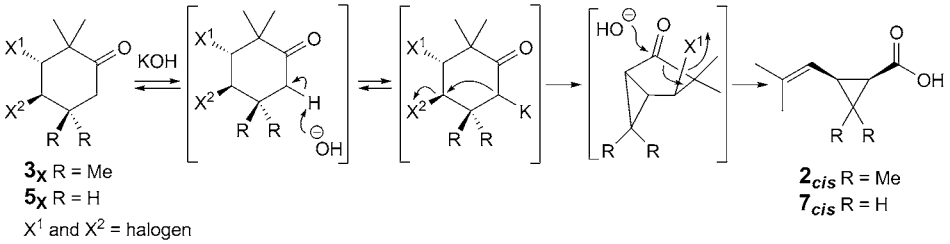


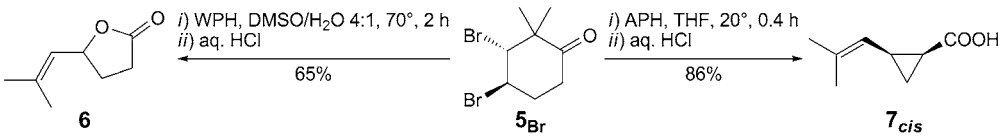
Table 2. *'One-Pot' Cyclization–Fragmentation of* $\mathbf{3_X}$

Entry	$X^1 = X^2$	Substrate	Conditions	Yield of $\mathbf{2}_{cis}$ [%]
a	Br	$\mathbf{3_{Br}}$	*i*) 6 equiv. KOH, DMSO/H_2O (4 : 1), 70°, 2 h. *ii*) H_3O^+.	87
b	Cl	$\mathbf{3_{Cl}}$	*i*) 6 equiv. KOH, DMSO/H_2O (4 : 1), 70°, 4 h. *ii*) H_3O^+.	64
c	Br	$\mathbf{3_{Br}}$	*i*) 6 equiv. ^{t}BuOK, 3 equiv. H_2O, THF, 20°, 0.4 h. *ii*) H_3O^+.	94
d	Cl	$\mathbf{3_{Cl}}$	*i*) 6 equiv. ^{t}BuOK, 3 equiv. H_2O, THF, 20°, 1 h. *ii*) H_3O^+.	80
e	Br	$\mathbf{3_{Br}}$	*i*) 6 equiv. ^{t}BuOK, 3 equiv. H_2O, DMSO, 20°, 0.5 h. *ii*) H_3O^+.	65

WHP or AHP in DMSO [8]. As expected $\mathbf{3_{Br}}$ reacts faster than $\mathbf{3_{Cl}}$ towards both AHP and WHP (*Scheme 2*, *cf. Entry a* to *b* and *c* to *d*).

It is interesting to notice that performing the reaction of $\mathbf{5_{Br}}$, the didemethyl analog of $\mathbf{3_{Br}}$, with WPH produces didemethyl-isopyrocine **6** instead of the didemethyl-vinyl-cyclopropanecarboxylic acid $\mathbf{7}_{cis}$. The latter is in fact produced when the reaction is carried out with APH in THF (*Scheme 3*).

Scheme 3. *'One-Pot' Cyclization–Fragmentation of* $\mathbf{5_{Br}}$

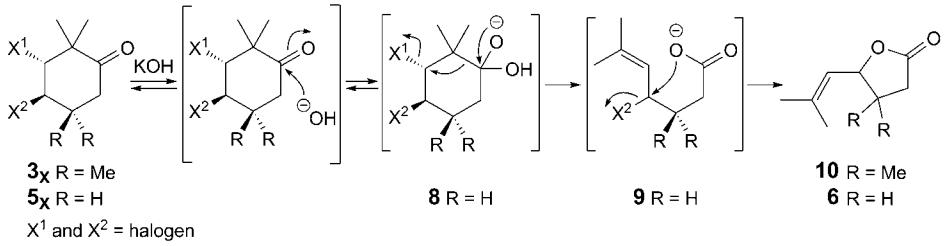


The transformation of $\mathbf{5_{Br}}$ to $\mathbf{7}_{cis}$ can be rationalized by assuming that the HO^- ion acts first as a *base* towards $\mathbf{5_{Br}}$ as outlined in *Scheme 2* (X^1, X^2 = Br; R = H). The transformation of $\mathbf{5_{Br}}$ to **6** is in turn rationalized (*Scheme 4*) by assuming that the HO^- ion reacts instead as a *nucleophile* on the CO group of $\mathbf{5_{Br}}$ leading to **8** that subsequently fragments to $\mathbf{9_{Br}}$ and collapses to **6** (R = H) *via* an intramolecular substitution of the allyl bromide by the carboxylate intermediate [8].

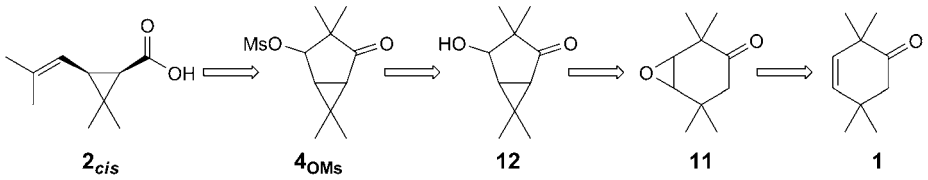
Results and Discussion. – We became next interested to carry out a related transformation on the 3,4-epoxycyclohexanone **11**, according to the retrosynthetic *Scheme 5*.

The challenging transformation is without doubt that of **1** to **12**, since the transformation of the latter to $\mathbf{2}_{cis}$ has been already achieved (*Scheme 6*) [9]. It involves mesylation of the alcohol **12** (1.2 equiv. MsCl, 1.5 equiv. Et_3N, CH_2Cl_2, $-10°$, 0.75 h,

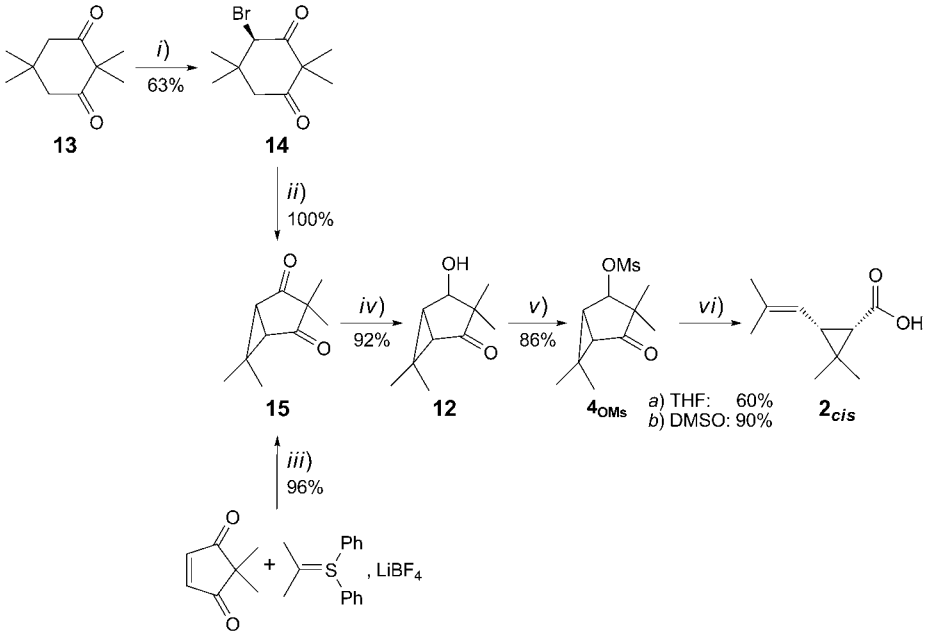
Scheme 4. *Rationalization for the Transformation of* $\mathbf{5_{Br}}$ *to* **6**



Scheme 5. *Retrosynthetic Scheme Involving* **11**



Scheme 6. *Synthesis of* $\mathbf{2_{cis}}$ *Involving* **12**?

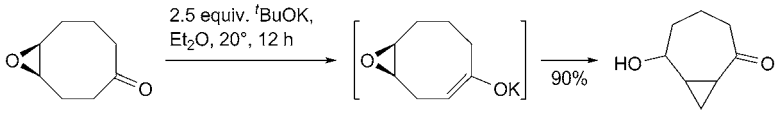


i) 1 equiv. Br_2, CCl_4, 0°, 2 h. *ii*) 1.2 equiv. ^{t}BuOK, −78° to r.t., 1 h. *iii*) 1,2-dimethoxyethane (DME), −78°, 1 h, then 20°, 1 h. *iv*) 1 equiv. $NaBH_4$, 1 equiv. $CeCl_3 \cdot 7\,H_2O$, MeOH, −78°, 1.5 h. *v*) 1.1 equiv. MsCl, 1.5 equiv. NEt_3, CH_2Cl_2, −10°, 0.75 h. *vi*) *a*) 6 equiv. ^{t}BuOK/3 equiv. H_2O, THF, 20°, 0.3 h; *b*) 6 equiv. ^{t}BuOK/3 equiv. H_2O, DMSO, 20°, 0.4 h.

86% yield) [9a] leading to $\mathbf{4_{OMs}}$, followed by reaction of the HO^- ion, leading *via Haller–Bauer* reaction/*Grob* fragmentation to *cis*-chrysanthemic acid ($\mathbf{2_{\textit{cis}}}$) after acid hydrolysis. We have shown that this transformation cannot be achieved using WPH in DMSO [9a], in contrast to what has been achieved with the related bicyclic halides $\mathbf{4_X}$ (*Scheme 1* and *Table 1*, *Entries a* and *d*; *Conditions 2*) [3], since polymeric substances are formed, beside minute amounts (7%) of *cis*-chrysanthemic acid ($\mathbf{2_{\textit{cis}}}$) [10]. The latter can be, however, efficiently produced using APH in THF or better in DMSO (*Scheme 6*) [10].

The more efficient transformation of **1** to **12** would have involved epoxidation of **1** and base promoted tandem metalation–epoxide ring opening of the resulting 7-oxabicyclo[4.1.0]heptane **11**. A related transformation has been successfully achieved on 9-oxabicyclo[6.1.0]nonane **16**, the higher homologue of **11**, which is expected, however, to involve a much less strained transition state (*Scheme 7*; $\mathbf{17_K}$ to **18**) [11].

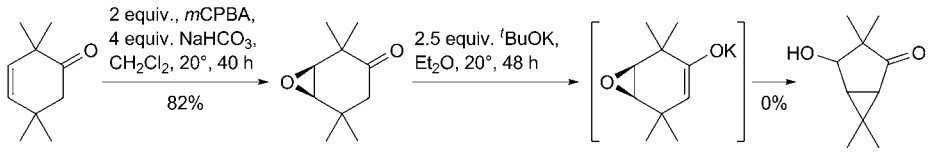
Scheme 7. *Synthesis of* **18** *from 9-Oxabicyclo[6.1.0]nonane* **16**



16 **17_K** **18**

3,4-Epoxycyclohexanone **11** has been prepared from **1** and *m*CPBA (2 equiv., 4 equiv. $NaHCO_3$, CH_2Cl_2, 20°, 40 h, 82% yield) [2c] but we were unable to achieve the epoxide ring opening and the subsequent carbocyclization using *a*) ^{t}BuOK as successfully used for its higher homolog **16** (*Scheme 8*, compare to *Scheme 7*); *b*) KOH in DMSO (5 equiv., 20°); *c*) EtONa in EtOH at reflux, or *d*) LDA in THF (– 78 to 20°) [12].

Scheme 8. *Attempt to Synthesize* **12** *from 3,4-Epoxycyclohexanone* **11**

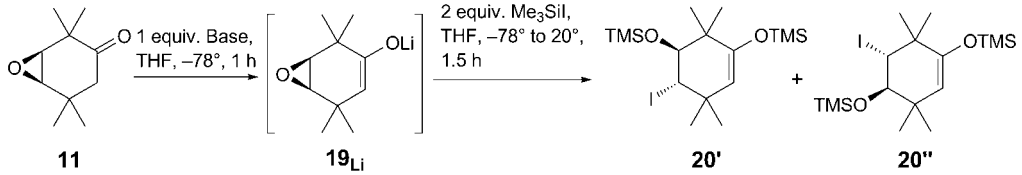


1 **11** **19_K** **12**

Since this could be ascribed to the extreme strain generated for the required alignment of the orbitals in the transition state of the planned substitution reaction, the only options left for achieving the desired transformation was to destroy, even partially, the C(4)–O bond of the epoxide ring, expecting the intermediate formation of a carbocation. The transformation of **11** to **12** could be achieved on treatment of *i*) the preformed lithium enolate $\mathbf{19_{Li}}$ (from LDA or LiHMDS on **11**) using *Lewis* acids such as $BF_3 \cdot Et_2O$ (1 to 5 equiv.), Et_2AlCl (5 equiv.), scandium(III) triflate (0.2 equiv.) or *ii*) the related enol $\mathbf{19_H}$ generated on reaction of **11** with $BF_3 \cdot Et_2O$ in $CHCl_3$ or with super acids such as ($BF_3 \cdot Et_2O$–HBF_4) or ($BF_3 \cdot Et_2O$–HBr) in the same solvent. Both approaches proved unsuccessful, the former leading to the recovery of **11** after acidification, and the latter to its destruction [5].

We, however, found that the required epoxide ring opening could be successfully achieved stepwise by reacting the lithium enolate **19$_{Li}$**, prepared from **11** and LDA (1 equiv.) with Me_3SiI (TMSI, 2 equiv.). We obtained evidence that the latter first traps the enolate intermediate then effects the epoxide ring opening [13] to finally produce a mixture of the two regioisomeric bis(silyloxy)-cyclohexenones **20′** and **20″** (*Scheme 9*).

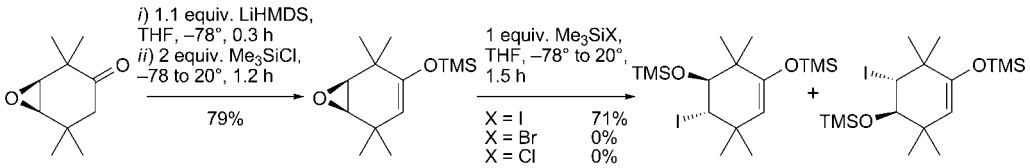
Scheme 9. *'One-Pot' Synthesis of Iodo-bis(silyloxy)-cyclohexenes* **20′** *and* **20″**. LiHMDS = Lithium hexamethyldisilazide, LDA = lithium diisopropylamide; LiTMP = lithium tetramethylpiperidide.



11		**19$_{Li}$**	**20'**	**20''**
	LiHMDS	26%	30	70
	LDA	50%	40	60
	LiTMP	60%	37	63

Lithium tetramethylpiperidide (LiTMP) [14], the strongest among the different bases tested (pK_a *ca.* 37) [15], provides the best yield of **20**. It nevertheless does not produce the highest percentage of the regioisomeric **20′**, the potential precursor of the bicyclo[3.1.0] derivative **4$_{OMs}$** and of **2$_{cis}$** (*Scheme 9*). A slightly improved ratio (**20′**/**20″** 58 : 42) has been achieved by reacting TMSI with the preformed silylenolate **19$_{TMS}$**, freed from the amine by-product resulting from the metalation of **11** (*Scheme 10*). We have not been able however, to promote the regioselective formation of **20′** using the strategy outlined in *Scheme 5*.

Scheme 10. *Two-Steps Synthesis of* **20′** *and* **20″**



11	**19$_{TMS}$**	**20'**	**20''**
		58	42

The synthesis of the silylenolate **19$_{TMS}$** is better achieved on reaction of the lithium enolate **19$_{Li}$** with Me_3SiCl (TMSCl), since it is not only cheaper than TMSI, but also it does not affect the epoxide ring opening observed above, even if it used in excess, a property that it shares with TMSBr (*Scheme 10*).

We have also successfully performed the epoxide ring opening on **11** using HBr [16], HCl [17], or Li_2NiBr_4 [18], in THF; Ph_3PHBr [19], $POCl_3$ + DMAP, titanium tetrahalides (X = Cl, Br) [20], or beryllium dichloride [21] in CH_2Cl_2, and have generated the corresponding regioisomeric β-chloro- and β-bromo-hydroxy-cyclohexanones **21′** and **21″** in reasonably good yields but as a stereoisomeric mixture (*Scheme 11* and *Table 3*).

Scheme 11. *Synthesis of Halogeno-hydroxy-cyclohexanones* **21′** *and* **21″**

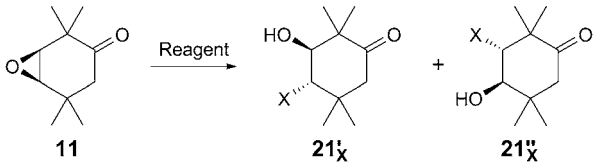
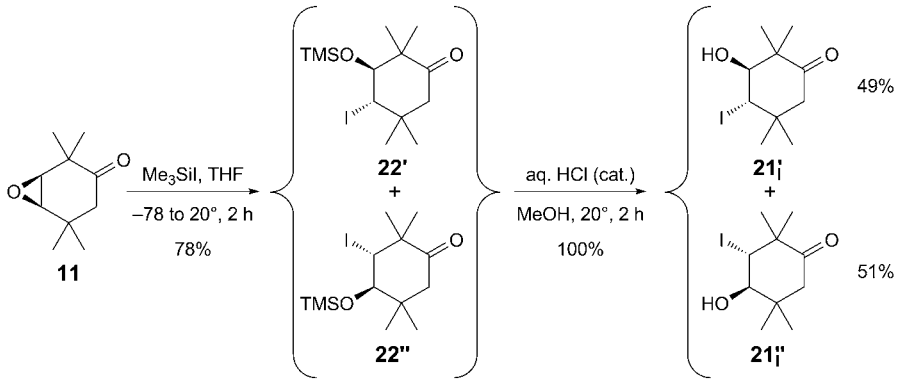


Table 3. S*ynthesis of β-Halogeno-hydroxy-cyclohexanones* **21′** *and* **21″**

Entry	Reagent	Solvent	Equiv.	*T* [°]	*t* [h]	X	$\mathbf{21_X}$	Yield of $\mathbf{21_X}$ [%]	**21′/21″** Ratio
a	$TiCl_4$	CH_2Cl_2	1	20	72	Cl	$\mathbf{21_{Cl}}$	92	58 : 42
b	$TiBr_4$	CH_2Cl_2	0.5	20	2	Br	$\mathbf{21_{Br}}$	96	43 : 57
c	$TiBr_4$	CH_2Cl_2	1	−78	5	Br	$\mathbf{21_{Br}}$	55	55 : 45
d	$TiBr_4$	CH_2Cl_2	1	20	1	Br	$\mathbf{21_{Br}}$	96	45 : 55
e	HBr [16]	THF	2	20	2	Br	$\mathbf{21_{Br}}$	75	65 : 35
f	HCl [17]	THF	2	20	3	Cl	$\mathbf{21_{Cl}}$	75	66 : 34
g	Li_2NiBr_4 [18]	THF	5	20	168	Br	$\mathbf{21_{Br}}$	41	75 : 25
h	$BeCl_2$ [21]	CH_2Cl_2	5	20	100	Cl	$\mathbf{21_{Cl}}$	83	80 : 20

Similarly, reaction of epoxy-cyclohexanone **11** with TMSI in THF and acid hydrolysis of the intermediate *β*-silyloxy-iodo-cyclohexanones **22** using aqueous HCl acid, also led to hydroxy-iodo-cyclohexanones $\mathbf{21_I}$, but as an almost 1 : 1 mixture of regioisomers (*Scheme 12*).

Scheme 12. *Synthesis of Hydroxy-iodo-cyclohexanones* $\mathbf{21_I'}$ *and* $\mathbf{21_I''}$

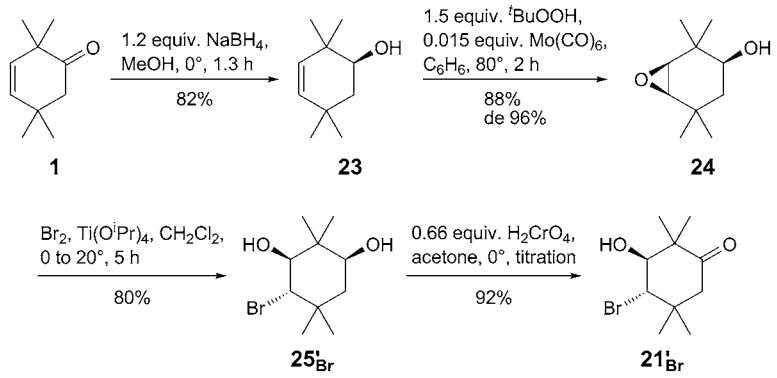


We have not been able to achieve the regioselective ring opening of **11**, and, except rare cases which are listed in *Table 3*, the reaction produces an almost 1 : 1 regioisomeric mixture **21**. The most valuable reagent for our purpose was beryllium dichloride but the de of the resulting products (60%) was far from excellent (*Scheme 11*; *Table 3*, *Entry h*) [21].

We, however, synthesized regioselectively 4-bromo-3-hydroxy-2,2,5,5-tetramethyl-cyclohexanone ($\mathbf{21_{Br}'}$) by a different strategy which involves a multistep process in which reduction of the CO group of **1** leads to the homoallylic alcohol **23** whose OH

group is able to direct the face selective epoxidation of the C=C bond and to achieve the regioselective ring opening of the resulting allylic epoxide **24** (*Scheme 13*). This was effectively achieved by: *i*) reduction of **1** with $NaBH_4$ (1.2 mol equiv., MeOH, 0°, 1.3 h, 82% yield); *ii*) stereoselective Mo-catalyzed epoxidation of the resulting homoallylic alcohol **23** (1.5 equiv. ^{t}BuOOH, 0.015 equiv. $Mo(CO)_6$, C_6H_6, 80°, 2 h) leading to the allylic epoxide **24** with the OH and epoxy moieties at the same face (88% yield, de 96%; *Scheme 13*) [22]; *iii*) regio- and stereoselective epoxide ring opening using the couple $Ti(O^iPr)_4$ and Br_2 [23], which almost exclusively leads to the diol $\mathbf{25'_{Br}}$ bearing the two OH moieties in a 1,3-*cis*-relationship, and a Br-atom with *trans*-relationships with the two OH groups, as unambiguously assessed by X-ray diffraction [24] (1.1 equiv. Br_2, 1.1 equiv. $Ti(O^iPr)_4$, CH_2Cl_2, 0 to 20°, 5 h, 93% yield, de 86%, *Schemes 13* and *14*; and *Table 4*, *Entry a*) [23], and *iv*) regioselective oxidation of the OH group of $\mathbf{25'_{Br}}$ bearing in δ position the Br-atom, when carried out by the *Jones* reagent [25] (0.66 equiv. H_2CrO_4, acetone, 0°, titration, *Scheme 13*). This reagent generated $\mathbf{21'_{Br}}$ in very high yield 92%, beside trace amount of 4-bromo-2,2,5,5-tetramethylcyclohexane-1,3-dione **14** (4%).

Scheme 13. *Synthesis of Bromo-hydroxy-cyclohexanone* $\mathbf{21'_{Br}}$



Scheme 14. *Synthesis of Diols* $\mathbf{25'_X}$ *and* $\mathbf{25''_X}$

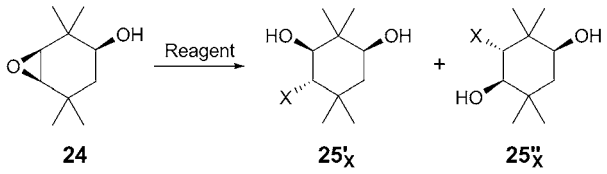


Table 4. *Regiocontrolled Epoxide Ring Opening of* **24** *Using* $Ti(O^iPr)_4$ *and Halogen*

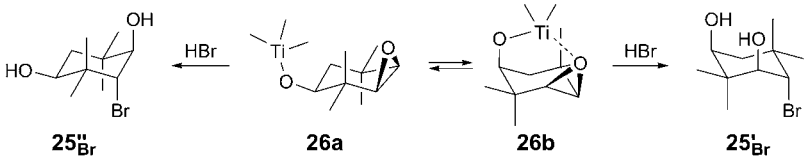
Entry	Reagent	Equiv.	T [°]	t [h]	X	Yield of **25′** + **25″** [%]	$\mathbf{25'_X/25''_X}$	Ratio
a	$Ti(O^iPr)_4 + Br_2$	1.1	0–20	5	Br	93	$\mathbf{25'_{Br}/25''_{Br}}$	93 : 7
b	$TiBr_4$	0.5	20	72	Br	87	$\mathbf{25'_{Br}/25''_{Br}}$	32 : 68
c	$Ti(O^iPr)_4 + I_2$	1.1	20	30	I	66	$\mathbf{25'_I/25''_I}$	73 : 27
d	$Ti(O^iPr)_4 + Cl_2$	1.1	20	24	Cl	0	$\mathbf{25'_{Cl}/25''_{Cl}}$–	

This series of transformations is quite exceptional, since, as it will be reported below, control of the regio- and stereochemistry cannot be easily achieved using reagents different from those we have selected. Thus, for example, epoxidation of **23** with *m*CPBA proved to be completely unselective [26] and led to 2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol (**24**) in excellent yield, but as a 1:1 mixture of the two diastereoisomers (1.5 equiv. *m*CPBA, 2 equiv. $NaHCO_3$, CH_2Cl_2, 20°, 4 h, 81% yield, de 0%) and reagents involving H_2O_2 or ^{t}BuOOH proved to be inefficient. This is, for example, the case of *i*) ^{t}BuOOH and $(^t BuO)_3Al$ (1.5 equiv. ^{t}BuOOH, 1.5 equiv. $(^t BuO)_3Al$, C_6H_6, 80°, 5 h, 0% yield) [27], *ii*) H_2O_2 in the presence of dicyclohexylcarbodiimide (8.8 equiv. H_2O_2, 2 equiv. DCC, 2 equiv. $KHCO_3$, MeOH, 20°, 23 h, 25%, de 94%) [28], or *iii*) ^{t}BuOOH and catalytic amounts of $VO(acac)_2$ (1.5 equiv. ^{t}BuOOH, 0.015 equiv. $VO(acac)_2$, C_6H_6, 80°, 5 h, 26% yield, de 98%). Although the latter reagents allowed the highly diastereoselective epoxidation of **23** to the 3,4-epoxycyclohexanol **24** bearing the epoxide ring on the same face as the OH group, as described when the reaction was instead catalyzed by $Mo(CO)_6$ (*Scheme 13*), the conversion rate was low, and using $VO(acac)_2$ competing formation of the epoxycyclohexanone **11** was observed. Such behavior has been already reported with alcohols whose OH group similarly is in equatorial position [29].

Similarly, we have been unable to achieve regiocontrolled epoxide ring opening using $TiBr_4$ (0.5 equiv. $TiBr_4$, 20°, 72 h; *Scheme 14*; *Table 4*, *Entry b*) or the related couples $Ti(O^iPr)_4$ and I_2 (*Table 4*, *Entry c*), or Cl_2 (*Table 4*, *Entry d*) [23], as we did using instead $Ti(O^iPr)_4$ and Br_2, which is known to produce $BrTi(O^iPr)_3$) [23] (*Schemes 13* and *14*; and *Table 4*, *Entry a* compared to *Entries b–d*).

We assume that the regioselective synthesis of $\mathbf{25'_{Br}}$ from $BrTi(O^iPr)_3$ (*Scheme 14*, and *Table 4*, *Entry a*) results, according to *Fürst–Plattner* rule [30], from the *trans*-diaxial nucleophilic ring opening of the epoxide ring of the less stable conformer **26b** (*Scheme 15*) stabilized through chelation by Ti^{IV} of the O-atom of the alcohol and the epoxide ring as well.

