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A Synthesis of (±)-*trans*-Chrysanthemic Acid

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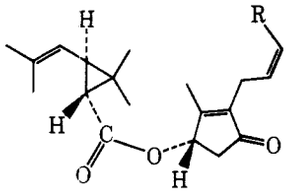
Received November 9, 1976

A synthesis of (±)-*trans*-chrysanthemic acid (8) from eucarvone (1) is described. Ozonolysis of 3-methylcar-4-en-2-one (2) in methanol at −78 °C followed by reduction with dimethyl sulfide and treatment with methanolic hydrogen chloride effects cleavage of the alkene, decarbonylation, and formation of acetal 3 in a single synthetic stage.

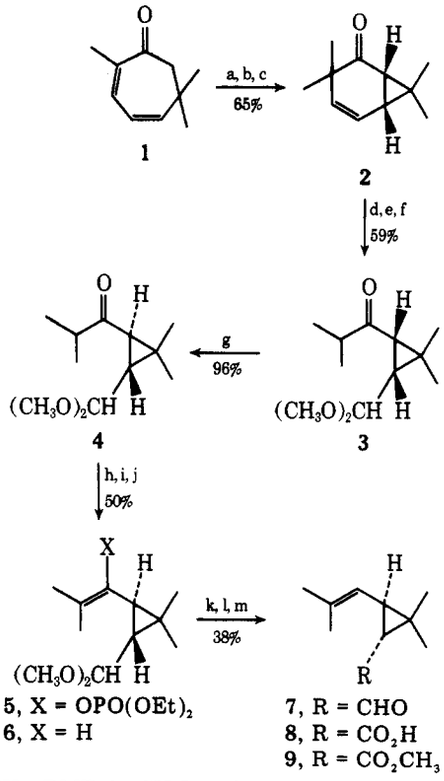
Pyrethrins are a family of naturally occurring insecticides from *Chrysanthemum cineriaefolium* (pyrethrum daises) which exhibit low mammalian toxicity and ready biodegradability.[1] Pyrethrins, such as pyrethrin I, are esters of *trans*-



pyrethrin I, R = CH_3, C_2H_5, or $CH{=}CH_2$

chrysanthemic acid (8) and various rethrolone alcohols.[2] A number of syntheses of *trans*-chrysanthemic acid (8) have been reported[3] presumably because of the usefulness of this substance in the preparation of commercial pyrethrins for pest insect control. We wish to report herein a synthesis of (±)-*trans*-chrysanthemic acid (8) from eucarvone (1).

Eucarvone (1), readily available from carvone,[4] upon alkylation using sodium amide in 1,2-dimethoxyethane (DME) followed by methyl iodide affords a 4:1 mixture of 3-methylcar-4-en-2-one (2) and 2,6,6,7-tetramethylcyclohepta-2,4-dienone, respectively.[5] These two ketones can be separated by preparative gas chromatography;[5] however, while investigating various methods of cleaving the alkenes in this mixture we discovered that the cycloheptadienone could be oxidized at an appreciably faster rate than ketone 2. Therefore, if this mixture of enones is stirred in a homogeneous solution of osmium tetroxide (catalytic amount) and sodium chlorate (2.62 equiv) in aqueous *tert*-butyl alcohol for 18 h,[6] followed by workup and simple bulb-to-bulb distillation, 3-methylcar-4-en-2-one (2) is then obtained pure in 65% overall yield from eucarvone (1). Ozonolysis of ketone 2 in methanol at −78 °C followed by reduction of the ozonide with dimethyl sulfide[7] and treatment with methanolic hydrogen chloride over anhydrous calcium sulfate affords keto acetal 3 in 59% yield. Methanolic hydrogen chloride not only converts the aldehyde group to an acetal, but it also affects decarbonylation of the intermediate nonenolizable β-keto aldehyde. Epimerization of keto acetal 3 using potassium *tert*-butoxide in dry *tert*-butyl alcohol gives keto acetal 4 in 96% yield. Treatment of keto acetal 4 with lithium diisopropylamide (1.1 equiv) in anhydrous tetrahydrofuran (THF) at −78 °C followed by diethyl chlorophosphate (1.1 equiv) at 0–25 °C produces enol phosphate 5 in 62% yield.[8] Reduction of enol phosphate 5 utilizing lithium metal (16 equiv) in anhydrous ethylamine in the presence of dry *tert*-butyl alcohol affords alkene 6 in 81% yield.[9] Hydrolysis of acetal 6 by simply stirring in aqueous acetone for 12 h gives aldehyde 7 in 98% yield. Oxidation of aldehyde 7 with chromium trioxide in wet pyridine for 78 h according to the procedure of Raphael and co-workers[3] produces (±)-*trans*-chrysanthemic acid (8) in 42% yield.[3] Other



