Novel Synthesis of Vinylcyclopropyl Ketones and Vinylcyclopropanecarboxylic Acids: Application to the Stereoselective Synthesis of *trans*-Chrysanthemic Acid

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Received October 28, 1996

Introduction

Some years ago, we designed[1a] a stereoselective synthesis of (1*RS*)-*cis*-chrysanthemic acid **1a** (R_1, R_2 = Me)[2] from dimethyldimedone **2a** (R_1, R_2 = Me) which uses cheap reagents compatible with industrial requirements. The key steps of this process are (i) the cyclopropanation of **2a**, which produced the bicyclo[3.1.0]hexa-2,4-dione[1a,3] **3a**, and (ii) the Grob fragmentation[4] on the mesylate **5a** derived from β-hydroxy ketone **4a**, itself resulting from the mono-reduction of **3a**. The stereochemical outcome of each individual step that is important for the success of the whole process is depicted in Scheme 1.[1]

Most of the reducing agents used, including sodium borohydride (methanol, −78 °C), efficiently achieved[5] monoreduction of the bicyclic dione **3a** but delivered, exclusively or mainly, the *endo* alcohol **4a**$_{endo}$. This alcohol, which results from the attack of the hydride from the least hindered *exo* face of **3a**,[1a,b] is unsuitable, however, for the synthesis of **1a**. This synthesis has been nevertheless successfully achieved from the *exo* stereoisomer **4a**$_{exo}$, readily available from the reduction of **3a**[1a,b] with sodium borohydride−cerium trichloride (methanol, −78 °C, Luche's reagent).[6]

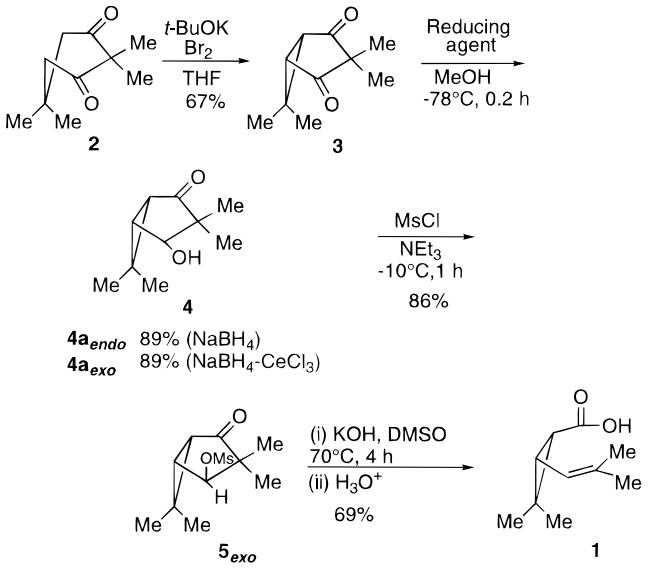
This synthetic approach has been successfully extended to homologous derivatives of **1** bearing one methyl group and one hydrogen or even two hydrogens on the cyclopropane ring. This approach is unsuitable, however, for the synthesis (for example) of derivatives **1** bearing one or two hydrogens on the terminal sp2 carbon, due to competing metalation at the position α to the carbonyl group of **2** and **4** (R_1 or/and R_2 = H).

Results and Discussion

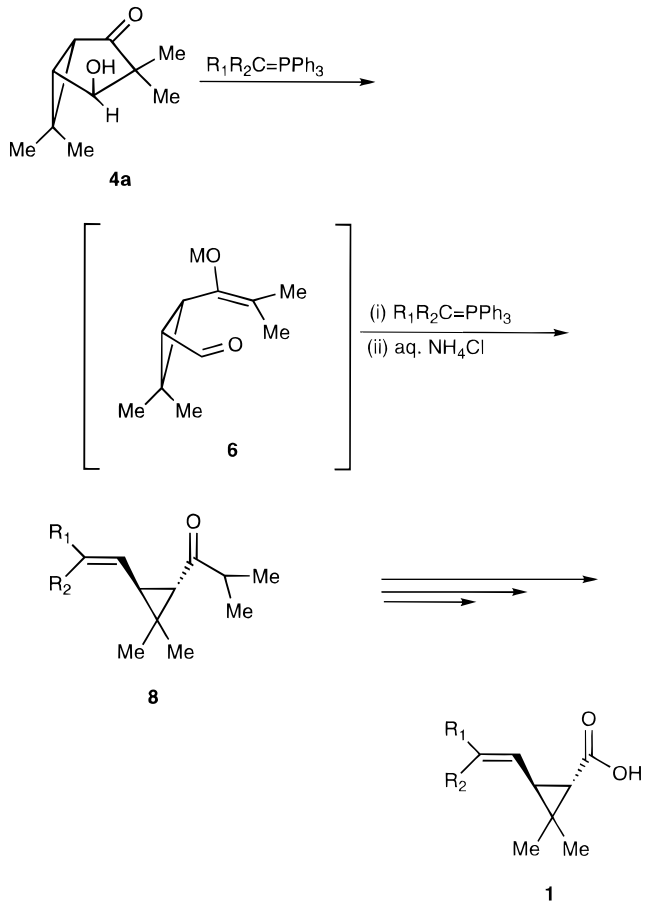
We now report a modified synthetic scheme which allows the synthesis of these chrysanthemic acid analogues bearing different substituents on the terminal vinylic carbon from the common intermediate **4a** (Scheme 2).

