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Diastereoselective Bromination of Compounds Bearing a Cyclohex-3-enol Moiety: Application to the Enantioselective Synthesis of (1R)-*cis*-Deltamethrinic Acid†

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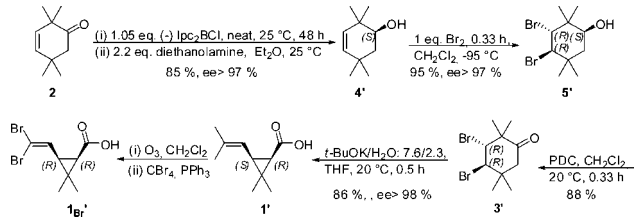
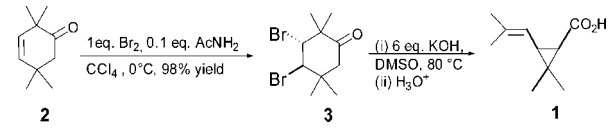


(1*R*)-*cis*-Chrysanthemic acid has been prepared in a few steps with complete control of the relative and absolute stereochemistry. Some mechanistic aspect of the addition of bromine to the C,C double bond of 2,2,5,5-tetramethylcyclohex-3-enol is disclosed.

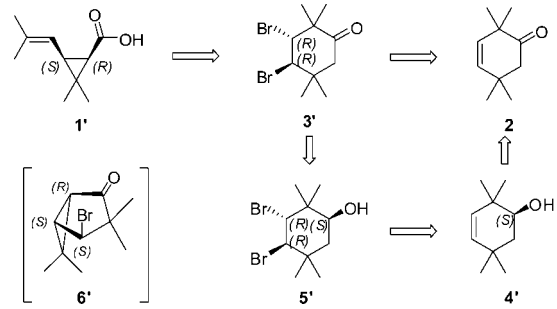
A few years ago, we described that the synthesis of (*d,l*)-*cis*-chrysanthemic acid **1** can be achieved in a few steps from 2,2,5,5-tetramethylcyclohex-3-enone **2**. These involve the *vic*-dibromination of **2** using elemental bromine followed by reaction with potassium hydroxide in DMSO which effect a cascade cyclopropane formation and fragmentation reaction (Scheme 1).[1]

This paper reports extension of our previous work to the enantioselective synthesis of (1*R*)-*cis*-chrysanthemic acid **1′** and of the related deltamethrinic acid $\mathbf{1_{Br}}'$ precursor of deltamethrin the most active commercially available insecticide (Scheme 3).[2] In fact, the planned transformation was not straightforward due to

SCHEME 1



SCHEME 2



the lack of enantioselective methods for *trans-vic*-dibromination of C,C double bonds.[3]

For that reason, we developed the strategy disclosed in Scheme 2, which instead involves the diastereoselective *vic*-dibromination of the C,C double bond of the (1*S*) homoallyl alcohol **4′** expecting to take advantage of the directing effect[4] of its hydroxyl group.

Enantioselective reduction of 2,2,5,5-tetramethylcyclohex-3-enone **2** using (−)-*B*-chlorodiisopinocampheylborane[5−7] (1.05 equiv, neat, 25 °C, 48 h) and quenching with diethanolamine (2.2 equiv) in anhydrous ether provides 1(*S*)-2,2,5,5-tetramethylcyclohex-3-enol **4′** in 85% yield, with very high stereocontrol (ee >97%,[8,9] Scheme 3).

vic-Dibromination of the resulting homoallyl alcohol **4a′** proved to be highly stereoselective (1 equiv of Br_2, −95 °C, 0.33 h, CH_2Cl_2) and leads to 3(*R*),4(*R*)-dibromo-2,2,5,5-tetramethyl-cy-

† Dedicated to the memory of Al Meyers for his excellence in chemistry and his acute sense of humor.