a, $NaNH_2$, DME; b, CH_3I; c, OsO_4 cat., $NaClO_3$, H_2O, *t*-BuOH; d, O_3, CH_3OH, −78°C; e, $(CH_3)_2S$; f, CH_3OH, HCl cat., $CaSO_4$; g, KO-*t*-Bu, *t*-BuOH; h, $LiN(i\text{-}Pr)_2$, THF; i, $(EtO)_2POCl$; j, Li, $EtNH_2$, *t*-BuOH; k, acetone, H_2O; l, CrO_3, pyridine, H_2O; m, CH_2N_2, Et_2O.

oxidizing agents were tried including Jones reagent[10] and silver oxide;[12] however, these latter methods proved to be less efficient than chromium trioxide in wet pyridine. Synthetic *trans*-chrysanthemic acid (8) was esterified to (±)-methyl

trans-crysanthemate (**9**) in 92% yield with ethereal diazomethane. Both acid **8** and ester **9** were found to be identical with respect to IR, NMR, TLC, and GLC with authentic samples obtained by epimerization (KO-*t*-Bu, *t*-BuOH), saponification (KOH, H_2O, EtOH), and esterification (CH_2N_2, Et_2O) of ethyl chrysanthemate (Aldrich 12,819-8).

Experimental Section

Melting points were determined on a Nalge No. 500 and/or Büchi melting point apparatus and are uncorrected. All boiling points are uncorrected. Analyses were performed by P.C.R. Laboratories, Inc., Gainsville, Fla., and Spang Microanalytical Laboratory, Ann Arbor, Mich. Analytical gas phase chromatography (GLC) was performed using the following types of columns and flow rates: (a) 6 ft, stainless steel, 0.125 in. column, packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian); (b) 6 ft, stainless steel, 0.125 in. column, packed with 5% FFAP on Varaport 30, 80/100 mesh (Varian); (c) 6-ft, stainless steel, 0.125 in. column, packed with 5% OV-17 on Varaport 30, 80/100 mesh (Varian); (d) 6 ft, stainless steel, 0.125 in. column, packed with 20% OV-101 on Chromosorb G, 80/100; (e) 6 ft, stainless steel, 0.125 in. column, packed with 5% SE-30 on Chromosorb W, 60/80 mesh; (f) 5 ft, stainless steel, 0.125 in. column, packed with 1.5% OV-101 on Chromosorb G, 100/120 mesh, all columns with a flow rate 15 mL/min at ambient temperature. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer. High-resolution mass spectra (HRMS) were obtained on a CEC Model 21-110-B spectrometer under the supervision of Dr. R. Grigsby, Department of Chemistry, Texas A & M University, College Station, Texas. Medium-resolution mass spectra (MRMS) were obtained on a Perkin-Elmer RMU-6H. Finally, for all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120 °C for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider.[10] The term "petroleum ether" refers to Baker "Analyzed Reagent", bp 30–60 °C. The general workup procedure was as follows: the aqueous layer was extracted with ether (three times), and the combined ethereal extracts were washed with water (four times) and saturated sodium chloride solution (once), and then dried (Na_2SO_4), filtered (through Na_2SO_4 or $MgSO_4$), and concentrated in vacuo.