This variation takes advantage of the special arrangement of the β-hydroxy ketone moiety in **4a** which can produce, via a retro-aldol reaction, the aldehydo enolate intermediate **6**. This should be susceptible to further

Scheme 1



Scheme 2[a]



[a] See Table 1.

(1) (a) Krief, A.; Surleraux, D.; Frauenrath, H. *Tetrahedron Lett.* **1988**, *29*, 6157. (b) Krief, A.; Surleraux, D. *Synlett* **1991**, 273. (c) Krief, A.; Surleraux, D.; Robson, M. J. *Synlett* **1991**, 276.

(2) (a) Krief, A. *Pestic. Sci.* **1994**, *41*, 237 (b) Krief, A. In *Stereocontrolled Organic Synthesis, Chemistry of the twenty first century*; Trost, B. M., Ed.; Blackwell: Oxford, U.K., 1994; pp 337−397. (c) Naumann, K. *Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel*; Springer-Verlag: Heidelberg, 1981 (ISBN 3-540-10452-6). (d) Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703. (e) Elliot, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473.

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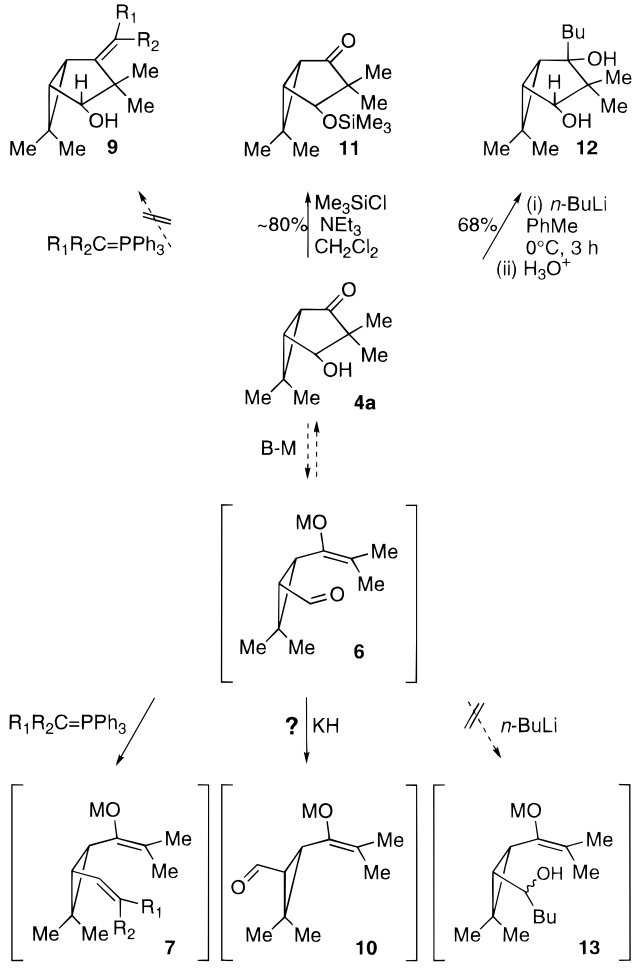
(4) (a) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535 and references cited therein. (b) Carruthers, W. In *Some Modern Methods of Organic Chemistry Synthesis*, 2nd ed.; Cambridge University Press: Cambridge, U.K., **1978**; p 141.

(5) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, **1972**. (b) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. (c) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.

(6) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

S0022-3263(96)02015-4 CCC: $14.00

Scheme 3



reaction with a phosphorus ylide to produce **7** and then **8** (Schemes 2 and 3).

However, the reactions we want to achieve are not exclusive, since several competing reactions can instead occur, as shown in Scheme 3. In fact, the β-hydroxy ketone **4a** possesses a schizophrenic behavior since, for example, on reaction with excess bases it (i) produces a polymer, probably *via* **10**, on reaction with KH, (ii) epimerizes (*exo*/*endo*: 60/40 from either $\mathbf{4a}_{exo}$ or $\mathbf{4a}_{endo}$) on reaction with KOH in DMSO, (iii) stereospecifically leads to the related β-silyloxy ketone **11** on reaction with triethylamine (1.1 equiv) or LiHDMS (2.3 equiv) and trimethylsilyl chloride, and (iv) generates the diol **12** on reaction with *n*-butyllithium in toluene in a process substantially different from that of the phosphorus ylides (see below).