Scheme 15. trans-*Diaxial Nucleophilic Ring Opening of* **26**



$\mathbf{25''_{Br}}$ **26a** **26b** $\mathbf{25'_{Br}}$

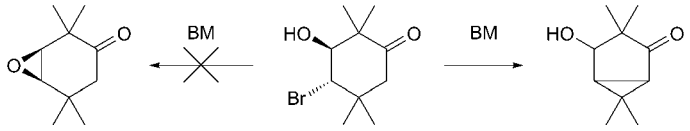
The same rule [30], applied to the non-chelated and more stable conformer **26a** (*Scheme 15*), can rationalize the reversed selectivity observed when $TiBr_4$ is instead used (*Scheme 14*, and *Table 4*, *Entry b*). Work is in progress to understand these discrepancies.

Finally, selective oxidation of the 1,3-diol $\mathbf{25'_{Br}}$ to the 3-hydroxyketone $\mathbf{21'_{Br}}$ which has been so efficiently achieved using the *Jones* reagent [25] (*Scheme 13*) proved to be extremely challenging, since the oxidation should take place selectively on one of the two alcohols whose OH groups are both equatorial, and competing 'over-oxidation' and '*retro*-aldol reaction' on $\mathbf{21'_{Br}}$ should be avoided. The first results involving pyridinium chlorochromate (PCC) [31] were disappointing, since the starting material

was recovered unchanged even after standing in CH_2Cl_2 for more than 3 d at 20°. ^{t}BuOOH in the presence of $VO(acac)_2$ [29], which was expected to produce 3,4-epoxy-2,2,5,5-tetramethylcyclohexanone (**11**) on reaction of 2,2,5,5-tetramethylcyclohex-3-enol (**23**) to 2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol (**24**), proved to be only slightly better although it effectively furnished the desired ketone $\mathbf{21'_{Br}}$ with complete regiocontrol, but the reaction was very slow and the yield extremely modest (C_6H_6, 80°, 84 h, 19%).

The transformation of $\mathbf{21'_{Br}}$ to **12**, which was the last goal to achieve, was not a simple task, since the base required to produce **12** could competitively generate the epoxide **11** instead (*Scheme 16*).

Scheme 16. *Selective Transformation of* $\mathbf{21'_{Br}}$ *to* **12**. BM = Base (M is the counter ion).



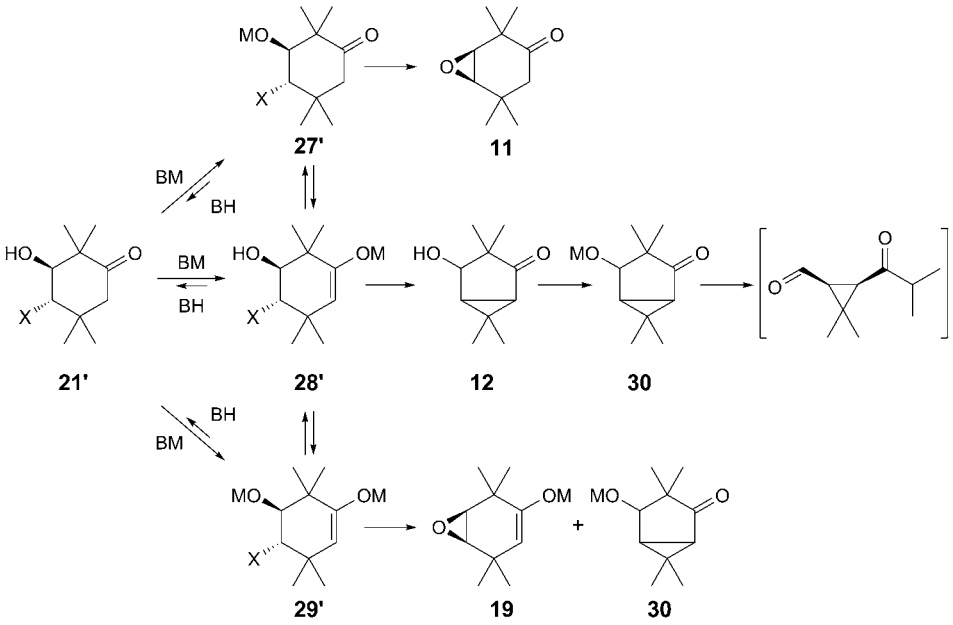
11 $\mathbf{21'_{Br}}$ **12**

These transformations involve first metallation of $\mathbf{21'_{Br}}$ which could either take place on its OH group, leading to $\mathbf{27'_{Br}}$, or on one of the CH_2 H-atoms leading to $\mathbf{28'_{Br}}$ under kinetic control then react to produce **11** by *O*-alkylation and the bicyclic cyclopropane derivative **12** by *C*-alkylation directly or after a pre-equilibrium (thermodynamic control; *Scheme 17*). Those can also be formed through the dimetallated intermediate $\mathbf{29'_{Br}}$ especially if more than 1 equiv. of base is used (*Scheme 17*). The nature of the leaving group X and of the counter ion M, the number of equivalent of base used, as well as the experimental conditions should, therefore, have a crucial impact on the chemioselectivity of the process. Furthermore the conditions should be mild enough to avoid a '*retro*-aldol reaction' on the resulting **30** which is known to lead to polymeric materials [10].

We first performed the reaction of lithium amides on $\mathbf{21'_{Br}}$, since it is not only the potential precursor of the required bicyclic derivative **30** but also the only halohydrin of the series which we have synthesized free from its regioisomer (*Scheme 18*). The highest percentage of bicyclo[3.1.0] derivative **12** was observed by adding, at −25° $\mathbf{21'_{Br}}$ in THF to an excess (≥2 equiv.) of base in the same solvent (*Table 5*, *Entries d* and *h*; *Conditions R*). Best results have been obtained by using LiTMP (*Table 5*, *Entry d*; *Conditions R*), the strongest among the various lithium amides used (LiTMP (pK_a = 37) [14][15] > LDA (pK_a = 36) [32] > lithium hexamethyldisilazide (LiHMDS, pK_a = 30) [12]).

The finding that some epoxide **11** was formed if the reverse order of addition was used (*Table 5*, *Conditions N*, *Entries c* and *d*) especially if a single equivalent of LiTMP was used (*Table 5*, *Conditions N*, *Entries b* and *d*) supports the assumption that metallation occurs first on the OH group of $\mathbf{21'_{Br}}$, and that epoxide formation is slow enough, to allow, if another equivalent of strong base is present, a second metallation to occur leading to the corresponding enolate $\mathbf{29'_{Br}}$. Apparently, substitution of the Br-atom by *O*-alkylation leading to epoxide formation is slow enough from $\mathbf{27'_{Br}}$ and $\mathbf{29'_{Br}}$

Scheme 17. O-*Alkylation* vs. C-*Alkylation from* $\mathbf{21'_{Br}}$. BH = Conjugate acid.



Scheme 18. *Synthesis of* **11** *and* **12** *from* $\mathbf{21'_{Br}}$

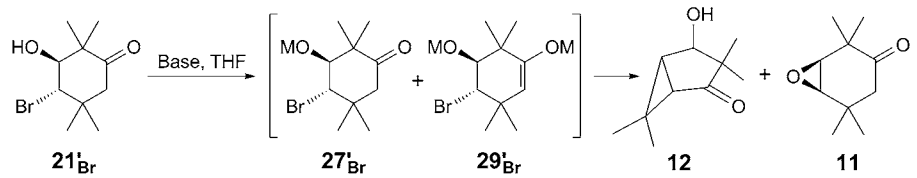


Table 5. *Synthesis of* **11** *and* **12** *from* $\mathbf{21'_{Br}}$

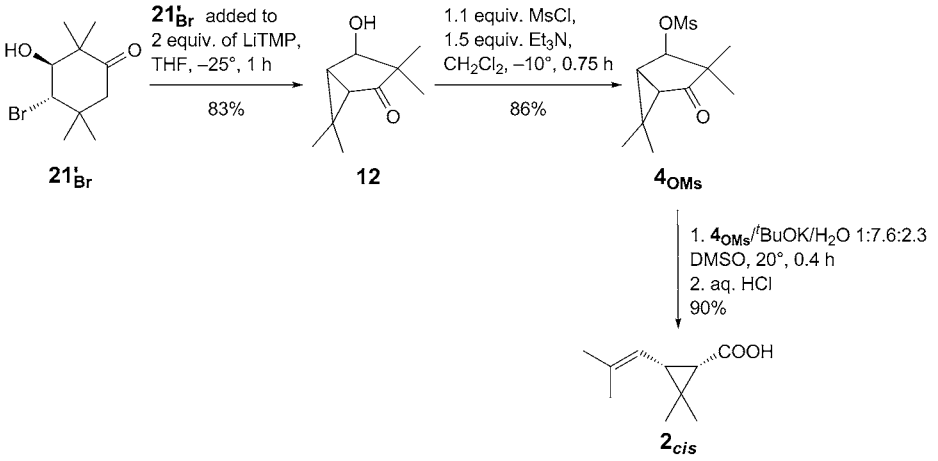
Entry	Reagent	Equiv.	Conditions [a])	*T* [°]	*t* [h]	**12**/**11** Ratio	Yield of **12** [%]	Yield of **11** [%]
a	LiTMP	1	*N*	20	0.5	10 : 90	–	86
b	LiTMP	1	*N*	−25	1	17 : 83	–	83
c	LiTMP	2	*N*	−25	1	77 : 23	77	21
d	LiTMP	2	*R*	−25	1	100 : 0	83	–
e	LDA	1	*N*	20	0.5	4 : 96	–	92
f	LDA	2	*N*	20	0.5	13 : 87	–	83
g	LDA	2	*R*	−25	1	70 : 30	57	21
h	LDA	3	*R*	−25	1	100 : 0	80	–
i	LiHMDS	3	*R*	20	3	30 : 70	32	63
j	KHMDS	3	*R*	20	0.3	0 : 100	–	83
k	KHMDS	3	*R*	−78	1	67 : 33	66	29

[a]) N = normal addition (of the base to **21'**), R = reverse addition (of **21'** to the base).

to favor *C*-alkylation leading to the selective cyclopropane formation. Epoxide formation, however, successfully compete if the reactivity of the alkoxide is enhanced (K instead of Li; *Table 5*, *Entries i* and *j*), if the lithium amide is not strong enough to achieve the second metallation rapidly (*Table 5*, *Entries g*,*i*, and *Entries d* and *h*) or missing (*Table 5*, *Entries a*,*b*, and *e*). We also found that, as expected, the temperature at which the reaction is carried out, influences the nature of the compounds formed (*Scheme 18* and *Table 5*).

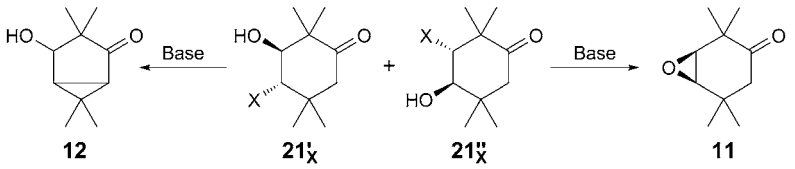
The transformation of the resulting bicyclic hydroxy ketone **12** to *cis*-chrysantemic acid (**2**$_{cis}$) has been successfully achieved according to published procedures as outlined in *Scheme 19* [10].

Scheme 19. *Synthesis of* **2**$_{cis}$ *from* **21**$'_{Br}$



The next goal to achieve was to carry out the desired reaction on the mixture **21′**/**21″** expecting to find conditions to selectively transform **21′** to bicyclic **12**, precursor of *cis*-chrysantemic acid **2**$_{cis}$, and its regioisomer **21″** to the epoxide **11**, respectively. This would take advantage of the easy separation of **12** from **11** by chromatography on SiO_2 due to the different functional groups present in each of the compounds and, therefore, allowing efficient recycling of **11** through the intermediate formation of the regioisomer mixture of **21′**/**21″** (*Scheme 20*).

Scheme 20. *Synthesis of* **11** *and* **12** *from a Mixture of* **21**$'_{X}$ *and* **21**$''_{X}$



We were rather surprised to find that the conditions successfully used to transform **21**$'_{Br}$ to **12** do not apply to the 1:1 mixture **21**$'_{Br}$/**21**$''_{Br}$, which provide an intractable

mixture of unidentified compounds, and this proved also to be the case if similar reaction was carried out on the regioisomer mixture $\mathbf{21'_I}/\mathbf{21''_I}$.

We could, however, transform the mixture $\mathbf{21'_{Cl}}/\mathbf{21''_{Cl}}$ to the mixture of the cyclopropane derivative **12** and epoxide **11** (*Scheme 21*; and *Table 6*, *Entry d*). This was fortunate, since chlorohydrins were the only halohydrins, among those we have produced, in which the amount of the regioisomer **21′** precursor of the bicyclo[3.1.0] carbocycle **12**, was the highest ($\mathbf{21'_{Cl}}/\mathbf{21''_{Cl}}$ 80 : 20) [2b].

Scheme 21. *Selective Cyclization of a Mixture of* $\mathbf{21'_{Cl}}$ *and* $\mathbf{21'_{Cl}}$

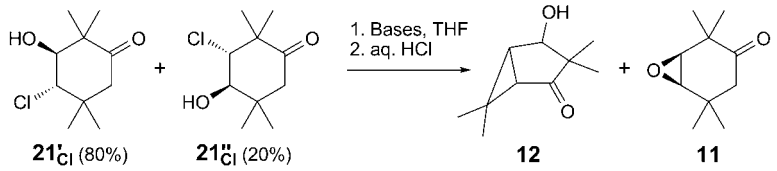


Table 6. *Selective Cyclization of a Mixture* $\mathbf{21'_{Cl}}/\mathbf{21''_{Cl}}$

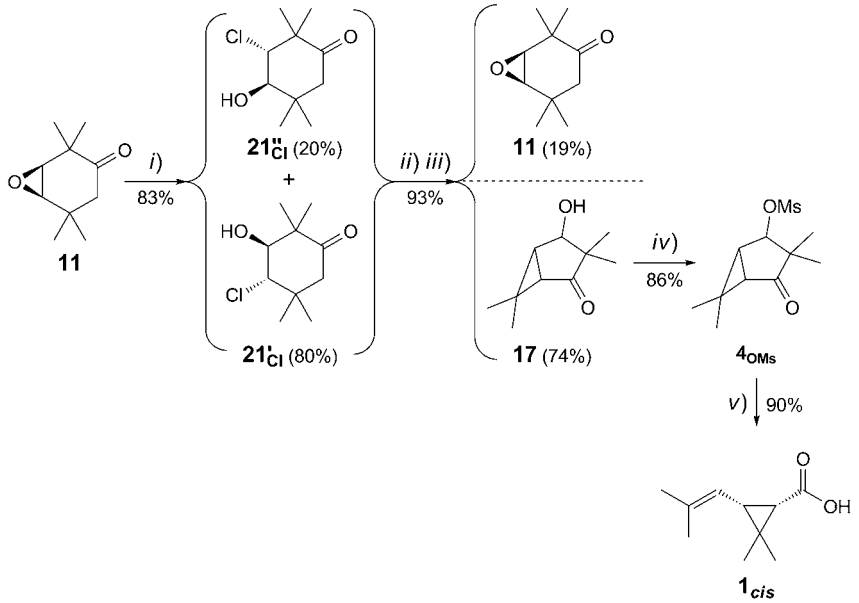
Entry	Reagent; equiv.; mode of addition	*T* [°]	*t* [h]	**12**/**11**/$\mathbf{21'_{Cl}}$/$\mathbf{21''_{Cl}}$ Ratio	Yield of isolated **12** [%]	Yield of isolated **11** [%]
a	LiTMP; 1; N	−25	1	21 : 0 : 58 : 21	20	
b	LiTMP; 1; N	20	0.5	67 : 8 : 8 : 16	66	
c	LiTMP; 2; R	−25	1	80 : 0 : 0 : 20	68	
d	*i*) LiTMP; 2; R; *ii*) ^{t}BuOK; 2; N	−25	1.5	80 : 20 : 0 : 0	74	19

We found that the mixture of $\mathbf{21'_{Cl}}/\mathbf{21''_{Cl}}$ (80 : 20) reacted with 2 equiv. of LiTMP to furnish the cyclopropane derivative **12** and recovered $\mathbf{21''_{Cl}}$ after acid hydrolysis, indicating that alkylation exclusively took place of the bromohydrin $\mathbf{21'_{Cl}}$, whereas *O*-alkylation of its stereoisomer $\mathbf{21''_{Cl}}$, which would have lead to the epoxide **11**, did not take place (*Scheme 21*, and *Table 6*, *Entry c*). The latter reaction was effectively achieved by replacing the Li^+ cation by K^+ after subsequent addition of an excess of ^{t}BuOK (*Scheme 21*, and *Table 6*, *Entry d*). This strategy is very convenient, since, after acid hydrolysis, it led not only to the desired compounds **11** and **12** in the same pot but also allowed their easy separation by chromatography on SiO_2 owing the difference of the functional groups present on each of the two products.

The formation of the bicyclo[3.1.0] compound **12** when reacting the same mixture with a single equivalent of LiTMP (20% at −25°; 66% at 20°; *Scheme 21*; *Table 6*, *Entries a* and *b*) suggests that each of the two β-chloro-alcoholate intermediates, $\mathbf{27'_{Cl}}$ and $\mathbf{27''_{Cl}}$, does not cyclize to the epoxide **11** and generate the enolate **28′**, if not directly formed, that efficiently cyclize already at −25°. Therefore, the behavior of LiTMP is different towards $\mathbf{21'_{Cl}}$ than towards $\mathbf{21'_{Br}}$ (compare *Scheme 21*, *Table 6*, *Entries a* and *b*, to *Scheme 18*, *Table 5*, *Entries a* and *b*).

We outline in *Scheme 22* the whole process that allows the synthesis of *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$) from the epoxide **11** *via* the intermediate formation of chlorohydrins $\mathbf{21'_{Cl}}$ and $\mathbf{21''_{Cl}}$, and recycling of the unwanted $\mathbf{21''_{Cl}}$ regioisomer [2b].

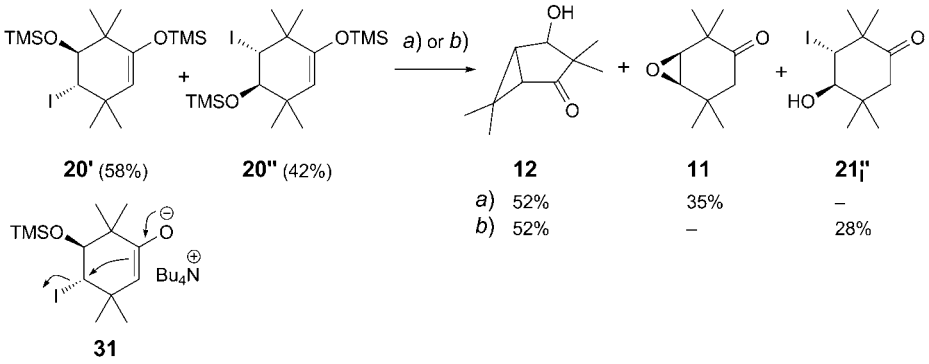
Scheme 22. *Synthesis of* $\mathbf{2}_{cis}$ *Involving a Mixture of* $\mathbf{21'_{Cl}}$ *and* $\mathbf{21''_{Cl}}$



i) 5 equiv. $BeCl_2$, CH_2Cl_2, 20°, 100 h. *ii*) *a*) 2 equiv. LiTMP; *b*) 2 equiv. ^{t}BuOK, THF, −25°, 1.5 h. *iii*) Separation by chromatography on SiO_2. *iv*) 1.2 equiv. MsCl, 1.5 equiv. Et_3N, CH_2Cl_2, −10°, 0.75 h. *v*) 6 equiv. ^{t}BuOK/3 equiv. H_2O, DMSO, 20°, 0.4 h.

Finally, we could transform the 58:42 regioisomer mixture **20′**/**20″** (*Scheme 10*) to the bicyclic *β*-hydroxy ketone **12** (90% from **20′**; *Scheme 23*, *a*) and the epoxide **11** (83% from **20″**, *Scheme 23*, *a*), respectively, by using Bu_4NF (2.2 equiv., THF, −25°, then acidic treatment).

Scheme 23. *Selective Cyclization of a Mixture of* **20′** *and* **20″**



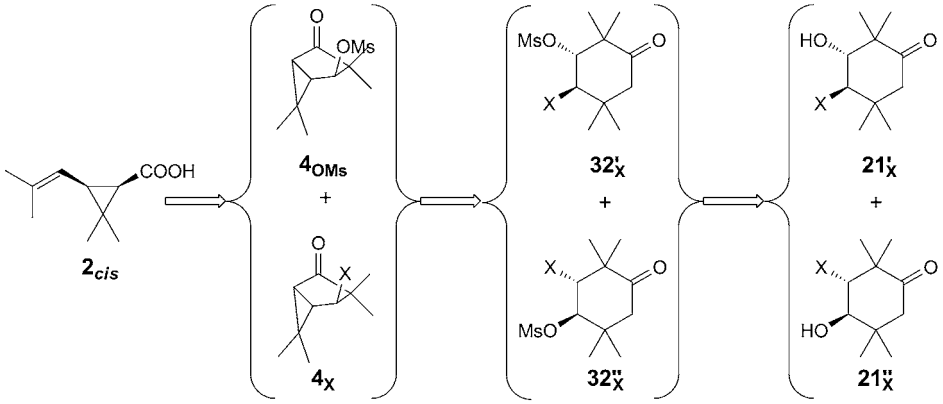
a) 1. 2.2 equiv. Bu_4NF, THF, −25°, 0.8 h. 2. H_3O^+. *b*) 1. 1 equiv. Bu_4NF, THF, −25°, 0.8 h. 2. H_3O^+.

To gain more insight into the intimate mechanism of such process, we reacted the mixture **20′**/**20″** with a single equiv. of Bu_4NF (*Scheme 23*, *b*) and observed the

formation, after acid hydrolysis, of the bicyclic **12** in very good yield (90% from **20′**) and $\mathbf{21}_{\mathbf{I}}''$ (67% from **20″**). This fully supports the hypothesis that the first equiv. of Bu_4NF selectively reacts on the silylenolate moieties of **20′** and **20″** leaving their silylether moieties untouched that play the role of protecting groups favoring the exclusive carbocyclization **31** (*Scheme 23*, *b*). It is interesting to notice that, in the presence of the second equiv. of Bu_4NF, carbocyclization of **31** occured faster than deprotection of its silylether moiety (*Scheme 23*, *a*) [2b].

The second route to *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$) that we have devised offers the advantage over the former to produce *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$) from both regiosiomers of **21**. It involves, as outlined in *Scheme 24: i*) activation of the regioisomer mixture **21′**/**21″** to afford the mixture of cyclohexanones **32** bearing two leaving groups at γ,δ-positions, *ii*) metallation of **32** favoring the annelation reaction leading to the bicyclo[3.1.0] cyclohexanones **4**, and *iii*) nucleophilic attack of a HO^- anion on the CO group of the ketones, followed by fragmentation of the intermediate to produce *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$) after acidic workup, as we already reported (*Schemes 1*, *19*, and *22*).

Scheme 24. *Synthesis of* $\mathbf{2}_{cis}$ *from Both Regioisomers of* **21**



The transformation of the mixtures of cyclohexanones **32** to chrysanthemic acid **2** could be achieved most conveniently by using:

1) A single reagent acting sequentially as a base to achieve, in a single pot, the selective carbocyclization of each of the regioisomers of **32** leading to $\mathbf{4}_{\mathbf{X}}$ and $\mathbf{4}_{\mathbf{OMs}}$, respectively, then as a nuleophile to affect the selective fragmentation of each of them to generate **2**. The choice is strictly limited to anhydrous KOH (APH) that is the only reagent able to transform the 'obliged' intermediate $\mathbf{4}_{\mathbf{OMs}}$ to **2**. APH, however, has been rarely used as a base [33], and most of the reports emphasize its exceptional nucleophilicity [4a].

2) Two distinct reagents that require the selection among various bases that are the most susceptible to achieve the selective carbocyclization of **32** to the mixture $\mathbf{4}_{\mathbf{X}}/\mathbf{4}_{\mathbf{OMs}}$. Two options still remain to achieve the synthesis of **2** from the crude mixture $\mathbf{4}_{\mathbf{X}}/\mathbf{4}_{\mathbf{OMs}}$ *a*) without separation in a single pot, the transformations again requires to use anhydrous KOH (APH) at the last stage (see above) or *b*) after separation of $\mathbf{4}_{\mathbf{X}}$ from $\mathbf{4}_{\mathbf{OMs}}$ that

can only be achieved in distinct pots. It should be easily achieved by chromatography owing the different polarity of $\mathbf{4_X}$ and $\mathbf{4_{OMs}}$. In such case, still APH is required for the transformation of $\mathbf{4_{OMs}}$ to **2**, but either WPH or APH can achieve the transformation of $\mathbf{4_X}$ to **2**.

The latter route, although slightly longer, offers the advantage to synthesize scalemic $\mathbf{2}_{cis}$ from $\mathbf{4_X}$ and $\mathbf{4_{OMs}}$ when those possess 'opposite chirality' as it will be disclosed in the last part of the article.

Reaction of the mixture of regioisomeric cyclohexanones **21** with MsCl in the presence of DMAP (2 equiv. MsCl, 2 equiv. Et_3N, 0.1 equiv. DMAP, CH_2Cl_2, -10 to 20°, 6 h) led to a mixture of cyclohexanones **32** in 80–86% yield. Reaction of $\mathbf{32'_{Br}}/\mathbf{32''_{Br}}$ (55:45) with KHMDS provided a mixture of $\mathbf{4_{OMs}}/\mathbf{4_{Br}}$ (55:45) in high overall yield (83%) that has been easily separated, by chromatography on SiO_2 ($\mathbf{4_{Br}}$: R_f (pentane/Et_2O 95:5) 0.52 and $\mathbf{4_{OMs}}$: R_f (pentane/Et_2O 60:40) 0.19). Each of them was transformed to *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$) using WPH or APH according to procedures described above. Each of the regioisomers **32′** and **32″** also separately reacted with an excess of commercial KOH in wet DMSO (DMSO/H_2O 4:1; WPH). The results are compiled in *Scheme 25* and *Table 7* [8] and commented below.

