Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Alexey V. Rukavishnikov & Alexey V. Tkaohev (1992) A Novel Synthetic Pathway to 1R- and 1S-Dihidro-Ghrisanthemolactone5 from (+)-3-Carene, Synthetic Communications, 22:7, 1049-1060, DOI: 10.1080/00397919208019296

To link to this article: http://dx.doi.org/10.1080/00397919208019296

SYNTHETIC COMMUNICATIONS, 22(7), 1049-1060 (1992)

A NOVEL SYNTHETIC PATHWAY TO 1R- AND 1S-DIHYDRO-CHRYSANTHEMOLACTONES FROM (+)-3-CARENE.

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ABSTRACT: A novel synthetic approach to the enantiomeric dihydrochrysanthemolactones is described.

Enantiomeric *(1S)*- 7 and *(1R)*- 11 dihydrochrysanthemolactones are the key intermediates in the synthesis of highly efficient pyrethroid insecticides [1]. We have worked out a new route to these compounds starting from a novel intermediate, *(1R,3S)*-2,2-dimethyl-3(2-oxopropyl)-cyclopropane acetonitrile 2, which is a readily available *seco*-derivative of the natural monoterpene hydrocarbon (+)-3-carene 1 [2,3]. Lactones 7 and 11 are prepared from

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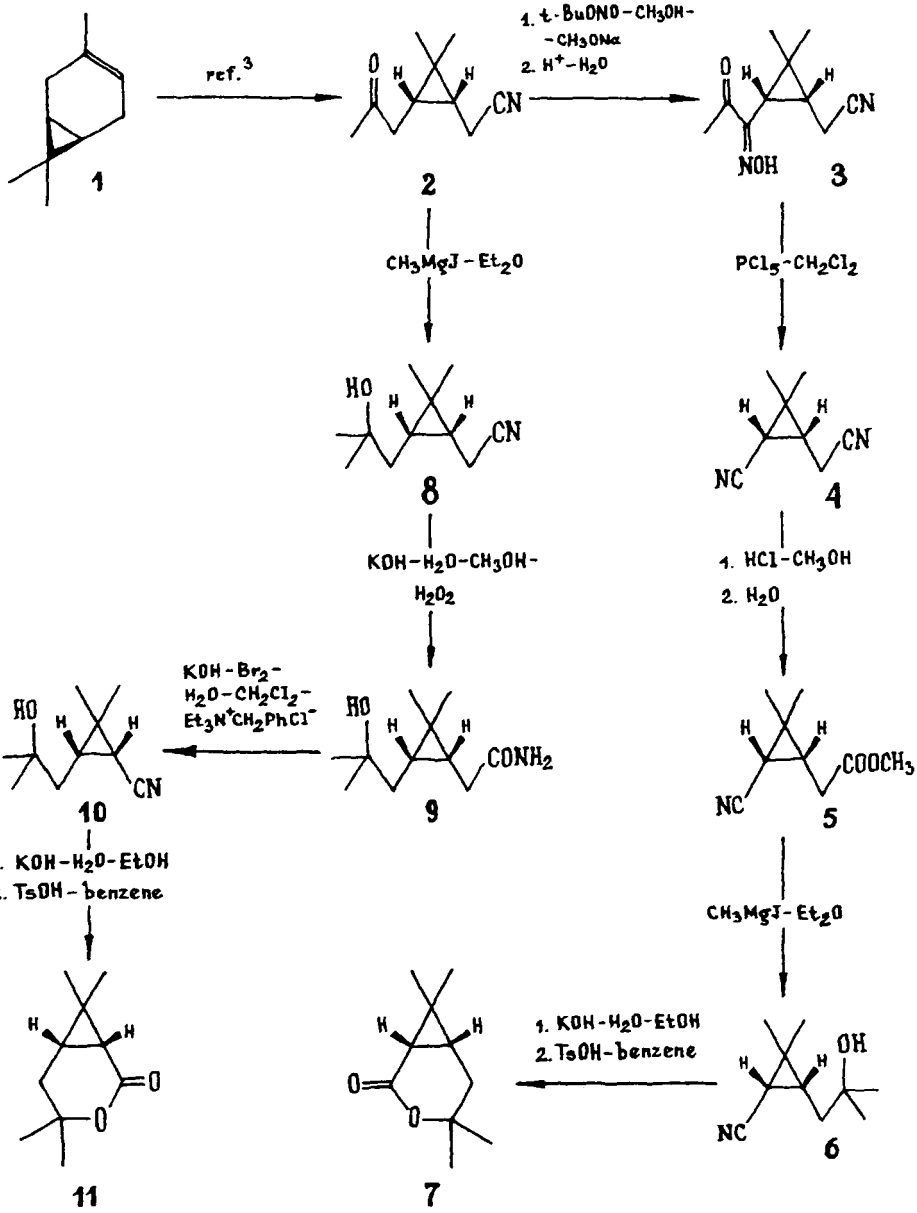
ketonitrile 2, as shown in the scheme. Ketonitrile 2 is condensed with alkyl nitrite to the oximino derivative 3 which is transformed to dinitrile 4 by Beckmann's fragmentation. Nitrile groups of dinitrile 4 essentially differ in reactivity, which allows the selective Pinner reaction to be performed with the subsequent hydrolysis of imino-ester to give ester 5. Treatment of cyano-ester 5 with excess methylmagnesium iodide leads to hydroxynitrile 6 whose alkaline hydrolysis with subsequent lactonization gives *(1S)*-dihydrochrysanthemolactone 7. The Grignard reaction at the keto group of ketonitrile 2 gives hydroxynitrile 8 which forms hydroxyamide 9 by the Radzishevsky reaction with alkaline hydrogen peroxide. On Hoffman rearrangement with excess hypobromite in a two-phase system in the presence of a phase transfer catalyst, amide 9 gives hydroxynitrile 10 being enantiomer of hydroxynitrile 6. Hydrolysis of nitrile 10 followed by lactonization leads to *(1R)*-dihydrochrysanthemolactone 11. These synthetic sequences give fair yields of target products: from ketonitrile 2 the yields of *(1S)*- 7 and *(1R)*- 11 dihydrochrysanthemolactones are 31 and 48% respectively.