The reaction of Wittig reagents with aldols bearing two substituents on the α-carbon has been scarcely disclosed and usually requires special conditions.[7] The best results have been obtained in our case from the *exo* derivative $\mathbf{4a}_{exo}$ and alkylidenetriphenylphosphoranes prepared in DMSO from the corresponding alkyltriphenylphosphonium iodide or bromide and dimsylsodium ($\mathbf{4a}_{exo}$, 2.1 equiv of $R_1R_2CHPPh_3^+\ X^-$ (X = Br, I), 2.1 equiv of dimsylsodium, DMSO, 0−20°C and then 20 °C, 1−3 h).[8] The tandem retro-aldol−Wittig reaction proved to be generally rather fast with acyclic derivatives (Scheme 2 and Table 1, entries a−c) but more difficult with cyclohexylidenetriphenylphosphorane which requires heating to go to completion (Scheme 2; compare entry e to entry d in Table 1). Under these conditions the isopropyl ketones **8** are produced, after hydrolysis, in reasonably good yield and with high stereocontrol both on the cyclopropane ring (Scheme 2 and Table 1, entries a−c and e) and on the CC double bond (Scheme 2 and Table 1, entry c). Although the *Z* stereochemistry of the CC double bond was expected,[7] we were surprised to obtain the *trans* derivative $\mathbf{8}_{trans}$ rather than its *cis* stereoisomer, which would have been produced if no epimerization had taken place on the cyclopropane ring.

In order to have some insight into the intimate mechanism of this reaction we have carried out the same reaction in DMSO-d_6 ($\mathbf{4a}_{exo}$, 2.1 equiv of $Me_2CHPPh_3^+I^-$, 2 equiv of dimsylsodium-d_5, 0−20 °C, 2 h, and then H_2O; 65% **8a′**; deuterium content C-3 89%, C-5 100%; Scheme 4) and found that it produces mainly, after hydrolysis, the dideuterated *trans*-cyclopropyl ketone **8a′** (Scheme 4). This proved unambiguously that epimerization is at least taking place on the cyclopropane ring α to the keto group. In a separate experiment we have found that metalation of **8a** occurs (i) nonselectively both on the isopropyl and on the cyclopropyl group with dimsylsodium-d_5 in DMSO-d_6 (**8a**,1.2 equiv of dimsylsodium-d_5, DMSO-d_6, 20 °C, 7 h and then H_2O, 55% **8a′**, deuterium content C-3 76%, C-5 100%; Scheme 4) and (ii) regioselectively on the isopropyl group with LDA (**8a**, 1.7 equiv of LDA, THF−hexanes, 0 °C, 0.3 h and then D_2O, 99% **8a″**, deuterium content C-3 76%, C-5 0%, Scheme 4). An equilibration which involves metalation of DMSO is therefore taking place in the transformation of **4a** to **8a**. This equilibration, however, does not occur if THF is used as the solvent. These results rule out, therefore, an epimerization at C-1.

The last results led us to envisage that isomerization could be avoided if the reaction could be carried out with lithium counterion in the absence of DMSO. The ylide generated from the corresponding phosphonium salts and butyllithium in THF[5a,10a] or THF−HMPA[7,10b] unfortunately did not effect the desired transformation, and the starting material was partially recovered. Performing the reaction in toluene−hexanes, under "salt free conditions",[9,10c] leads however to the isopropyl ketone **8a** now possessing the *cis* stereochemistry, but we have not been able, even after systematic work, to find conditions allowing reproducible results.

It would have been particularly interesting to extend the conditions which proved successful for $\mathbf{4a}_{exo}$ to its $\mathbf{4a}_{endo}$ stereoisomer, whose synthesis avoids the use of cerium trichloride. We found, however, that the *endo* diastereoisomer $\mathbf{4a}_{endo}$ reacted less efficiently than $\mathbf{4a}_{exo}$ with isopropylidenetriphenylphosphorane to provide under similar conditions the same *trans*-cyclopropyl ketone $\mathbf{8}_{trans}$ in 30% yield (2.1 equiv of $Me_2CHPPh_3^+I^-$, 2.1 equiv of dimsylsodium, DMSO, 0−20 °C, 2−3 h). A higher yield of $\mathbf{8}_{trans}$ (50% yield) was obtained, however, if the reaction was carried out for the same time with 3.3 instead of 2.1 equiv of isopropylidenetriphenylphosphorane.

We planned to transform the isopropyl keto group of

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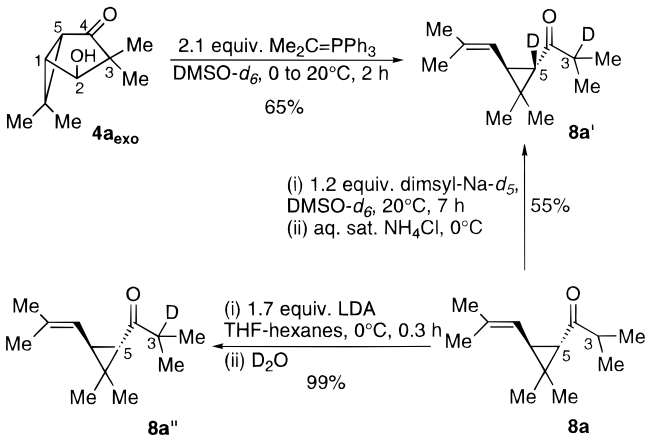
(8) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(9) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823.