3-Methylcar-4-en-2-one (2).[4,5] Ketone **2** was prepared according to the procedures in ref 4 and 5 starting with eucarvone (9.90 g, 65.9 mmol) and substituing 1,2-dimethoxyethane for 1,4-dioxane as the solvent. Distillation of the crude product gave 9.95 g (92%) of a pale yellow mixture of 3-methylcar-4-en-2-one (**2**) and 2,6,6,7-tetramethylcyclohepta-2,4-dienone in a 4:1 ratio, respectively, by GLC analysis on column a (column temperature 115 °C), retention times 6.8 and 8.9 min, respectively, bp 82–84 °C (0.8 mm) [lit. 86–90 °C (12 mm)].[3] The cycloheptadienone impurity was removed by the following procedure.[6] A solution of the distilled mixture (10.0 g, 60.9 mmol), water (400 mL), *tert*-butyl alcohol (200 mL), sodium chlorate (34.20 g, 159.8 mmol), and a catalytic amount of osmium tetroxide (0.005 g/mL, 4 mL) was allowed to stir at room temperature. The selective cleavage of the cycloheptadienone impurity was monitored by GLC analysis on column a (column temperature 115 °C). After 18 h the resulting pale yellow solution was taken up in an equal volume of water (600 mL) and extracted with dichloromethane (6 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL) and saturated sodium chloride solution (150 mL), and then dried ($MgSO_4$) and concentrated in vacuo to yield 9.84 g of a dark yellow liquid. Distillation gave 7.04 g (70.4%) of pure 3-methylcar-4-en-2-one (**2**): bp 66–70 °C (6 mm) [lit. 70 °C (5 mm)];[3] IR (film) 1695 (CO), 3020, and 995 cm^{-1} (cyclopropyl); NMR (CCl_4) δ 5.74 (2 q, 5-H) as the X part of an ABX system, $J_{4,5}$ = 10 Hz), 5.46 (d, 4-H), 1.66 (m, 2-H, 1- and 6-H as the AB parts of an ABX system, $J_{1,6}$ = 7, $J_{5,6}$ = 4, $J_{1,5}$ = 1 Hz), 1.26, 1.06, 1.03, and 0.95 ppm (4 s, 3,3-7, and 7-CH_3); GLC analysis on column a (column temperature 80 °C, retention time 6.8 min) and spectroscopic evidence show ketone **2** to have less than 0.4% impurity.

(±)-*cis*-3-Isobutyryl-2,2-dimethylcyclopropanecarboxyaldehyde Dimethyl Acetal (3).[7] Ozone was bubbled through a solution of ketone **2** (6.34 g, 38.7 mmol) in absolute methanol (150 mL) at −78 °C for 35 min. Nitrogen was bubbled through the blue purple solution for 15 min to remove any excess ozone. The solution was transferred to a 1-L round-bottomed flask, stirred, and allowed to warm to room temperature while methyl sulfide (2 equiv or until it gave a negative potassium starch–iodide test) was added. This reaction mixture was concentrated in vacuo to approximately one-third its original volume and a catalytic amount of methanolic hydrogen chloride was added (1 mL) with a few crystals of anhydrous calcium sulfate (white Drierite, 8 mesh), then allowed to stand in a refrigerator at 3 °C for 48 h. The solution was diluted with ether (100 mL), shaken with a small amount of solid sodium bicarbonate to remove any traces of acid, washed with water (3 × 40 mL), and then dried (Na_2SO_4, 1 drop of pyridine), filtered (Na_2SO_4), and concentrated in vacuo to give 7.85 g (95%) of a crude product. A portion of the crude product (9.265 g) was chromatographed immediately before use on silica gel (30 g, 70–230 mesh, E. Merck) in a 2.5-cm diameter column. A solution of 30% ether–70% petroleum ether (with a few drops of pyridine) was used to develop the column, taking 15-mL sized fractions. Fractions 12–18 gave 0.211 g (62.5%) of pure keto acetal **3** as a colorless oil: by 40–42 °C (6 mm); IR (film) 1690 (CO), 1370, 1380 (*gem*-CH_3), 3020 (cyclopropyl), 1115, 1090, 1055, and 1020 cm^{-1} (acetal); NMR (CCl_4) δ 4.77 [d, 1, J = 8 Hz, **CH**$(OCH_3)_2$], 3.28 and 3.23 [2 s, 6, –CH$(OCH_3)_2$], 1.07 (d, 6, J = 7.6 Hz, isopropyl), 1.22 (bs, 6, *gem*-CH_3), and 1.83 ppm (d, 1, J = 8 Hz, –COCH); mass spectrum, HRMS (70 eV) *m/e* (rel intensity) 214 (1), 183 (18), 139 (89), 112 (23), 111 (19), 97 (34), 75 (100), 73 (94), 71 (89), 79 (20), 57 (25), 47 (23), 43 (88), 41 (55), 39 (19), 27 (23).