EXPERIMENTAL

NMR spectra were obtained using a **Varian 56/60** spectrometer (^{1}H 60 MHz) and a **Bruker WP 200 SY** spectrometer (^{13}C 50.32 MHz). IR spectra were obtained using a **UR-20**



spectrometer. Mass spectra were obtained using a **Finnigan MAT 8200** instrument with EI ionization. Optical rotation was measured in $CHCl_3$ using polarimeter **POLAMAT A** *(Carl Zeiss JENA)*.

(1R,3S)-2,2-Dimethyl-3(2-oxopropyl)-cyclopropaneacetonitrile 2 with $[\alpha]_{580}^{25}$ -12° (pure liquid) was prepared from (+)-3-carene 1 as described in ref.[3]

(1R,3S)-2,2-Dimethyl-3(1-hydroxyimino-2-oxopropyl)-cyclopropaneacetonitrile 3.

To a stirred solution of ketonitrile 2 (20.0 g, 121 mmol) in CH_3OH (80 mL) t-$BuONO$ (12.6 g, 122 mmol) and 3 N CH_3ONa (50 mL, in CH_3OH) are added. The reaction mixture is heated to 50°C and allowed to cool down spontaneously. After the mixture was allowed to stay during 15 h at room temperature, methanol is evaporated at reduced pressure, the resulting mixture is diluted with H_2O (100 mL) and washed with Et_2O (2×30 mL). The aqueous phase is acidified with 1 N HCl (200 mL) and extracted with Et_2O (50, 30 mL). The combined ethereal solutions are washed with brine (20 mL) and dried ($MgSO_4$). The solvent is evaporated at reduced pressure to give the crude oxime 3 (21.0 g, 89% yield) as brown viscous oil solidifying when staying. The analytical sample of oxime 3 is prepared by crystallization of the crude product from Et_2O-hexane: mp 87°C; $[\alpha]_D^{21}$ +103.5° (c 4.3, $CHCl_3$); found C 62.0, H 7.3, N 14.5 (calc. for $C_{10}H_{14}N_2O_2$: C 61.84, H 7.27, N 14.42);

MS (*m/z*, %): 177 (11), 154 (12), 135 (12), 108 (10), 194 (12), 85 (13), 83 (18), 43 (100); IR (1% in CCl_4, cm^{-1}): 3570 and 3340 (O-H), 2260 (C≡N), 1700 (C=O); NMR^{1}H (δ, ppm in $CDCl_3$): 0.89 *s* 3H, 1.26 *s* 3H, 2.34 *s* 3H; NMR^{13}C (δ, ppm, in $CDCl_3$): 15.53 *t*, 16.02 *q*, 18.85 *s*, 23.24 *d*, 23.25 *d*, 25.56 *q*, 26.78 *q*, 119.31 *s*, 155.20 *s*, 197.95 *s*.