(10) Conditions: (a) 2 equiv of $MePPh_3$,I, 2 equiv of *n*-BuLi, THF−hexanes, 20 °C, 17 h, $\mathbf{8a}_{trans}$ 0%, recovery 49%; (b) 2 equiv of $MePPh_3I$, 2 equiv of *n*-BuLi, THF−hexanes−8 equiv of HMPA, 0 °C for 1 h, 20 °C for 23 h, $\mathbf{8a}_{trans}$ 0%, $\mathbf{4a}_{exo}$ recovery 62%; (c) 3 equiv of Me_2CHPPh_3,-Br, 3 equiv of *n*-BuLi, toluene, 80 °C, 5 h, $\mathbf{8c}_{cis}$ 0−55%.

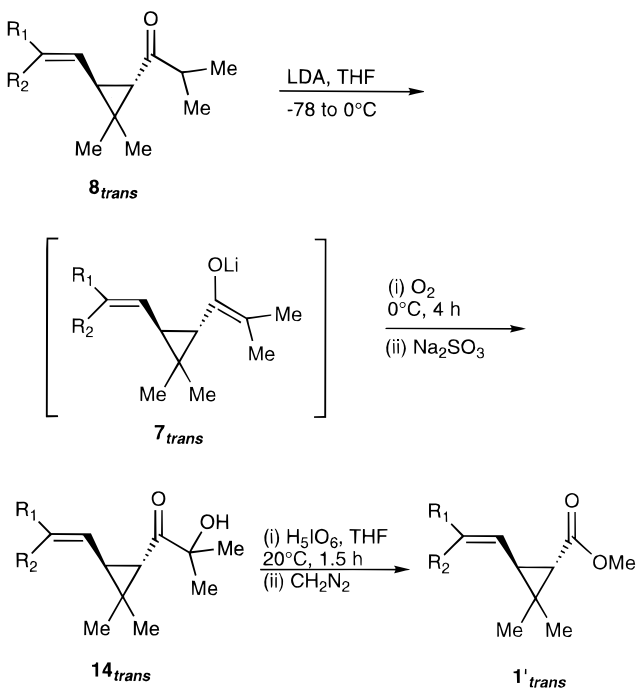
Table 1

entry	R_1		R_2	conditions	$\mathbf{8}_{trans}$	yield **8**, %	(*trans*/*cis*) *Z*/*E* ratio	recovery of **4**, %
a	Me		Me	2.1 equiv of *i*-$PrPPh_3^+I^-$, 2.1 equiv of $MeS(O)CH_2Na$, DMSO, 0−20 °C, 1 h	8a	75	(100/0)	0
b	H		H	2.1 equiv. $MePPPh_3^+I^-$, 2.1 equiv of $MeS(O)CH_2Na$, DMSO, 0−20 °C, 24 h	8b	71	(84/16)	0
c	H		Et	2.1 equiv of *n*-$PrPPh_3^+I^-$, 2.1 equiv of $MeS(O)CH_2Na$, DMSO, 0−20 °C, 3 h	8c	54	(100/0), 84/16	0
d	CH_2	$-(CH_2)_3-$	CH_2	2.1 equiv of *c*-Hex$PPh_3^+Br^-$, 2.1 equiv of $MeS(O)CH_2Na$, DMSO, 0−20 °C, 50 h	8d	0		76
e	CH_2	$-(CH_2)_3-$	CH_2	2.1 equiv of *c*-HexPPh3$^+Br^-$, 2.1 equiv of $MeS(O)CH_2Na$, DMSO, 0−60 °C, 15 h	8d	40	(100/0)	0

Scheme 4



Scheme 5[a]



[a] See Table 2.

$\mathbf{8}_{trans}$ to the carboxylic acid functionality using the Baeyer-Villiger reaction, but oxidation exclusively took place on the CC double bond (1.5 equiv of *m*-CPBA, 4 equiv of K_2CO_3, CH_2Cl_2, 20 °C, 44%, dr 65/35). The synthesis of the *trans*-vinylcyclopropane carboxylic acids **1**, including *trans*-chrysanthemic acid **1a**, has been achieved by taking advantage of the regioselective formation of the enolates $\mathbf{7}_{trans}$ from the corresponding isopropyl ketone $\mathbf{8}_{trans}$. The desired transformation was achieved in two steps from $\mathbf{8}_{trans}$ by reaction of the corresponding enolates $\mathbf{7}_{trans}$ with oxygen to give α-hydroxy ketones $\mathbf{14}_{trans}$ ((i) LDA, THF, −78 °C; (ii) −78 to 0 °C; (iii) O_2, 0°C, 4 h; (iv) Na_2SO_3)[11] and further oxidation with periodic acid (Scheme 5 and Table 2).[12]

Experimental Section

General Considerations. Anhydrous DMSO (Acros Chimica) was obtained by distillation from CaH_2. THF was dried by the sodium−benzophenone method immediately prior to use. Other reagents were purchased from commercial sources and used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively, and chemical shifts are reported in δ relative to the reference (δ 0.0 for ^1H and δ 77.0 for ^{13}C). The deuterium content at different positions on **8a′** and **8a″** has been determined by relative integration of their ^1H NMR spectra.