Anal. Calcd for $C_{12}H_{22}O_3$ ($M^+ - OCH_3$, peak at 214 too weak for high-resolution measurement): 183.139309. Found: 183.138495 (MS), 4.4 ppm error.

(±)-*trans*-3-Isobutyryl-2,2-dimethylcyclopropanecarboxaldehyde Dimethyl Acetal (4). Keto acetal **3** (250 mg, 1.17 mmol) in dry *tert*-butyl alcohol (3 mL) was added to a solution of potassium *tert*-butoxide (26.2 mg, 0.233 mmol) in dry *tert*-butyl alcohol (10 mL, freshly distilled from calcium hydrid)). The resulting light yellow solution was allowed to stir at gentle reflux (90 ± 5 °C) for 48 h. The resulting yellow solution was taken up in water (40 mL) and worked up in the usual way. The remaining traces of *tert*-butyl alcohol were removed by codistillation in vacuo with benzene (3 × 40 mL containing a trace of pyridine) to give 248.4 mg of pale yellow crude oil. Distillation of the crude product afforded 241 mg (96%) of colorless epimerized keto acetal **4**: bp 40 °C (5 mm, bulb to bulb, external temperature); IR (film) 1690 (CO), 1370, 1380 (*gem*-CH_3), 1140, 1100, 1055, 1035 cm^{-1} (acetal); NMR (CCl_4) δ 4.16 [d, 1, J = 5 Hz, **CH**$(OCH_3)_2$], 3.26, 3.23 [2 s, 6, –CH$(OCH_3)_2$], 1.20 (d, 6, J = 6 Hz, isopropyl), and 1.07 ppm (bs, 6, *gem*-CH_3); mass spectrum, MRMS (70 eV) 214 (4) 183 (40), 139 (100), 113 (39), 112 (39), 108 (60), 100 (32), 98 (48), 126 (19), 90 (47), 89 (95), 82 (30), 80 (33), 77 (19), 76 (96), 74 (90), 72 (85), 71 (41), 70 (25), 67 (23), 61 (21), 59 (20), 58 (37), 55 (37), 53 (19), 47 (25), 45 (41), 44 (21), 43 (81), 41 (86), 39 (29), 32 (56), 31 (51).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.25. Found: C, 67.64; H, 10.62.

(±)-*trans*-3-(1-Hydroxy-2-methylpropenyl)-2,2-dimethylcyclopropanecarboxaldehyde Dimethyl Acetal Diethyl Phosphate (5).[8] To a solution of methyllithium (0.372 mL, 0.770 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (5 mL, freshly distilled from lithium aluminum hydride) containing a few crystals of bipyridine (used as an indicator) at −40 °C was added freshly distilled diisopropylamine (0.113 mL, 1.15 equiv, 0.806 mmol, distilled from calcium hydride). Stirring was continued for 0.5 h and the temperature allowed to rise to 0 °C. The solution was again cooled to −78 °C and a solution of keto acetal **4** (0.150 g, 0.700 mmol) in anhydrous tetrahydrofuran (3 mL) was added all at once. The resulting yellow orange solution was stirred for an additional 0.75 h and the temperature was allowed to rise to 0 °C. Diethyl chlorophosphate (0.094 mL, 1.1 equiv, 0.771 mmol) was added. The reaction mixture was stirred at room temperature for 1 h, and the solution turned a pale yellow color. The reaction mixture was poured into ice–water (40 mL) and worked up in the usual way to give 0.172 g of a colorless oil. Preparative thin layer chromatography on a 20 × 20 cm silica gel plate using 90% ether–10% petroleum ether eluent (with a drop of pyridine) gave 0.152 g (62%) of enol phosphate **5** (R_f 0.34): bp 90–94 °C (2 mm); IR (film) 1680 (C=C), 1370, 1380 (*gem*-CH_3), 1135, 1095, 1035 (acetal), and 1260 cm^{-1} [P(OC)$_2$]; NMR (CCl_4) δ 4.08 [m, 5, **CH**$(OCH_3)_2$ and P$(OCH_2-)_2$], 3.28 and 3.26 [s, s, 6, CH$(OCH_3)_2$], 1.70 [bs, 6, $(CH_3)_2C$=C], 1.35 [t, 6, J = 7.6 Hz, P$(OCH_2CH_3)_2$], 1.17 and 1.03 ppm (s, s, 6, *gem*-CH_3); mass spectrum, HRMS (70 eV) *m/e* (rel intensity) 350 (2), 319 (17), 318 (43), 169 (32), 165 (44), 164 (95), 155 (32), 150 (26), 149 (94), 133 (31), 124 (89), 122 (26), 121 (29), 109 (46), 107 (83), 105 (25), 99 (45), 91 (38), 75 (100), 73 (56), 41 (41).