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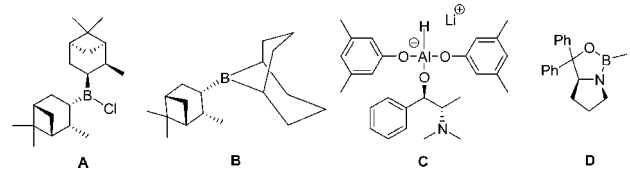
(6) In addition to (−)-*B*-chlorodiisopinocampheylborane A,[5] other reducing agents have been tested unsuccessfully, such as (a) (*R*)-alpine-borane **B**,[7a] (b) modified aluminum hydride C,[7b,c] (THF, 20 °C, 96 h, 0%), and (c) Corey's oxazaborolidine D[7d,e] complexed with borane (cat. **10d**, BH_3,−78 °C, 0% yield). The later reagent reacts, however, at higher temperature with **2** but leads to a mixture of compounds resulting from the reduction of both the C,C and C,O double bonds of **2**.



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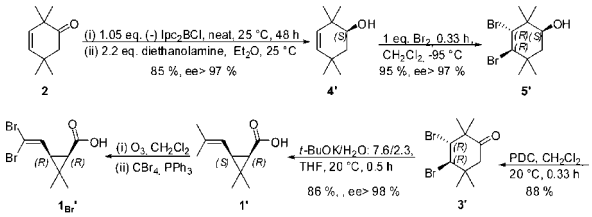
SCHEME 3



SCHEME 4

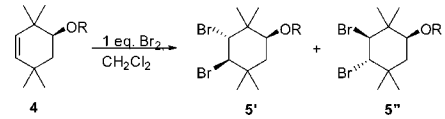


TABLE 1

entry	4	R	*T* (°C)	de (%)
a	**4a′**	H	−95	97
b	**4a′**	H	−78	90
c	**4a′**	H	0	76
d	**4b**	CH═O	−78	84.2
e	**4b**	CH═O	0	64.6
f	**4c**	MeC═O	−78	76.9
g	**4c**	MeC═O	0	61.5
h	**4d**	*t*-BuC═O	−95	76.0
i	**4d**	*t*-BuC═O	−78	73.2
j	**4d**	*t*-BuC═O	0	60.6
k	**4e**	$SiMe_3$	−78	82.8
l	**4e**	$SiMe_3$	0	62.4

clohexan-1(*S*)-ol **5a′** in high yield and with very high stereocontrol (95% yield; de 97%, Scheme 3).

The relative and absolute stereochemistry of the **5a′** has been deducted from the DRX[10] of its acetate **5c′** (9 equiv of Ac_2O, 9 equiv of Pyr, 0.1 equiv of DMAP, CH_2Cl_2, 0−20 °C, 36 h; 92% yield).

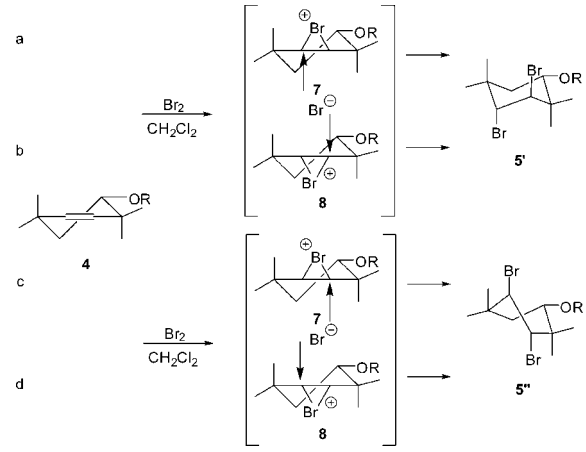
The synthesis of scalemic (1*R*)-*cis*-chrysanthemic acid **1′** was readily achieved from that stage by oxidation to the scalemic 3(*R*),4(*R*)-dibromo-2,2,5,5-tetramethylcyclohexanone **3′** (PDC,[11] CH_2Cl_2, 20 °C, 0.33 h, 88% yield) followed by reaction with the Gassman reagent[12] (*t*-BuOK/H_2O: 7.6/2.3, THF, 20 °C, 0.5 h) and acid hydrolysis of the resulting potassium carboxylate (86% yield in **1′**, ee >98%, Scheme 3).

The reaction involving the Gassman reagent[12] is remarkable since it sequentially allows the formation of the [3.1.0] bicyclic skeleton by intramolecular substitution leading to **6′** and the high-yielding Grob-type fragmentation reaction[1,13] leading to the potassium chrysanthemate.