General Method for the Preparation of Isopropyl Ketones 8. A 2 M solution of dimsylsodium[8] was prepared by heating (70−75 °C), under argon, a suspension of sodium hydride (80% mineral oil dispersion, Acros Chimica) in dimethyl sulfoxide. This solution was cooled to 0 °C and stirred at that temperature while a solution containing stoichiometric amounts of alkyltriphenylphosphonium halides (1 M in dimethyl sulfoxide) was added dropwise, leading to a deep red solution of alkylidenetriphenylphosphorane. This was stirred at room temperature for 0.75 h.

The keto alcohol $\mathbf{4a}_{exo}$ (1 M in dimethyl sulfoxide) was added to the ylide solution and the coloration of the solution faded. After it was stirred at room temperature for 1−24 h, the reaction mixture was hydrolyzed with H_2O (3 mL) washed with a saturated aqueous solution of NH_4Cl (10 mL), and then extracted with Et_2O (20 mL). The Et_2O phase was separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with water (2 × 5 mL), and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave the crude reaction mixture. Addition of pentane, filtration of triphenylphosphine oxide, concentration under reduced pressure, and then purification by preparative layer chromatography (SiO_2, pentane or pentane/ether as the eluent) gave **8**.

Isopropyl Ketone 8a. This compound was prepared, according to the typical procedure described above, from isopropyltriphenylphosphonium iodide (4.536 g, 10.5 mmol), dimsylsodium (10.5 mmol) in dimethyl sulfoxide (5 mL) and the keto alcohol $\mathbf{4a}_{exo}$ (0.841 g, 5.0 mmol) in dimethyl sulfoxide (5 mL). Purification on SiO_2 (pentane, R_f 0.36) gave 0.733 g (75 %) of **8a** as a colorless oil: ^1H NMR δ 1.08 (d, 3 H, J = 7 Hz), 1.10 (s, 3 H), 1.11 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 1.74 (d, 1 H, J = 5 Hz), 2.21 (dd, 1 H, J = 8, 5.5 Hz), 2.67 (qq, 1 H), 4.92 (d, 1 H, J = 8 Hz); ^{13}C NMR δ 17.64, 18.15, 18.48, 19.89, 22.28, 25.57, 31.99, 33.24, 41.96, 42.16, 121.44, 135.10, 211.56; IR (film) $\nu_{C=O}$ 1691 cm^{-1}; MS (EI) *m*/*e* 123, 71, 55. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.44. Found: C, 80.25; H, 11.64.

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(12) Gosmini, C.; Sauvêtre, R.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1993**, *130*, 236.

Table 2

entry	R_1		R_2	**14**$_{trans}$	yield %	**1′**$_{trans}$	yield %
a	Me		Me	**14a**$_{trans}$	70	**1a′**$_{trans}$	60
c	H		Et	**14c**$_{trans}$	62		
d	CH_2	$-(CH_2)_3-$	CH_2	**14d**$_{trans}$	60		

Isopropyl Ketone 8b. This compound was prepared, according to the typical procedure described above, from the keto alcohol **4a**$_{exo}$ (0.336 g, 2.0 mmol), methyltriphenylphosphonium iodide (1.620 g, 4.0 mmol), and dimsylsodium (4.0 mmol). After 24 h of reaction at room temperature, the usual workup, and purification on SiO_2 (pentane, R_f 0.25), 0.200 g (60%) of **8b** was obtained as a colorless oil: ^{1}H NMR δ 1.09 (d, 3 H, J = 6.8 Hz), 1.10 (s, 3 H), 1.12 (d, 3 H, J = 7.3 Hz), 1.21 (s, 3 H), 1.90 (d, 1 H (major diast), J = 5.9 Hz), 2.02 (d, 1 H (minor diast), J = 8.3 Hz), 2.20 (dd, 1 H, J = 8.3, 5.4 Hz), 2.69 (qq, 1 H), 5.08 (m, 2 H), 5.58 (m, 1 H (major diast)), 6,20 (m, 1H (minor diast)); ^{13}C NMR δ 17.51, 17.62, 18.02, 19.74, 21.90, 29.63, 29.91, 31.88, 37.22, 37.53, 38.45, 40.72, 42.14, 42.75, 115.59, 116.01, 133.44, 135.52, 210.89, 211.58; IR (film) $\nu_{C=O}$ 1689 cm^{-1}; MS (EI) m/e 95, 71.