Anal. Calcd for $C_{16}H_{31}O_6P$ ($M^+ - OCH_3$, peak at 350 too weak for high-resolution measurement): 319.167414. Found: 319.168674 (MS), 3.9 ppm error.

(±)-*trans*-2,2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde Dimethyl Acetal (6).[9] Freshly cut lithium wire (80 mg, 11 mg-atoms, 16 equiv) was introduced into anhydrous

monoethylamine (25 mL, distilled from lithium metal) with stirring, and stirring continued for 20 min to allow dissolution of the metal. While stirring was continued a solution of enol phosphate (256 mg, 0.731 mmol) in dry *tert*-butyl alcohol (0.27 mL, freshly distilled from calcium hydride) was added all at once. The blue-colored solution was stirred for 10 min and then carefully quenched with ethyl alcohol (2–5 mL). The monoethylamine was then allowed to evaporate. The reaction mixture was transferred to a separatory funnel with a mixture of ether (50 mL) and water (50 mL), and worked up in the usual way to give 0.1245 g of a colorless oil. This crude product was chromatographed on silica gel (14 g, 70–230 mesh, E. Merck) in a 1.0-cm diameter column using 15% ether–85% petroleum ether to develop the column, taking 7-mL sized fractions. Fractions 5–7 gave 0.118 g (81%) of pure olefin acetal **6**: bp 48–51 °C (4 mm, external temperature); IR (film) 1660 (C=C), 1375, 1360 (*gem*-CH_3), 1190, 1125, 1085, 1050 (acetal), 970 cm^{-1} (C=CH); NMR (CCl_4) δ 4.81 (dm, 1, J = 7 Hz, C=CH), 4.05 [d, 1, J = 6 Hz, C**H**C$(CH_3)_2$], 3.21 [s, 6, $(OCH_3)_2$], 1.70 [s, 6, $(CH_3)_2$C=C], 1.12, 1.03 ppm (s, s, 6, *gem*-CH_3); mass spectrum, MRMS (70 eV) *m/e* (rel intensity) 198 (2), 75 (100), 74 (62), 73 (53), 59 (79), 45 (77), 43 (76), 41 (68), 31 (57), 30 (97).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.68; H, 11.24.

(±)-*trans*-2-Dimethyl-3-(2-methylpropenyl)cyclopropanecarboxaldehyde (7).[3] A solution of olefin acetal **6** (100 mg, 0.50 mmol) in reagent acetone (5 mL) and water (about 2 drops) was allowed to stir at room temperature while the progress of the acetal hydrolysis was monitored by TLC [R_f 0.63 (acetal)–9.39 (aldehyde) using 5% ether–95% petroleum ether to develop the slides].

After 12 h the reaction mixture was taken up in water (20 mL) and worked up in the usual way to give 79.4 mg (98%) of colorless olefin aldehyde **7**; bp 38–40 °C (5 mm, external temperature); IR (CCl_4) 2720 (-CHO), 1700 (-CHO), 1375 (*gem*-CH_3), and 975 cm^{-1} (C=CH); NMR (CCl_4) δ 9.5 (d, 1, J = 5 Hz, -CHO), 4.88 (dm, 1, J = 7 Hz, HC=C), 1.72 [s, 6, $(CH_3)_2$C=C], 1.28, 1.18 ppm (s, s, 6, *gem*-CH_3); mass spectrum, HRMS (70 eV) *m/e* (rel intensity) 152 (12), 123 (100), 81 (73), 69 (26), 67 (36), 55 (32), 43 (39), 41 (64), 39 (40).

Anal. Calcd for $C_{10}H_{16}O$: 152.120110. Found: 152.119776 (2.9 ppm error).