Scheme 25. *Reactivity of 2,2-Dimethylcyclohexanones* $\mathbf{32_X}$ *towards Aq. KOH in DMSO* (WPH)

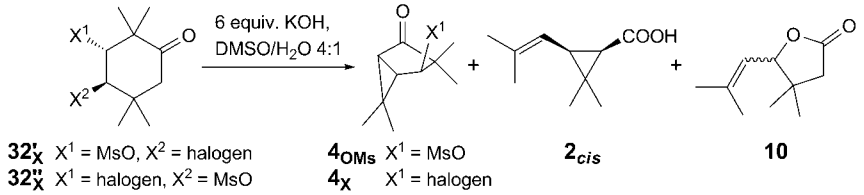


Table 7. *Reactivity of 2,2-Dimethylcyclohexanones* $\mathbf{32_X}$ *towards Aq. KOH in DMSO* (WPH)

Entry	$\mathbf{32_X}$	X^1	X^2	T [°]	t [h]	**4**	Yield of **4** [%]	Yield of $\mathbf{2}_{cis}$ [%]	Yield of **10** [%]	$\mathbf{10}/\mathbf{2}_{cis}$ Ratio
a	$\mathbf{32'_{Cl}}$	MsO	Cl	70	0.6 h	$\mathbf{4_{OMs}}$	71			
b	$\mathbf{32'_{Br}}$	MsO	Br	70	0.6 h	$\mathbf{4_{OMs}}$	65			
c	$\mathbf{32'_{I}}$	MsO	I	70	0.5 h	$\mathbf{4_{OMs}}$	64			
d	$\mathbf{32''_{Cl}}$	Cl	MsO	20	1 h	$\mathbf{4_{Cl}}$	76			
e	$\mathbf{32''_{Cl}}$	Cl	MsO	70	6 h	$\mathbf{4_{Cl}}$	6	57		
f	$\mathbf{32''_{Br}}$	Br	MsO	20	8 h			7	61	90:10
g	$\mathbf{32''_{Br}}$	Br	MsO	70	1 h			26	53	67:33
h	$\mathbf{32''_{I}}$	I	MsO	20	3 h			4	67	95:5
i	$\mathbf{32'_{I}}$	I	MsO	70	1 h			7	66	90:10

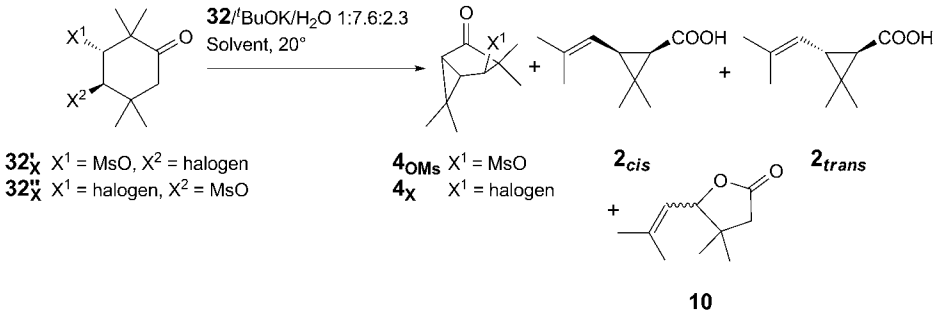
The reaction involving 4-halogeno-3-(mesyloxy)-2,2,5,5-tetramethylcyclohexanones $\mathbf{32'_X}$ was best achieved at 70° for a short time (0.6 h) and furnished 3,3,6,6-tetramethyl-4-oxobicyclo[3.1.0]hex-2-yl methanesulfonate ($\mathbf{4_{OMs}}$) in reasonably good yields in all the cases (*Scheme 25*, and *Table 7*, *Entries a–c*). Performing the reaction of $\mathbf{32'_X}$ with WPH for a much longer time led to the disappearance of $\mathbf{4_{OMs}}$ and formation, as expected, of a polymeric material [10].

WPH could also achieve the carbocyclization from the regioisomeric 3-chloro-4-(mesyloxy)-2,2,5,5-tetramethylcyclohexanone ($\mathbf{32''_{Cl}}$) to afford, at low temperature, 4-chloro-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one ($\mathbf{4_{Cl}}$) chemoselectively and in high yield (20°, *Scheme 25*; and *Table 7*, *Entry d*), and *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$), if the reaction is carried out at higher temperature (70° instead of 20°; *Scheme 25*, *Table 7*, *Entry e*).

The reaction took however, another course, when performed on the related bromide $\mathbf{32''_{Br}}$ and iodide $\mathbf{32''_{I}}$, since it delivered, after acid hydrolysis, the unsaturated lactone **10** beside some *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$; *Table 7*, *Entries f–i*). Apparently, KOH in aqueous DMSO (WPH) no longer acts as a base towards $\mathbf{32''_{Br}}$ and $\mathbf{32''_{I}}$ but as a nucleophile as it has been already observed for the dibromide $\mathbf{5_{Br}}$ (*Schemes 3* and *4*). It is interesting to notice that a higher percentage of *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$) is observed if the transformation is performed at higher temperature on $\mathbf{32''_{Br}}$, but that this is no longer the case for the related iodinated derivative $\mathbf{32''_{I}}$.

To achieve the desired transformations of **32″** to *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$), we performed the reaction with APH that proved so successful to produce the vinyl-cyclopropane derivative $\mathbf{7}_{cis}$ instead of the vinyl-lactone **6** from the related $\mathbf{5_{Br}}$ (*Scheme 3*). We were delighted to find that, as we had expected, APH in THF allowed, under very mild conditions (20°), efficient access to chrysanthemic acid **2**, from the whole series of cyclohexanones **32″**, even those that proved reluctant to do so using WPH instead (*Scheme 26* and *Table 8*, *Entries a–c*, compare to *Scheme 25*, *Table 7*), and, in only one case, a few percent of vinyl-lactone was also produced (*Scheme 26* and *Table 8*, *Entry c*). The reactions were so fast that isolation of the bicyclic intermediates $\mathbf{4_X}$ was not feasible except in the case of the chloride $\mathbf{32''_{Cl}}$ which delivered small amounts of the bicyclic derivative $\mathbf{4_{Cl}}$, besides *cis*-chrysanthemic acid $\mathbf{2a}_{cis}$ (*Table 8*, *Entry a*).

Scheme 26. *Reactivity of 2,2-Dimethylcyclohexanones* **32** *towards* ^{t}BuOK/H_2O (APH)



Performing the reaction in DMSO instead of THF did not offer advantages, since it was slower and gave lower yield of chrysanthemic acid, especially from the iodide $\mathbf{32_I}$. Surprisingly, however, in the case of $\mathbf{32''_{Br}}$ and $\mathbf{32''_{I}}$, chrysanthemic acid was obtained as a *cis*/*trans* diastereoisomer mixture.

We could not find the origin of the *trans*-chrysanthemic acid ($\mathbf{2}_{trans}$) formed in this process. We have, however, secured, by independent reactions, that 'AHP' in DMSO is

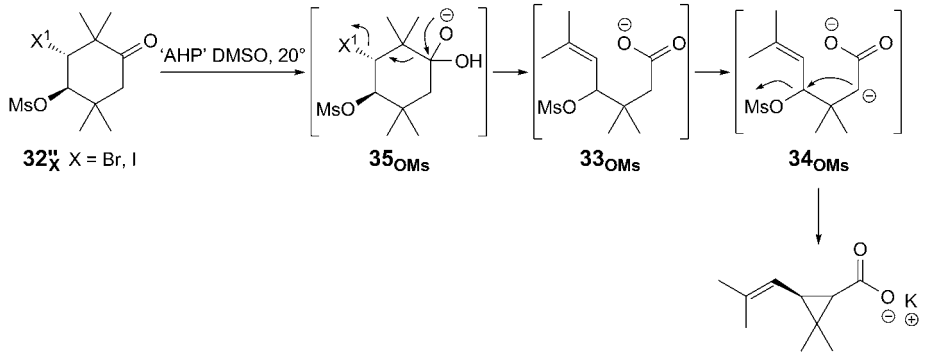
Table 8. *Reactivity of 2,2-Dimethylcyclohexanones* **32** *towards* ^{t}*BuOK-H$_2$O (APH)*

Entry	$\mathbf{32_X}$	X^1	X^2	Time [h]	Solvent	Yield of **1** + **4** + **10** [%]	Yield of **4** [%]	Yield of **10** [%]	Yield of **1** [%] (*cis*/*trans*)	**1**/**10** Ratio
a	$\mathbf{32''_{Cl}}$	Cl	MsO	1.5	THF	90	18	0	72 (100 : 0)	100 : 0
b	$\mathbf{32''_{Br}}$	Br	MsO	0.6	THF	89	0	0	89 (100 : 0)	100 : 0
c	$\mathbf{32''_{I}}$	I	MsO	1	THF	93	0	4	89 (100 : 0)	96 : 4
d	$\mathbf{32''_{Cl}}$	Cl	MsO	2	DMSO	75	0	0	75 (100 : 0)	100 : 0
e	$\mathbf{32''_{Br}}$	Br	MsO	2	DMSO	81	0	5	76 (83 : 17)	94 : 6
f	$\mathbf{32''_{I}}$	I	MsO	2	DMSO	41	0	5	36 (30 : 70)	88 : 12
g	$\mathbf{32'_{Cl}}$	MsO	Cl	1.5	THF	38	0	0	38 (100 : 0)	100 : 0
h	$\mathbf{32'_{Br}}$	MsO	Br	1.6	THF	48	0	0	48 (100 : 0)	100 : 0
i	$\mathbf{32'_{I}}$	MsO	I	2	THF	10	0	0	10 (100 : 0)	100 : 0
j	$\mathbf{32'_{Cl}}$	MsO	Cl	2.5	DMSO	67	0	0	67 (100 : 0)	100 : 0
k	$\mathbf{32'_{Br}}$	MsO	Br	0.75	DMSO	80	0	0	80 (100 : 0)	100 : 0
l	$\mathbf{32'_{I}}$	MsO	I	2	DMSO	30	0	0	30 (100 : 0)	100 : 0

unable to *i*) epimerize potassium *cis*- to potassium *trans*-chrysanthemate or to *ii*) transform the lactone **10** to $\mathbf{2}_{trans}$ [8].

Another hypothesis, which involves a completely different mechanism, is tentatively presented in *Scheme 27*. It implies metallation of the intermediate $\mathbf{33_{OMs}}$, resulting from the attack of 'APH' on the CO group of $\mathbf{32''_X}$, followed by cyclization of $\mathbf{34_{OMs}}$. We have not been able, however, to experimentally support this proposal [8].

Scheme 27. *Hypothesis for the Formation of* $\mathbf{2}_{trans}$



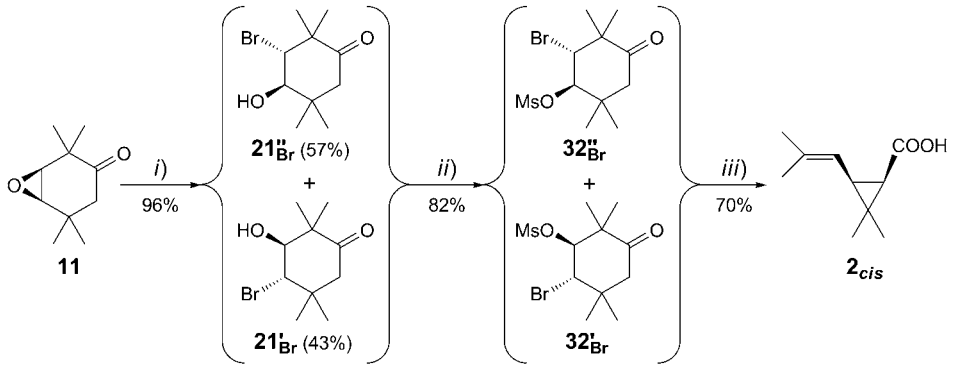
We also carried out the reaction of **32′** with APH to get the whole reactivity pattern of each of the two partner in order to select the best conditions to perform *in fine* the tandem carbocyclization/*Haller–Bauer* reaction/*Grob* fragmentation reaction on the mixture **32″**/**32′**.

We were delighted to find that chrysanthemic acid $\mathbf{2}_{cis}$ was chemoselectively and stereoselectively formed from all **32′** derivatives, whatever the solvent used (*Scheme 26*, and *Table 8*, *Entries g–l*). We were, however, surprised to observe that, except in the case of $\mathbf{32'_{Br}}$ (*Table 8*, *Entry k*), the yields in **2**, were lower than those obtained from their regioisomers **32″** under similar conditions (*Table 8*, compare *Entries g–l* to *a–f*). Surprisingly better yields were generated when the reaction of **32′** with APH was

carried out in DMSO instead of THF (*Table 8*, compare *Entries j–l* to *Entries g–i*) and, therefore, the behavior of **32′** towards APH markedly differs from that of their regioisomers **32″** (*Table 8*, compare *Entries j–l* to *Entries d–f* and to *Entries a–c*).

Accordingly, the reaction of the epoxy-cyclohexanone **11** sequentially with $TiBr_4$, H_2O and MsCl led to the mixture of the two isomeric bromo-methanesulfonates (57:43) in high yield (80%), which was transformed in a single pot to *cis*-chrysanthemic acid (**2**$_{cis}$) on reaction with APH in THF (70% yield, *Scheme 28*).

Scheme 28. *Synthesis of* **2**$_{cis}$ *Involving a Mixture of* **21**′$_{Br}$ *and* **21**″$_{Br}$



i) 0.5 equiv. $TiBr_4$, CH_2Cl_2, 20°, 2 h, then aq. $NaHCO_3$. *ii*) 2 equiv. MsCl, 2 equiv. Et_3N, 0.1 equiv. 4-(dimethylamino)pyridine (DMAP), −10 to 20°, 6 h. *iii*) **32**/^{t}BuOK/H_2O, 1:7.6:2.3, THF, 20°, 2 h.

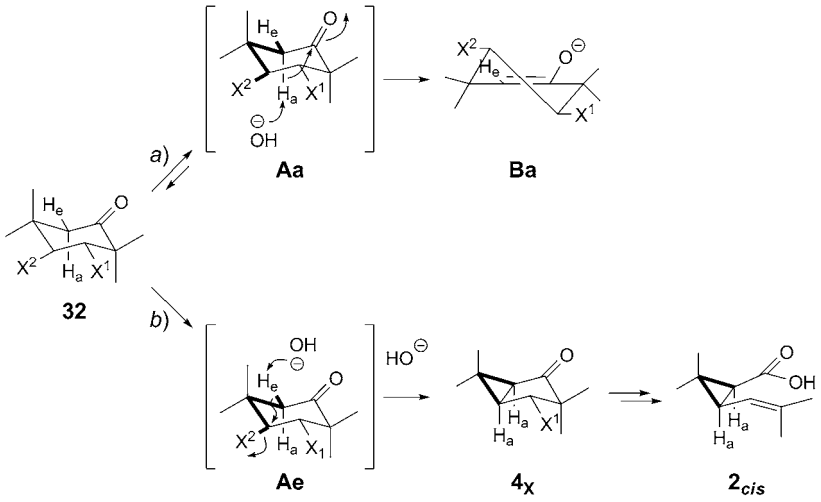
We were interested to rationalize the difference between WPH and APH to act as nucleophile or base toward **32**. The formal mechanism outlined in *Schemes 2* and *4*, to be more accurate, should take into account stereochemical features. Those are presented in *Schemes 29* and *30*. Thus, attack of HO^- anion can take place at the H-atom at C(6) or at the CO C-atom of **32**.

We assume that:

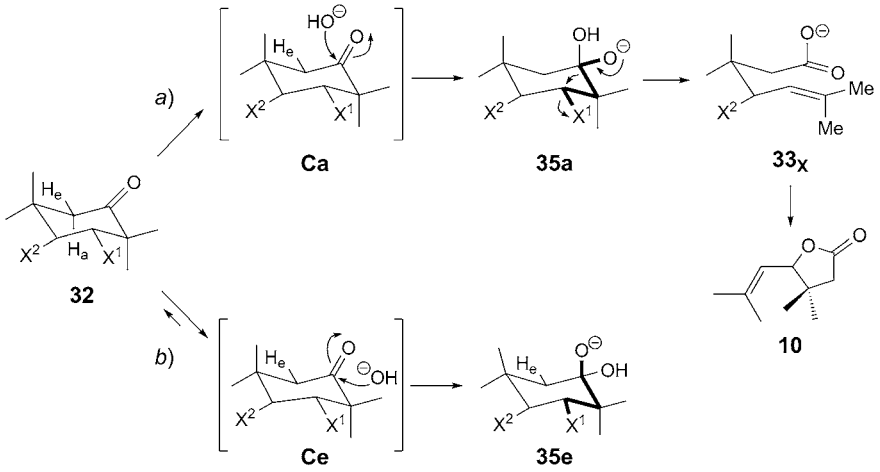
1) Metallation of **32** is best achieved at the more acidic H_{ax}–C(6) and should provide, under kinetic control, the corresponding enolate **Ba** by constant overlap of the orbitals involved (*Scheme 29*,*a*) [34]. Metallation of H_{eq}, however, the less acidic of the two H-atoms at C(6), achieves the antiperiplanar arrangement of atoms and bonds suitable for the cyclization leading to cyclopropane ring present in *cis*-chrysanthemic acid (**2**$_{cis}$; *Scheme 29*, *Entry*) and, therefore, successful cyclization is expected to involve an equilibrium [8].

2) Addition of the HO^- ion onto the CO C-atom [35] from the top-face is expected to generate the intermediate **35a**, whose alkoxide ion is adequately positioned to favor through an antiperiplanar conformation [36], the fragmentation reaction leading to the open-chain intermediate **33**$_X$, precursor of the vinyl lactone **10** (*Scheme 30*,*a*). This approach could be hampered with a bulky Me group (1,3-diaxial interaction as in **3**$_{Br}$ (*Scheme 2*) compared to **5**$_{Br}$ (*Scheme 4*)). Addition from the bottom-face, however, provides instead **35e**, whose fragmentation is expected to be much less favored (*Scheme 30*,*b*) [8].

Scheme 29. *Rationalization for the Formation of* $\mathbf{2}_{cis}$



Scheme 30. *Rationalization for the Formation of* **10**



APH apparently reacts faster in the process outlined in *Scheme 29*, *a*, than WPH. It favors all the time, the *cis*-vinyl-cyclopropanecarboxylic acid $\mathbf{2}_{cis}$, even when WPH instead produces the vinyl lactone **10**, probably because the 'more reactive' APH is more able than WPH to react *via* the process described in *Scheme 29*, *b*, on H_{eq} of **Ae**, leading to $\mathbf{4}_{X}$, the precursor of *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$; *Scheme 29*, *b*).

To have a better insight on the more suitable species required for successful synthesis of *cis*-chrysanthemic acid ($\mathbf{2}_{cis}$), we carried out the reaction of 3-bromo-4-(mesyloxy)cyclohexanone $\mathbf{32}''_{Br}$ with KOH generated by *i*) dehydration, on heating, of powdered commercial KOH, or *ii*) reacting stoichiometric amounts of H_2O on KH

(1 equiv. KH, 1 equiv. H_2O, THF, 20°) [37]. These reagents lack ^{t}BuOK as well as ^{t}BuOH.

We found that both reactions carried out in THF at 20°, were slower (18 h and 66 h, resp.) than that involving APH (0.5 h). Using dried KOH, the β-bromo bicyclo[3.1.0] cyclohexanone $\mathbf{4_{Br}}$ (70%) and the vinyl-lactone **10** (30%) were formed, whereas using KOH from KH, $\mathbf{4_{Br}}$ (19%) and *cis*-chrysanthemic acid ($\mathbf{2_{\textit{cis}}}$; 81%) were obtained after acid hydrolysis.

'Dried KOH' in THF behaves as KOH in aqueous DMSO, whereas KOH from KH in THF behaves as AHP in chemoselectivity but not in reactivity. AHP, therefore, possesses an exceptional reactivity, which differentiates it from the two 'anhydrous KOH' and wet KOH reagents tested in this study [8].

We took the opportunity of this work to slightly modify the routes disclosed in order to achieve the enantioselective synthesis of (1*R*)-*cis*-chrysanthemic acid ((1*R*)-$\mathbf{2_{\textit{cis}}}$), or its methyl ester, (1*R*)-$\mathbf{2_{\textit{cis}\text{-}\mathbf{Me}}}$, respectively, which, after adequate replacement of the isopropylidene moiety by the dibromovinyl, allows the synthesis of deltamethrin (**36**), the most powerful commercial insecticide for outdoor uses (*Scheme 31*, *Path a*). We also synthesized (1*R*)-*trans*-chrysanthemic acid ((1*R*)-$\mathbf{2_{\textit{trans}}}$), the constituent of the naturally occurring pyrethrin I or the related commercially available insecticide (*S*)-bioallethrin (**37**), suitable for indoor use. The latter transformation involves epimerization at C(1) of (1*S*)-*cis*-chrysanthemic acid (1*S*)-$\mathbf{2_{\textit{cis}}}$, or better of one of its ester, especially the ^{t}butyl ester (*Scheme 31*, *Path b*). The individual steps used for those transformations are outlined in *Scheme 31*.

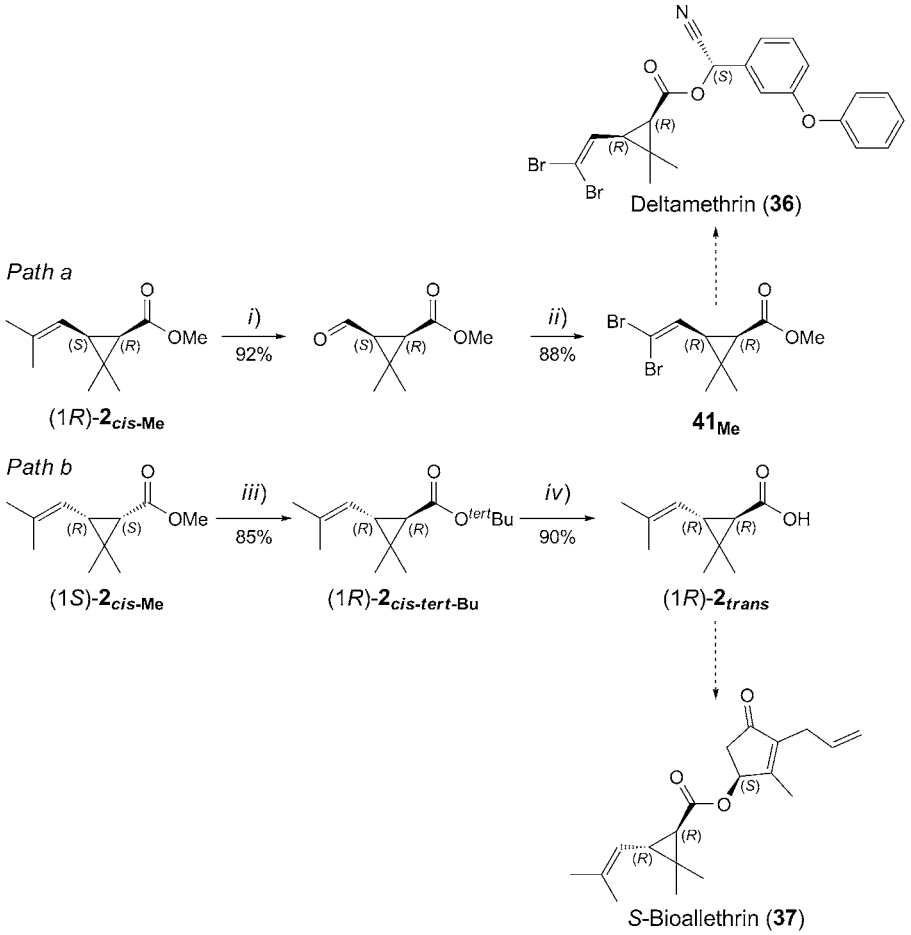
Thus, the most straightforward route to those compounds would have been the enantioselective additions on the C=C bond of 2,2,5,5-tetramethylcyclohex-3-enone **1** which would have led to the corresponding scalemic epoxide **11***, dihalides **3***, or *pseudo*-halides **32***. We have been, however, unable to achieve it. We could, however, perform the desired transformations in a three-step sequence which involves *i*) enantioselective reduction of the CO group of **1** leading to the scalemic (1*S*)-2,2,5,5-tetramethylcyclohex-3-enol (*S*)-**23**, *ii*) diastereoselective additions across the C=C bond of the resulting homoallyl alcohol, *iii*) regioselective oxidation of the resulting saturated alcohol to the functionalized ketones **11***, **3***, and **32***.

The enantioselective reduction of 2,2,5,5-tetramethylcyclohex-3-en-1-one (**1**) to scalemic (1*S*)-2,2,5,5-tetramethylcyclohex-3-enol (*S*)-**23**, which is the key step in this transformation, was conveniently achieved in high yield (85%) and very high stereocontrol (ee >97%) by using (−)-β-chlorodiisopinocampheylborane (Ipc_2BCl) [38] (*i*) 1.05 equiv., neat, 25°, 48 h, *ii*) 2.2 equiv. diethanolamine, Et_2O, 25°, 85% yield, ee >97%, *Scheme 32*).

Vicinal dibromination of the homoallyl alcohol (*S*)-**23** proved to be highly stereoselective if carried out at very low temperature (1 equiv. Br_2, CH_2Cl_2, −95°, 0.33 h) and led to (*R*,*R*)-**38** in high yield and with very high stereocontrol (95% yield; de 97%; *Scheme 32*). Its structure has been secured by X-ray crystallography of the corresponding acetate (*R*,*R*)-**39** (*Scheme 33*) [2d].

The selective formation of (*R*,*R*)-**38** over (*S*,*S*)-**38** could be rationalized by assuming the attack of the Br^- ion at C(4) of **40a** or at C(3) of its diastereoisomer **40b** to reach a chair (*Scheme 34*,*a* and *b*) rather than a twisted boat transition state (*Scheme 34*,*c* and *d*) [39].

Scheme 31. *Synthesis of Deltamethrine* (**36**) *and S-Bioallethrin* (**37**) *from* cis-*Chrysanthemic Acid* (**2**$_{cis}$)

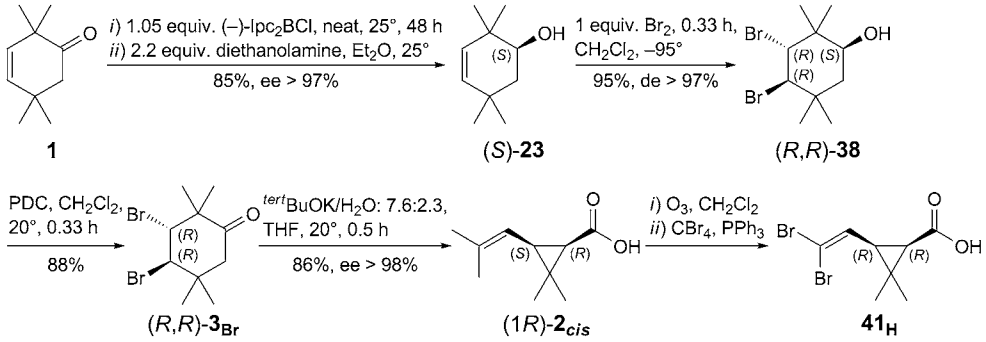


i) *a*) O_3, MeOH, $-80°$; *b*) Me_2S, $-40°$ to $20°$; *c*) aq. AcOH, $80°$, 0.25 h. *ii*) CBr_4, PPh_3, CH_2Cl_2, $25°$, 0.15 h. *iii*) ^{t}BuOK, THF, $20°$, 2 h. *iv*) KOH, MeOH, $65°$, 24 h, then H_3O^+.

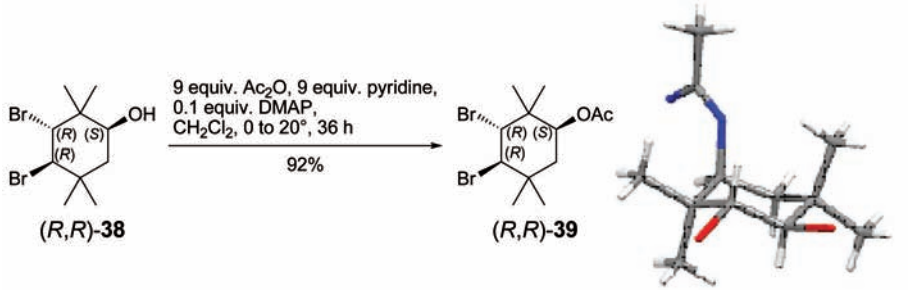
We have used these results to produce (1*R*)-*cis*-dibromovinyl-cyclopropanecarboxylic acid **41**$_{H}$ in more than 98% ee conducting known reactions that we already disclosed (*Scheme 32*).