(1R,3S)-2,2-Dimethyl-3-cyanocyclopropaneacetonitrile **4**.

To a stirred solution of the crude oxime **3** (17.9 *g*, 92 mmol) in CH_2Cl_2 (80 mL) pounded PCl_5 (19.3 g, 93 mmol) is added at 0°C in small portions over 20 min. The resulting solution is poured into ice water (60 mL). The organic phase is separated, washed consecutively with 0.5 N Na_2CO_3 (3×10 mL) and brine (20 mL) and dried ($MgSO_4$). The solvent is evaporated at reduced pressure to give the crude dinitrile **4** (11.7 g, 95% yield) as brown liquid solidifying when staying. The analytical sample of dinitrile **4** is prepared by crystallization of the crude product from EtOAc: mp 63°C; $[\alpha]_D^{21}$ +74.9° (c 5.2, $CHCl_3$); found C 72.1, H 7.8, N 21.2 (calc. for $C_8H_{10}N_2$: C 71.61, H 7.51, N 20.88); MS (*m/z*, %): 134 (42), 133 (38), 94 (100), 67 (67), 41 (28); IR (1% in CCl_4, cm^{-1}): 2260 and 2240 (C≡N); NMR^{1}H (δ, ppm in CCl_4): 1.21 *s* 3H, 1.27 *s* 3H, 1.3-1.8 *m* 2H, 2.3-2.8 *m* 2H; NMR^{13}C (δ, ppm, in $CDCl_3$): 14.23 *t*, 14.30 *d*, 15.44 *q*, 23.30 *s*, 24.64 *d*, 25.29 *q*, 117.03 *s*, 117.11 *s*.

Methyl (1R,3S)-2,2-dimethyl-3-cyano-cyclopropaneacetate 5.

A solution of the crude dinitrile 4 (6.7 g, 50 mmol) in CH_3OH (40 mL) is saturated with HCl (gas) at 0÷-5°C and allowed to stay at room temperature overnight. Brown solution is separated from the crystalline precipitate and concentrated at reduced pressure (T≤40°C) to a viscous oil, which is combined with the crystalline product and stirred with H_2O (30 mL) over 20 min at room temperature. The reaction mixture is extracted with Et_2O (50 mL), the aqueous phase is saturated with NaCl and extracted with Et_2O (2×30 mL). The combined ethereal extracts are washed with brine (20 mL), dried ($MgSO_4$), and concentrated at reduced pressure to a brown oil, which is passed through a silica gel column (30×4 cm, 100-200 mesh, Et_2O- hexane 1:1) to give the crude ester 5 (4.6 g, 55% yield). The analytical sample of ester 5 is prepared by chromatography of the crude product on a silica gel column (10-50% Et_2O in hexane): $[\alpha]_D^{21}$ +26.6° (c 10.0, $CHCl_3$); found C 64.5, H 7.6, N 8.4 (calc. for $C_9H_{13}NO_2$: C 64.65, H 7.84, N 8.38); MS (*m/z*, %): 167 (3), 135 (60), 108 (60), 107 (100), 94 (50); IR (1% in CCl_4, cm^{-1}): 2240 (C≡N), 1740 (C=O); NMR^{1}H (δ, ppm in CCl_4): 1.26 *s* 6H, 2.3-2.6 *m* 2H, 3.66 *s* 3H; NMR^{13}C (δ, ppm, in $CDCl_3$): 14.16 *d*, 15.93 *q*, 22.94 *s*, 25.11 *d*, 25.84 *q*, 30.32 *t*, 51.30 *q*, 118.04 *s*, 171.36 *s*.