Isopropyl Ketone 8c. This compound was prepared, according to the typical procedure described above, from the keto alcohol **4a**$_{exo}$ (0.841 g, 5.0 mmol), *n*-propyltriphenylphosphonium iodide (4.539 g, 10.5 mmol), and dimsylsodium (10.5 mmol). After 3.25 h of reaction at room temperature, the usual workup and purification on SiO_2 (pentane/ether 95/5, R_f 0.57) gave 0.527 g (54%) of **8c** as a colorless oil: ^{1}H NMR δ 0.97 (t, 6 H, J = 2.75 Hz), 1.10 (m, 9 H), 1.20 (s, 3 H), 1.79 (d, J = 5 Hz, 1 H major diast)), 1.83 (d, J = 5 Hz, 1 H (minor diast)), 2.07 (m, 2 H (minor diast)), 2.14 (m, 2 H (major diast)), 2.30 (dd, 1 H, J = 8.5, 5 Hz), 2.68 (qq, 1 H, J = 2.75 Hz), 5.10 (dd, 1 H, J = 10.3, 8.5 Hz (major diast)), 5.19 (dd, 1 H, J = 15.1, 6.8 Hz (minor diast)), 5,48 (dt, 1 H, J = 10.3, 7.3 Hz (major diast)), 5,61 (dt, 1 H, J = 15.1, 6.4 Hz (minor diast)); ^{13}C NMR δ 14.12, 17.57, 18.06, 19.79, 21.10, 22.18, 31.86, 32.20, 42.06, 42.14, 125.85, 134.42, 211.21; IR (film) $\nu_{C=O}$ 1691 cm^{-1}; MS (EI) m/e 123, 95, 71. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.44. Found: C, 80.23; H, 11.43.

Isopropyl Ketone 8d. This compound was prepared, according to the typical procedure described above, from the keto alcohol **4a**$_{exo}$ (0.841 g, 5.0 mmol), cyclohexyltriphenylphosphonium bromide (4.466 g, 10.5 mmol), and dimsylsodium (10.5 mmol). After the mixture was stirred for 15 h at 60 °C, the workup procedure and purification on SiO_2 (pentane/ether 95/5, R_f 0.44) gave 0.461 g (40%) of **8d** as a colorless oil: ^{1}H NMR δ 1.08 (d, 3 H, J = 6.8 Hz), 1.10 (s, 3 H), 1.11 (d, 3 H, J = 6.8 Hz), 1.18 (s, 3 H), 1.50 (m, 6 H), 1.72 (d, 1 H, J = 5.4 Hz), 2.06 (m, 2 H), 2.18 (t, 2 H, J = 5.5 Hz), 2.24 (dd, 1 H, J = 7.7, 5.6 Hz), 2,67 (qq, 1 H, J = 6.8 Hz), 4.86 (d, 1 H, J = 7.7 Hz); ^{13}C NMR δ 17.40, 17.87, 19.58, 22.06, 26.52, 27.42, 28.35, 29.16, 31.77, 32.19, 32.23, 36.58, 41.83, 117.82, 142.98, 211.20; IR (film) $\nu_{C=O}$ 1690 cm^{-1}; MS (EI) m/e 163. Anal. Calcd for $C_{16}H_{26}O$: C, 81.98; H, 11.20. Found: C, 81.99; H, 11.39.

Isopropyl Ketone 8a′ from the Keto Alcohol 4a$_{exo}$**.** Isopropyltriphenylphosphonium iodide (1.81 g, 4.2 mmol) in dimethyl-d_6 sulfoxide (4 mL) was added dropwise under argon to a stirred solution of dimsylsodium (from sodium hydride, 0.120 g, 4.0 mmol) in dimethyl-d_6 sulfoxide (2 mL) maintained at 0 °C. The reaction mixture instantly became deep red and was then stirred at room temperature for 0.25 h. A solution of the keto alcohol **4a**$_{exo}$ (0.340 g, 2.0 mmol) in dimethyl-d_6 sulfoxide (2 mL) was then added dropwise to this mixture, which slowly turned pale brown. After it was stirred at room temperature for 2 h, the reaction mixture was hydrolyzed with H_2O (3 mL), washed with a saturated aqueous solution of NH_4Cl (10 mL) and then extracted with Et_2O (20 mL). The Et_2O phase was separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined, washed with water (2 × 5 mL), and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave a crude reaction mixture. Addition of pentane, filtration of triphenylphosphine oxide, concentration under reduced pressure, and purification of the resulting crude mixture on SiO_2 (pentane, R_f 0.36) gave 0.250 g (65%) of **8a′** as a colorless oil: ^{1}H NMR δ 1.07 (s, 3 H), 1.10 (s, 3 H), 1.11 (s, 3 H), 1.19 (s, 3 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 2.21 (d, 1 H, J = 8.3 Hz), 4.92 (d, 1 H, J = 8.3 Hz); ^{13}C NMR δ 17.56, 18.07, 18.49, 19.88, 22.24, 25.60, 31.93, 33.21, 41.29, 41.55, 41.75, 41.95, 42.17, 121.43, 135.11, 211.65; IR (film) $\nu_{C=O}$ 1691 cm^{-1}; MS (EI) m/e 196 (M), 124. Anal. Calcd for $C_{13}H_{20}D_2O$: C, 79.53; (H + D/2), 11.29. Found: C, 79.48; H, 11.31.

Isopropyl Ketone 8a′ from Isopropyl Ketone 8a. A solution of dimsylsodium was prepared under argon from sodium hydride (0.046 g, 1.53 mmol) and dimethyl-d_6 sulfoxide (1.3 mL). A solution of the isopropyl ketone **8a** (0.248 g, 1.28 mmol) in dimethyl sulfoxide (1.3 mL) was then added dropwise to the mixture, which slowly turned pale brown. After it was stirred at room temperature for 7 h, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (3 × 5 mL). The organic layers were combined, washed with water (2 × 5 mL), and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave 0.136 g (55%) of pure isopropyl ketone **8a′** as a colorless oil.