The dibromination of (*S*)-**23** involves *i*) attack of the bromonium ion on its C=C bond *syn* or *anti* to the OH group, and leading to the intermediate formation of bromoniums **40a** or **40b**, *ii*) ring opening of **40** which can take place either at the γ- or δ-positions relative to the C-atom bearing the OH group as already discussed (*Scheme 34*). To distinguish amongst those possibilities, we have carried out a model study involving the bromohydroxylation of (*S*)-**42**, the acetate of (*S*)-**23** (*Scheme 35*). Best results were obtained by using NBS in aqueous acetone [40]. The reaction was slower than that involving the same reagent in aqueous ^{t}BuOH [41] but provided better

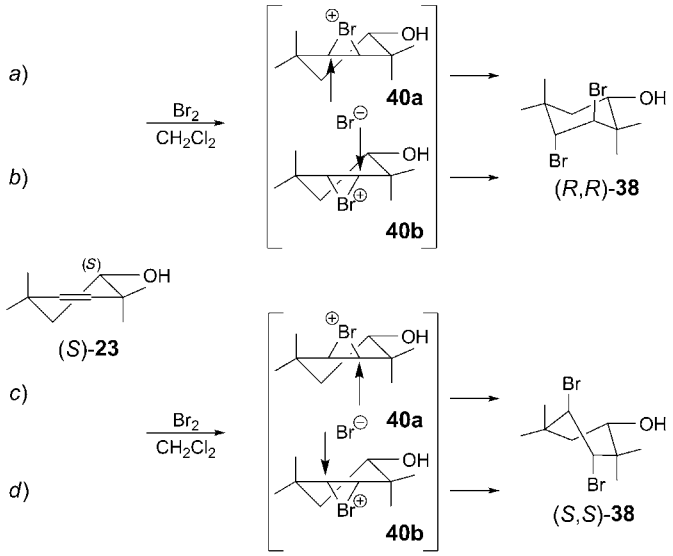
Scheme 32. *Enantioselective Synthesis of* cis-*Chrysanthemic Acid (1*R*)-***2***$_{cis}$ *Involving (1*S*)-2,2,5,5-Tetramethylcyclohex-3-en-1-ol* ((*S*)-**23**). Diethanolamine = 2,2′-Iminodiethanol, Ipc_2BCl = chloro-bis(2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)borane; PDC = pyridinium dichromate.



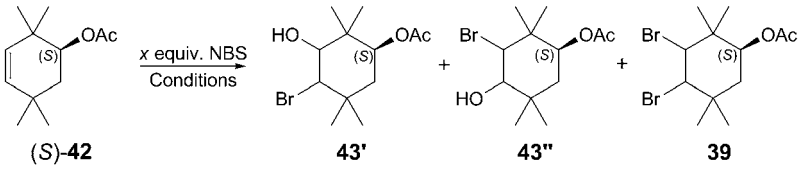
Scheme 33. *Synthesis of Acetate* (*R*,*R*)-**39**



Scheme 34. *Hypothesis for the Selective Formation of* (R,R)-**38** *over* (S,S)-**38**



Scheme 35. *Bromohydroxylation of* (S)-**42**. NBS = *N*-Bramosuccinimide.



(*S*)-**42** **43'** **43"** **39**

Table 9. *Bromohydroxylation of* (S)-**42**

Entry	*x* equiv. of NBS	Conditions	*T* [h]	Yield of **43′** + **43″** [%]	Yield of **42** [%]	Yield of **39** [%]
a	1.1	^{t}BuOH/H_2O 1 : 2, 20°	0.75	57	0	6
b	2	DMSO + 2 equiv. H_2O, 20°	168	26	34	27
c	4	DME/H_2O 4 : 1, 20°	168	34	24	19
d	1.5	Acetone/H_2O 1 : 4	168	86	0	*ca.* 2

yield of **43** than when carried out in aqueous DMSO [42] or DME [43] (*Scheme 35*, *Table 9*).

The ^{1}H-NMR studies coupled with the results disclosed in *Schemes 37* and *38*, led us to conclude that *i*) the resulting crude compound is in fact a mixture (*R*,*R*)-**43″**/(*R*,*R*)-**43′**/(*S*,*S*)-**43″**/(*S*,*S*)-**43′** in a 55 : 32 : 10 : 3 ratio, and the formation of bromonium **44a**, which results from the attack of the bromonium ion on the face opposite to that where the Ac group lies, is slightly favored (58%) over the other (42%; *Scheme 36*).

On the basis of these results, we devised new routes to scalemic *cis*-chrysanthemic acid (**2**$_{cis}$) from the mixture **43′**/**43″** (**43***) (*Schemes 37* and *38*).

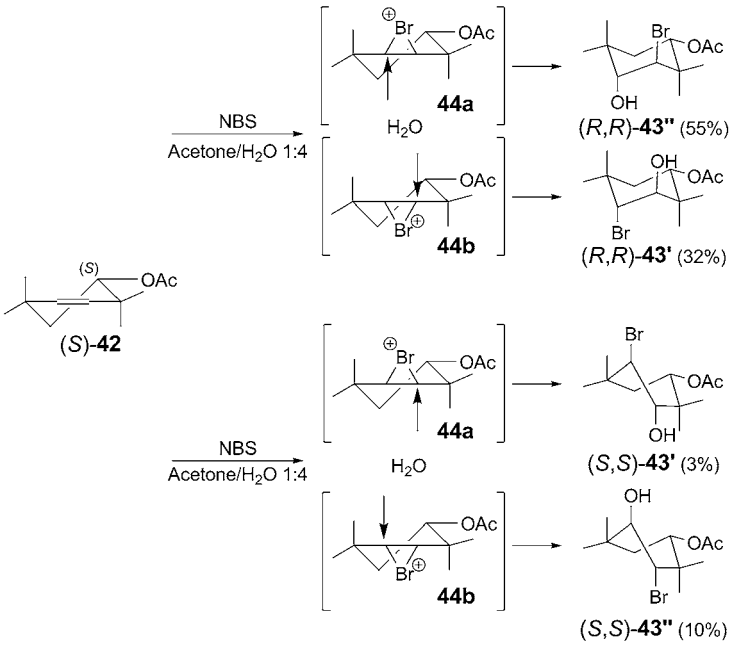
Thus reaction of mesylchloride with **43′**/**43″** led to the β-bromomesylates **45′**/**45″** (**45***) whose deacetylation, followed by oxidation with PDC, provided a mixture of regioisomeric ketones, **32**$'_{Br}$/**32**$''_{Br}$. Reaction of **32**$^*_{Br}$ mixture with APH in THF, followed by acid hydrolysis, provided in one pot (1*R*)-*cis*-chrysanthemic acid ((1*R*)-**2**$_{cis}$) in 64% yield and 76% ee (*Scheme 37*).

Alternatively, reaction of the same mixture of **32**$^*_{Br}$ with KHMDS afforded a mixture of the bicyclic derivatives, **4**$^*_{OMs}$/(*S*)-**4**$^*_{Br}$ in 78% yield. Those have been easily separated by column chromatography on SiO_2 ((*S*)-**4**$_{OMs}$: 36%, ee 82%; (*S*)-**4**$_{Br}$: 64%, ee 74%; *Scheme 38*). These results support those disclosed in *Scheme 36*, indicating that asymmetric induction in the reaction of (*S*)-**42** with NBS in aqueous acetone that leads to the bromohydrin **43′** is higher than the one which instead produces in the same pot its regioisomer **43″** (*Scheme 36*).

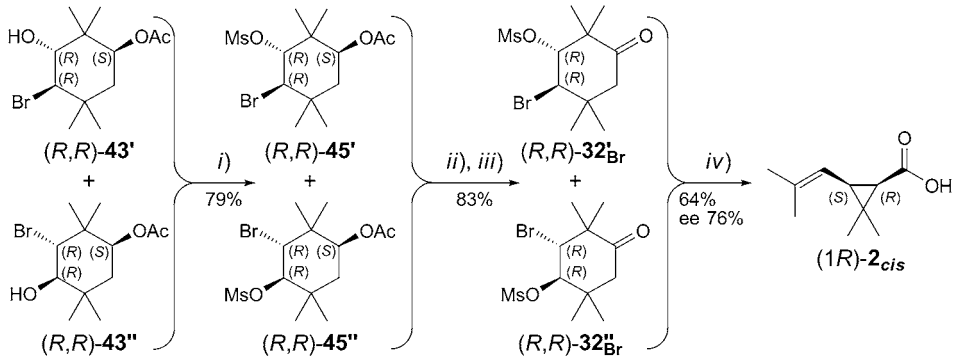
We have then achieved the transformation of (*S*)-**4**$_{OMs}$ and (*S*)-**4**$_{Br}$ to *cis*-chrysanthemic acid by using APH in DMSO (*Scheme 6*) and THF (*Scheme 1*, and *Table 1*, *Entry b*), respectively (*Scheme 38*).

We next synthesized enantioselectively (1*S*)-*cis*-chrysanthemic acid ((1*S*)-**2**$_{cis}$) from scalemic homoallyl alcohol (*S*)-**23** using the series of reactions outlined in *Schemes 13* and *19*, which involve *i*) stereoselective epoxidation of (*S*)-**23** leading to **24*** (*Scheme 13*), *ii*) regioselective ring opening of the epoxide **24*** leading exclusively to

Scheme 36. *Rationalization for the Bromohydroxylation of* (S)-**42**



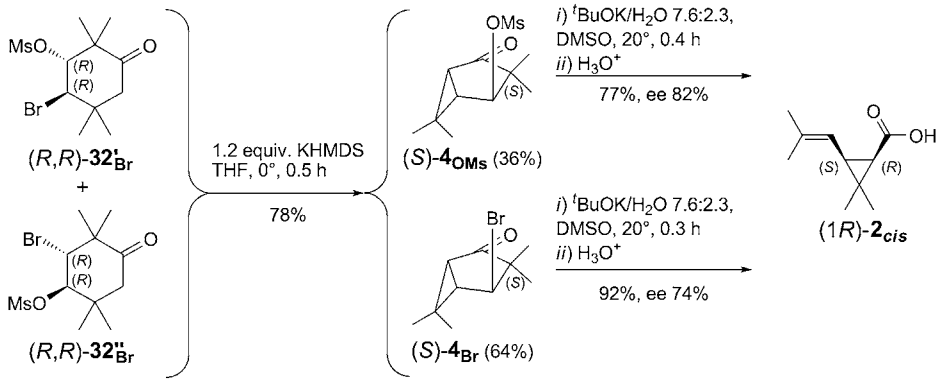
Scheme 37. *Synthesis of scalemic* cis-*Chrysanthemic Acid* ($\mathbf{2}^{*}_{cis}$) *from the Mixture of the Bromohydrines* **43*** *Involving 'One-Pot' Cyclization–Fragmentation*



i) 2 equiv. MsCl, 2 equiv. Et_3N, 0.2 equiv. DMAP, CH_2Cl_2, −10 to 20°, 55 h. *ii*) 5 equiv. K_2CO_3, THF/MeOH 1:1, 0 to 20°, 5.5 h. *iii*) 1.4 equiv. PDC, mol. sieves (MS; 4 Å), CH_2Cl_2, 0 to 20°, 4 h. *iv*) 7.6 equiv. ^{t}BuOK, 2.3 equiv. H_2O, THF, 20°, 2.5 h, then H_3O^+.

the bromohydrin $\mathbf{25'}^{*}_{Br}$ (*Scheme 13*), *iii*) regioselective oxidation to $\mathbf{21'}^{*}_{Br}$ (*Scheme 13*), *iv*) carbocyclization producing the bicyclic *β*-hydroxy-cylopentanone **12*** (*Scheme 19*), and *v*) cascade *Haller–Bauer* reaction-*Grob* fragmentation of the corresponding methanesulfonate $\mathbf{4}^{*}_{OMs}$ leading finally to (1*S*)-*cis*-chrysanthemic acid (1*S*)-$\mathbf{2}_{cis}$ in very

Scheme 38. *Synthesis of Scalemic* cis-*Chrysanthemic Acid* ($\mathbf{2}^{*}_{cis}$) *from the Mixture of the Bromohydrines* **43*** *Involving Sequential Cyclization–Fragmentation.* KHMDS = Potassium hexamethyldisilazide.



good yield (90%), and extremely high de (100%) and ee (93%) values (*Scheme 19*) [2a].

A variation of *Scheme 13* implies the oxidation of the scalemic homoallyl alcohol (*S*,*R*)-**24** to the corresponding β-oxo epoxide (*S*,*R*)-**11** (90% overall yield, 94% ee; *Scheme 39*) which, on reaction with $TiBr_4$ as disclosed in the racemic version (*Scheme 28*), produced a mixture of scalemic bromohydrins $\mathbf{21}'_{Br}/\mathbf{21}''_{Br}$ ($\mathbf{21}^{*}_{Br}$), resulting from epoxide ring opening (*Scheme 39*). Mesylation of mixture of $\mathbf{21}^{*}_{Br}$, followed by treatment of the resulting methanesulfonate $\mathbf{32}'_{Br}/\mathbf{32}''_{Br}$ (**32***) sequentially with APH in THF and HCl led to (1*S*)-*cis*-chrysanthemic acid ((1*S*)-$\mathbf{2}_{cis}$) in good overall yield but very poor enantioslectivity (9%, *Scheme 39*) [2c] due to 10% excess of the methanesulfonate (*R*)-$\mathbf{4}_{OMs}$ over the bromide (*S*)-$\mathbf{4}_{Br}$ that are *pseudo*-enantiomers.

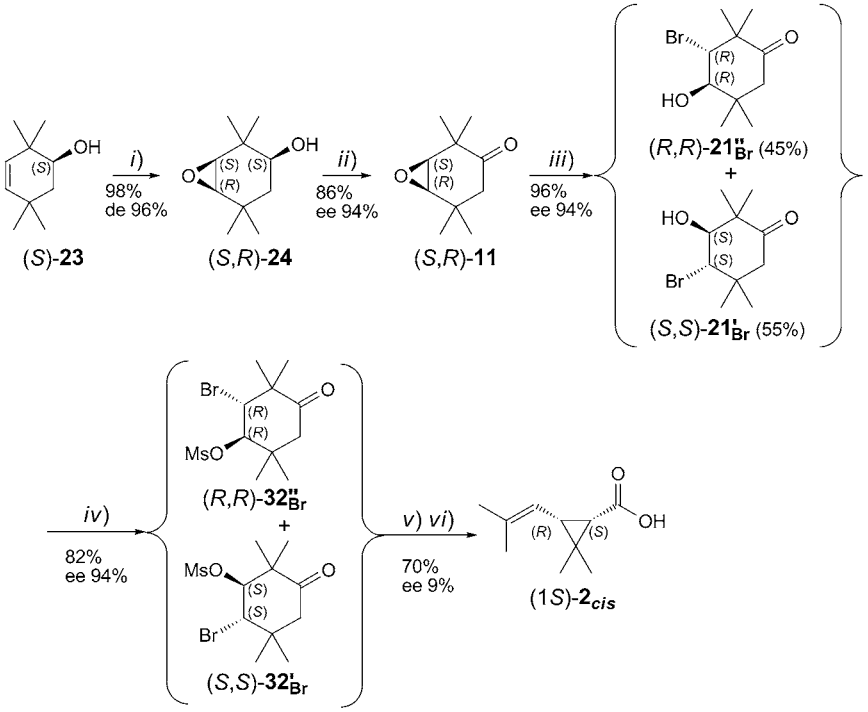
A slight change in the above strategy that involves *i*) isolation of the mixture (*S*)-$\mathbf{4}_{Br}$/(*R*)-$\mathbf{4}_{OMs}$ using KHMDS instead of APH, *ii*) easy separation by column chromatography on SiO_2, and *iii*) fragmentation of each bicyclic derivative using APH ((*S*)-$\mathbf{4}_{Br}$ in THF; *Scheme 40*; (*R*)-$\mathbf{4}_{OMs}$ in DMSO; *Scheme 40*) [2c] furnished, in high yield and very high ee, (1*R*)-*cis*-chrysanthemic acid ((1*R*)-$\mathbf{2}_{cis}$), precursor of deltamethrin (*Scheme 31*) and (1*S*)-*cis*-chrysanthemic acid ((1*S*)-$\mathbf{2}_{cis}$) precursor of (*S*)-bioallethrin (*Scheme 31*), respectively.

A related transformation carried out on the scalemic mixture $\mathbf{21}^{*}_{Cl}$ obtained by epoxide ring opening of scalemic (1*S*,6*R*)-2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-one (*S*,*R*)-**11** by $BeCl_2$ (*Scheme 11*, and *Table 3*, *Entry g*) led to the mixture (*S*,*S*)-$\mathbf{21}'_{Cl}$/(*R*,*R*)-$\mathbf{21}''_{Cl}$ (80:20) that then provided, as outlined in *Scheme 41*, a mixture of (1*S*)-*cis*-chrysanthemic acid ((1*S*)-$\mathbf{2}_{cis}$; ee: 94%) and (1*S*,6*R*)-2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-one ((*S*,*R*)-**11**; ee: 94%) [2b].

Acid/base treatment allowed the separation of (1*S*)-$\mathbf{2}_{cis}$, the precursor of *S*-bioallethrin (*Scheme 31*, *Entry b*) from (*S*,*R*)-**11**, which has been then recycled (*Scheme 41*).

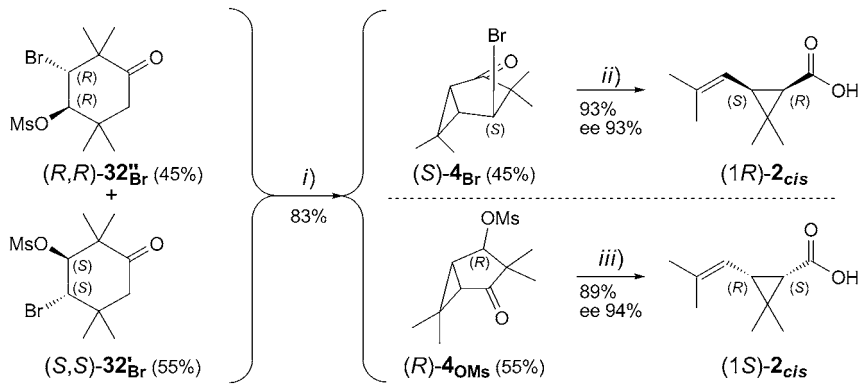
Conclusions. – In this article, we have described a series of reactions that allow the enantioselective transformation of the prochiral 2,2,5,5-tetramethylcyclohex-3-enone **1**

Scheme 39. *Synthesis of Scalemic* cis-*Chrysanthemic Acid* ($\mathbf{2}^{*}_{cis}$) *from the Mixture of the Bromohydrines* **21*** *Involving 'One-Pot' Cyclization–Fragmentation*



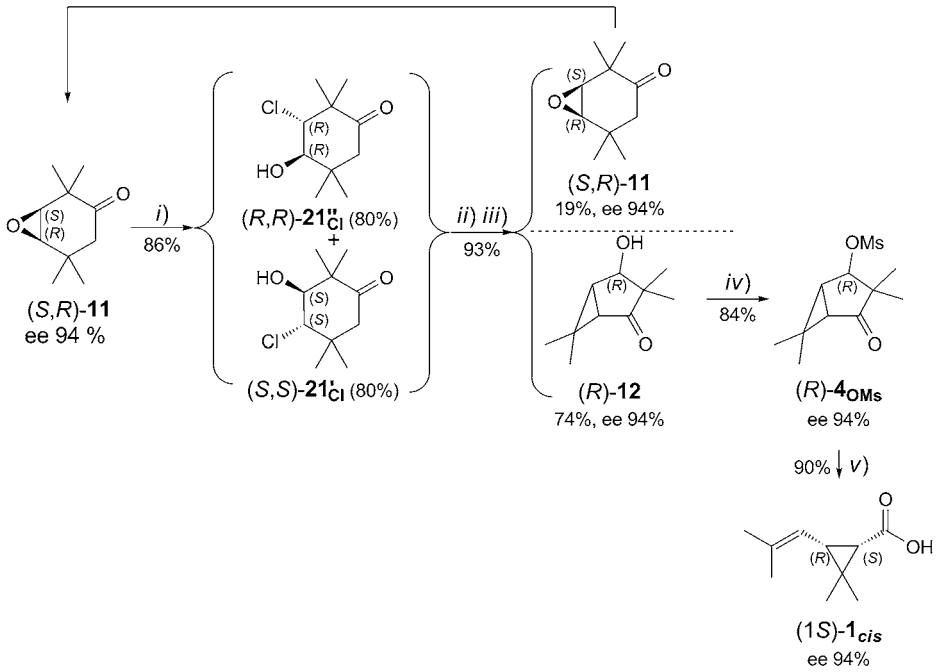
i) 1.5 equiv. ^{t}BuOOH, 0.015 equiv. $Mo(CO)_6$, C_6H_6, 80°, 2 h. *ii*) 1.5 equiv. PDC, MS (4 Å) CH_2Cl_2, 0 to 20°, 18 h. *iii*) 0.5 equiv. $TiBr_4$, CH_2Cl_2, 20°, 2 h. *iv*) 2 equiv. MsCl, 2 equiv. Et_3N, 0.1 equiv. DMAP, CH_2Cl_2, −10 to 20°, 18 h. *v*) 7.6 equiv. ^{t}BuOK, 2.3 equiv. H_2O, THF, 20°, 2 h. *vi*) H_3O^+.

Scheme 40. *Synthesis of Both Enantiomers of Scalemic* cis-*Chrysanthemic Acid* ($\mathbf{2}^{*}_{cis}$) *from the Mixture of the Bromohydrines* **21*** *Involving Sequential Cyclization–Fragmentation*



i) 1.2 equiv. KMHDS, THF, 0°, 1 h. *ii*) 7.6 equiv. ^{t}BuOK, 2.3 equiv. H_2O, THF, 20°, 0.6 h, then H^3O^+. *iii*) 7.6 equiv. ^{t}BuOK, 2.3 equiv. H_2O, DMSO, 20°, 0.6 h, then H_3O^+.

Scheme 41. *Synthesis of Scalemic* cis-*Chrysanthemic Acid* ($\mathbf{2}^{*}_{cis}$) *from the Mixture of the Chlorohydrines* **21***



i) 5 equiv. $BeCl_2$, CH_2Cl_2, 20°, 100 h. *ii*) *a*) 2 equiv. LiTMP; *b*) 2 equiv. ^{t}BuOK, THF, −25°, 1.5 h. *iii*) Separation by chromatography on SiO_2. *iv*) 1.1 equiv. MsCl, 1.5 equiv. Et_3N, CH_2Cl_2, −10°, 2 h. *v*) 6 equiv. ^{t}BuOK, 3 equiv. H_2O, DMSO, 20°, 1 h, then H_3O^+.

to (1*S*)-2,2,5,5-tetramethylcyclohex-3-enol ((*S*)-**23**) using (−)-*β*-chlorodiisopinocampheylborane [38] then to *i*) (1*R*)-*cis*-chrysanthemic acid ((1*R*)-$\mathbf{2}_{cis}$), the precursor of deltamethrin **38** (*Scheme 31*, *a*), *via* diastereoselective dibromination of (*S*)-**23** (*Scheme 32*) [2d] or *ii*) (1*S*)-*cis*-chrysanthemic acid ((1*S*)-$\mathbf{2}_{cis}$), the precursor of (*S*)-bioalletrin **40** (*Scheme 31*, *b*), by *a*) diastereoselective epoxidation of (*S*)-**23**, followed by epoxide ring opening on the epoxyalcohol (*S*,*R*)-**24** to produce, after regioselective oxidation, the ketone (*S*,*S*)-$\mathbf{21}'_{\mathbf{Br}}$ (scalemic version of *Schemes 13* and *19*) [2a] or *b*) epoxide ring opening of the related epoxy ketones (*S*,*R*)-**11** by $BeCl_2$ to give mainly (*S*,*S*)-$\mathbf{21}'_{\mathbf{Cl}}$ (Scalemic version of *Scheme 22*) [2b].

It is interesting to notice that the strategy described above is very flexible, since starting from the same 2,2,5,5-tetramethylcyclohex-3-enone **1**, (1*S*)-*cis*-chrysanthemic acid ((1*S*)-$\mathbf{2}_{cis}$) can be obtained using the reactions disclosed in *i* in the above paragraph), and its regioisomer (1*R*)-*cis*-chrysanthemic acid ((1*R*)-$\mathbf{2}_{cis}$) can be prepared by using the reactions disclosed in *ii* in the above paragraph by simply using the dextrogyre (+)-*B*-chlorodiisopinocampheylborane [38] instead of its enantiomer. Both are commercially available for about the same cost.

Experimental Part

General. For the procedures of syntheses presented in *Schemes 32* and *33*, see reference [2d]. Reactions requiring an inert atmosphere were carried out in two-neck flask fitted with a magnetic stirrer, a rubber cap and an Ar-inflated balloon. Unless otherwise mentioned, solvents and commercial reagents were used without further purification. Et_2O and THF were distilled from Na/benzophenone/cetyl, C_6H_6 was refluxed over Na, and CH_2Cl_2 was refluxed over P_2O_5. Column chromatography (CC): 30 g of silica gel (SiO_2; *Merck silica 7734*) per g crude sample. M.p.: *Büchi B-545* in open capillary tubes; uncorrected. Specific rotations $[\alpha]_D$: *Perkin-Elmer 241* polarimeter; at 20°; with a Na lamp (589 nm) and a sample tube of 10-cm length. ^{1}H- and ^{13}C-NMR: *Jeol JNM EX-400* at 400.0 and 100.4 MHz, respectively; chemical shifts refer to $\delta(\text{TMS}) = 0$ for ^{1}H and to $\delta(CDCl_3) = 77.0$ ppm for ^{13}C. GC/MS: *Hewlett-Packard 5890 series II* gas chromatograph coupled to a *Hewlett-Packard 5989B* mass spectrometer, at 70 eV.

2,2,5,5-Tetramethylcyclohex-3-en-1-one (**1**). In a 250-ml round-bottom neck flask, $TsNHNH_2$ (9.3 g, 50 mmol) was added to a stirred soln. of *2,2-dimethyldimedone* (**13**; 8.4 g, 50 mmol) in abs. EtOH (100 ml) at r.t. without any special care. The $TsNHNH_2$ did not solubilize totally, and more precipitate appeared during the reaction. After 7 d, the mixture was placed under reduced pressure to furnish a white solid as crude product. In a 500-ml round-bottom two-neck flask fitted with a condenser under Ar, the crude product was added to a soln. of ethylene glycol/sodium glycolate (from 250 ml of ethylene glycol and 5.75 g of Na, 250 mmol) and was heated at 180° until evolution of N_2 had ceased (*ca.* 0.5 h). The cooled soln. was poured onto 350 ml of ice and extracted with pentane (5×120 ml). The extracts were combined, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give a brown liquid (the product obtained was quite volatile). The crude product was purified by CC (pentane/Et_2O 98:2) to furnish 1.44 g (50%) of slightly yellow, volatile liquid. Spectral properties were identical with those described in [44].

3,4-Dibromo-2,2,5,5-tetramethylcyclohexanone ($\mathbf{3_{Br}}$) *in* CH_2Cl_2 *at* −78°. In a 25-ml round-bottom two-neck flask under Ar, at −78°, a 1M soln. of Br_2 in CH_2Cl_2 (1 ml, 1 mmol) was added to a stirred soln. of **1** (152 mg, 1 mmol) in CH_2Cl_2 (5 ml). At the end of the addition, the mixture was evaporated under reduce pressure, while it was allowed to warm to r.t. to furnish 311 mg (100%) of $\mathbf{3_{Br}}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{3_{Br}}$ *in* CCl_4 *at 0°*. In a 50-ml round-bottom two-neck flask under Ar, acetamide (30 mg, 0.5 mmol) was added to a stirred soln. of **1** (760 mg, 5 mmol) in CCl_4 (20 ml). The soln. was cooled to 0° before adding dropwise a soln. of Br_2 (800 mg, 5 mmol) diluted with CCl_4 (5 ml). After 1 h at 0°, aq. sat. $NaHCO_3$ (10 ml) was added, and the mixture extracted with Et_2O (3×30 ml). The combined org. extracts were washed with aq. sat. $Na_2S_2O_5$ (10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish 1.53 g (98%) of $\mathbf{3_{Br}}$. White solid. Spectral properties were identical with those described in [2d].