(1S,3R)-2,2-Dimethyl-3(2-hydroxy-2-methylpropyl)-cyclopropanecarbonitrile **6.**

A solution of ester **5** (1.5 g, 9 mmol) in Et_2O (10 mL) is added dropwise at room temperature to a stirred solution of CH_3MgI (30 mmol) in Et_2O (30 mL) over 10 min, and stirring is continued at the same temperature for 4 h. H_2O (20 mL) is added dropwise followed by 1 N HCl (30 mL). The organic phase is separated. The aqueous phase is saturated with NaCl and extracted with Et_2O (2×20 mL). The combined ethereal extracts are washed with brine (20 mL), dried ($MgSO_4$). The solvent is evaporated at reduced pressure to give the crude hydroxynitrile **6** (1.4 g, 93% yield). The analytical sample of hydroxynitrile **6** is prepared by chromatography of the crude product on a silica gel column (40-90% Et_2O in hexane): $[\alpha]_D^{21}$ -2.2° (c 6.2, $CHCl_3$); found C 71.6, H 10.1, N 8.1 (calc. for $C_{10}H_{17}NO$: C 71.82, H 10.25, N 8.37); MS (*m/z*, %): 94(27), 82 (30), 59 (100), 56 (21), 43 (53), 41 (22); IR (1% in CCl_4, cm^{-1}): 3620 (O-H), 2240 (C≡N); NMR ^1H (δ, ppm in CCl_4): 1.17 *s* 6H, 1.22 *s* 3H, 1.26 *s* 3H, 1.57 *d J=7 Hz* 2H; NMR ^{13}C (δ, ppm, in $CDCl_3$): 14.24 *d*, 16.59 *q*, 23.05 *s*, 26.35 *d*, 26.40 *q*, 28.79 *q*, 29.17 *q*, 38.90 *t*, 70.45 *s*, 119.29 *s*.

(1S)-Chrysanthemolactone **7.**

To a solution of the crude nitrile **6** (0.16 g, 1 mmol) in EtOH (2 mL) a solution of KOH (0.75 g, 13 mmol) in H_2O

(2 mL) is added. The reaction mixture is stirred under reflux for 24 h. Ethanol is evaporated at reduced pressure, the resulting syrup is diluted with water (30 mL) and washed with Et_2O (2×10 mL). 1N HCl (20 mL) is added and the mixture is extracted with Et_2O (3×20 mL). The ethereal extract is washed with brine (10 mL), dried ($MgSO_4$), and concentrated at reduced pressure to a brown oil, which is dissolved in benzene (3 mL), *p*-TsOH (0.05 g, 0.3 mmol) is added, and the reaction mixture is refluxed for 1 h. The resulting solution is washed with ice-cold 0.5 N Na_2CO_3 (2 mL), dried ($MgSO_4$). The solvent is evaporated at reduced pressure to give the crude lactone 7 (0.12 g, 71% yield) as brown oil, which solidifies after staying overnight. The analytical sample of lactone 7 is prepared by crystallization of the crude lactone from Et_2O–hexane: mp 81-82°C, $[\alpha]_{580}^{22}$ -78° (c 8.6, $CHCl_3$), (lit.[4] 82-83°C, $[\alpha]_D^{23}$ -72° ($CHCl_3$)). ^1H NMR spectrum of the lactone is identical with that described in ref.[5]

(1R,3S)-2,2-Dimethyl-3(2-hydroxy-2-methylpropyl)-cyclopropaneacetonitrile 8.

Keto nitrile 2 (5.0 g, 30 mmol) in Et_2O (20 mL) is added dropwise over 15 min to a cold (0°C) stirred solution of CH_3MgJ (41 mmol) in Et_2O (250 mL), and stirring is continued at the same temperature for 1 h, then at room temperature for 1 h, and under reflux for 3 h. The reaction mixture is cooled down, H_2O (30 mL) and 1 N

HCl (50 mL) are consecutively added dropwise under vigorous stirring. The organic layer is separated, the aqueous phase is extracted with Et_2O (50 mL). The combined ethereal solutions are washed with brine (60 mL), dried ($MgSO_4$). The solvent is evaporated at reduced pressure to give the crude product 8 (4.8 g, 88% yield). The analytical sample of hydroxynitrile 8 is prepared by chromatography of the crude product on a silica gel column (20-50% CH_3CN in C_6H_6): $[\alpha]_D^{21}$ +18.5° (c 8.4, $CHCl_3$); found C 72.8, H 10.6, N 7.8 (calc. for $C_{11}H_{19}NO$: C 72.88, H 10.57, N 7.73); MS (*m/z*, %): 108 (20), 99 (25), 59 (100), 43 (22); IR (1% in $CHCl_3$, cm^{-1}): 3600 (O-H), 2260 (C≡N); NMR ^1H (δ, ppm in $CDCl_3$): 0.97 *s* 3H, 1.11 *s* 3H, 1.24 *s* 6H, 1.42 *d* *J=7 Hz* 2H, 2.24 *d* *J=7 Hz* 2H; NMR ^{13}C (δ, ppm, in $CDCl_3$): 13.35 *t*, 14.51 *q*, 17.29 *s*, 21.58 *d*, 22.00 *d*, 28.12 *q*, 28.70 *q*, 29.60 *q*, 37.37 *t*, 70.39 *s*, 119.53 *s*.

