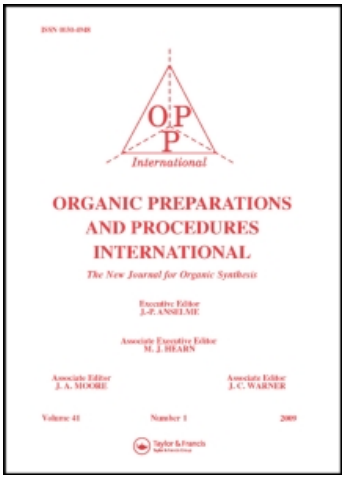


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

IMPROVED SYNTHESIS OF 7,7-DIMETHYL-1,4-DIOXO-2,3,4,5,6,7-HEXAHYDROINDEN-2-YL-ACETIC AND PROPIONIC ACID FROM CITRAL

István Kádas[a]; Géza Árvai[a]; Gabriella Horváth[a]
[a] Department of Organic Chemical Technology, Technical University of Budapest, Budapest, HUNGARY

To cite this Article Kádas, István , Árvai, Géza and Horváth, Gabriella(1998) 'IMPROVED SYNTHESIS OF 7,7-DIMETHYL-1,4-DIOXO-2,3,4,5,6,7-HEXAHYDROINDEN-2-YL-ACETIC AND PROPIONIC ACID FROM CITRAL', Organic Preparations and Procedures International, 30: 1, 79 — 85
To link to this Article: DOI: 10.1080/00304949809355262
URL: http://dx.doi.org/10.1080/00304949809355262

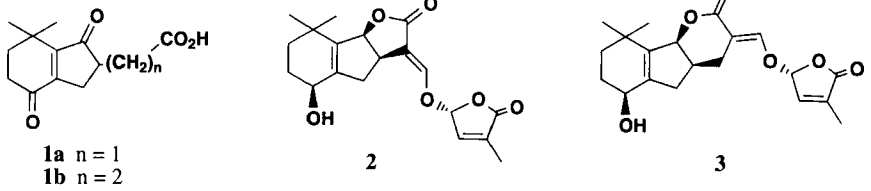
ORGANIC PREPARATIONS AND PROCEDURES INT., 30 (1), 79-85 (1998)

IMPROVED SYNTHESIS OF 7,7-DIMETHYL-1,4-DIOXO-2,3,4,5,6,7-HEXAHYDROINDEN-2-YL-ACETIC AND PROPIONIC ACID FROM CITRAL

István Kádas*, Géza Árvai, Gabriella Horváth

Department of Organic Chemical Technology, Technical University of Budapest
H-1521 Budapest, PO Box 91, HUNGARY

7,7-Dimethyl-1,4-dioxo-2,3,4,5,6,7-hexahydroinden-2-yl-acetic acid[1-3] (**1a**, thereafter shortly referred to as hydrindanacetic acid) is an important intermediate in various syntheses of the powerful plant stimulant strigol (**2**). We set out to elaborate an improved procedure for its preparation and extend the route to the homologous propionic acid **1b**, which can be used in the synthesis of homostrigol analogue **3** (*Fig. 1*).

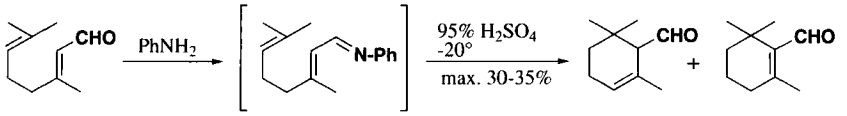


1a n = 1
1b n = 2

2 **3**

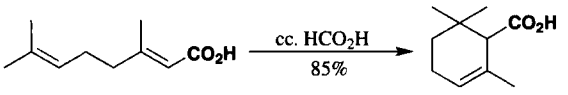
Fig. 1

For this purpose, the synthesis of Sih[2] was modified based on some recent progress.[4-8] Sih's approach makes use of the readily available citral (**4**). We have found, however, that cyclization of citral *via* the corresponding anil (**5**, *Eq. 1*) was unsuitable for scale-up, mainly because of the low temperature employed (-20°), considerable tar formation and difficulties in stirring.



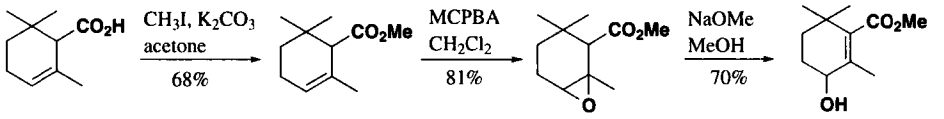
4 **5** **6** **7** (1)

It is known[9] that geranic acid can readily be cyclized into α-cyclogeranic acid (**9**) in good yield (*Eq. 2*) upon treatment with formic acid. Geranic acid (**8**) is in turn synthesized from citral with silver oxide.[9] We found no difficulties in scaling up this reaction in 93% yield. Recycling of silver oxide with a loss of only 3% renders this route feasible.

