Selected regiocontrolled transformations applied to the synthesis of (1S)-cis-chrysanthemic acid from (1S)-3,4-epoxy-2,2,5,5-tetramethylcyclohexanol†

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**(1S)-cis-Chrysanthemic acid has been prepared in a few steps with complete control of the relative and absolute stereochemistry using regiocontrolled epoxide ring opening, diol mono-oxidation and cyclopropanation.**

In the course of a study involving the enantioselective synthesis of chrysanthemic acids[1,2] from 2,2,5,5-tetramethylcyclohex-3-enone **2**, we needed to open the epoxide ring present in **5** to generate the bromohydrin **7**. This reaction has been carried out with several reagents but it was unselective and produced a mixture of the two regioisomeric bromohydrins **6** and **7** (Scheme 1).[2a]

We therefore developed a novel strategy, shown in Scheme 2. This takes advantage of the efficient enantioselective reduction of the β,γ-unsaturated enone **2** using (−)-Ipc$_2$BCl[2,3] and the molybdenum-catalysed epoxidation of the resulting homoallyl alcohol **3** by *t*-butylhydroperoxide that we have already performed (Scheme 1).[2a,4] We expected that the hydroxyl group in **4**, which is *cis* to the epoxide ring, will control the regiochemistry of the epoxide ring opening, leading to **8**.

Oxidation of the 1,3-diol **8** to the β-hydroxyketone **7**, followed by base-promoted carbocyclisation, was expected to produce **11**, a known[5] precursor of (1S)-cis-chrysanthemic acid **1S$_{cis}$**. The latter delivers, on epimerisation at C-1, the
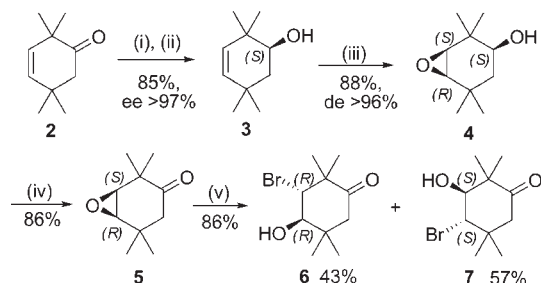

Scheme 1 *Reagents and conditions*: (i) 1.05 eq. (−)-Ipc$_2$BCl, neat, 25 °C, 48 h; (ii) 2.2 eq. diethanolamine, Et$_2$O, 25 °C; (iii) 1.5 eq. *t*-BuOOH, 0.015 eq. Mo(CO)$_6$, C$_6$H$_6$, 80 °C, 2 h; (iv) PDC, CH$_2$Cl$_2$, 20 °C, 0.33 h; (v) 0.5 eq. TiBr$_4$, CH$_2$Cl$_2$, 20 °C, 2 h.

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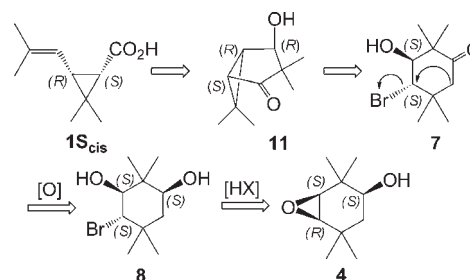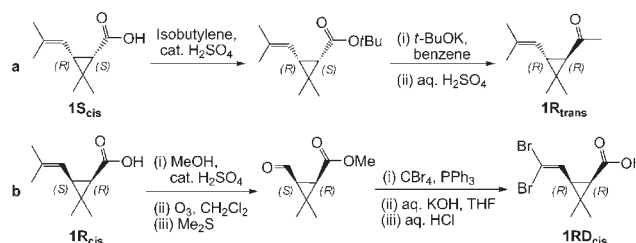

Scheme 2

related (1R)-trans-chrysanthemic acid **1R$_{trans}$**, a precursor of the natural pyrethrin I or S-bioallethrin, the most powerful indoor insecticide[1] (Scheme 3a).