Isopropyl Ketone 8a″. A solution of isopropyl ketone **8a** (0.388 g, 2.0 mmol) in THF (4 mL) was added dropwise at 0 °C under argon to a stirred solution of LDA prepared from *n*-butyllithium (2.27 mL, 1.50 M, 3.4 mmol) and diisopropylamine (0.51 mL, 0.367 g, 3.6 mmol) in THF (4 mL). The resulting brown solution was stirred at room temperature for an additional 0.3 h and then was quenched with D_2O (1 mL). The colorless solution was immediately extracted with ether (3 × 10 mL). The organic layers were combined, washed with water (2 × 5 mL), and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave 0.386 g (99%) of pure **8a″** as a colorless oil: ^{1}H NMR δ 1.07 (s, 3 H), 1.10 (s, 3 H), 1.11 (s, 3 H), 1.19 (s, 3 H), 1.68 (s, 3 H), 1.71 (s, 3 H), 1.73 (d, 1 H, J = 5.86 Hz), 2.22 (dd, 1 H, J = 7.8, 5.86 Hz), 4.92 (d, 1 H, J = 7.8 Hz); IR (film) $\nu_{C=O}$ 1691 cm^{-1}; MS (EI) m/e 195 (M + 1), 123.

Ketone 11. Trimethylsilyl chloride (0.42 mL, 0.360 g, 3.3 mmol) and then triethylamine (0.46 mL, 0.334 g, 3.3 mmol) were added, at room temperature, to a solution of the keto alcohol **4a**$_{exo}$ (0.505 g, 3.0 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at that temperature for 1 h before adding sequentially ether (15 mL) and a saturated aqueous solution of $NaHCO_3$. The ether phase was separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with water (1 mL), and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave 0.697 g (97%) of pure ketone **11** as a colorless oil: ^{1}H NMR δ 0.16 (s, 9 H), 0.96 (s, 3 H), 1.00 (s, 3 H), 1.01 (s, 3 H), 1.13 (s, 3 H), 1.61 (d, 1 H, J = 5.6 Hz), 1.86 (d, 1 H, J = 5.6 Hz), 3.79 (s, 1 H); IR (film) $\nu_{C=O}$ 1724 cm^{-1}; MS (EI) m/e 240 (M). Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.08. Found: C, 64.80; H, 10.19.

Diol 12. *n*-Butyllithium (3.12 mL, 1.6 M, 5.0 mmol) was added dropwise with stirring at 0 °C under argon to a suspension of the keto alcohol **4a**$_{endo}$ (0.168 g, 1.0 mmol) in toluene (5 mL). The mixture slowly turned pale yellow and was stirred at 0 °C for 3 h. A saturated aqueous solution of $NaHCO_3$ was then added to the mixture. The organic phase was separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with water (3 × 1 mL), and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave 0.207 g of a crude reaction mixture. Purification on SiO_2 (pentane/ether 50/50, R_f 0.74) gave 0.155 g (68%) of **12**: ^{1}H NMR δ 0.97 (m, 12 H), 1.20 (d, 1 H, J = 7.81 Hz), 1.44 (m, 7 H), 1.69 (m, 4 H), 2.19 (bs, 1 H), 3.96 (d, 1 H, J = 6.35 Hz); ^{13}C NMR δ 14.14, 16.92, 19.17, 23.31, 25.94, 26.36, 32.01, 35.71, 37.64, 41.12, 58.91, 84.10, 85.32; IR (film) ν_{OH} 3416 cm^{-1}; MS (EI) m/e 193. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.27; H, 11.60. Found: C, 74.27; H, 11.46.

Hydroxy ketone 14a$_{trans}$**.** A solution of isopropyl ketone **8a** (0.170 g, 0.87 mmol) in THF (1.5 mL) was added dropwise at −78 °C under argon to a stirred solution of LDA prepared at −78 °C from *n*-butyllithium (0.67 mL, 1.50 M, 1.0 mmol) and diisopropylamine (0.14 mL, 0.101 g, 1.00 mmol) in THF (1.5 mL). After a further 0.2 h the temperature was raised to 0 °C and a balloon of oxygen was attached to the reaction flask. The

resulting yellow mixture was stirred at room temperature for 1 h, then hydrolyzed with a saturated aqueous solution of NH_4Cl (5 mL), and extracted with Et_2O (3 × 5 mL). The organic layers were combined, washed with a saturated aqueous solution of Na_2SO_3 and water, and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave 0.138 g of a crude reaction mixture. Purification on SiO_2 (pentane/ether 80/20, R_f 0.31) gave 0.130 g (70%) of **14a**$_{trans}$ as a colorless oil: ^{1}H NMR δ 1.13 (s, 3 H), 1.22 (s, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 1.68 (s, 3 H), 1.72 (s, 3 H), 1.83 (d, 1 H, J = 5.37 Hz), 2.33 (dd, 1 H, J = 7.3, 5.4 Hz), 4.07 (s, 1 H), 4.95 (d, 1 H, J = 7.3 Hz); ^{13}C NMR δ 18.35, 19.50, 22.01, 25.37, 25.74, 26.43, 33.38, 34.33, 38.10, 75.83, 120.56, 135.85, 211.00; IR (film) ν_{OH} 3467, $\nu_{C=O}$ 1685 cm^{-1}; MS (EI) m/e 123. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.57. Found: C, 74.38; H, 10.67.