3,4-Dichloro-2,2,5,5-tetramethylcyclohexanone ($\mathbf{3_{Cl}}$). In a 50-ml round-bottom two-neck flask under Ar, acetamide (47 mg, 0.8 mmol) was added to a stirred soln. of **1** (1.22 g, 8 mmol) in CCl_4 (8 ml). The soln. was cooled to −40° before adding dropwise a soln. of Cl_2 (1.3M in CCl_4, 6.15 ml, 8.0 mmol). At the end of the addition, the reaction was quenched with aq. sat. $NaHCO_3$ (25 ml), and the mixture was allowed to warm to r.t. and extracted with CH_2Cl_2 (3×20 ml). The combined org. extracts were washed with aq. sat. $Na_2S_2O_5$ (10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield 1.70 g (95%) of $\mathbf{3_{Cl}}$. White solid. M.p. 99°. IR (KBr): 2987, 2937, 2879, 1708, 1462, 1391, 1370, 1306, 1263, 1248, 1196, 1123, 1080, 973, 949, 900, 874, 817, 784, 740. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.22 (*d*, $J = 11.2$, 1 H); 4.01 (*d*, $J = 11.2$, 1 H); 2.74 (*dd*, $J = 14.4$, 0.8, 1 H); 2.27 (*d*, $J = 14.4$, 1 H); 1.27 (*s*, 3 H); 1.25 (*s*, 3 H); 1.24 (*s*, 3 H); 0.95 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 209.0; 71.2; 70.8; 52.2; 50.0; 39.1; 29.9; 22.5; 21.7; 20.0.

4-exo-*Bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* ($\mathbf{4_{Br}}$) *with LDA.* In a 25-ml round-bottom two-neck flask under Ar, at −78°, a 0.57M soln. of LDA in THF (1.75 ml, 1 mmol) was added dropwise to a soln. of $\mathbf{3_{Br}}$ (312 mg, 1 mmol) in THF (3 ml). After 1 h at −78°, the mixture was hydrolyzed with 20 ml of H_2O and extracted with Et_2O (3×20 ml). The combined org. extracts were washed with brine ($2 \times$ 10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish 199 mg (86%) of $\mathbf{4_{Br}}$. Colorless liquid. IR (film): 3043, 2969, 2931, 2871, 1731, 1462, 1380, 1360, 1280, 1236, 1195, 1109, 1028,

1008, 974, 870, 837, 785, 746. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.01 (*d*, *J* = 1.2, 1 H); 2.15 (*dd*, *J* = 5.6, 1.6, 1 H); 1.98 (*d*, *J* = 6.0, 1 H); 1.23 (*s*, 3 H); 1.16 (*s*, 3 H); 1.01 (*s*, 3 H); 1.00 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 212.3; 56.1; 54.4; 38.9; 38.0; 27.5; 26.8; 26.4; 19.0; 16.9. Due to the instability of the product, further analyses were not performed.

Compound $\mathbf{4_{Br}}$ *with* ^{t}*BuOK*. In a 250-ml round-bottom two-neck flask under Ar, at −78°, ^{t}BuOK (2.69 g, 24 mmol) was added in one portion to a stirred soln. of $\mathbf{3_{Br}}$ (6.24 g, 20 mmol) in dry THF (200 ml), and the mixture was stirred while warming up to r.t. After 1 h, the reaction was quenched with aq. sat. NH_4Cl (20 ml), the org. layer was decanted and the aq. layer extracted with Et_2O (3 × 50 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 95:05) to furnish 4.34 g (94%) of $\mathbf{4_{Br}}$. Colorless liquid. Spectral properties were identical with those already reported.

Compound $\mathbf{4_{Br}}$ *with MeOLi*. In a 25-ml round-bottom two-neck flask equipped with a reflux condenser under Ar, BuLi (1.6M in hexane, 3.75 ml, 6 mmol) was added to freshly dried MeOH (5 ml). The mixture was then evaporated under reduce pressure in order to remove the solvents. Freshly dried MeOH (1 ml) and $\mathbf{3_{Br}}$ (332 mg, 1 mmol) were then added successively, and the soln. was heated at 65° under Ar. After 48 h, the reaction was quenched with aq. sat. NH_4Cl (15 ml), and the mixture was extracted with Et_2O (3 × 20 ml). The combined org. extracts were washed with brine (20 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish 113 mg (49%) of $\mathbf{4_{Br}}$. Colorless liquid. Spectral properties were identical with those already reported.

4-exo-*Chloro-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* ($\mathbf{4_{Cl}}$) *with LDA*. In a 25-ml round-bottom two-neck flask under Ar, at −78°, a 0.57M soln. of LDA in THF (1.75 ml, 1 mmol) was added dropwise to a soln. of $\mathbf{3_{Cl}}$ (223 mg, 1 mmol) in THF (3 ml). After 1 h at −78°, the mixture was hydrolyzed with 20 ml of H_2O and extracted with Et_2O (3 × 20 ml). The combined org. extracts were washed with brine (2 × 10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish 164 mg (88%) of $\mathbf{4_{Cl}}$. Colorless liquid. IR (film): 3042, 2970, 2931, 2871, 1732, 1463, 1381, 1360, 1279, 1263, 1198, 1110, 1029, 974, 882, 842, 788, 712. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.98 (*s*, 1 H); 1.98 (*d*, *J* = 0.8, 2 H); 1.18 (*s*, 3 H); 1.16 (*s*, 3 H); 1.04 (*s*, 3 H); 1.02 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 213.3; 62.8; 56.4; 38.8; 37.7; 26.9; 25.6; 24.4; 19.2; 17.0. Due to the instability of the product, further analyses were not performed.

Compound $\mathbf{4_{Cl}}$ *with* ^{t}*BuOK*. In a 50-ml round-bottom two-neck flask under Ar, at −78°, ^{t}BuOK (404 mg, 3.6 mmol) was added in one portion to a stirred soln. of $\mathbf{3_{Cl}}$ (669 mg, 3 mmol) in dry THF (30 ml), and the mixture was stirred while warming up to r.t. After 1 h, the reaction was quenched with aq. sat. NH_4Cl (10 ml), the org. layer was decanted, and the aq. layer was extracted with Et_2O (3 × 20 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 90:10) to furnish 500 mg (89%) of $\mathbf{4_{Cl}}$. Colorless liquid. Spectral properties were identical with those already reported.

cis-*Chrysanthemic Acid* ($\mathbf{2_{\mathit{cis}}}$) *from* $\mathbf{4_{Br}}$ *with WPH* (*General Procedure 1* (*GP 1*)). In a 25-ml round-bottom two neck flask equipped with a reflux condenser under Ar, $\mathbf{4_{Br}}$ (116 mg, 0.5 mmol) was added to a stirred soln. of KOH (168 mg, 3 mmol) in DMSO/H_2O 4:1 (2 ml). The mixture was then heated to 70° for 0.8 h. A orange-brown color appeared, and the reaction was monitored by TLC (pentane/Et_2O 80:20). The mixture was acidified to pH 2 with aq. HCl (10%; discoloration) and extracted with Et_2O (4 × 15 ml). The combined org. extracts were washed with H_2O (2 × 5 ml), dried ($MgSO_4$), filtered, and evaporated under reduce pressure. The crude product was purified by CC (pentane/Et_2O 80:20) to furnish 73 mg (87%) of $\mathbf{2_{\mathit{cis}}}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2_{\mathit{cis}}}$ *from* $\mathbf{4_{Br}}$ *with APH in THF* (*General Procedure 2* (*GP 2*)). In a 25-ml round-bottom two-neck flask under Ar, H_2O (21 mg, 1.15 mmol) was added to a stirred soln. of freshly sublimed ^{t}BuOK (426 mg, 3.8 mmol) in dry THF (4 ml), and the mixture was stirred at r.t. After 10 min, a soln. of $\mathbf{4_{Br}}$ (116 mg, 0.5 mmol) in dry THF (2 ml) was added dropwise. A yellow color appeared, and the reaction was monitored by TLC (pentane/Et_2O 80:20). After 0.5 h at r.t., ice (8 ml) was added, the mixture was acidified to pH 2 with aq. HCl (10%; discoloration) and extracted with Et_2O (4 × 15 ml). The combined org. extracts were washed with H_2O (2 × 5 ml), dried ($MgSO_4$), filtered, and evaporated under reduce pressure. The crude product was purified by CC (pentane/Et_2O 80:20) to furnish 79 mg (94%) of $\mathbf{2_{\mathit{cis}}}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{4}_{Br}$ *with APH in DMSO* (*General Procedure 3* (*GP 3*)). In a 25-ml round-bottom two-neck flask under Ar, H_2O (42 mg, 2.3 mmol) was added to a stirred soln. of freshly sublimed ^{t}BuOK (852 mg, 7.6 mmol) in dry DMSO (4 ml), and the mixture was stirred at r.t. After 10 min, $\mathbf{4}_{Br}$ (231 mg, 1 mmol) was added. An orange color appeared, and the reaction was monitored by TLC (pentane/Et_2O 80:20). After 0.3 h at r.t., the mixture was poured into a 25-ml *Erlenmeyer* flask containing Et_2O (10 ml) and ice (5 ml), acidified to pH 2 with aq. HCl (10%; discoloration), and extracted with Et_2O (4 × 15 ml). The combined org. extracts were washed with H_2O (2 × 5 ml), dried ($MgSO_4$), filtered, and evaporated under reduce pressure. The crude product was purified by CC (pentane/Et_2O 80:20) to furnish 89 mg (53%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{4}_{Cl}$ *with WPH. GP 1*, $\mathbf{4}_{Cl}$ (187 mg, 1 mmol), KOH (336 mg, 6 mmol), DMSO/H_2O 4:1 (4 ml), 0.8 h at 70°. CC (pentane/Et_2O 80:20): 126 mg (75%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{4}_{Cl}$ *with APH in THF. GP 2*, $\mathbf{4}_{Cl}$ (187 mg, 1 mmol), ^{t}BuOK (852 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry THF (12 ml), 0.5 h at r.t. CC (pentane/Et_2O 80:20): 153 mg (91%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{3}_{Br}$ *with WPH. GP 1*, $\mathbf{3}_{Br}$ (312 mg, 1 mmol), KOH (336 mg, 6 mmol), DMSO/H_2O 4:1 (3 ml), 2 h at 70°. CC (pentane/Et_2O 80:20)): 146 mg (87%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{3}_{Cl}$ *with WPH. GP 1*, $\mathbf{3}_{Cl}$ (223 mg, 1 mmol), KOH (336 mg, 6 mmol), DMSO/H_2O 4:1 (3 ml), 4 h at 70°. CC (pentane/Et_2O 80:20): 108 mg (64%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{3}_{Br}$ *with APH in THF. GP 2*, $\mathbf{3}_{Br}$ (312 mg, 1 mmol), ^{t}BuOK (852 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry THF (12 ml), 0.4 h at r.t. CC (pentane/Et_2O 80:20): 158 mg (94%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{3}_{Cl}$ *with APH in THF. GP 2*, $\mathbf{3}_{Cl}$ (223 mg, 1 mmol), ^{t}BuOK (852 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry THF (12 ml), 1 h at r.t. CC (pentane/Et_2O 80:20): 134 mg (80%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{3}_{Br}$ *with APH in DMSO. GP 3*, $\mathbf{3}_{Br}$ (312 mg, 1 mmol), ^{t}BuOK (852 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry DMSO (4 ml), 0.5 h at r.t. CC (pentane/Et_2O 80:20): 109 mg (65%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

*5-(2-Methylprop-1-en-1-yl)dihydrofuran-2(3*H*)-one* (**6**) *from* $\mathbf{5}_{Br}$ *with WPH.* In a 5-ml round-bottom two-neck flask equipped with a reflux condenser under Ar, *3,4-dibromo-2,2-dimethylcyclohexanone* ($\mathbf{5}_{Br}$; 142 mg, 0.5 mmol) was added to a stirred soln. of KOH (168 mg, 3 mmol) in DMSO/H_2O 4:1 (2 ml). The mixture was then heated to 70° for 2 h. A orange-brown color appeared, and the reaction was monitored by TLC (pentane/Et_2O 80:20). The mixture was poured into a 25-ml *Erlenmeyer* flask containing Et_2O (10 ml) and ice (4 ml), acidified to pH 2 with aq. HCl (10%; discoloration), and stirred overnight (cyclization of allylic alcohol).The mixture was extracted with Et_2O (4 × 10 ml). The combined org. extracts were washed with H_2O (2 × 5 ml), dried ($MgSO_4$), filtered, and evaporated under reduce pressure. The crude product was purified by CC (pentane/Et_2O 70:30) to furnish 46 mg (65%) of **6**. Colorless liquid. IR (film): 2976, 2935, 1770, 1678, 1451, 1424, 1380, 1328, 1293, 1218, 1179, 1130, 1057, 1007, 977, 915, 878, 833, 801. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.26–5.26 (*m*, 2 H); 2.58–2.53 (*m*, 2 H); 2.38 (*m*, 1 H); 1.92 (*m*, 1 H); 1.78 (*s*, 3 H); 1.74 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.4; 140.0; 122.9; 77.8; 29.8; 29.4; 29.3; 18.5. EI-MS: 140, 125, 97, 85.

Didemethyl-cis-*chrysanthemic Acid* ($\mathbf{7}_{cis}$) *from* $\mathbf{5}_{Br}$ *with APH in THF. GP 2*, $\mathbf{5}_{Br}$ (142 mg, 0.5 mmol), ^{t}BuOK (426 mg, 3.8 mmol), H_2O (21 mg, 1.15 mmol), dry THF (6 ml), 0.4 h at r.t. CC (pentane/Et_2O 80:20): 60 mg (86%) of $\mathbf{7}_{cis}$. Colorless liquid. IR (film): 2960, 2918, 2702, 2551, 1698, 1437, 1374, 1356, 1300, 1235, 1134, 1093, 1064, 984, 944, 916, 882, 854, 801, 740. ^{1}H-NMR (400 MHz, $CDCl_3$): 11.9 (br., 1 H); 5.10 (*dt*, *J* = 8.9, 1.4, 1 H); 2.15–2.01 (*m*, 1 H); 1.94–1.82 (*m*, 1 H); 1.72 (*d*, *J* = 0.9, 3 H); 1.70 (*d*, *J* = 0.9, 3 H); 1.28–1.15 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 178.5; 135.1; 120.6; 25.8; 21.2; 20.5; 18.2; 15.0. EI-MS: 140, 125, 95, 79.

4-Bromo-2,2,5,5-tetramethylcyclohexane-1,3-dione (**14**). In a 500-ml round-bottom two-neck flask fitted with a $CaCl_2$ tube, at 0°, a soln. of Br_2 (19.8 g, 124 mmol) in CCl_4 (50 ml) was added dropwise over

1.5 h, to a stirred soln. of *2,2,5,5-tetramethylcyclohexane-1,3-dione* (**13**; 20.9 g, 124 mmol) in CCl_4 (250 ml). After 0.5 h, the mixture was treated with aq. sat.$NaHCO_3$ (100 ml) and extracted with Et_2O (4 × 150 ml). The combined org. extracts were washed with H_2O (3 × 75 ml), dried ($MgSO_4$), filtered, and evaporated under reduce pressure. The crude product was purified by CC (toluene) to furnish 19.3 g (63%) of **14**. White solid. Spectral properties were identical with those described in [45].

3,3,6,6-Tetramethylbicyclo[3.1.0]hexane-2,4-dione (**15**). In a 50-ml round-bottom two-neck flask under Ar, a soln. of ^{t}BuOK (806 mg, 7.2 mmol) in THF (8 ml) was added dropwise over 0.5 h, at −78°, to a stirred soln. of **14** (1.48 g, 6 mmol) in THF (10 ml). The soln. was then stirred at r.t. After 0.5 h, the reaction was quenched with aq. sat. NH_4Cl (10 ml), and the mixture was extracted with pentane (4 × 50 ml). The combined org. extracts were washed with H_2O (3 × 20 ml), dried ($MgSO_4$), filtered, and evaporated under reduce pressure to furnish 994 mg (100%) of **15**. Colorless liquid. Spectral properties were identical with those described in [45].

4-exo-*Hydroxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* (**12**). In a 250-ml round-bottom two-neck flask fitted with a $CaCl_2$ tube, $CeCl_3 \cdot 7\ H_2O$ (7.46 g, 20 mmol) was added to a stirred soln. of **15**; 3.32 g, 20 mmol) in MeOH (150 ml). After complete dissolution of the Ce salt, at −78°, $NaBH_4$ (760 mg, 20 mmol) was added in portions (4 × 190 mg). After 1.5 h at −78°, the mixture was poured into an *Erlenmeyer* flask containing Et_2O (100 ml) and aq. HCl (10%, 40 ml) and allowed to warm to r.t. The org. layer was decanted, and the aq. layer was extracted with Et_2O (3 × 60 ml). The combined org. extracts were washed with H_2O (2 × 20 ml) and brine (20 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 60:40) to furnish 3.11 g (92%) of **12**. Colorless liquid. IR (film): 3430, 3036, 2967, 2932, 2874, 1711, 1465, 1380, 1281, 1122, 1059, 1028, 862. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.91 (*d*, *J* = 6.0, 1 H); 1.99 (*d*, *J* = 6.0, 1 H); 1.91 (*dd*, *J* = 5.6, 1.2, 1 H); 1.70 (*dd*, *J* = 5.6, 1.2, 1 H); 1.15 (*s*, 3 H); 1.07 (*s*, 3 H); 1.03 (*s*, 3 H); 1.00 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 216.2; 75.3; 55.8; 39.1; 37.7; 27.1; 24.3; 21.0; 19.6; 17.3. EI-MS: 168, 153, 125, 123, 107, 98, 96, 83, 81, 69, 67, 55, 43, 41, 39. Anal. calc. for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.73, H 9.49.

4-exo-*Mesyloxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* (*=3,3,6,6-Tetramethyl-4-oxobicyclo[3.1.0]hex-2-yl Methanesulfonate*; $\mathbf{4}_{\mathbf{OMs}}$). In a 25-ml round-bottom two-neck flask under Ar, Et_3N (303 mg, 3 mmol) was added to a stirred soln. of **12** (336 mg, 2 mmol) in dry CH_2Cl_2 (12 ml). The soln. was cooled to −10° before adding dropwise a soln. of MsCl (253 mg, 2.2 mmol) in dry CH_2Cl_2 (2 ml). After 1.5 h at −10°, the reaction was quenched with ice (5 ml), and the mixture was extracted with Et_2O (3 × 20 ml). The combined org. extracts were washed with aq. HCl (10%, 5 ml) and aq. sat. $NaHCO_3$ (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 50:50) to furnish 423 mg (86%) of $\mathbf{4}_{\mathbf{OMs}}$. White solid. M.p. 60°. IR (KBr): 3026, 2978, 2877, 1720, 1466, 1356, 1305, 1175, 1124, 1032, 977, 956, 895, 846, 831, 786, 755, 734. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.72 (*s*, 1 H); 3.11 (*s*, 3 H); 2.01 (*d*, *J* = 5.2, 1 H); 1.95 (*d*, *J* = 5.2, 1 H); 1.18 (*s*, 3 H); 1.14 (*s*, 3 H); 1.12 (*s*, 3 H); 1.06 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 212.5; 82.9; 55.4; 38.4; 38.3; 34.6; 26.7; 24.1; 22.1; 19.0; 16.9. EI-MS: 246, 231, 208, 204, 153, 150, 123, 107, 96, 81, 72, 69, 55, 43. Anal. calc. for $C_{11}H_{18}O_4S$: C 53.64, H 7.37; found: C 53.43, H 7.25.

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{4}_{\mathbf{OMs}}$ *with APH in THF. GP 2*, $\mathbf{4}_{\mathbf{OMs}}$ (246 mg, 1 mmol), ^{t}BuOK (672 mg, 6 mmol), H_2O (54 mg, 3 mmol), dry THF (12 ml), 0.3 h at r.t. CC (pentane/Et_2O 80:20): 101 mg (60%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{2}_{cis}$ *from* $\mathbf{4}_{\mathbf{OMs}}$ *with APH in DMSO. GP 3*, $\mathbf{4}_{\mathbf{OMs}}$ (246 mg, 1 mmol), ^{t}BuOK (672 mg, 6 mmol), H_2O (54 mg, 3 mmol), dry DMSO (4 ml), 0.4 h at r.t. CC (pentane/Et_2O 80:20): 152 mg (90%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

2,2,5,5-Tetramethyl-7-oxabicyclo[4.1.0]heptan-3-one (**11**). In a 250-ml round-bottom two-neck flask fitted with a $CaCl_2$ tube, $NaHCO_3$ (3.70 g, 44 mmol) and *m*CPBA (70%, 5.43 g, 22 mmol) were added to a stirred soln. of **1** (1.68 g, 11 mmol), in CH_2Cl_2 (110 ml), and the mixture was stirred at r.t. After 40 h, aq. sat. $NaHCO_3$ (20 ml) was added, the org. layer was decanted, and the aq. layer was extracted with pentane (3 × 20 ml). The combined org. extracts were washed with aq. sat. $Na_2S_2O_3$ (15 ml) and aq. sat. $NaHCO_3$ (15 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 90:10) to furnish 1.51 g (82%) of **11**. Colorless liquid. IR (film): 2966, 2935, 2912, 2873, 1711, 1469, 1448, 1414, 1391, 1368, 1295, 1260, 1216, 1177, 1168, 1141, 1094, 1055, 1008, 965, 942. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.05 (*dd*, *J* = 4.0, 1.5, 1 H); 2.99 (*d*, *J* = 3.9, 1 H); 2.48 (*d*, *J* = 14.2,

1 H); 1.87 (*dd*, *J* = 14.2, 1.5, 1 H); 1.21 (*s*, 3 H); 1.17 (*s*, 3 H); 1.16 (*s*, 3 H); 0.98 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 212.9; 61.6; 60.6; 47.3; 42.3; 34.2; 27.8; 24.8; 23.8; 22.8. EI-MS: 168, 153, 85. Anal. calc. for $C_{10}H_{16}O_2$: C 71.39, H 9.59; found: C 71.43, H 9.72.

4-Iodo-3,3,6,6-tetramethyl-1,5-bis[(trimethylsilyl)oxy]cyclohexene (**20′**) *and 5-Iodo-3,3,6,6-tetramethyl-1,4-bis[(trimethylsilyl)oxy]cyclohexene* (**20″**) *from* **11**. In a 25-ml round-bottom two-neck flask under Ar, a soln. of LiTMP (0.3M in THF, 0.67 ml, 0.2 mmol) was added dropwise, at −78° to a soln. of **11** (34 mg, 0.2 mmol) in dry THF (1 ml). After 1 h, Me_2SiI (79 mg, 0.4 mmol) was added, and the mixture was stirred at −78° for 1 h and at r.t. for 0.5 h. The mixture was concentrated under reduced pressure, and the crude product was purified by CC (pentane/Et_2O 100:0 to 98:2) to furnish 53 mg (60%) of **20′**/**20″** 37:63. Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): Major product: 4.58 (*s*, 1 H); 4.32 (*d*, *J* = 11.4, 1 H); 3.77 (*d*, *J* = 11.7, 1 H); 1.15 (*s*, 3 H); 1.09 (*s*, 6 H); 0.96 (*s*, 3 H); 0.26 (*s*, 9 H); 0.18 (*s*, 9 H); minor product: 4.44 (*d*, *J* = 11.4, 1 H); 4.38 (*s*, 1 H); 3.67 (*d*, *J* = 11.7, 1 H); 1.20 (*s*, 3 H); 1.14 (*s*, 3 H); 1.05 (*s*, 3 H); 0.91 (*s*, 3 H); 0.25 (*s*, 9 H); 0.19 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 153.6; 149.4; 125.5; 125.0; 111.8; 108.6; 78.1; 77.3; 56.2; 55.5; 43.4; 42.6; 38.4; 36.4; 33.3; 30.4; 29.8; 28.3; 27.0; 25.4; 23.8; 20.4; 1.4; 0.4. EI-MS: 313, 225, 223, 197, 185, 133, 131, 127, 107, 75, 73. HR-MS: 440.1075 ($C_{16}H_{33}O_2Si_2I^+$; calc. 440.1064).

Trimethyl[(2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]hept-3-en-3-yl)oxy]silane (**19$_{TMS}$**). In a 25-ml round-bottom two-neck flask under Ar, at −78°, a soln. of LiHMDS (1.0M in THF, 2.2 ml, 2.2 mmol) was added dropwise, to a soln. of **11** (336 mg, 2 mmol) in dry THF (6 ml). After 0.3 h, a soln. of Me_3SiCl (435 mg, 4 mmol) in dry THF (2 ml) was added dropwise, and the soln. was allowed to warm to r.t. over 1.2 h. The reaction was quenched by aq. sat. $NaHCO_3$ (20 ml), and the mixture was extracted with Et_2O (4 × 25 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 95:05) to furnish 379 mg (79%) of **19$_{TMS}$**. Pale-yellow liquid. IR (film): 2962, 2908, 2869, 1734, 1666, 1472, 1360, 1339, 1254, 1214, 1149, 1119, 913, 874, 847, 758. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.19 (*d*, *J* = 2.0, 1 H); 2.95 (*d*, *J* = 3.9, 1 H); 2.90 (*dd*, *J* = 3.9, 2.0, 1 H); 1.15 (*s*, 3 H); 1.11 (*s*, 3 H); 1.10 (*s*, 3 H); 1.07 (*s*, 3 H); 0.16 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 151.1; 107.8; 62.5; 61.0; 35.7; 33.8; 28.1; 27.1; 25.1; 22.7; 0.44.

Compounds **20′**/**20″** *from* **19$_{TMS}$**. In a 25-ml round-bottom two-neck flask under Ar, at −78°, Me_3SiI (79 mg, 0.4 mmol) was added dropwise, to a soln. of **19$_{TMS}$** (95 mg, 0.4 mmol) in dry THF (1 ml). The mixture was stirred at −78° for 0.5 h and 1 h at r.t., and then concentrated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 97/03 to 50:50) to furnish 125 mg (71%) of **20′**/**20″** 58:42. Colorless liquid. Spectral properties were identical with those already reported.

Opening of the Epoxy Ring of **11**. *With 1 equiv. of $TiCl_4$ at r.t.* (*General Procedure 4*, *GP 4*). In a 25-ml round-bottom two-neck flask under Ar, at r.t., a soln. of **11** (168 mg, 1 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise, to a soln. of $TiCl_4$ (190 mg, 1 mmol) in dry CH_2Cl_2 (4 ml). After 72 h at r.t., the mixture was poured into an *Erlenmeyer* flask containing aq. sat. $NaHCO_3$ (4 ml) and CH_2Cl_2 (4 ml). The org. layer was decanted, and the aq. layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish 188 mg (92%) of a mixture *4-chloro-3-hydroxy-2,2,5,5-tetramethylcyclohexanone* (**21′$_{Cl}$**)/*3-chloro-4-hydroxy-2,2,5,5-tetramethylcyclohexanone* (**21″$_{Cl}$**) 58:42. White solid. M.p. 131°. IR (KBr): 3517, 2977, 2940, 2893, 1699, 1461, 1387, 1366, 1246, 1197, 1122, 1054, 998, 903, 866, 820, 761, 673, 613. ^{1}H-NMR (400 MHz, $CDCl_3$): **21′$_{Cl}$**: 4.16 (*d*, *J* = 10.6, 1 H); 3.59 (*d*, *J* = 10.3, 1 H); 2.69 (*d*, *J* = 14.2, 1 H); 2.48 (br., 1 H); 2.24 (*d*, *J* = 14.4, 1 H); 1.21 (*s*, 3 H); 1.19 (*s*, 3 H); 1.16 (*s*, 3 H); 0.93 (*s*, 3 H). **21″$_{Cl}$**: 3.91 (*d*, *J* = 10.3, 1 H); 3.81 (*d*, *J* = 10.3, 1 H); 2.65 (*d*, *J* = 14.9, 1 H); 2.41 (br., 1 H); 2.14 (*d*, *J* = 14.2, 1 H); 1.24 (*s*, 3 H); 1.20 (*s*, 3 H); 1.18 (*s*, 3 H); 0.85 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 211.1; 210.0; 76.9; 76.6; 73.8; 73.5; 51.6; 51.1; 50.4; 49.7; 37.4; 36.9; 29.5; 28.7; 22.4; 21.8; 21.7; 20.5; 19.5; 18.9. EI-MS: **21′$_{Cl}$**: 206, 204, 169, 158, 146, 144, 139, 121, 119, 114, 105, 103, 101; **21″$_{Cl}$**: 206, 204, 169, 168, 153, 123, 113, 109. Anal. calc. for $C_{10}H_{17}ClO_2$: C 58.68, H 8.37; found: C 58.86, H 8.63.