(1R,3S)-2,2-Dimethyl-3(2-hydroxy-2-methylpropyl)-cyclopropaneacetamide 9.

To a stirred solution of KOH (2.5 g, 45 mmol) in H_2O (20 mL) a solution of the crude hydroxy nitrile 8 (4.8 g, 26 mmol) in CH_3OH (35 mL) is added, and 30% H_2O_2 (33 mL) is then added dropwise, the temperature of the reaction mixture is not allowed to rise higher than 35÷40°C during the addition of H_2O_2. The reaction mixture is saturated with NaCl and the resulting solution is extracted with $CHCl_3$ (4×50 mL). The combined organic extracts are dried

($MgSO_4$) and the solvent is removed at reduced pressure to give the crude hydroxy amide **9** (4.5 g, 87% yield) as a yellowish viscous oil crystallizing when staying. The analytical sample of amide **9** is prepared by crystallization of the crude product from Et_2O–hexane: mp 103–104°C, $[\alpha]_D^{21}$ -2.4° (c 3.7, $CHCl_3$); found C 66.9, H 11.1, N 6.5 (calc. for $C_{11}H_{21}NO_2$: C 66.30, H 10.62, N 7.03); MS (*m/z*, %): 140 (57), 83 (22), 59 (100), 55 (24), 43 (29); IR (1% in $CHCl_3$, cm^{-1}):3600 (O-H), 3520 and 3410 (N-H), 1680 and 1590 (C=O); NMR^{1}H (δ, ppm in $CDCl_3$): 0.91 *s* 3H, 1.09 *s* 3H, 1.22 *s* 6H, 1.41 *m* 2H, 2.16 *m* 2H; NMR^{13}C (δ, ppm, in acetone-d_6): 22.63 *d*, 38.42 *t*, 70.08 *s*, 175.73 *s*, 31.75 *s*, 23.00 *d*, 16.96 *s*, 28.91 *q*, 15.56 *q*, 29.07 *q*, 30.48 *q*.

(1R,3S)-2,2-Dimethyl-3(2-hydroxy-2-methylpropyl)-cyclopropanecarbonitrile **10**.

To a solution of KOH (13.5 g, 240 mmol) in H_2O (30 mL) Br_2 (4.16 mL, 81 mmol) is added dropwise over 30 min with vigorous stirring and with the temperature kept (cooling with ice water) between 0 and +5°C. $Et_3N^+CH_2PhCl^-$ (0.3 g, 1.3 mmol) is added. A solution of the crude hydroxy amide **9** (4.0 g, 20 mmol) in CH_2Cl_2 (30 mL) is then added dropwise over 10 min at 0°C and stirring is continued at room temperature for 1 h, and then under reflux for 2 h. The organic layer is separated and the aqueous phase is extracted with CH_2Cl_2 (20 mL). The combined organic

extracts are washed with brine (20 mL), dried ($MgSO_4$). Removal of solvent at reduced pressure gives the crude hydroxy nitrile **10** (3.1 g, 93% yield). The analytical sample of nitrile **10** is prepared by chromatography of the crude product on a silica gel column (40–90% Et_2O in hexane): $[\alpha]_D^{21}$ +5.7° (c 5.6, $CHCl_3$); found C 71.5, H 10.4, N 8.2 (calc. for $C_{10}H_{17}NO$: C 71.82, H 10.25, N 8.37); spectral data are identical with those of hydroxynitrile **6**.

(1R)-Chrysanthemolactone **11**.

Hydrolysis and lactonization of nitrile **10** (as described above for the transformation of nitrile **6** to *(1S)*-lactone **7**) result in the formation of *(1R)*-lactone **11** (68% yield): mp 81–82°C; $[\alpha]_{580}^{18}$+73° (c 5.0, $CHCl_3$) (Lit.[8] mp 82–83°C, $[\alpha]_D^{28}$ +72° (c 1.5, $CHCl_3$)); ^1H NMR spectrum of the lactone is identical with that described in ref.[5]

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(Accepted in The Netherlands 25 October, 1991)