The dibromination of the equatorial homoallyl alcohol **4a′** is even more remarkable since the high stereocontrol reported above is only observed when the reaction is performed at quite low temperature (−95 °C, Schemes 4, Table 1, compare entry a to b,c), and interestingly, dilution does not affect this stereocontrol.

We have also performed the bromination either of the corresponding formiate **4b**, acetate **4c**, pivalate **4d**, or trimethylsilyl derivative **4e** (Table 1, entries d−l) but the results were disappointing since we never reached the high stereoselectivity observed from the free alcohol **4a** (Table 1, compare entry b to d,f,i,k). We have not been able to determine why the stereocontrol is poorer with **4b**−**d** possessing carboxy groups which have a higher propensity to lie in equatorial position than the hydroxyl group.

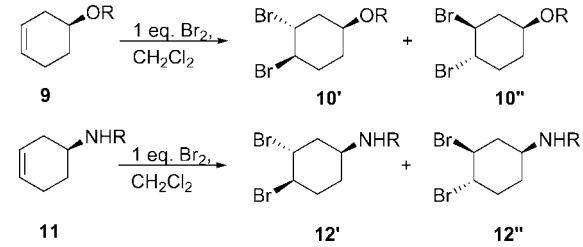
SCHEME 5



The selective formation of **5a′** over **5a″** could be rationalized by assuming the attack of the bromide ion at C-4 of the bromiranium **7a** or at C-3 of its diastereoisomers **8a** so that it leads to a chair (Scheme 5, entries a,b) rather than a twisted boat transition state (Scheme 5, entries c,d).[14]

Dibromation of related 4-trideuteromethoxy- **9a**, 4-acetoxy- **9b**, and 4-trifluoromethylcyclohexenes **9c** was carried out 25 years ago[15] ($CHCl_3$, 0 °C) and produces the corresponding dibromides in quantitative yields but as a 65/35, 60/40, and 60/40 mixture of **10′/10″** diastereoisomers, respectively (Scheme 6).

SCHEME 6



Related results have been also reported[16] on the dibromation of *tert*-butyl *N*-(cyclohex-3-enyl)carbamate **11a** and *N*-(cyclohex-3-enyl)trifluoroacetamide **11b** with bromine in methylene dichloride (−78 °C) and produce **12** in about 90% yields and in 83/17 and 77/23 ratios of **12′/12″** diastereoisomers, respectively (Scheme 6).

Those results are related to those reported in this work, but diastereoselections are far poorer than we have observed from the homoallyl alcohol **4a**.

Preliminary results on the addition of hypobromous acid on **4** lead us to suspect that the addition of bromenium ion (Br^+) is not stereoselective and produces a 60/40 mixture of **7/8**. We will report in due course this work and its uses for another synthesis of (1*R*)-*cis*-chrysanthemic acid **1′**.

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Experimental Section

2,2,5,5-Tetramethylcyclohex-3-enone **2** was prepared according to the literature procedure.[1]

(*S*)-2,2,5,5-Tetramethylcyclohex-3-enol 4a′. Into a 25 mL round-bottomed two-necked flask under a bell of Ar were added 2,2,5,5-tetramethylcyclohex-3-enone **2** (3.040 g, 20 mmol) and (−)-Ipc$_2$BCl (6.74 g, 21 mmol), and the solution was stirred at rt. After 3 days, liberated α-pinene was removed by vacuum (0.1 mmHg) at 40 °C. Dry ether (70 mL) was added followed by diethanolamine (4.62 g, 44 mmol) and the solution stirred for 2 h at rt. The white precipitate that appeared was filtered through a Büchner funnel, and the filter cake was washed with dry ether (4 × 25 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 95/5) to furnish 2.61 g (85%) of (*S*)-2,2,5,5-tetramethylcyclohex-3-enol **4a′** as a white solid with an odor close to that of menthol: mp 47 °C; $[\alpha]^{20}$D −64.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 2H), 3.67 (dd, J = 11.2, 4.8 Hz, 1H), 1.58 (m, 2H), 1.38 (broad, 1H), 1.08 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 133.9, 73.6, 42.1, 36.9, 34.6, 31.0, 29.4, 27.6, 21.3; IR (KBr): ν (cm^{-1}) 3372, 3005, 2959, 2931, 2868, 1469, 1361, 1185, 1076, 1041, 912, 764, 736.