Furthermore, this strategy can be easily adapted (by using (+)-Ipc$_2$BCl[3]) to the stereoselective synthesis of (1R)-cis-chrysanthemic acid **1R$_{cis}$**, a precursor of scalemic *cis*-deltametrinic acid **1RD$_{cis}$** (Scheme 3b) and to deltamethrin, the most active outdoor insecticide.[1]

A successful synthesis faces the following challenges: (i) Regioselective epoxide ring opening (**4** to **8**) (Scheme 4a); (ii) Oxidation of an alcohol to a ketone (**8** to **7**) with the requirement that it should exclusively involve the hydroxyl group farthest from the halogen atom (Scheme 4b); (iii) Selective 1,3-carbocyclisation of **7** to **11** possessing the cyclopropane ring, rather than 1,3-O-cycloalkylation generating the epoxide present in **5** (Scheme 4c).

We expected that the halogen would play an important role in each of the processes shown in Scheme 4, and therefore we tested a series of reagents able to perform the epoxide ring opening regioselectively (Scheme 5). The yields of halohydrins were usually good to excellent, but the regioselectivity was extremely poor. For example, reaction of **4** with titanium tetrabromide[6] mainly provided the bromohydrin **9$_{Br}$** possessing the unwanted regiochemistry (Table 1, entry a).

Scheme 3
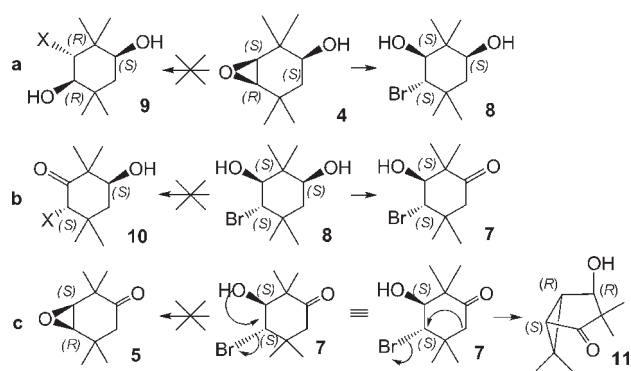
Scheme 4
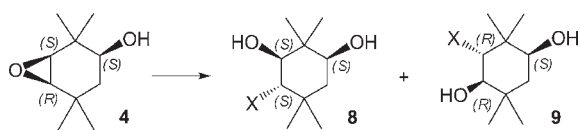
Scheme 5

The reagent pair titanium isopropoxide and bromine (giving BrTi(O*i*Pr)$_3$)[7] was, among those tested, the only one that delivered 8_{Br} in extremely good yield with high regiocontrol (Table 1, entry b); the structure of 8_{Br} was unambiguously assessed by XRD.[8] In addition, 8_{Br} was easily separated from 9_{Br} by silica gel chromatography.[9]

We assume that the regioselective synthesis of 8_{Br} from BrTi(O*i*Pr)$_3$ (Table 1, entry b) results, according to the Fürst–Plattner rule,[10] from the *trans*-diaxial nucleophilic ring opening of the epoxide ring of the less stable conformer **4B** stabilised through chelation of the oxygen atoms of the alcohol and of the epoxide by Ti(IV) (Scheme 6).

The same rule,[10] applied to the non-chelated and more stable conformer **4A**, can rationalise the reversed selectivity observed when TiBr$_4$ is instead used (Scheme 6; Table 1, entry a). Work is in progress to understand these discrepencies.

The selective oxidation of the 1,3-diol 8_{Br} to the 3-hydroxy-ketone **7** (Scheme 4b) was the next goal to achieve. This step was extremely challenging since the oxidation needed to take place selectively at one of the two alcohols, which are both equatorial. Furthermore, competing over-oxidation and potential "retro-aldol" reaction of **7** needed to be avoided.

Table 1 Epoxide ring-opening of **4** (see Scheme 5)