With 0.5 Equiv. of $TiBr_4$ at r.t. GP 4, **11** (1.68 g, 10 mmol), dry CH_2Cl_2 (60 ml), $TiBr_4$ (1.84 g, 5 mmol), 2 h at r.t.: 2.39 g (96%) of a mixture *4-bromo-3-hydroxy-2,2,5,5-tetramethylcyclohexanone* (**21′$_{Br}$**)/*3-bromo-4-hydroxy-2,2,5,5-tetramethylcyclohexanone* (**21″$_{Br}$**) 43:57. White solid.

Data of **21′$_{Br}$**. M.p. 112°. IR (KBr): 3526, 2975, 2939, 2888, 1700, 1461, 1430, 1387, 1365, 1350, 1283, 1245, 1193, 1144, 1122, 1079, 1050, 997, 945, 902. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.37 (*d*, *J* = 10.6, 1 H); 3.68

(d, J = 10.5, 1 H); 2.72 (dd, J = 14.4, 0.8, 1 H); 2.46 (br., 1 H); 2.29 (d, J = 14.3, 1 H); 1.21 (s, 3 H); 1.19 (s, 3 H); 1.15 (s, 3 H); 0.96 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 208.0; 66.7; 66.3; 52.6; 49.7; 40.2; 31.9; 23.7; 23.6; 21.0. EI-MS: 250, 248, 204, 202, 169, 165, 163, 151, 139, 136, 134, 123, 109. Anal. calc. for $C_{10}H_{17}BrO_2$: C 48.21, H 6.88; found: C 48.14, H 6.88.

Data of $\mathbf{21''_{Br}}$. M.p. 104°. IR (KBr): 3420, 2991, 2970, 2957, 2933, 2899, 2872, 1693, 1461, 1451, 1408, 1386, 1367, 1339, 1317, 1272, 1248, 1199, 1171, 1140, 1125, 1100, 1078, 1045, 861. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.12 (d, J = 10.5, 1 H); 3.89 (d, J = 10.5, 1 H); 2.66 (d, J = 14.2, 1 H); 2.37 (br., 1 H); 2.12 (d, J = 14.2, 1 H); 1.26 (s, 3 H); 1.20 (s, 3 H); 1.18 (s, 3 H); 0.83 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 212.6; 76.5; 71.0; 51.4; 49.5; 38.1; 28.9; 23.6; 23.4; 18.6. EI-MS: 169, 151, 123, 113, 109. Anal. calc. for $C_{10}H_{17}BrO_2$: C 48.21, H 6.88; found: C 48.14, H 6.88.

With 1 Equiv. of $TiBr_4$ *at* −78°. *GP 4*, **11** (84 mg, 0.5 mmol), dry CH_2Cl_2 (3 ml), $TiBr_4$ (184 mg, 0.5 mmol), 5 h at −78°: 68 mg (55%) of $\mathbf{21'_{Br}}/\mathbf{21''_{Br}}$ 55:45. White solid. Spectral properties were identical with those already reported. The main by-product was starting **11** (43%).

With 1 Equiv. of $TiBr_4$ *at r.t. GP 4*, **11** (84 mg, 0.5 mmol), dry CH_2Cl_2 (3 ml), $TiBr_4$ (184 mg, 0.5 mmol), 1 h at r.t.: 120 mg (96%) of $\mathbf{21'_{Br}}/\mathbf{21''_{Br}}$ 45:55. White solid. Spectral properties were identical with those already reported.

With 2 Equiv. of HBr at r.t. GP 4, **11** (84 mg, 0.5 mmol), dry THF (1 ml), HBr (48% in H_2O, 1 mmol), 2 h at r.t. CC (pentane/Et_2O 80:20 to 50:50): 95 mg (75%) of $\mathbf{21'_{Br}}/\mathbf{21''_{Br}}$ 65:35. White solid. Spectral properties were identical with those already reported.

With 2 Equiv. of HCl at r.t. GP 4, **11** (1.68 g, 10 mmol), dry THF (48 ml), HCl (36% in H_2O, 2.02 g, 20 mmol), 3 h at r.t. CC (pentane/Et_2O 95:5 to 50:50): 1.53 g (75%) of $\mathbf{21'_{Cl}}/\mathbf{21''_{Cl}}$ 66:34. White solid. Spectral properties were identical with those already reported.

With 5 Equiv. of Li_2NiBr_4 *at r.t. GP 4*, **11** (67 mg, 0.4 mmol), dry THF (1 ml), Li_2NiBr_4 (0.4M in THF, 5 ml, 2 mmol), 168 h at r.t. CC (pentane/Et_2O 80:20 to 50:50): 41 mg (41%) of $\mathbf{21'_{Br}}/\mathbf{21''_{Br}}$ 75:25. White solid. Spectral properties were identical with those already reported. The main by-product was starting **11**.

With 5 Equiv. of $BeCl_2$ *at r.t. GP 4*, **11** (504 mg, 3 mmol), dry CH_2Cl_2 (30 ml), $BeCl_2$ (1.20 g, 15 mmol), 100 h at r.t. CC (pentane/Et_2O 95:5 to 50:50) to furnish 511 mg (83%) of $\mathbf{21'_{Cl}}/\mathbf{21''_{Cl}}$ 80:20. White solid. Spectral properties were identical with those already reported.

With 1 Equiv. of Me_3SiI. In a 25-ml round-bottom two-neck flask under Ar, at −78°, Me_3SiI (2.00 g, d 1.4, 1.43 ml, 10 mmol) was added dropwise, to a soln. of **11** (1.68 g, 10 mmol) in THF (17 ml). The mixture was stirred at −78° for 1 h and at r.t. for 1 h, and concentrated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 95:5) to furnish 2.87 g (78%) of a mixture *4-iodo-2,2,5,5-tetramethyl-3-[(trimethylsilyl)oxy]cyclohexanone* (**22′**)/*3-iodo-2,2,5,5-tetramethyl-4-[(trimethylsilyl)oxy]cyclohexanone* (**22″**) 49:51. White solid. M.p. 68°. IR (KBr): 3408, 2969, 1708, 1462, 1386, 1367, 1250, 1110, 1064, 1003, 886, 837, 756, 728, 639, 608. ^{1}H-NMR (400 MHz, $CDCl_3$): **22′**: 4.47 (d, J = 10.5, 1 H); 3.82 (d, J = 10.5, 1 H); 2.75 (d, J = 13.7, 1 H); 2.30 (d, J = 13.4, 1 H); 1.19 (s, 3 H); 1.14 (s, 3 H); 1.07 (s, 3 H); 0.96 (s, 3 H); 0.26 (s, 9 H); **22″**: 4.26 (d, J = 10.8, 1 H); 3.98 (d, J = 10.5, 1 H); 2.65 (d, J = 14.0, 1 H); 2.06 (d, J = 14.0, 1 H); 1.27 (s, 3 H); 1.19 (s, 3 H); 1.08 (s, 3 H); 0.77 (s, 3 H); 0.28 (s, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 212.1; 207.8; 81.4; 80.3; 54.5; 52.1; 51.3; 49.2; 47.9; 40.1; 36.7; 34.3; 30.2; 27.5; 25.8; 24.2; 22.5; 20.0; 18.9; 1.6; 1.4. EI-MS: 353, 283, 242, 241, 185, 157, 151, 144, 123, 109, 103. Anal. calc. for $C_{13}H_{25}IO_2Si$: C 42.39, H 6.84; found: C 42.18, H 6.63.

3-Hydroxy-4-iodo-2,2,5,5-tetramethylcyclohexanone ($\mathbf{21'_I}$) *and 4-Hydroxy-3-iodo-2,2,5,5-tetramethylcyclohexanone* ($\mathbf{21''_I}$). In a 25-ml round-bottom two-neck flask under Ar, aq. HCl (10%, 5 drops) was added to a stirred soln. of **22′**/**22″** 49:51 (790 mg, 2.2 mmol) in MeOH (10 ml). After 2 h at r.t., MeOH was evaporated under reduce pressure, H_2O (5 ml) was added, and the mixture was extracted with $CHCl_3$ (5 × 10 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish 640 mg (100%) of $\mathbf{21'_I}/\mathbf{21''_I}$ 49:51. White solid. M.p. 95°. IR (KBr): 3408, 2972, 1690, 1459, 1385, 1368, 1315, 1238, 1108, 1069, 1044, 856, 733, 610. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.62 (d, J = 11.0, 1 H, $\mathbf{21'_I}$); 4.37 (d, J = 11.0, 1 H, $\mathbf{21''_I}$); 3.93 (d, J = 11.0, 1 H, $\mathbf{21''_I}$); 3.75 (d, J = 10.8, 1 H, $\mathbf{21'_I}$; 2.77 (dd, J = 14.0, 0.7, 1 H, $\mathbf{21'_I}$); 2.65 (d, J = 14.0, 1 H, $\mathbf{21''_I}$); 2.35 (br., 1 H, $\mathbf{21'_I}$); 2.33 (d, J = 14.0, 1 H, $\mathbf{21''_I}$); 2.23 (br., 1 H, $\mathbf{21''_I}$); 2.09 (d, J = 14.0, 1 H, $\mathbf{21'_I}$); 1.27 (s, 3 H); 1.22 (s, 3 H); 1.19 (s, 6 H); 1.18 (s, 3 H); 1.14 (s, 3 H); 0.98 (s, 3 H); 0.81 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 211.6; 207.2; 78.0; 77.3; 57.9; 57.5; 51.5;

50.7; 49.4; 47.9; 39.0; 37.0; 33.7; 29.4; 27.2; 25.7; 24.2; 22.0; 19.1; 18.3. EI-MS: $\mathbf{21}_{\mathbf{I}}'$: 296, 211, 170, 169, 168, 151, 139, 127, 123, 113, 109; $\mathbf{21}_{\mathbf{I}}''$: 169, 152, 151, 127, 123, 113, 109. HR-MS: 296.0267 ($C_{10}H_{17}O_2I^+$; calc. 296.0273).

2,2,5,5-Tetramethylcyclohex-3-en-1-ol (**23**). In a 25-ml round-bottom neck flask fitted with a $CaCl_2$ tube, at 0°, $NaBH_4$ (228 mg, 6 mmol) was added, to a stirred soln. of **1** (760 mg, 5 mmol) in MeOH (15 ml). After 1.3 h at 0°, the reaction was quenched with aq. HCl (10%, 10 ml), and the mixture was extracted with Et_2O (5 × 25 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 80:20) to furnish 628 mg (82%) of **23**. White solid. Spectral properties were identical with those described in [46].

cis-*2,2,5,5-Tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol* (**24**). In a 25-ml round-bottom two-neck flask equipped with a reflux condenser under Ar, $Mo(CO)_6$ (4 mg, 0.015 mmol) was added to a stirred soln. of **23** (154 mg, 1 mmol) in dry C_6H_6 (4 ml), and the mixture was heated at 80° before adding dropwise over a period of 0.5 h a soln. ^{t}BuOOH (70% in H_2O, 193 mg, 1.5 mmol) in dry C_6H_6 (1 ml). After 2 h at 80°, the mixture was cooled, aq. sat. $NaHCO_3$ (5 ml) was added, and the mixture was extracted with pentane (4 × 10 ml). The combined org. extracts were washed with aq. sat. $Na_2S_2O_3$ (5 ml) and aq. sat. $NaHCO_3$ (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 80:20 to 50:50) to furnish 149 mg (88%) of **24**/*trans*-2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol 98:2 (de 96%).

Data of **24**. White solid. M.p. 53°. IR (KBr): 3468, 3304, 2966, 1476, 1423, 1361, 1325, 1259, 1085, 1034, 929, 910, 850, 825, 773, 643, 554. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.36 (*dd*, *J* = 8.7, 3.2, 1 H); 2.90 (*d*, *J* = 3.7, 1 H); 2.83 (*d*, *J* = 3.7, 1 H); 1.77 (br., 1 H); 1.51 (*dd*, *J* = 13.4, 8.9, 1 H); 1.27 (*dd*, *J* = 13.4, 3.4, 1 H); 1.14 (*s*, 3 H); 1.10 (*s*, 3 H); 1.08 (*s*, 3 H); 1.07 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 73.8; 63.1; 62.7; 38.7; 33.9; 31.1; 28.4; 26.9; 26.0; 19.8. Anal. calc. for $C_{10}H_{18}O_2$: C 70.55, H 10.66; found: C 70.91, H 10.72.

Data of trans-*2,2,5,5-Tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol.* Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.59 (*dd*, *J* = 10.8, 5.5, 1 H); 2.93 (*d*, *J* = 3.6, 1 H); 2.74 (*d*, *J* = 3.6, 1 H); 1.59 (br., 1 H); 1.38–1.22 (*m*, 2 H); 1.20 (*s*, 3 H); 1.11 (*s*, 3 H); 1.08 (*s*, 3 H); 0.93 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 70.3; 65.0; 61.4; 41.6; 38.7; 35.5; 29.6; 25.9; 24.3; 17.0.

4-Bromo-2,2,5,5-tetramethylcyclohexane-1,3-diol ($\mathbf{25}_{\mathbf{Br}}'$; *General Procedure 5* (*GP 5*)). In a 250-ml round-bottom two-neck flask under Ar, was added $Ti(O^iPr)_4$ (4.92 g, 16.8 mmol) to a soln. of Br_2 (2.46 g, 15.4 mmol) in dry CH_2Cl_2 (140 ml). The mixture was cooled to 0° before adding dropwise a soln. of **24** (2.38 g, 14 mmol) in dry CH_2Cl_2 (30 ml). After 1 h at 0° and 4 h at r.t., the reaction was quenched with aq. tartaric acid (15%, 280 ml) and solid $Na_2S_2O_5$ (6.38 g) with vigorous stirring until clear phases were obtained. The org. layer was decanted, and the aq. layer was extracted with CH_2Cl_2 (4 × 30 ml). The combined org. extracts were washed with aq. sat. $NaHCO_3$ (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product, $\mathbf{25}_{\mathbf{Br}}'/\mathbf{25}_{\mathbf{Br}}''$ 93:7, was purified by CC (pentane/Et_2O 85:15 to 50:50) to furnish 2.81 g (80%) of $\mathbf{25}_{\mathbf{Br}}'$. White solid. M.p. 88°. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.04 (*d*, *J* = 10.8, 1 H); 3.58 (*dd*, *J* = 12.2, 4.4, 1 H); 3.46 (*d*, *J* = 10.8, 1 H); 1.76 (*dd*, *J* = 13.3, 4.4, 1 H); 1.57 (*t*, *J* = 12.7, 1 H); 1.55 (br., 2 H); 1.20 (*s*, 3 H); 1.10 (*s*, 3 H); 1.09 (*s*, 3 H); 0.86 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 76.3; 73.3; 72.1; 43.5; 35.9; 31.8; 31.0; 25.8; 22.9; 11.2. Anal. calc. for $C_{10}H_{19}BrO_2$: C 47.82, H 7.63; found: C 48.06, H 7.67.

Compound $\mathbf{21}_{\mathbf{Br}}'$ *from* $\mathbf{25}_{\mathbf{Br}}'$. In a volumetric flask, H_2O was added, to adjust the volume to 10.0 ml, to CrO_3 (2.672 g, 26.7 mmol) and conc. H_2SO_4 (4.210 g, 42.9 mmol). A 2.672M soln. of H_2CrO_4 was obtained.

In a 100-ml round-bottom two-neck flask fitted with a $CaCl_2$ tube, an aq. soln. of H_2CrO_4 (2.672M, 1.18 ml, 3.15 mmol) was added, as in a titration (20 × 59 µl, red to green color between each addition), to a stirred soln. of $\mathbf{25}_{\mathbf{Br}}'$ (1.26 g, 5 mmol) in acetone (48 ml). The reaction was quenched by aq. sat. $NaHSO_3$ (10 ml) and H_2O (10 ml), and the mixture was extracted with CH_2Cl_2 (6 × 10 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 70:30) to furnish 1.15 g (92%) of $\mathbf{21}_{\mathbf{Br}}'$. White solid. Spectral properties were identical with those already reported.

Opening of the Epoxy Ring of **24**. *With* $TiBr_4$. *GP 4*, **24** (170 mg, 1 mmol), dry CH_2Cl_2 (10 ml), $TiBr_4$ (184 mg, 0.5 mmol), 72 h at r.t. CC (pentane/Et_2O 70:30 to 40:60): 70 mg (28%) of $\mathbf{25}_{\mathbf{Br}}'$ and 149 mg

(59%) of *3-bromo-2,2,5,5-tetramethylcyclohexane-1,4-diol* (**25″$_{Br}$**) as white solids. Spectral properties of **25′$_{Br}$** were identical with those already reported.

Data of **25″$_{Br}$**: M.p. 75°. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.48 (*d*, *J* = 10.8, 1 H); 3.73 (*t*, *J* = 3.0, 1 H); 3.57 (*d*, *J* = 10.8, 1 H); 2.27 (br., 1 H); 1.79 (*dd*, *J* = 15.1, 3.3, 1 H); 1.57 (*dd*, *J* = 15.4, 2.6, 1 H); 1.52 (br., 1 H); 1.18 (*s*, 3 H); 1.12 (*s*, 3 H); 1.08 (*s*, 3 H); 1.05 (*s*, 3 H).

Base-Promoted Carbocyclization of **21′$_{Br}$**. *With 1 Equiv. of LiTMP at r.t., Normal Addition* (*General Procedure 6* (GP 6)). In a 25-ml round-bottom two-neck flask under Ar, at r.t., a soln. of LiTMP (0.3M in THF, 0.67 ml, 0.2 mmol) was added dropwise, to a soln. of **21′$_{Br}$** (50 mg, 0.2 mmol) in dry THF (2 ml). After 0.5 h at r.t., the mixture was hydrolyzed with sat. NH_4Cl in MeOH (1.5 ml) and H_2O (5 ml). The mixture was extracted with Et_2O (4 × 10 ml), the combined org. extracts were washed with aq. HCl (10%, 2 ml) and brine (2 ml), dried ($MgSO_4$), filtered, and evaporated under reduced to furnish a crude mixture **12**/**11** 10:90. CC (pentane/Et_2O 70:30): 29 mg (86%) of **11**. Spectral properties were identical with those already reported.

With 1 Equiv. of LiTMP at −25°, Normal Addition. GP 6, **21′$_{Br}$**; 50 mg, 0.2 mmol), dry THF (2 ml), LiTMP (0.3M in THF, 0.67 ml, 0.2 mmol), 1 h at −25° to furnish a crude mixture **12**/**11** 17:83. CC (pentane/Et_2O 70:30): 28 mg (83%) of **11**. Spectral properties were identical with those already reported.

With 2 Equiv. of LiTMP at −25°, Normal Addition. GP 6, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), LiTMP (0.3M in THF, 1.33 ml, 0.4 mmol), 1 h at −25° to furnish a crude mixture **12**/**11** in a 77:23. CC (pentane/Et_2O 80:20 to 0:100): 33 mg (98%) of **12**/**11** 79:21. Spectral properties were identical with those already reported.

With 2 Equiv. of LiTMP at −25°, Reverse Addition (*General Procedure 7* (*GP 7*)). In a 25-ml round-bottom two-neck flask under Ar, at −25°, a soln. of **21′$_{Br}$** (125 mg, 0.5 mmol) in dry THF (2.5 ml) was added dropwise, to a soln. of LiTMP (0.3M in THF, 3.3 ml, 1 mmol). After 1 h at −25°, the mixture was hydrolyzed with sat. NH_4Cl in MeOH (1.5 ml) and H_2O (5 ml). The mixture was extracted with Et_2O (4 × 10 ml), the combined org. extracts were washed with aq. HCl (10%, 2 ml) and brine (2 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish exclusively crude **12**. CC (Et_2O): 70 mg (83%) of **12**). Spectral properties were identical with those already reported.

With 1 Equiv. of LDA at r.t., Normal Addition. GP 6, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), LDA (2.0M in THF, 0.1 ml, 0.2 mmol), 0.5 h at r.t. to furnish a crude mixture **12**/**11** 4:96. CC (pentane/Et_2O 70:30): 31 mg (92%) of **11**. Spectral properties were identical with those already reported.

With 2 Equiv. of LDA at r.t., Normal Addition. GP 6, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), LDA (2.0M in THF, 0.2 ml, 0.4 mmol), 0.5 h at r.t. to furnish a crude mixture **12**/**11** 13:87. CC (pentane/Et_2O 80:20): 28 mg (83%) of **11**. Spectral properties were identical with those already reported.

With 2 Equiv. of LDA at −25°, Reverse Addition. GP 7, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), LDA (2.0M in THF, 0.2 ml, 0.4 mmol), 1 h at −25° to furnish a crude mixture **12**/**11** 70:30. CC (pentane/Et_2O 90:10 to 50:50): 19 mg (57%) of **12** and 7 mg (21%) of **11**. Spectral properties were identical with those already reported.

With 3 Equiv. of LDA at −25°, Reverse Addition. GP 7, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), LDA (2.0M in THF, 0.3 ml, 0.6 mmol), 1 h at −25° to furnish exclusively crude **12**. CC (pentane/Et_2O 30:70): 27 mg (80%) of **12**. Spectral properties were identical with those already reported.

With 3 Equiv. of LiHMDS at r.t., Reverse Addition. GP 7, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), LiHMDS (1.0M in THF, 0.6 ml, 0.6 mmol), 3 h at r.t. to furnish a crude mixture **12**/**11** 30:70. CC (pentane/Et_2O 70:30 to 50:50): 32 mg (95%) of **12**/**11** 34:66. Spectral properties were identical with those already reported.

With 3 Equiv. of KHMDS at r.t., Reverse Addition. GP 7, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), KHMDS (0.5M in toluene, 1.2 ml, 0.6 mmol), 0.3 h at r.t. to furnish exclusively crude **11**. CC (pentane/Et_2O 80:20): 28 mg (83%) of **11**. Spectral properties were identical with those already reported.

With 3 Equiv. of KHMDS at −78°, Reverse Addition. GP 6, **21′$_{Br}$** (50 mg, 0.2 mmol), dry THF (2 ml), KHMDS (0.5M in toluene, 1.2 ml, 0.6 mmol), 1 h at −78° to furnish a crude mixture **12**/**11** 67:33. CC (pentane/Et_2O 20/80): 32 mg (95%) of **12**/**11** 67:33. Spectral properties were identical with those already reported.

Base-Promoted Carbocyclization of the Mixture **21′$_{Cl}$/21″$_{Cl}$**. *With 1 Equiv. of LiTMP at* $-25°$, *Normal Addition. GP 6*, **21′$_{Cl}$/21″$_{Cl}$** (80:20, 41 mg, 0.2 mmol), dry THF (1 ml), LiTMP (0.3M in THF, 0.67 ml, 0.2 mmol), 1 h at $-25°$ to furnish a crude mixture **12/21′$_{Cl}$/21″$_{Cl}$** 21:58:21. Purification by CC (pentane/Et_2O 50:50 to 0:100): 7 mg (20%) of **12**. Spectral properties were identical with those already reported.

With 1 Equiv. of LiTMP at r.t., Normal Addition. GP 6, mixture **21′$_{Cl}$/21″$_{Cl}$** 80:20 (41 mg, 0.2 mmol), dry THF (1 ml), LiTMP (0.3M in THF, 0.67 ml, 0.2 mmol), 0.5 h at r.t. to furnish a crude mixture **12/11/21′$_{Cl}$/21″$_{Cl}$** 67:8:8:16. CC (pentane/Et_2O 60:40 to 0:100): 22 mg (66%) of **12**. Spectral properties were identical with those already reported.

With 2 Equiv. of LiTMP at $-25°$, *Reverse Addition. GP 7*, mixture of **21′$_{Cl}$/21″$_{Cl}$** 80:20 (102 mg, 0.5 mmol), dry THF (2.5 ml), LiTMP (0.3M in THF, 3.3 ml, 1 mmol), 1 h at $-25°$ to furnish a crude mixture **12/21″$_{Cl}$** 80:20. CC (pentane/Et_2O 50:50 to 0:100): 57 mg (68%) of **12**. Spectral properties were identical with those already reported.

With 2 Equiv. of LiTMP at $-25°$, *Reverse Addition Followed by Normal Addition of 2 Equiv. of* ^{t}*BuOK*. In a 25-ml round-bottom two-neck flask under Ar, at $-25°$, a soln. of a mixture of **21′$_{Cl}$/21″$_{Cl}$** 80:20 (41 mg; 0.2 mmol) in dry THF (1 ml) was added dropwise, to a soln. of LiTMP (0.3M in THF, 1.33 ml, 0.4 mmol). After 1 h at $-25°$, a soln. of ^{t}BuOK (46 mg, 0.4 mmol) in dry THF (1 ml) was added dropwise. After 0.5 h at $-25°$, the mixture was hydrolyzed with sat. NH_4Cl in MeOH (1.5 ml) and H_2O (5 ml). The mixture was extracted with Et_2O (4 × 10 ml), the combined org. extracts were washed with aq. HCl (10%, 2 ml) and brine (2 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish a crude mixture **12/11** 80:20. CC (pentane/Et_2O 80:20 to 30:70): 25 mg (74%) of **12** and 6.6 mg (19%) of **11**. Spectral properties were identical with those already reported.

Reaction of **20′** *and* **20″**. *With 2.2 Equiv. of* Bu_4NF (*General Procedure 8* (*GP 8*)). Into a 25-ml round-bottom two-neck flask under Ar, at $-25°$, a soln. of a mixture of **20′/20″** 58:42 (44 mg, 0.1 mmol) in dry THF (1 ml) was added dropwise to a soln. of Bu_4NF (1.0M in THF, 0.22 ml, 0.22 mmol). After 0.8 h at $-25°$, the mixture was concentrated under reduced pressure, and the crude product was purified by CC (pentane/Et_2O 95:5 to 0:100) to furnish 14.6 mg (87%) of a mixture **12/11** in a 60:40 ratio, resp. Colorless liquid. Spectral properties were identical with those already reported.

With 1 Equiv. of Bu_4NF. *GP 8*, **20′/20″** (58:42, 44 mg, 0.1 mmol), dry THF (1 ml), Bu_4NF (1.0M in THF, 0.1 ml, 0.1 mmol), 0.8 h at $-25°$. CC (pentane/Et_2O 50:50 to 0:100): 17.0 mg (80%) of **12/21″$_I$** 65:35. Spectral properties were identical with those already reported.

Synthesis of Compounds **32**. *6-Chloro-2,2,5,5-tetramethyl-3-oxocyclohexyl Methanesulfonate* (**32′$_{Cl}$**) *and 6-Chloro-2,2,5,5-tetramethyl-4-oxocyclohexyl Methanesulfonate* (**32″$_{Cl}$**; *General Procedure 9* (*GP 9*)). In a 25-ml round-bottom two-neck flask under Ar, Et_3N (808 mg, 8 mmol) and DMAP (49 mg, 0.4 mmol) were added to a stirred soln. of **21′$_{Cl}$/21″$_{Cl}$** 66:34 (818 mg, 4 mmol) in dry CH_2Cl_2 (13 ml). The soln. was cooled to $-10°$ before adding dropwise a soln. MsCl (916 mg, 8 mmol) in dry CH_2Cl_2 (3 ml). After 0.5 h at $-10°$ and 20 h at r.t., the mixture was diluted with CH_2Cl_2 (50 ml), washed with aq. HCl (10%, 2 × 5 ml) and aq. sat. $NaHCO_3$ (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/AcOEt 95:05), followed by recristallization from CH_2Cl_2/pentane to furnish 537 mg (47%) of **32′$_{Cl}$** and 307 mg (27%) of **32″$_{Cl}$** as white solids.