(±)-*trans*-Chrysanthemic Acid (8) and (±)-Methyl *trans*-Chrysanthemate (9).[3] **Method A.** Chromium trioxide (1.0 g, 10 mmol) was added carefully to pyridine (10 mL) at 0 °C. The olefin aldehyde **7** (380 mg, 2.50 mmol) in pyridine (3 mL) was added in one portion, followed by water (5 drops). The mixture was stirred at room temperature. The slow oxidation of aldehyde **7** to the acid **8** was monitored by thin layer chromatography, by taking small aliquots of the mixture and diluting it in ether–water (3:1) prior to spotting the plate. Ether–petroleum ether (70:30, respectively) was used to develop the silica gel slides (R_f 0.89, aldehyde; 0.32, acid). After 78 h the mixture was poured into water (25 mL) and ether (5 mL). The reaction mixture was acidified with 10% hydrochloric acid solution until the pH reached 3–4 (approximated by litmus paper), and this mixture was worked up in the usual way to give 189 mg of the crude product as a viscous, colorless oil. Bulb to bulb distillation afforded 178 mg (42.3%) of pure acid **8**, bp 97–99 °C (6 mm, external temperature). The product failed to crystallize even after storing in the refrigerator (3 °C) overnight. Crystallization was induced by taking up a simple sample (50 mg) of the above distilled product in an ethyl acetate–petroleum ether (5 mL, 10:1 ratio, respectively). Removal of the solvent afforded 48 mg of a white, crystalline solid, which was further recrystallized from the same ethyl acetate–petroleum ether solvent system: mp 47–49 °C (lit. 46–48 °C);[3] IR (CCl_4) 2960 (COOH), 1690 (CO), 1740 weak shoulder (H bonding of dimer), 1375 (*gem*-CH_3), 850 cm^{-1} (C=CH); NMR (CCl_4) δ 4.86 (dm, 1, J = 8 Hz, HC=C), 1.95 (dd, 1, J = 8, 5 Hz, -C=CHC**H**), 1.73 [s, 6, $(CH_3)_2$C=C], 1.31, 1.17 (s, s, 6, *gem*-CH_3), 1.33 ppm (d, 1, J = 5 Hz).

Method B. Excess Jones reagent[11] (0.3 mL) was added dropwise to a solution of olefin aldehyde **58** (51.14 mg, 0.337 mmol) in anhydrous reagent acetone (3 mL) at 0 °C (ice bath). After 30 min the reaction mixture was checked by TLC (silica gel slides) developed using 30% ether–70% petroleum ether eluent. The presence of a spot with a high R_f of 0.83 indicated the presence of unoxidized aldehyde. There was also one other unidentified spot of R_f 0.45 besides the acid spot (R_f 0.3). Additional Jones reagent (0.1 mL) was added and the stirring continued at 0 °C. After 30 min the ice bath was removed and the solution stirred at room temperature for an additional 30 min. At this time the excess Jones reagent was quenched with 2-propanol (1 mL) added dropwise. The mixture was poured into water (10 mL) and worked up in the usual way to give 40.4 mg of a colorless, viscous oil. Preparative thin layer chromatography on a 10 × 20 cm silica gel plate using 30% ether–70% petroleum ether eluent gave 16 mg of the acid **8** (28%) and 16.4 mg of an unidentified material (R_f 0.3, acid; 0.41, other product), NMR spectrum of which lacked the doublet at δ 4.8 and the singlet at δ 1.73, characteristic signals of the vinyl H (C=CH) and the isopropylidene 6 H [$(CH_3)_2$C=C], respectively. The pure acid fraction 1 was crystallized from ethyl acetate–petroleum ether (10:1) solvent system, mp 45–47 °C.