Entry	Reagent	Eq.	$T/°C$	$t/$h	X	8 + 9 (%)	8/9
a	TiBr$_4$	0.5	20	72	Br	87	32 : 68
b	Ti(O*i*Pr)$_4$ + Br$_2$	1.1	0 → 20	5	Br	87	93 : 7
c	Ti(O*i*Pr)$_4$ + I$_2$	1.1	20	30	I	66	73 : 27
d	Ti(O*i*Pr)$_4$ + Cl$_2$	1.1	20	24	Cl	0	—
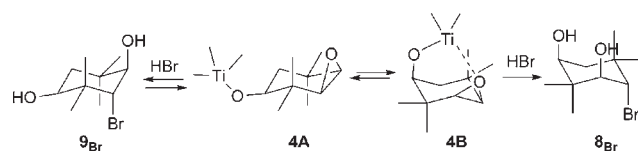
Scheme 6
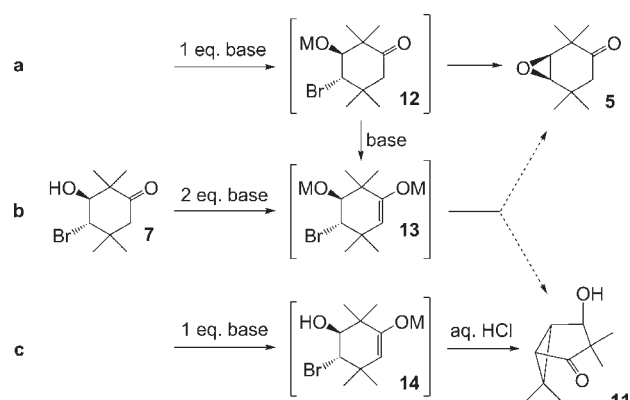
Scheme 7

The first results involving pyridinium chlorochromate (PCC)[11] were disappointing, since the starting material was recovered unchanged even after standing in dichloromethane for more than 3 days at 20 °C. *tert*-Butyl hydroperoxide in the presence of vanadium di(acetylacetonate),[12] which so readily produced 3,4-oxido-2,2,5,5-tetramethylcyclohexanone when we tried to epoxidise (1*S*)-2,2,5,5-tetramethylcyclohexanol to 3,4-oxido-2,2,5,5-tetramethylcyclohexanol,[2b] proved only slightly better: although it effectively produced the desired ketone **7** with complete regiocontrol, the reaction was very slow and the yield very modest (C$_6$H$_6$, 80 °C, 84 h, 19%).

We also tested an alternative method involving selective monoacetylation of **8** and oxidation of the resulting 3-(acetyloxy)cyclohexanol. Since acetylation was extremely slow and poorly regioselective, we did not follow this "protection–deprotection" strategy.

We ultimately found that the Jones reagent[13] led to formation of **7** in 91% yield (0.66 eq. H$_2$CrO$_4$, acetone, 0 °C, 0.75 h), together with 4% 4-bromo-2,2,5,5-tetramethylcyclohexane-1,3-dione. By following the reaction by GC, we found that over-oxidation of **7** only occurs once 8_{Br} has completely disappeared.

The final goal was to find conditions for the 1,3-elimination of **7** providing the cyclopropane moiety present in *exo*-4-hydroxy-3,3,6,6-tetramethylbicyclo[3.1.0]hexan-2-one **11**. This transformation is not a simple task, since mono-metallation is expected to occur under kinetically controlled conditions at the hydroxyl hydrogen (Scheme 7a) rather than α to the carbonyl group (Scheme 7c) of **7**, suggesting that the unwanted epoxide **5** will be produced at the expense of **11**.

Table 2 Reaction of **7** with base (see Scheme 7)

Entry	Reagent	Eq.	N/R[a]	$T/°C$	$t/$h	5/11	5 (%)	11 (%)
a	LDA	1	N	20	0.5	96 : 4	92	—
b	LDA	2	N	20	0.5	87 : 13	83	—
c	LDA	2	R	20	0.5	24 : 76	20	60
d	LDA	3	R	20	0.3	5 : 95	0	85
e	LiTMP	1	N	20	0.5	90 : 10	86	—
f	LiTMP	2	N	−25	1	23 : 77	21	77
g	LiTMP	2	R	−25	1	0 : 100	—	83
h	LiHMDS[17]	3	R	20	3	70 : 30	63	32
i	KHMDS[17]	3	R	20	0.3	100 : 0	83	—
j	KOH	2	N	20	12	90 : 10	90	—