Data of **32′$_{Cl}$**. M.p. 207°. IR (KBr): 2982, 1711, 1464, 1349, 1328, 1169, 1129, 950, 914, 878, 834, 777, 714, 522. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.71 (*d*, *J* = 10.8, 1 H); 4.26 (*d*, *J* = 10.8, 1 H); 3.23 (*s*, 3 H); 2.69 (*d*, *J* = 14.4, 1 H); 2.30 (*d*, *J* = 14.6, 1 H); 1.27 (*s*, 3 H); 1.22 (*s*, 3 H); 1.21 (*s*, 3 H); 0.95 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 208.2; 87.8; 68.4; 52.0; 50.0; 39.4; 36.8; 29.5; 21.9; 21.1; 20.5. EI-MS: 284, 282, 247, 197, 186, 163, 151, 144, 123, 109. Anal. calc. for $C_{11}H_{19}ClO_4S$: C 46.72, H 6.77; found: C 46.80, H 6.64.

Data of **32″$_{Cl}$**. M.p. 211°. IR (KBr): 2982, 1711, 1464, 1349, 1328, 1169, 950, 914, 878, 834, 777, 714, 522. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.96 (*d*, *J* = 10.8, 1 H); 4.07 (*d*, *J* = 10.8, 1 H); 3.23 (*s*, 3 H); 2.75 (*d*, *J* = 14.4, 1 H); 2.21 (*d*, *J* = 14.4, 1 H); 1.28 (*s*, 3 H); 1.24 (*s*, 3 H); 1.23 (*s*, 3 H); 0.90 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 208.3; 87.5; 68.1; 51.5; 49.1; 39.5; 37.8; 28.7; 22.4; 21.9; 20.2. EI-MS: 284, 282, 247, 197, 186, 179, 163, 151, 144, 139, 123, 119, 109, 103. Anal. calc. for $C_{11}H_{19}ClO_4S$: C 46.72, H 6.77, S 11.34; found: C 46.44, H 6.69, S 11.68.

6-Bromo-2,2,5,5-tetramethyl-3-oxocyclohexyl Methanesulfonate (**32′$_{Br}$**) *and 6-Bromo-2,2,5,5-tetramethyl-4-oxocyclohexyl Methanesulfonate* (**32″$_{Br}$**). *GP 9*, **21′$_{Br}$/21″$_{Br}$** 50:50 (1.74 g, 7 mmol), dry CH_2Cl_2

(50 ml), Et_3N (1.42 g, 14 mmol), DMAP (85 mg, 0.7 mmol), MsCl (1.60 g, 14 mmol), 0.5 h at $-10°$ and 5 h at r.t. CC (pentane/AcOEt 95:05): 976 mg (43%) of **32′$_{Br}$** and 834 mg (36%) of **32″$_{Br}$**. White solids.

Data of **32′$_{Br}$**. M.p. 169°. IR (KBr): 2984, 2936, 1710, 1463, 1347, 1326, 1167, 1127, 948, 912, 875, 832, 798, 769, 711, 668, 567, 530, 520. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.83 (*d*, *J* = 10.8, 1 H); 4.40 (*d*, *J* = 10.8, 1 H); 3.27 (*s*, 3 H); 2.72 (*d*, *J* = 14.4, 1 H); 2.36 (*d*, *J* = 14.4, 1 H); 1.30 (*s*, 3 H); 1.24 (*s*, 3 H); 1.20 (*s*, 3 H); 0.99 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 208.3; 88.0; 63.0; 52.2; 49.6; 39.6; 36.8; 31.0; 22.0; 21.7; 21.0. EI-MS: 232, 230, 190, 188, 179, 163, 151, 135, 123, 110, 109.

Data of **32″$_{Br}$**. M.p. 175°. IR (KBr): 3323, 2983, 2940, 1717, 1466, 1389, 1374, 1346, 1327, 1248, 1174, 1129, 962, 939, 901, 882, 823, 770, 736, 668, 608, 565, 522. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.06 (*d*, *J* = 11.0, 1 H); 4.20 (*d*, *J* = 11.0, 1 H); 3.28 (*s*, 3 H); 2.77 (*d*, *J* = 14.4, 1 H); 2.20 (*d*, *J* = 14.4, 1 H); 1.31 (*s*, 3 H); 1.26 (*s*, 3 H); 1.24 (*s*, 3 H); 0.89 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 207.4; 87.4; 62.7; 51.4; 48.9; 39.7; 38.8; 28.9; 23.8; 23.4; 19.9. EI-MS: 247, 232, 230, 190, 188, 163, 152, 151, 124, 123, 110, 109.

6-Iodo-2,2,5,5-tetramethyl-3-oxocyclohexyl Methanesulfonate (**32′$_{I}$**) *and 6-Iodo-2,2,5,5-tetramethyl-4-oxocyclohexyl Methanesulfonate* (**32″$_{I}$**). *GP 9*, **21′$_{I}$**/**21″$_{I}$** 51:49 (840 mg, 2.8 mmol), dry CH_2Cl_2 (45 ml), Et_3N (434 mg, 4.3 mmol), MsCl (390 mg, 3.4 mmol), 1 h at $-10°$ and 5 h at r.t. CC (pentane/AcOEt 95:05), followed by recristallization from CH_2Cl_2/pentane: 377 mg (36%) of **32′$_{I}$** and 403 mg (38%) of **32″$_{I}$**. White solids.

Data of **32′$_{I}$**. M.p. 128°. IR (KBr): 3023, 2974, 2944, 1711, 1460, 1370, 1346, 1327, 1172, 1122, 938, 868, 829, 789, 766, 708, 527, 516. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.91 (*d*, *J* = 11.2, 1 H); 4.56 (*d*, *J* = 11.2, 1 H); 3.36 (*s*, 3 H); 2.76 (*d*, *J* = 14.2, 1 H); 2.42 (*d*, *J* = 14.4, 1 H); 1.34 (*s*, 3 H); 1.23 (*s*, 3 H); 1.20 (*s*, 3 H); 1.00 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 208.9; 89.1; 51.9; 47.7; 46.4; 40.1; 36.9; 34.0; 23.9; 22.1; 20.7. EI-MS: 163, 151, 123, 110, 109, 95, 81, 79, 69, 67, 55, 43, 41, 39. Anal. calc. for $C_{11}H_{19}IO_4S$: C 35.30, H 5.12, S 8.57; found: C 35.08, H 5.14, S 8.94.

Data of **32″$_{I}$**. M.p. 120°. IR (KBr): 3009, 2963, 2933, 2880, 1715, 1464, 1392, 1375, 1345, 1327, 1239, 1174, 1114, 931, 898, 877, 821, 770, 536, 518. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.12 (*d*, *J* = 11.2, 1 H); 4.39 (*d*, *J* = 11.2, 1 H); 3.37 (*s*, 3 H); 2.77 (*d*, *J* = 14.2, 1 H); 2.17 (*d*, *J* = 14.4, 1 H); 1.31 (*s*, 3 H); 1.28 (*s*, 3 H); 1.24 (*s*, 3 H); 0.89 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 205.6; 88.1; 51.3; 49.0; 45.9; 40.5; 40.0; 29.4; 27.1; 25.6; 19.5. EI-MS: 169, 151, 123, 110, 109, 95, 85, 83, 81, 79, 69, 67, 55, 43, 41, 39. Anal. calc. for $C_{11}H_{19}IO_4S$: C 35.30, H 5.12, S 8.57; found: C 35.58, H 5.11, S 8.28.

Reactivity of **32** *towards WPH. 6-Chloro-2,2,5,5-tetramethyl-3-oxocyclohexyl Methanesulfonate* (**32′$_{Cl}$**). *GP 1*, **32′$_{Cl}$** (28.3 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4:1 (1 ml), 0.6 h at 70°. CC (pentane/Et_2O 40:60): to furnish 17.5 mg (71%) of **4$_{OMs}$**. White solid. Spectral properties were identical with those already reported.

Compound **32′$_{Br}$**. *GP 1*, **32′$_{Br}$** (32.7 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4:1 (1 ml), 0.6 h at 70°. CC (pentane/Et_2O 40:60): 16.0 mg (65%) of **4$_{OMs}$**. White solid. Spectral properties were identical with those already reported.

Compound **32′$_{I}$**. *GP 1*, **32′$_{I}$** (37.4 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4:1 (1 ml), 0.5 h at 70°. CC (pentane/Et_2O 40:60): 15.7 mg (64%) of **4$_{OMs}$**. White solid. Spectral properties were identical with those already reported.

6-Chloro-2,2,5,5-tetramethyl-4-oxocyclohexyl Methanesulfonate (**32″$_{Cl}$**) *at r.t. GP 1*, **32″$_{Cl}$** (28.3 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4:1 (1 ml), 1 h at r.t. CC (pentane/Et_2O 95:5): 14.2 mg (76%) of **4$_{Cl}$**. Colorless liquid. Spectral properties were identical with those already reported.

Compound **32″$_{Cl}$** *at 70°. GP 1*, **32″$_{Cl}$** (28.3 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4:1 (1 ml), 6 h at 70°. CC (pentane/Et_2O 50:50): 10.7 mg (63%) of **4$_{Cl}$**/**2$_{cis}$** 10:90. Spectral properties of **4$_{Cl}$** were identical with those already reported, and spectral properties of **2$_{cis}$** were identical with those described in [2d].

Compound **32″$_{Br}$** *at r.t. GP 1*, **32″$_{Br}$** (32.7 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O (4:1, 1 ml), 8 h at r.t. CC (pentane/Et_2O 50:50): 11.4 mg (68%) of **2$_{cis}$**/*4,4-dimethyl-5-(2-methylprop-1-en-1-yl)oxolan-2(3*H*)-one* (**10**) 10:90. Spectral properties of **2$_{cis}$** were identical with those described in [2d].

Data of **10**. Colorless liquid. IR (film): 2967, 2932, 2874, 1761, 1751, 1467, 1456, 1419, 1321, 1287, 1254, 1235, 1198, 1155, 1021, 993, 972, 928. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.22 (*dt*, *J* = 9.0, 1.0, 1 H); 4.82 (*d*, *J* = 9.0, 1 H); 2.43 (*d*, *J* = 17.2, 1 H); 2.35 (*d*, *J* = 17.2, 1 H); 1.81 (*d*, *J* = 1.0, 3 H); 1.73 (*d*, *J* = 1.0, 3 H); 1.13

(*s*, 3 H); 1.02 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 176.5; 145.1; 118.3; 85.3; 44.5; 40.6; 26.1; 25.1; 21.8; 18.4. EI-MS: 168, 153, 123, 109, 85, 83, 81, 69, 56, 41, 32, 28; HR-MS: 168.1149 ($C_{10}H_{16}O_2^+$; calc. 168.1150).

Compound $\mathbf{32''_{Br}}$ *at 70°. GP 1*, $\mathbf{32''_{Br}}$ (32.7 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4 : 1 (1 ml), 1 h at 70°. CC (pentane/Et_2O 50 : 50): 13.3 mg (79%) of $\mathbf{2}_{cis}$/**10** 33 : 67. Spectral properties of **10** were identical with those already reported, and spectral properties of $\mathbf{2}_{cis}$ were identical with those described in [2d].

Compound $\mathbf{32''_I}$ *at r.t. GP 1*, $\mathbf{32''_I}$ (37.4 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4 : 1 (1 ml), 3 h at r.t. CC (pentane/Et_2O 50 : 50): 11.9 mg (71%) of $\mathbf{2}_{cis}$/**10** 5 : 95. Spectral properties of **10** were identical with those already reported and spectral properties of $\mathbf{2}_{cis}$ were identical with those described in [2d].

Compound $\mathbf{32''_I}$ *at 70°. GP 1*, $\mathbf{32''_I}$ (37.4 mg, 0.1 mmol), KOH (33.6 mg, 0.6 mmol), DMSO/H_2O 4 : 1 (1 ml), 1 h at 70°. CC (pentane/Et_2O 50 : 50): 12.3 mg (73%) of $\mathbf{2}_{cis}$/**10** 10 : 90. Spectral properties of **10** were identical with those already reported, and spectral properties of $\mathbf{2}_{cis}$ were identical with those described in [2d].

Reactivity of **32** *towards APH. Compound* $\mathbf{32''_{Cl}}$ *in THF. GP 2*, $\mathbf{32''_{Cl}}$ (28.3 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry THF (1.2 ml), 1.5 h at r.t. CC (pentane/Et_2O 50 : 50): 15.6 mg (90%) of $\mathbf{4}_{Cl}$/$\mathbf{2}_{cis}$ 20 : 80. Spectral properties of $\mathbf{4}_{Cl}$ were identical with those already reported, and spectral properties of $\mathbf{2}_{cis}$ were identical with those described in [2d].

Compound $\mathbf{32''_{Br}}$ *in THF. GP 2*, $\mathbf{32''_{Br}}$ (32.7 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry THF (1.2 ml), 0.6 h at r.t. CC (pentane/Et_2O 70 : 30): 15.0 mg (89%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{32''_I}$ *in THF. GP 2*, $\mathbf{32''_I}$ (37.4 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry THF (1.2 ml), 1 h at r.t. CC (pentane/Et_2O 70 : 30): 15.6 mg (93%) of $\mathbf{2}_{cis}$/**10** 96 : 4. Spectral properties of **10** were identical with those already reported and spectral properties of $\mathbf{2}_{cis}$ were identical with those described in [2d].

Compound $\mathbf{32''_{Cl}}$ *in DMSO. GP 3*, $\mathbf{32''_{Cl}}$ (28.3 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry DMSO (1 ml), 2 h at r.t. CC (pentane/Et_2O 50 : 50): 13.2 mg (75%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{32''_{Br}}$ *in DMSO. GP 3*, $\mathbf{32''_{Br}}$ (32.7 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry DMSO (1 ml), 2 h at r.t. CC (pentane/Et_2O 50 : 50): 13.6 mg (81%) of $\mathbf{2}_{cis}$/trans-*chrysanthemic acid* ($\mathbf{2}_{trans}$)/**10** 78 : 16 : 6. Spectral properties of **10** were identical with those already reported, and spectral properties of $\mathbf{2}_{cis}$ were identical with those described in [2d].

Data of $\mathbf{2}_{trans}$. Colorless liquid. IR (film): 2954, 2928, 2676, 1688, 1446, 1379, 1349, 1319, 1290, 1245, 1218, 1184, 1115, 1062, 952, 857, 703. ^{1}H-NMR (400 MHz, $CDCl_3$): 11.42 (br., 1 H); 4.90 (*dt*, *J* = 7.6, 1.2, 1 H); 2.10 (*dd*, *J* = 7.6, 5.2, 1 H); 1.72 (*s*, 3 H); 1.70 (*d*, *J* = 1.2, 3 H); 1.38 (*d*, *J* = 5.2, 1 H); 1.30 (*s*, 3 H); 1.15 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 179.2; 135.9; 120.8; 34.5; 33.5; 29.8; 25.5; 22.2; 20.4; 18.4. EI-MS: 168, 153, 125, 123, 111, 107.

Compound $\mathbf{32''_I}$ *in DMSO. GP 3*, $\mathbf{32''_I}$ (37.4 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry DMSO (1 ml), 1.5 h at r.t. CC (pentane/Et_2O 50 : 50): 6.9 mg (41%) of $\mathbf{2}_{cis}$/$\mathbf{2}_{trans}$/**10** 26 : 62 : 12. Spectral properties of $\mathbf{2}_{trans}$ and **10** were identical with those already reported and spectral properties of $\mathbf{2}_{cis}$ were identical with those described in [2d].

Compound $\mathbf{32'_{Cl}}$ *in THF. GP 2*, $\mathbf{32'_{Cl}}$ (28.3 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry THF (1.2 ml), 1.5 h at r.t. CC (pentane/Et_2O 70 : 30): 6.4 mg (38%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{32'_{Br}}$ *in THF. GP 2*, $\mathbf{32'_{Br}}$ (32.7 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry THF (1.2 ml), 1.6 h at r.t. CC (pentane/Et_2O 70 : 30): 8.1 mg (48%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{32'_I}$ *in THF. GP 2*, $\mathbf{32'_I}$ (374 mg, 1 mmol), ^{t}BuOK (850 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry THF (12 ml), 2 h at r.t. CC (pentane/Et_2O 70 : 30): 17.0 mg (10%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound $\mathbf{32'_{Cl}}$ *in DMSO. GP 3*, $\mathbf{32'_{Cl}}$ (28.3 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry DMSO (1 ml), 2.5 h at r.t. CC (pentane/Et_2O 60 : 40): 11.3 mg (67%) of $\mathbf{2}_{cis}$. White solid. Spectral properties were identical with those described in [2d].

Compound **32′$_{Br}$** *in DMSO. GP 3*, **32′$_{Br}$** (32.7 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry DMSO (1 ml), 0.75 h at r.t. CC (pentane/Et_2O 60:40): 13.4 mg (80%) of **2$_{cis}$**. White solid. Spectral properties were identical with those described in [2d].

Compound **32′$_I$** *in DMSO. GP 3*, **32′$_I$** (37.4 mg, 0.1 mmol), ^{t}BuOK (85 mg, 0.76 mmol), H_2O (4.2 mg, 0.23 mmol), dry DMSO (1 ml), 2 h at r.t. CC (pentane/Et_2O 60:40): 5.0 mg (30%) of **2$_{cis}$**. White solid. Spectral properties were identical with those described in [2d].

Mixture of **32″$_{Br}$/32′$_{Br}$**. *GP 9*, **21′$_{Br}$/21′$_{Br}$** (57:43, 1.25 g, 5 mmol), dry CH_2Cl_2 (30 ml), Et_3N (1.01 g, 10 mmol), DMAP (60 mg, 0.5 mmol), MsCl (1.15 g, 10 mmol), 2 h at $-10°$ and 4 h at r.t. CC (pentane/Et_2O 90:10 to 50:50): 1.34 g (82%) of **32″$_{Br}$/32′$_{Br}$** 57:43. Spectral properties were identical with those already reported.

Compound **2$_{cis}$** *from* **32″$_{Br}$/32′$_{Br}$**. *GP 2*, **32″$_{Br}$/32′$_{Br}$** (57:43, 327 mg, 1 mmol), ^{t}BuOK (851 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry THF (12 ml), 2 h at r.t. CC (pentane/Et_2O 80:20): 118 mg (70%) of **2$_{cis}$**. White solid. Spectral properties were identical with those described in [2d].

*(1*S*)-Acetoxy-2,2,5,5-tetramethylcyclohex-3-ene* (=*(1*S*)-2,2,5,5-Tetramethylcyclohex-3-en-1-yl Acetate*; (*S*)-**42**). In a 100-ml round-bottom two-neck flask under Ar, pyridine (3.55 g, 45 mmol) and DMAP (182 mg, 1.5 mmol) were added to a stirred soln. of (*S*)-**23** (2.31 g, 15 mmol) in dry CH_2Cl_2 (35 ml). The soln. was cooled to 0° before adding dropwise a soln. of freshly dist. Ac_2O (6.12 g, 60 mmol) in dry CH_2Cl_2 (15 ml). After 1.5 h at 0°, the reaction was quenched with aq. HCl (10%, 10 ml), and the mixture was extracted with Et_2O (4 × 20 ml). The combined org. extracts were washed with aq. HCl (10%, 10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 95:05) to furnish 2.80 g (95%) of (*S*)-**42**. Colorless liquid. $[\alpha]_D^{20} = +13.9$ (*c* 1.0, $CHCl_3$). IR (film): 3008, 2962, 2870, 1737, 1469, 1368, 1241, 1175, 1121, 1079, 1031, 958, 888, 764. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.26 (*d*, *J* = 10.1, 1 H); 5.23 (*d*, *J* = 9.6, 1 H); 4.91 (*dd*, *J* = 10.1, 5.4, 1 H); 2.07 (*s*, 3 H); 1.61 (*m*, 2 H); 1.07 (*s*, 3 H); 1.01 (*s*, 3 H); 0.98 (*s*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.0; 134.9; 133.3; 75.9; 38.4; 35.7; 34.3; 30.8; 29.3; 27.6; 22.7; 21.3. EI-MS: 196, 136, 121, 110, 95.

*Addition of HBrO to (*S*)-***42***. In ^{t}BuOH* (*General Procedure 10* (*GP 10*)). In a 25-ml round-bottom two-neck flask protected from light and under Ar, H_2O (10 ml) and NBS (98 mg, 0.55 mmol) were added to a soln. of (*S*)-**42** (98 mg, 0.5 mmol) in ^{t}BuOH (5 ml). After 0.75 h at r.t., H_2O was added (10 ml), and the mixture was extracted with Et_2O (4 × 15 ml). The combined org. extracts were washed with H_2O (5 ml) and brine (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduce pressure. The crude product was purified by CC (pentane/Et_2O 70:30) to furnish 83 mg (57%) of a mixture *(1*S*)-1-acetoxy-4-bromo-3-hydroxy-2,2,5,5-tetramethylcyclohexane* (=*(1*S*)-4-bromo-3-hydroxy-2,2,5,5-tetramethylcyclohexyl acetate*; **43′**)/*(1*S*)-1-acetoxy-3-bromo-4-hydroxy-2,2,5,5-tetramethylcyclohexane* (=*(1*S*)-3-bromo-4-hydroxy-2,2,5,5-tetramethylcyclohexyl acetate*; **43″**). White solid. Ratio (*R*,*R*)-**43′**/(*R*,*R*)-**43″**/((*S*,*S*)-**43′** + (*S*,*S*)-**43″**) 30:54:16. The main by-product was *(1S)-1-acetoxy-3,4-dibromo-2,2,5,5-tetramethylcyclohexane* (=*(1*S*)-3,4-dibromo-2,2,5,5-tetramethylcyclohexyl acetate*; **39**; 6%). IR (KBr; mixture): 3504, 2975, 2937, 2891, 1712, 1469, 1380, 1253, 1165, 1129, 1086, 1020, 992, 971, 921, 874, 809, 761, 717, 679, 633, 607, 521. ^{1}H-NMR (400 MHz, $CDCl_3$): (*R*,*R*)-**43′**: 4.72 (*t*, *J* = 4.4, 1 H); 4.15 (*d*, *J* = 15.7, 1 H); 3.84 (*d*, *J* = 15.7, 1 H); 2.05 (*s*, 3 H); 1.84–1.50 (*m*, 3 × 1 H); 1.20–0.9 (4*s*, 4 × 3 H); (*R*,*R*)-**43″**: 4.84 (*t*, *J* = 4.4, 1 H); 4.40 (*d*, *J* = 16.1, 1 H); 3.59 (*d*, *J* = 16.1, 1 H); 2.04 (*s*, 3 H); 1.84–1.50 (*m*, 3 H); 1.20–0.9 (4*s*, 4 × 3 H); (*S*,*S*)-**43′** + (*S*,*S*)-**43″**: 4.84–4.74 (*m*, 2 × 1 H); 4.00 (*d*, *J* = 15.7, 2 × 1 H); 3.48 (*d*, *J* = 15.7, 2 × 1 H); 2.05 (s, 2 × 3 H); 1.84–1.50 (*m*, 6 H); 1.20–0.9 (8 × 3 H).

In DMSO. GP 10, (*S*)-**42** (196 mg, 1 mmol), DMSO (2.2 ml), H_2O (36 mg, 2 mmol), NBS (356 mg, 2 mmol), 7 d at r.t. CC (pentane/Et_2O 90:10): 38 mg (26%) of **43′**/**43″**. White solid. Ratio (*R*,*R*)-**43′**/(*R*,*R*)-**43″**/((*S*,*S*)-**43′** + (*S*,*S*)-**43″**) 35:54:11. Starting (*S*)-**42** was also recovered (34%), and the main by-product was **39** (27%). Spectral properties were identical with those already reported.

In DME. GP 10, (*S*)-**42** (196 mg, 1 mmol), DME (2 ml), H_2O (0.5 ml), NBS (712 mg, 4 mmol), 7 d at r.t. CC (pentane/Et_2O 80:20): 50 mg (34%) of **43′**/**43″**. White solid. Ratio (*R*,*R*)-**43′**/(*R*,*R*)-**43″**/((*S*,*S*)-**43′** + (*S*,*S*)-**43″**) 32:50:18. Starting (*S*)-**42** was also recovered (24%), and the main by-product was **39** (19%). Spectral properties were identical with those already reported.

In Acetone: GP 10, (*S*)-**42** (2.74 g, 14 mmol), acetone (14 ml), H_2O (56 ml), NBS (3.74 g, 21 mmol), 7 d at r.t. CC (pentane/Et_2O 70:30): 3.57 g (86%) of **43′**/**43″**. White solid. Ratio (*R*,*R*)-**43′**/(*R*,*R*)-**43″**/(*S*,*S*)-**43′**/(*S*,*S*)-**43″** 32:55:3:10. Spectral properties were identical with those already reported.

*(1*S*,3*R*,4*R*)-1-Acetoxy-4-bromo-3-(mesyloxy)-2,2,5,5-tetramethylcyclohexane* (=*(1*S*,3*R*,4*R*)-4-Bromo-2,2,5,5-tetramethyl-3-[(methylsulfonyl)oxy]cyclohexyl Acetate*; (*R*,*R*)-**45′**) *and (1*S*,3*R*,4*R*)-1-Acetoxy-3-bromo-4-mesyloxy-2,2,5,5-tetramethylcyclohexane* (=*(1*S*,3*R*,4*R*)-3-Bromo-2,2,5,5-tetramethyl-4-[(methylsulfonyl)oxy]cyclohexyl Acetate*; (*R*,*R*)-**45″**). In a 100-ml round-bottom two-neck flask under Ar, Et_3N (2.32 g, 23 mmol) and DMAP (278 mg, 2.3 mmol) were added to a stirred soln. of *(1*S*,3*R*,4*R*)-1-acetoxy-4-bromo-3-hydroxy-2,2,5,5-tetramethylcyclohexane* (=*(1*S*,3*R*,4*R*)-4-bromo-3-hydroxy-2,2,5,5-tetramethylcyclohexyl acetate*; (*R*,*R*)-**43′**)/*(1*S*,3*R*,4*R*)-1-acetoxy-3-bromo-4-hydroxy-2,2,5,5-tetramethylcyclohexane* (=*(1*S*,3*R*,4*R*)-3-bromo-4-hydroxy-2,2,5,5-tetramethylcyclohexyl acetate*; (*R*,*R*)-**43″**) (ratio (*R*,*R*)-**43′**/(*R*,*R*)-**43″**/(*S*,*S*)-**43′**/(*S*,*S*)-**43″** 32:55:3:10; 3.38 g, 11.5 mmol) in dry CH_2Cl_2 (40 ml). The soln. was cooled to $-10°$ before adding dropwise a soln. MsCl (2.64 g, 23 mmol) in dry CH_2Cl_2 (10 ml). After 0.5 h at $-10°$ and 55 h at r.t., H_2O (30 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined org. extracts were washed with aq. HCl (10%, 10 ml), sat. aq. $NaHCO_3$ (10 ml) and brine (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 80:20): 3.37 g (79%) of a mixture *(1*S*,3*R*,4*R*)-1-acetoxy-4-bromo-3-(mesyloxy)-2,2,5,5-tetramethylcyclohexane* ((*R*,*R*)-**45′**)/*(1*S*,3*R*,4*R*)-1-acetoxy-3-bromo-4-mesyloxy-2,2,5,5-tetramethylcyclohexane* ((*R*,*R*)-**45″**). White solid. Ratio (*R*,*R*)-**45′**/(*R*,*R*)-**45″**/((*S*,*S*)-**45′** + (*S*,*S*)-**45″**) 33:54:13. IR (KBr; mixture): 2978, 2939, 1735, 1466, 1375, 1347, 1240, 1168, 1123, 1098, 1024, 957, 897, 826, 777, 739, 716, 668, 632, 563, 540, 524, 505. ^{1}H-NMR (400 MHz, $CDCl_3$): (*R*,*R*)-**45′**: 5.02 (*d*, *J* = 11.4, 1 H); 4.81 (*t*, *J* = 2.7, 1 H); 4.17 (*d*, *J* = 11.4, 1 H); 3.26 (*s*, 3 H); 2.07 (*s*, 3 H); 1.90–1.50 (*m*, 3 × 1 H); 1.25–1.00 (4*s*, 4 × 3 H); (*R*,*R*)-**45″**: 4.85 (*t*, *J* = 2.8, 1 H); 4.77 (*d*, *J* = 11.0, 1 H); 3.42 (*d*, *J* = 11.0, 1 H); 3.24 (*s*, 3 H); 2.06 (*s*, 3 H); 1.90–1.50 (*m*, 3 × 1 H); 1.25–1.00 (4*s*, 4 × 3 H); (*S*,*S*)-**45′** + (*S*,*S*)-**45″**: 4.86–4.78 (*m*, 2 × 1 H); 4.69 (*d*, *J* = 11.0, 2 × 1 H); 4.07 (*d*, *J* = 11.0, 2 × 1 H); 3.26 (*s*, 2 × 3 H); 2.06 (*s*, 2 × 3 H); 1.90–1.50 (*m*, 6 H); 1.20–1.00 (8 × 3 H).