Method C.[12] A solution of silver nitrate (1.7 g, 0.1 mol) in water (50 mL) was treated dropwise, with stirring, with a solution of 80% sodium hydroxide solution [prepared from 4 g (0.1 mol) of NaOH and 5.0 mL of H_2O]. The mixture was stirred for 10 min and the brown precipitate (silver oxide) was collected by decantation and washed free of nitrates with distilled water (3 × 20 mL). The wet, freshly precipitated silver oxide was covered with water (2 mL) and stirred while olefin aldehyde **7** (224 mg, 1.47 mmol) in tetrahydrofuran (20 mL) was added all at once followed by addition of a 50% solution of sodium hydroxide (4 drops). After stirring for 36 h the raction mixture was taken up in ether (50 mL) and the aqueous layer separated. The ether portion was washed with 10% sodium hydroxide solution (5 × 20 mL), then worked up in the usual way to give 118 mg of a crude product. The combined aqueous layers were cooled to 0 °C, acidified with concentrated hydrochloric acid (2–4 drops), and worked up in the usual way to give 95.4 mg of a viscous, colorless oil. Distillation of the crude product afforded 83.4 mg (34%) of the pure acid, bp 96–99 °C (6 mm, external temperature). The other 118.2 mg of crude product obtained from the neutral fraction comprised 48% of the theoretical yield and was recognized by the NMR doublet at δ 9.5 as a mixture of unoxidized aldehyde **7** and an unidentified third product. The pure acid **1** obtained by this method was crystallized by ethyl acetate–petroleum ether (10:1) solvent system, mp 47–49 °C. The spectral data of this acid sample are identical with those observed for the other samples obtained via method A and B.

Synthetic *trans*-chrysanthemic acid (**8**, 80 mg, 0.476 mmol) was transformed to its methyl ester by dissolving in ether (10 mL) and adding an ethereal solution of diazomethane at 0 °C in small increments until the yellow color persisted. The solution was maintained at 0 °C for 30 min, then allowed to rise to room temperature. Excess of diazomethane was quenched with glacial acetic acid (2 drops), then the solution was added to an equal volume of ether (15 mL) and washed with water (2 × 10 mL). The ether layer was separated and then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 82 mg of a slightly yellow oil. Distillation of this crude product gave 79 mg (92%) of methyl ester **9**: bp 86–90 °C (12 mm, external temperature) [lit. 90–92 °C (12 mm)];[3] IR (film) 1730 (CO), 3020 (cyclopropyl), 1375, 1350 cm^{-1} (*gem*-CH_3); NMR (CCl_4) δ 4.86 (dm, 1, J = 8 Hz, HC=C), 3.62 (s, 3, CO_2CH_3), 1.73 [s, 6, $(CH_3)_2$C=], 1.93 (dd, 1, J = 7, 8 Hz, C=CHC**H**), 1.25, 1.14 (s, s, 6, *gem*-CH_3) 1.26 ppm (d, 1, J = 7 Hz).

Synthetic (±)-*trans*-chrysanthemic acid (**8**) was found to have identical retention times and R_f values with a sample of authentic *trans*-chrysanthemic acid which was obtained by the epimerization and saponification of ethyl chrysanthemumate[13] (Aldrich 12,819-8). The methyl esters were also found to be identical with respect to IR, NMR, TLC, and GLC.[2,3]

Acknowledgment. We graciously thank The Robert A. Welch Foundation (Grant E-518) and The University of Houston New Research Opportunities Program for their generous support.

Registry No.—**1**, 503-93-5; **2**, 62057-37-8; **3**, 62006-18-2; **4**, 62005-88-3; **5**, 62005-89-4; **6**, 62005-90-7; **7**, 62057-35-6; **8**, 705-16-8; **9**, 15543-70-1; 2,6,6,7-tetramethylcyclohepta-2,4-dienone, 62005-91-8; diethyl chlorophosphate, 814-49-3.

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Vinylketenes. Synthesis of (+)-Actinidine‡

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Received July 13, 1976

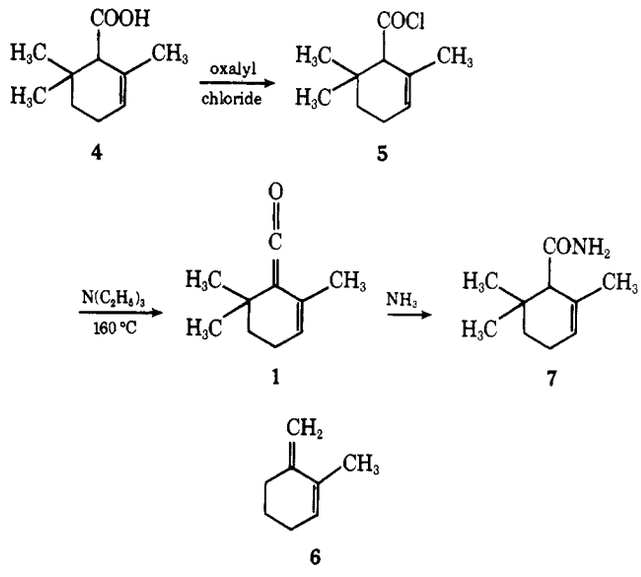
Dehydrochlorination of 2,6,6-trimethylcyclohex-2-ene-1-carbonyl chloride (**5**) yielded 2,6,6-trimethyl-1-carbonylcyclohex-2-ene (**1**), a vinylketene which could be isolated and characterized. Dehydrochlorination of (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carbonyl chloride (**9**) led presumably to (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**), but this vinylketene quickly rearranged by a [1,5] migration of hydrogen into (*R*)-5-methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (**10**). Aldehyde **10** could be converted directly into (+)-actinidine (**12**).