(1*S*)-(3*R*,4*R*)-Dibromo-2,2,5,5-tetramethylcyclohexanol 5a′. Into a 50 mL round-bottomed two-necked flask under Ar was added dropwise, at −95 °C, a solution of bromine (480 mg, 3 mmol) in dry CH_2Cl_2 (12 mL) to a stirred solution of (*S*)-2,2,5,5-tetramethylcyclohex-3-enol **4a′** (462 mg, 3 mmol) in dry CH_2Cl_2 (18 mL). After 0.25 h at −95 °C, 10 mL of satd aq $Na_2S_2O_5$ was added, and the reaction mixture was allowed to warm to room temperature and diluted with CH_2Cl_2 (100 mL). The organic layer was decanted, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 90/10) to furnish 895 mg (95%) of (^{1}S)-(3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexanol **5a′** as a white solid: mp 119 °C; $[\alpha]^{20}_D$ −48.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (d, J = 11.6 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 3.78 (dd, J = 3.0, 2.8 Hz, 1H), 1.88 (m, 2H), 1.56 (s, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.9, 69.5, 66.0, 43.9, 41.0, 39.0, 33.3, 28.0, 25.4, 21.5; IR (KBr) ν (cm^{-1}) 3576, 2973, 2932, 2881, 1464, 1452, 1391, 1367, 1347, 1288, 1245, 1205, 1166, 1114, 1079, 1048, 1014, 998, 933, 916, 881; EIMS *m*/*z* 235, 233, 153, 135, 111, 95, 69, 55. Anal. Calcd for $C_{10}H_{18}Br_2O$: C, 38.24; H 5.78. Found: C, 38.64; H, 4.78.

(1*S*)-Acetoxy-(3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexane 5c′. Into a 25 mL round-bottomed two-necked flask under Ar were added dry pyridine (240 mg, 3 mmol) and DMAP (4 mg, 0.04 mmol) to a stirred solution of (^{1}S)-(3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexanol **5a′** (105 mg, 0.33 mmol) in dry CH_2Cl_2 (3 mL). The solution was cooled to 0 °C before freshly distilled acetic anhydride (306 mg, 3 mmol) diluted with 2 mL of dry CH_2Cl_2 was added dropwise. After 36 h at room temperature, the reaction mixture was quenched with aq HCl (10%, 3 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with an aq satd solution of $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 95/5) to furnish 108 mg (92%) of (^{1}S)-acetoxy-(3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexane **5c′** as a white solid: mp 121 °C; $[\alpha]^{20}_D$ −52.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (t, = 3.0 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.7 Hz, 1H), 2.08 (s, 3H), 1.96 (d, J = 3.2 Hz, 1H), 1.91 (d, J = 3.2 Hz, 1H), 1.22 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 76.8, 68.6, 65.4, 42.8, 38.9, 38.3, 33.1, 27.7, 25.0, 21.5, 21.1; IR (KBr) ν (cm^{-1}) 2989, 2973, 2940, 2879, 1735, 1464, 1451, 1432, 1393, 1373, 1351, 1240, 1198, 1163, 1076, 1060, 1022, 994; EIMS *m*/*z* 217, 215, 153, 149, 147, 136, 135, 121, 120, 119, 107. Anal. Calcd for $C_{12}H_{20}Br_2O_2$: C, 40.48; H, 5.66. Found: C, 41.16; H, 5.69.

The product was crystallized, without special care, by evaporation of isopropyl alcohol solution over a period of 2 days for X-ray diffraction analysis.