[a] N = normal addition; R = reverse addition.
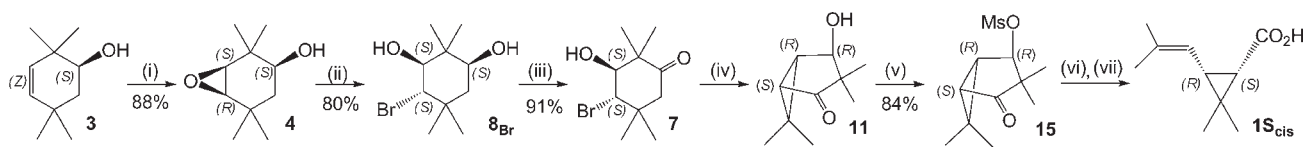
Scheme 8 *Reagents and conditions*: (i) 1.05 eq. $tBuO_2H$, 0.015 eq. $Mo(CO)_6$, C_6H_6, 80 °C, 2 h; (ii) $Ti(OiPr)_4$ + Br_2, CH_2Cl_2, 0 → 20 °C, 5 h; (iii) 0.66 eq. H_2CrO_4, acetone, 0 °C, 0.75 h; (iv) 2 eq. LiTMP, reverse addition, −25 °C, 1 h; (v) 1.1 eq. MsCl, CH_2Cl_2; (vi) 6 eq. $tBuOK$, 3 eq. H_2O; (vii) aq. HCl.

This proved to be the case when metallation of **7** was carried out by adding a single equivalent of LDA[14,15] or LiTMP[15,16] to **7** dissolved in THF (Scheme 7; Table 2, entries a and e), since **5** was produced almost exclusively (**5**/**11**: 96 : 4). Similar results were obtained when potassium amides were used instead under similar conditions (Table 2, entry i).

Taking into account those preliminary results, we initially considered trapping the first-formed alcoholate using trimethylsilyl chloride, expecting to prevent epoxide formation and allowing the synthesis of the cyclopropane ring present in **11**. However, we did not favour this option because it would require a lengthy protection–deprotection strategy.

We then envisaged a strategy involving metallation of the β-alkoxyketone **12** to generate the dialkoxide **13**, expecting that C-alkylation (producing the cyclopropane ring) would favorably compete with the epoxide formation. This would only be feasible if enolate formation (**12** to **13**) was faster than epoxide formation (**12** to **5**). In order to preclude epoxide formation, we decided to perform the reaction with an excess of base. The choice of reverse addition of the reactants became obvious (addition of **7** to the base; "R" mode), and proved to be highly beneficial.

We found that the whole process could be successfully achieved by simply performing the addition ("R" mode) of two equivalents of particularly strongly basic LiTMP (Scheme 7; Table 2, entry g). We were not surprised to find that LDA (Table 2, entry c) and LiHMDS (Table 2, entry h), which are not as strong bases as LiTMP,[16a] deliver, under similar conditions, a lower amount of **11**. Although the formation of a much higher amount of **11** can be achieved when 3 equivalents of LDA are used (Table 2, entry d), this is not the case for LiHMDS, which is known to be an even poorer base than LDA (Table 2, entry h).

The beneficial effect of using the "R" rather than the "N" mode of addition of the reagents (so that **7** is always kept in an excess of base) proved to be, as expected, extremely important (Table 2, compare entries g to f and c to b), especially when the less reactive LDA is used.

The cooperative effect of the lithium cation has to be pointed out, since to a certain extent it is playing the role of a hydroxyl "protecting group" (as could have the trimethylsilyl group), avoiding or lowering competing epoxide ring formation. This is not the case when potassium bases are used (Table 2, entries i and j), since the higher ionic character of the first-formed metal alcoholate increases the rate of epoxide formation, precluding the formation of **13** (Scheme 7; Table 2, entry i; compare with entry h).

We proved the identity of compound **11** by comparison with an authentic sample,[18a] and transformed it according to a known procedure to (1S)-cis-chrysanthemic acid **1S_cis** (Scheme 8).[2a,5,18b]

In the course of this work, we found that the results described for the bromohydrin **7** cannot be systematically transposed to the related chlorohydrin because the lithium alcoholate has a lower propensity to cyclise to **5**. Those results will be reported in due course.

Notes and references

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17 We trapped the mixture with MeOD and found incorporation of one equivalent of deuterium α to the carbonyl group of **5**.
18 (a) $[\alpha]_D^{20} = -51.8$ (c = 1.11 in $CHCl_3$; (b) $[\alpha]_D^{20} = -78.1$ (c = 1.00 in $CHCl_3$).