Hydroxy Ketone 14c$_{trans}$**.** A solution of isopropyl ketone **8c** (0.420 g, 2.16 mmol) was added dropwise at −78 °C under argon to a stirred solution of LDA prepared at −78 °C from *n*-butyllithium (2.00 mL, 1.58 M, 3.21 mmol) and diisopropylamine (0.45 mL, 0.325 g, 3.21 mmol) in THF (1.5 mL). After a further 0.2 h, the temperature is allowed to rise 0 °C and a balloon of oxygen was attached to the reaction flask. The resulting yellow mixture was allowed to stir at room temperature for 4.5 h then hydrolyzed with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. Purification of the resulting crude mixture on SiO_2 (pentane/ether 80/20, R_f = 0.31) gave 0.281 g (62%) of **14c**$_{trans}$ as a colorless oil: ^{1}H NMR δ 0.98 (t, 3 H, J = 7.6 Hz), 1.14 (s, 3 H), 1.23 (s, 3 H), 1.37 (s, 3 H), 1.43 (s, 3 H), 1.90 (d, 1 H (major diast), J = 5.4 Hz), 1.94 (d, 1 H (minor diast), J = 5.4 Hz), 2.04 (m, 2 H (minor diast)), 2.13 (m, 2 H (major diast)), 2.28 (dd, 1 H (minor diast), J = 8.5, 5.6 Hz), 2.41 (dd, 1 H (major diast), J = 8.3, 5.4 Hz), 4.05 (s, 1 H), 5.13 (ddt, 1 H (major diast), J = 10, 8.5 Hz, 1 Hz), 5.24 (dd, 1 H (minor diast), J = 15.1, 6.8 Hz), 5.53 (dt, 1 H (major diast), J = 10, 7.3 Hz), 5.64 (dt, 1 H (minor diast), J = 15.1, 6.3 Hz); ^{13}C NMR δ 14.12, 17.57, 18.06, 19.79, 21.10, 22.18, 31.86, 32.20, 42.06, 42.14, 125.85, 134.42, 211.21; IR (film) ν_{OH} 3467, $\nu_{C=O}$ 1684 cm^{-1}; MS (EI) m/e 123. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.57. Found: C, 74.20; H, 10.63.

Hydroxy Ketone 14d$_{trans}$**.** A solution of isopropyl ketone **8d** (0.330 g, 1.4 mmol) was added dropwise at −78 °C under argon to a stirred solution of LDA prepared at −78 °C from *n*-butyllithium (1.36 mL, 1.54 M, 2.1 mmol) and diisopropylamine (0.30 mL, 0.217 g, 2.1 mmol) in THF (1 mL). After a further 0.2 h the temperature was raised to 0 °C and a balloon of oxygen was attached to the reaction flask. The resulting yellow mixture was stirred at room temperature for 4.5 h, hydrolyzed with a saturated aqueous solution of NH_4Cl, and extracted with Et_2O. Purification of the resulting crude mixture on SiO_2 (pentane/ether 80/20, R_f 0.40) gave 0.209 g (60%) of **14d**$_{trans}$ as a colorless oil: ^{1}H NMR δ 1.13 (s, 3 H), 1.22 (s, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 1.50 (m, 6 H), 1.82 (d, 1 H, J = 5.37 Hz), 2.07 (m, 2 H), 2.17 (m, 2 H), 2.35 (dd, 1 H, J = 6, 5.37 Hz), 4.09 (s, 1 H), 4.90 (d, 1 H, J = 6.8 Hz); ^{13}C NMR δ 19.36, 21.93, 25.65, 26.27, 26.43, 27.38, 28.30, 29.23, 33.36, 33.55, 36.49, 38.16, 75.74, 117.01, 143.99, 210.98; IR (film) ν_{OH} 3268, $\nu_{C=O}$ 1690 cm^{-1}; MS (EI) m/e 163. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.74; H, 10.49. Found: C, 76.14; H, 10.41.

Chrysanthemic Acid 1a$_{trans}$**.** Periodic acid (0.324 g, 1.4 mmol) was added at 20 °C to a stirred solution of the hydroxy ketone **14a**$_{trans}$ (0.230 g, 1.09 mmol) in THF (5 mL). The reaction mixture was stirred for 1.5 h then extracted with ether (4×). The organic layers were combined, washed with water (2 × 2 mL), and then dried over magnesium sulfate. Filtration and concentration under reduced pressure gave 0.205 g of a crude reaction mixture that was directly esterified with diazomethane. Purification on SiO_2 (pentane/ether 90/10, R_f 0.80) gave 0.118 g (60%) of **1a′**$_{trans}$ as a colorless oil: spectroscopic data are identical with published data.[13]

Acknowledgment. We thank the "Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture" (FRIA) for financial support to T.O.

JO962015E

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