Valence isomerizations of cyclobutenones[1a] and cyclohexadienones,[1b] [1,5] sigmatropic migrations of hydrogen in α,β-γ,δ-unsaturated aldehydes,[2] and pyrolyses of β,γ-unsaturated acid chlorides[2] apparently produce vinylketenes. Although these reactive intermediates have been detected spectroscopically and trapped chemically, the isolation and complete characterization of a vinylketene has not yet been reported. We therefore would like to describe the synthesis and physical properties of 2,6,6-trimethyl-1-carbonylcyclohex-2-ene (**1**), the behavior of (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**), and an application of our observations in a synthesis of the enantiomer of (−)-actinidine (**3**), a natural product of *Actinidia polygama*[3] and *Valeriana officinalis*.[4] Actinidine, first synthesized by Sakan,[5] has received some special attention since it is one of the rare monoterpenoid alkaloids,[6] since it has been reported to be an attractant of cats,[3] and since it is a close structural relative of the principal alkaloid of the medicinal plant *Valeriana officinalis* L.[7]

Results and Discussion

Vinylketene **1** was synthesized by the sequence of reactions described in Scheme I. 2,6,6-Trimethylcyclohex-2-ene-1-carboxylic acid (**4**) was prepared from geranic acid[8] and converted into 2,6,6-trimethylcyclohex-2-ene-1-carbonyl chloride (**5**). This acid chloride strongly resisted dehydrochlorination but was transformed by the action of triethylamine in benzene at 160 °C into compound **1**, which could be isolated and purified by molecular distillation. The infrared spectrum contained bands at 2115 and 1645 cm^{-1}, and the ultraviolet spectrum, which consisted of absorptions at 234 (ϵ 10 100) and 404 nm (ϵ 33), was simply the sum of the spectra expected for the butadiene **6** (λ_{max} 236 nm)[9] and the ketene portion of a diarylketene (λ_{max} 405 nm).[10] In the ^1H NMR spectrum of compound **1**, a sharp singlet replaced the doublet attributable to the diastereotopic methyl groups at C_6 in compounds **4** and **5**. In addition, treatment with ethereal ammonia converted

Scheme I



the ketene into 2,6,6-trimethylcyclohex-2-ene-1-carboxamide (**7**), which was identical with a sample of the amide prepared by the method of Bouveault.[11]

Applied to (1*S*,5*R*)-5-methyl-2-(1-methylethylidene)cyclopentane-1-carboxylic acid (**8**), derived from (+)-pulegone by the procedure of Achmad and Cavill,[12] a similar sequence of reactions did not lead to (*R*)-5-methyl-2-(1-methylethylidene)-1-carbonylcyclopentane (**2**). Instead, (*R*)-5-methyl-2-(1-methylethenyl)cyclopent-1-ene-1-carboxaldehyde (**10**) was isolated. A [1,5] sigmatropic migration of hydrogen in ketene **2**, a rearrangement which has been observed recently by others,[1,2] accounts for the formation of aldehyde **10**; and, in fact, when the dehydrochlorination was interrupted, a ketene was detected spectroscopically by an absorption at 2090 cm^{-1} which vanished slowly at 25 °C. However, no bases, including tetramethylethylenediamine, triethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-bis(dimethylamino)-naphthalene, pyridine, lithium diisopropylamide, and po-

‡ Dedicated to Professor Robert Burns Woodward on the occasion of his sixtieth birthday.