*(1*R*,6*R*)-6-Bromo-2,2,5,5-tetramethyl-3-oxocyclohexyl Methanesulfonate* ((*R*,*R*)-**32′$_{Br}$**) *and (1*R*,6*R*)-6-Bromo-2,2,5,5-tetramethyl-4-oxocyclohexyl methanesulfonate* ((*R*,*R*)-**32″$_{Br}$**). In a 50-ml round-bottom one neck flask under Ar, at 0°, K_2CO_3 (5.52 g, 40 mmol) was added, to a stirred soln. of a mixture (*R*,*R*)-**45′**/(*R*,*R*)-**45″** ((*R*,*R*)-**45′**/(*R*,*R*)-**45″**/((*S*,*S*)-**45′** + (*S*,*S*)-**45″**) 33:54:13, 2.97 g, 8 mmol) in dry THF/dry MeOH 1:1 (20 ml). After 1.25 h at 0° and 4 h at r.t., H_2O was added (20 ml), and the mixture was extracted with CH_2Cl_2 (5 × 20 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was diluted with dry CH_2Cl_2 (30 ml), and PDC (3.46 g, 9.2 mmol) and powdered molecular sieves (4 Å; 3.46 g) mixed together were added at 0°. After 2 h at 0° and 2 h at r.t., the mixture was filtered through *Celite*, the *Celite* cake was washed with CH_2Cl_2 (3 × 30 ml), and the filtrate was concentrated under reduce pressure. The crude product was purified by CC (Et_2O) to furnish 2.21 g (83%) of (*R*,*R*)-**32′$_{Br}$**/(*R*,*R*)-**32″$_{Br}$** 36:64. Spectral properties were identical with those already reported.

*(1*R*,3*S*)*-cis-*Chrysanthemic Acid* ((1*R*)-**2$_{cis}$**) *from (3*R*,4*R*)-4-Bromo-3-(mesyloxy)-2,2,5,5-tetramethylcyclohexanone* ((*R*,*R*)-**32′$_{Br}$**)/*(3*R*,4*R*)-3-Bromo-4-mesyloxy-2,2,5,5-tetramethylcyclohexanone* ((*R*,*R*)-**32″$_{Br}$**). *GP 2*, (*R*,*R*)-**32′$_{Br}$**/(*R*,*R*)-**32″$_{Br}$** 36:64 (327 mg, 1 mmol), ^{t}BuOK (851 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry THF (12 ml), 2.5 h at r.t. CC (pentane/Et_2O 80:20): 108 mg (64%) of (1*R*)-**2$_{cis}$**. White solid. $[\alpha]_D^{20} = +62.9$ (*c* = 1.00, $CHCl_3$), ee 76%; (lit. [2]: $[\alpha]_D^{20} = +83.0$ (*c* = 1.75, $CHCl_3$)). Spectral properties were identical with those described in [2d].

*(1*R*,4*S*,5*S*)*-4-exo-*(Mesyloxy)-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* (=*(1*S*,2*S*,5*R*)-3,3,6,6-Tetramethyl-4-oxobicyclo[3.1.0]hex-2-yl Methanesulfonate*; (*S*)-**4$_{OMs}$**) *and (1*R*,4*S*,5*S*)*-4-exo-*Bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* (=*(1*R*,4*S*,5*S*)-4-Bromo-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one*; (*S*)-**4$_{Br}$**) *from (*R,R*)-**32′$_{Br}$**/(*R,R*)-**32″$_{Br}$**.* In a 100-ml round-bottom two-neck flask under Ar, at 0°, a soln. of KHMDS (0.5M in toluene, 8.3 ml, 4.1 mmol) was added dropwise, to a stirred soln. of (*R*,*R*)-**32′$_{Br}$**/(*R*,*R*)-**32″$_{Br}$** 36:64, (1.12 g, 3.4 mmol) in dry THF (50 ml). After 0.5 h at 0°, sat. aq. NH_4Cl (10 ml) and H_2O (5 ml) were added, and the mixture was extracted with Et_2O (4 × 20 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 95:5 to 60:40) to furnish 400 mg (80%) of (*S*)-**4$_{Br}$** ($[\alpha]_D^{23} = +12.9$ (*c* = 1.00, $CHCl_3$)) and 230 mg (77%) of (*S*)-**4$_{OMs}$** ($[\alpha]_D^{23} = +44.6$ (*c* = 1.11, $CHCl_3$)). Spectral properties were identical with those already reported.

*(1*R,*3*S*)*-cis-*Chrysanthemic Acid* ((1*R*)-**2**$_{cis}$) *from* (S)-**4**$_{OMs}$. *GP 3*, (*S*)-**4**$_{OMs}$ (123 mg, 0.5 mmol), *t*BuOK (426 mg, 3.8 mmol), H_2O (21 mg, 1.2 mmol), dry DMSO (3 ml), 0.4 h at r.t. CC (pentane/Et_2O 70:30): 65 mg (77%) of (1*R*)-**2**$_{cis}$. White solid. $[\alpha]_D^{20} = +68.0$ ($c = 1.00$, $CHCl_3$), ee 82%; lit. [2] $[\alpha]_D^{20} = +83.0$ ($c = 1.75$, $CHCl_3$). Spectral properties were identical with those described in [2d].

*(1*R,*3*S*)*-cis-*Chrysanthemic Acid* ((1*R*)-**2**$_{cis}$) *from* (S)-**4**$_{Br}$. *GP 2*, (S)-**4**$_{Br}$ (116 mg, 0.5 mmol), *t*BuOK (426 mg, 3.8 mmol), H_2O (21 mg, 1.2 mmol), dry THF (6 ml), 0.3 h at r.t. CC (pentane/Et_2O 70:30): 77 mg (92%) of (1*R*)-**2**$_{cis}$. White solid. $[\alpha]_D^{20} = +61.2$ (*c* 1.00, $CHCl_3$), ee = 74%; lit. [2] $[\alpha]_D^{20} = +83.0$ (*c* 1.75, $CHCl_3$). Spectral properties were identical with those described in [2d].

*(1*S,*3*S,*6*R*)-2,2,5,5-Tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol* ((*S*,*R*)-**24**). In a 100-ml round-bottom two-neck flask equipped with a reflux condenser under Ar, $Mo(CO)_6$ (62 mg, 0.24 mmol) was added to a stirred soln. of (*S*)-**23** (2.43 g, 15.7 mmol) in dry C_6H_6 (60 ml), and the mixture was heated to reflux before adding dropwise a soln. *t*BuOOH (70% in H_2O, 3.03 g, 23.6 mmol) diluted with dry C_6H_6 (15 ml) over a period of 0.5 h. The reaction was monitored by GC of aliquots. After 2 h at reflux (no more starting material), the mixture was cooled, aq. sat. $NaHCO_3$ (15 ml) was added, and the mixture was extracted with pentane (4 × 25 ml). The combined org. extracts were washed with aq. sat. $Na_2S_2O_3$ (10 ml) and aq. sat. $NaHCO_3$ (10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 90:10 to 70:30) to furnish 2.32 g (88%) of a mixture (*S*,*R*)-**24**/*(1*R,*3*S,*6*S*)*-*trans-2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol* 98:2. Spectral properties were identical with those already reported.

*(1*S,*6*R*)-2,2,5,5-Tetramethyl-7-oxabicyclo[4.1.0]heptan-3-one* ((*S*,*R*)-**11**). In a 50-ml round-bottom neck flask under Ar, at 0°, PDC (2.82 g, 7.5 mmol) and powdered molecular sieves 4 Å (2.82 g) mixed together were added, to a stirred soln. of a mixture (*S*,*R*)-**24**/*(1*R,*3*S,*6*S*)-trans-2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptan-3-ol* (98:2, 850 mg, 5 mmol) in CH_2Cl_2 (20 ml) After 2 h at 0° and overnight at r.t., the mixture was filtered through *Celite*, the *Celite* cake was washed with CH_2Cl_2 (3 × 10 ml), and the filtrate was concentrated under reduce pressure. The crude product was purified by CC (pentane/Et_2O 80:20) to furnish 725 mg (86%) of (*S*,*R*)-**11**. $[\alpha]_D^{23} = -151.3$ ($c = 1.15$, $CHCl_3$). Spectral properties were identical with those already reported.

*(3*R,*4*R*)-3-Bromo-4-hydroxy-2,2,5,5-tetramethylcyclohexanone* ((*R*,*R*)-**21**$''_{Br}$) *and (3*S,*4*S*)-4-Bromo-3-hydroxy-2,2,5,5-tetramethylcyclohexanone* ((*S*,*S*)-**21**$'_{Br}$). *GP 4*, (*S*,*R*)-**11** (722 mg, 4.3 mmol), dry CH_2Cl_2 (25 ml), $TiBr_4$ (790 mg, 2.2 mmol), 2 h at r.t. to furnish 1.03 g (96%) of a mixture (*R*,*R*)-**21**$''_{Br}$/(*S*,*S*)-**21**$'_{Br}$ 45:55. White solid. Spectral properties were identical with those already reported.

*(3*R,*4*R*)-3-Bromo-4-mesyloxy-2,2,5,5-tetramethylcyclohexanone* (=*(1*R,*6*R*)-6-Bromo-2,2,5,5-tetramethyl-4-oxocyclohexyl Methanesulfonate*; (*R*,*R*)-**32**$''_{Br}$) *and (3*R,*4*R*)-4-bromo-3-mesyloxy-2,2,5,5-tetramethylcyclohexanone* (=*(1*R,*6*R*)-6-Bromo-2,2,5,5-tetramethyl-3-oxocyclohexyl Methanesulfonate*; (*R*,*R*)-**32**$'_{Br}$). *GP 9*, (*R*,*R*)-**21**$''_{Br}$/(*S*,*S*)-**21**$'_{Br}$ (45:55, 1.02 g, 4.1 mmol), dry CH_2Cl_2 (25 ml), Et_3N (828 mg, 8.2 mmol), DMAP (50 mg, 0.4 mmol), MsCl (940 mg, 8.2 mmol), 2 h at −10° and 16 h at r.t. CC (pentane/Et_2O 90:10 to 50:50): 1.10 g (82%) of (*R*,*R*)-**32**$''_{Br}$/(*S*,*S*)-**32**$'_{Br}$ 45:55. Spectral properties were identical with those already reported.

*(1*S,*3*R*)*-cis-*Chrysanthemic Acid* ((1*S*)-**2**$_{cis}$) *from* (R,R)-**32**$''_{Br}$/(R,R)-**32**$'_{Br}$. *GP 2*, (*R*,*R*)-**32**$''_{Br}$/(*S*,*S*)-**32**$'_{Br}$ (45:55 (327 mg, 1 mmol), *t*BuOK (851 mg, 7.6 mmol), H_2O (42 mg, 2.3 mmol), dry THF (12 ml), 2 h at r.t. CC (pentane/Et_2O 80:20): 118 mg (70%) of (1*S*)-**2**$_{cis}$. White solid. $[\alpha]_D^{20} = -7.5$ (*c* 1.00, $CHCl_3$), ee = 9%; lit. [2] $[\alpha]_D^{20} = +83.0$ ($c = 1.75$, $CHCl_3$). Spectral properties were identical with those described in [2d].

Compounds (*S*)-**4**$_{Br}$ *and* (R)-**4**$_{OMs}$ *from* (R,R)-**32**$''_{Br}$/(S,S)-**32**$'_{Br}$. In a 100-ml round-bottom two-neck flask under Ar, at 0°, a soln. of KHMDS (0.5 M in toluene, 8.3 ml, 4.1 mmol) was added dropwise, to a stirred soln. of (*R*,*R*)-**32**$''_{Br}$/(*S*,*S*)-**32**$'_{Br}$ 45:55 (1.01 g, 3.4 mmol) in dry THF (40 ml). After 1 h at 0°, sat. aq. NH_4Cl (10 ml) and H_2O (5 ml) were added, and the mixture was extracted with Et_2O (4 × 25 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (pentane/Et_2O 95:5 to 70:30) to furnish 290 mg (87%) of (*S*)-**4**$_{Br}$ ($[\alpha]_D^{23} = +16.3$ (*c* 1.00, $CHCl_3$)) and 377 mg (80%) of (*R*)-**4**$_{OMs}$ ($[\alpha]_D^{23} = +55.1$ ($c = 1.11$, $CHCl_3$)). Spectral properties were identical with those already reported.

*(1*R,*3*S*)*-cis-*Chrysanthemic Acid* ((1*R*)-**2**$_{cis}$) *from* (S)-**4**$_{Br}$. *GP 2*, (*S*)-**4**$_{Br}$ (116 mg, 0.5 mmol), *t*BuOK (426 mg, 3.8 mmol), H_2O (21 mg, 1.2 mmol), dry THF (6 ml), 0.6 h at r.t. CC (pentane/Et_2O 70:30):

78 mg (93%) of (1*R*)-**2**$_{cis}$. White solid. $[\alpha]_D^{20} = +77.1$ ($c = 1.00$, $CHCl_3$), ee 93%; lit. [2] $[\alpha]_D^{20} = +83.0$ ($c = 1.75$, $CHCl_3$). Spectral properties were identical with those described in [2d].

*(1*S*,3*R*)*-cis-*Chrysanthemic Acid* ((1*S*)-**2**$_{cis}$) *from (*R*)-***4***$_{OMs}$. *GP 3*, (*R*)-**4**$_{OMs}$ (123 mg, 0.5 mmol), ^{t}BuOK (426 mg, 3.8 mmol), H_2O (21 mg, 1.2 mmol), dry DMSO (3 ml), 0.6 h at r.t. CC (pentane/Et_2O 70:30): 75 mg (89%) of (1*S*)-**2**$_{cis}$. White solid. $[\alpha]_D^{20} = -77.5$ ($c = 1.00$, $CHCl_3$), ee = 94%; lit. [2] $[\alpha]_D^{20} = +83.0$ ($c = 1.75$, $CHCl_3$). Spectral properties were identical with those described in [2d].

*Compounds (*R,R*)-***21***$''_{Cl}$*/(*S,S*)-***21***$'_{Cl}$. *GP 4*, (*S*,*R*)-**11** (722 mg, 4.3 mmol), dry CH_2Cl_2 (43 ml), $BeCl_2$ (1.72 g, 21.5 mmol), 100 h at r.t. CC (pentane/Et_2O 50:50): 756 mg (86%) of (*R*,*R*)-**21**$''_{Cl}$/(*S*,*S*)-**21**$'_{Cl}$ 20:80. White solid. Spectral properties were identical with those already reported.

*Compounds (*S,R*)-***11*** and (1*S*,4*R*,5*R*)-4-*exo-*Hydroxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* ((*R*)-**12**). In a 100-ml round-bottom two-neck flask under Ar, at $-25°$, a soln. of a mixture (*R*,*R*)-**21**$''_{Cl}$/(*S*,*S*)-**21**$'_{Cl}$ 20:80, (695 mg, 3.4 mmol) in dry THF (15 ml) was added to a soln. of LiTMP (0.3M in THF, 22.7 ml, 6.8 mmol). After 1 h at $-25°$, a soln. of ^{t}BuOK (762 mg, 6.8 mmol) in dry THF (20 ml) was added dropwise. After 0.5 h at $-25°$, the mixture was hydrolyzed with sat. NH_4Cl in MeOH (15 ml) and H_2O (15 ml). The mixture was extracted with Et_2O (4 × 40 ml), the combined org. extracts were washed with aq. HCl (10%, 10 ml) and brine (10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to furnish a crude mixture (*S*,*R*)-**11**/(*R*)-**12** 20:80. CC (pentane/Et_2O 80:20 to 30:70): 103 mg (19%) of (*S*,*R*)-**11** ($[\alpha]_D^{23} = -150.9$ ($c = 1.15$, $CHCl_3$), ee 94%) and 425 mg (74%) of (*R*)-**12** ($[\alpha]_D^{23} = -130.3$ ($c = 0.92$, $CHCl_3$), ee 94%). Spectral properties were identical with those already reported.

*(1*S*,4*R*,5*R*)-4-*exo-*Mesyloxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one* ((*R*)-**4**$_{OMs}$). In a 25-ml round-bottom two-neck flask under Ar, Et_3N (263 mg, 2.6 mmol) was added to a stirred soln. of (*R*)-**12** (287 mg, 1.7 mmol) in dry CH_2Cl_2 (10 ml). The soln. was cooled to $-10°$ before adding dropwise a soln. of MsCl (234 mg, 2.1 mmol) in dry CH_2Cl_2 (4 ml). After 2 h at $-10°$, the reaction was quenched with ice (5 ml), and the mixture extracted with Et_2O (3 × 20 ml). The combined org. extracts were washed with aq. HCl (10%, 5 ml) and aq. sat. $NaHCO_3$ (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by CC (CH_2Cl_2) to furnish 351 mg (84%) of (*R*)-**4**$_{OMs}$. White solid. $[\alpha]_D^{23} = -51.8$ ($c = 1.11$, $CHCl_3$), ee 94%). Spectral properties were identical with those already reported.

*(1*S*,3*R*)*-cis-*Chrysanthemic Acid* ((1*S*)-**2**$_{cis}$) *from (*R*)-***4***$_{OMs}$. *GP 3*, (*R*)-**4**$_{OMs}$ (197 mg, 0.8 mmol), ^{t}BuOK (681 mg, 6.1 mmol), H_2O (33 mg, 1.9 mmol), dry DMSO (3.5 ml), 1 h at r.t. CC (pentane/Et_2O 60:40): 121 mg (90%) of (1*S*)-**2**$_{cis}$. White solid. $[\alpha]_D^{20} = -78.1$ ($c = 1.00$, $CHCl_3$), ee 94%; lit. [2] $[\alpha]_D^{20} = +83.0$ ($c = 1.75$, $CHCl_3$). Spectral properties were identical with those described in [2d].

REFERENCES

[1] A. Krief, S. Jeanmart, A. Kremer, *Bioorg. Med. Chem.* **2009**, *17*, 2555; A. Krief, A. Froidbise, *Mini-Rev. Org. Chem.* **2005**, *2*, 299; K. Chamberlain, N. Matsuo, H. Kaneko, B. P. S. Khambay, in 'Chirality in Agrochemicals', Eds. N. Kurihara, J. Miyamoto, Wiley, New York, 1998, p. 9; A. Krief, in 'Stereocontrolled Organic Syntheses', Ed. B. M. Trost, Blackwell, Oxford, UK, 1994, p. 337; A. Krief, *Pestic. Sci.* **1994**, *41*, 237; G. M. R. Tombo, D. Belluš, *Angew. Chem., Int. Ed.* **1991**, *30*, 1193; K. Naumann, 'Synthetic Pyrethroid Insecticides: Chemistry and Patents', Springer-Verlag Berlin Heidelberg, 1990; Roussel-Uclaf, 'Deltamethrin: Monograph', Ed. J. L' Hoste, Roussel-Uclaf, Paris, 1982; J. Tessier, *Chem. Ind.* **1984**, 199; D. Arlt, M. Jautelat, R. Lantzsch, *Angew. Chem., Int. Ed.* **1981**, *20*, 703; L. Crombie, M. Elliott, 'Progress in the Chemistry of Natural Products', Ed. L. Zechmeister, Springer-Verlag, Vienna, 1961, Vol. 19, p. 120.

[2] a) A. Krief, H. Y. Gondal, A. Kremer, *Chem. Commun.* **2008**, 4753; b) A. Krief, A. Kremer, *Tetrahedron Lett.* **2010**, *51*, 1942; c) A. Krief, S. Jeanmart, A. Kremer, *Heterocycles* **2008**, *76*, 1075; d) A. Krief, S. Jeanmart, A. Kremer, *J. Org. Chem.* **2008**, *73*, 9795.

[3] A. Krief, G. Lorvelec, S. Jeanmart, *Tetrahedron Lett.* **2000**, *41*, 3871.

[4] a) A. Krief, A. Kremer, *Chem. Rev.* **2010**, *110*, 4772; b) G. Mehta, R. V. Venkateswaran, *Tetrahedron* **2000**, *56*, 1399; c) K. Prantz, J. Mulzer, *Chem. Rev.* **2010**, *110*, 3741.

[5] S. Jeanmart, Ph.D. Thesis, Facultés Universitaires Notre-Dame de la Paix, Namur, 2004.

[6] G. A. Swan, *J. Chem. Soc.* **1948**, 1408; P. G. Gassman, J. T. Lumb, F. V. Zalar, *J. Am. Chem. Soc.* **1967**, *89*, 946; P. G. Gassman, W. N. Schenk, *J. Org. Chem.* **1977**, *42*, 918.
[7] A. Krief, A. Kremer, *Tetrahedron Lett.* **2010**, *51*, 3045.
[8] A. Krief, A. Kremer, *Tetrahedron Lett.* **2010**, *51*, 4306.
[9] a) A. Krief, D. Surleraux, H. Frauenrath, *Tetrahedron Lett.* **1988**, *29*, 6157; b) A. Krief, D. Swinnen, *Tetrahedron Lett.* **1996**, *37*, 7123.
[10] A. Krief, A. Kremer, *Synlett* **2007**, 607.
[11] J. K. Crandall, R. D. Huntington, G. L. Brunner, *J. Org. Chem.* **1972**, *37*, 2911.
[12] M. W. Rathke, *J. Am. Chem. Soc.* **1970**, *92*, 3222.
[13] J. N. Denis, A. Krief, *Tetrahedron Lett.* **1981**, *22*, 1429; M. R. Detty, M. D. Seidler, *J. Org. Chem.* **1981**, *46*, 1283; H. Sakurai, K. Sasaki, A. Hosomi, *Tetrahedron Lett.* **1980**, *21*, 2329.
[14] M. W. Rathke, R. Kow, *J. Am. Chem. Soc.* **1972**, *94*, 6854; R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 582.
[15] D. B. Collum, *Acc. Chem. Res.* **1993**, *26*, 227.
[16] D. Terakado, T. Oriyama, *Org. Synth.* **2006**, *83*, 70.
[17] B. D. Brandes, E. N. Jacobsen, *J. Org. Chem.* **1994**, *59*, 4378; M. Chini, P. Crotti, L. A. Flippin, F. Macchia, *J. Org. Chem.* **1990**, *55*, 4265; Y. Naruse, T. Esaki, H. Yamamoto, *Tetrahedron* **1988**, *44*, 4747; G. D. Price, J. J. Pluth, J. V. Smith, J. M. Bennett, R. L. Patton, *J. Am. Chem. Soc.* **1982**, *104*, 5971.
[18] R. D. Dawe, T. F. Molinski, J. V. Turner, *Tetrahedron Lett.* **1984**, *25*, 2061.
[19] C. A. M. Afonoso, N. M. L. Vieira, W. B. Motherwell, *Synlett* **2000**, 382.
[20] M. Shimizu, A. Yoshida, T. Fujisawa, *Synlett* **1992**, 204.
[21] S. Halazy, F. Zutterman, A. Krief, *Tetrahedron Lett.* **1982**, *23*, 4385.
[22] K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc.* **1973**, *95*, 6136.
[23] E. Alvarez, M. T. Nunez, V. S. Martin, *J. Org. Chem.* **1990**, *55*, 3429.
[24] A. Kremer, B. Norberg, A. Krief, J. Wouters, *Acta Crystallogr.* **2012**, submitted.
[25] K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weedon, *J. Chem. Soc.* **1946**, 39.
[26] H. A. J. Carless, G. K. Fekarurhobo, *Tetrahedron Lett.* **1983**, *24*, 107.
[27] K. Takai, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1983**, 3791.
[28] G. Majetich, R. Hicks, G.-R. Sun, P. McGill, *J. Org. Chem.* **1998**, *63*, 2564.
[29] R. B. Dehnel, G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1* **1979**, 953; T. Itoh, K. Jitsukawa, K. Kaneda, S. Teranishi, *J. Am. Chem. Soc.* **1979**, *101*, 159.
[30] E. L. Eliel, N. L. Allinger, S. J. Angyal, G. A. Morisson, 'Conformational Analysis', Wiley, New York, 1965, p. 102; A. Fürst, P. A. Plattner, Abstract of Papers, 12th International Congress of Pure and Applied Chemistry, 1951, p. 409.
[31] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647.
[32] C. Kowalski, S. Creary, A. J. Rollin, M. C. Burke, *J. Org. Chem.* **1978**, *43*, 2602; M. T. Reetz, W. F. Maier, *Liebigs Ann. Chem.* **1980**, 1471.
[33] I. E. Markó, J.-C. Vanherck, A. Ates, B. Tinant, J.-P. Declercq, *Tetrahedron Lett.* **2003**, *44*, 3333.
[34] S. M. Behnam, S. E. Behnam, K. Ando, N. S. Green, K. N. Houk, *J. Org. Chem.* **2000**, *65*, 8970; E. J. Corey, R. A. Sneen, *J. Am. Chem. Soc.* **1956**, *78*, 6269.
[35] H. B. Bürgi, J. D. Dunitz, J.-M. Lehn, G. Wipff, *Tetrahedron* **1974**, *30*, 1563.
[36] P. S. Wharton, G. A. Hiegel, *J. Org. Chem.* **1965**, *30*, 3254; R. Zurflüh, E. N. Wall, J. B. Sidall, J. A. Edwards, *J. Am. Chem. Soc.* **1968**, *90*, 6224; C. H. Heathcock, R. A. Badger, *J. Org. Chem.* **1972**, *37*, 234.
[37] W. F. Erman, E. Wenkert, P. W. Jeffs, *J. Org. Chem.* **1969**, *34*, 2196.
[38] H. C. Brown, J. Chandrasekharan, P. V. Ramachandran, *J. Am. Chem. Soc.* **1988**, *110*, 1539.
[39] G. H. Alt, D. H. R. Barton, *J. Chem. Soc.* **1954**, 4284; J. Valls, E. Toromanoff, *Bull. Soc. Chim. Fr.* **1961**, 758.
[40] S. Elango, T.-H. Yan, *Tetrahedron* **2002**, *58*, 7335.
[41] R. P. Hanzlik, *Org. Synth.* **1977**, *56*, 112.
[42] D. R. Dalton, V. P. Dutta, D. G. Jones, *J. Am. Chem. Soc.* **1968**, *90*, 5498.
[43] E. J. Corey, J. Das, *Tetrahedron Lett.* **1982**, *23*, 4217.

[44] Y. Gaoni, E. Wenkert, *J. Org. Chem.* **1966**, *31*, 3809.
[45] T. Okada, K. Kamogawa, M. Kawanisi, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2908.
[46] Y. Gaoni, *Tetrahedron* **1972**, *28*, 5533.

Received July 25, 2012