(3*R*,4*R*)-Dibromo-2,2,5,5-tetramethylcyclohexanone 3′. Into a 25 mL round-bottomed two-necked flask under Ar were added at 0 °C PDC (1.13 g, 3 mmol) and powdered molecular sieves 4 Å (1.13 g) mixed together with a stirred solution of (^{1}*S*)-(3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexanol **5a′** (785 mg, 2.5 mmol) in dry CH_2Cl_2 (15 mL), and the reaction mixture was stirred at rt. After 0.33 h, the reaction mixture was filtered through Celite, the Celite cake was washed with CH_2Cl_2 (2 × 25 mL), and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 90/10) to furnish 886 mg (88%) of (3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexanone **3′** as a white solid: mp 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (d, J = 11.6 Hz, 1H), 4.25 (d, J = 11.6 Hz, 1H), 2.78 (d, J = 14.0 Hz, 1H), 2.32 (d, J = 14.0 Hz, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 66.8, 66.5, 52.7, 49.8, 40.4, 32.0, 23.9, 23.8, 21.2; IR (KBr) ν (cm^{-1}) 2982, 2941, 2879, 1712, 1460, 1389, 1371, 1345, 1298, 1245, 1185, 1122, 1076, 945, 893, 856, 806, 733; EIMS *m*/*z* 233, 231, 205, 203, 191, 189, 151, 149, 147, 123, 110, 109. Anal. Calcd for $C_{10}H_{16}Br_2O$: C, 38.49; H, 5.17. Found: C, 38.88; H, 4.95.

(1*R*)-*cis*-Chrysanthemic Acid 1′ with the Gassman Reagent. Into a 25 mL round-bottomed two-necked flask under Ar was added water (21 mg, 1.15 mmol) to a stirred solution of freshly sublimed potassium *tert*-butoxide (426 mg, 3.8 mmol) in dry THF (4 mL), and the reaction mixture was stirred at rt. After 10 min, a solution of (3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexanone **3′** (156 mg, 0.5 mmol) in dry THF (2 mL) was added dropwise. A yellow coloration appeared, and the reaction was monitored by TLC (pentane/ether: 80/20). After 0.5 h at rt, ice (8 mL) was added and the reaction mixture acidified to pH 2 with aq HCl (10%) (discoloration) and extracted with ether (4 × 15 mL). The combined organic extracts were washed with water (2 × 5 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 80/20) to furnish 72 mg (86%) of (^{1}*R*)-*cis*-chrysanthemic acid **1′** as a white solid: mp 108 °C; $[\alpha]^{20}_D$ +82.3 (*c* 1.0, $CHCl_3$) (lit.[17] $[\alpha]^{20}_D$ +83.0 (*c* 1.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (broad, 1H), 5.36 (dt, J = 8.8, 1.3 Hz, 1H), 1.96 (dd, *J* 8.5, 8.6 Hz, 1H), 1.74 (s, 3H), 1.69 (s, 3H), 1.64 (d, J = 9.1 Hz, 1H), 1.24 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 135.2, 117.9, 33.1, 30.9, 28.8, 27.4, 25.9, 18.2, 14.7; IR (KBr) ν (cm^{-1}) 3037, 2928, 2559, 1693, 1438, 1394, 1376, 1326, 1305, 1229, 1148, 1120, 1090, 1061, 1004, 979, 940, 852, 838, 786, 718.

(1*R*)-*cis*-Chrysanthemic Acid 1′ with KOH in DMSO/Water Mixture. Into a 25 mL round-bottomed two-necked flask under Ar,was added (3*R*,4*R*)-dibromo-2,2,5,5-tetramethylcyclohexanone **3′** (156 mg, 0.5 mmol) to a stirred solution of potassium hydroxide (168 mg, 3 mmol) in a mixture of dimethyl sulfoxide and water (4:1, 2 mL). The reaction mixture was then heated to 70 °C for 2.5 h. The reaction was monitored by TLC (pentane/ether: 80/20). The reaction was hydrolyzed to pH 2 with aq HCl (10%) and extracted with ether (4 × 15 mL). The combined organic extracts were washed with water (2 × 5 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (pentane/ether: 80/20) to furnish 69 mg (82%) of (^{1}*R*)-*cis*-chrysanthemic acid **1′** as a white solid. Spectral properties were identical with those already reported.

Acknowledgment. S.J. thanks the FRIA for financial support.

Supporting Information Available: NMR spectra (^{1}H and ^{13}C) for compounds **4a′**, **5a′**, **5c′**, **3′**. and **1′**. Experimental procedures, characterizations, and NMR spectra (^{1}H) for compounds **4b**−**e** and relative bromine adducts **5b**, **5d**, and **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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