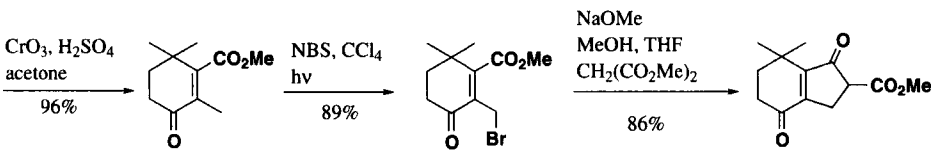


8 9 (2)

A further observation in our sequence was that the formic acid cyclization can be achieved on a 2.5 mole scale in 78% yield. The small amount of isomeric cyclogeranic acid is removed by crystallization from 75% aqueous ethanol. The α-cyclogeranic acid (**9**) is esterified with methyl iodide (acetone, K_2CO_3)[2] on a 1.5 mole scale. Epoxidation with *m*-CPBA, followed by ring opening with sodium methoxide in methanol furnishes the corresponding allylic alcohol **12** (*Eq. 3*).[8]

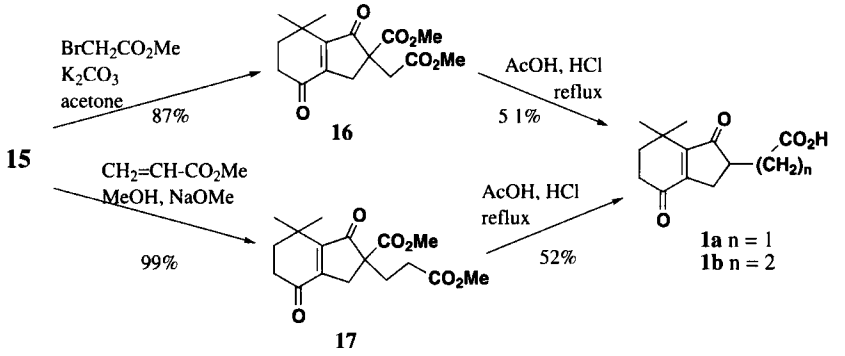


9 10 11 12



13 14 15 (3)

By use of the modified version[8] of the original synthesis,[2] this alcohol (**12**) is converted *via* ketone **13** and the corresponding bromo derivative **14** to hydrindane carboxylic ester **15**,[2] which is transformed to hydrindanacetic (**1a**) and propionic acid (**1b**), respectively. The latter is employed for the synthesis of the corresponding C-homo-strigol 3.[10] The method described here furnished the corresponding hydrindane acids on a 10-20 g scale for further synthetic steps (*Eq. 4*).[12]



(4)

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined on either a Büchi 510 or a Gallenkamp apparatus in open capillary tubes. Infrared spectra were recorded on a Nicolet FT-IR or a Perkin Elmer 1600 Series FT-IR apparatus. ^1H and ^{13}C NMR spectra were obtained on either of the following NMR spectrometers:

Perkin Elmer R12 (^{1}H: 60 MHz), Bruker AW (^{1}H: 80 MHz), Jeol FX (^{1}H: 100 MHz), Varian Unity (^{1}H: 300 MHz), Bruker AC (^{1}H: 250 MHz, 400 MHz) and AM (^{1}H: 500 MHz) (δ, ppm, TMS). Merck Kieselgel 60 was used for tlc and column chromatography. During work-up organic extracts were dried over anhydrous magnesium sulfate. Elemental analyses were performed on automated analyzers by the Richter Gedeon Chemical Co. Ltd or the EGIS Pharmaceutical Co. Ltd. (Budapest, Hungary).

Geranic Acid (8).- Sodium hydroxide (120.0 g, 3.0 mol) in distilled water (750 mL) was added to a suspension of silver oxide (Ag_2O) (695.2 g, 3.0 mol) in distilled water (750 mL). To this suspension freshly distilled citral (**4**) (380.6 g, 2.5 mol) was added with ice cooling and vigorous stirring during a period of 2.5 h. After the addition was complete, the reaction mixture was stirred for a further 8 h. The metallic silver precipitate was removed by filtration and washed thoroughly with distilled water. The combined filtrate was then extracted three times with 50 mL portions of diethyl ether to remove the unreacted citral. The aqueous layer was acidified to pH 1.0 with 20% hydrochloric acid and extracted with diethyl ether (4 x 500 mL).

The ethereal extract from the alkaline solution gave upon distillation 16.0 g of a colorless oil, bp. 44-48°0.1 torr, n_D^{22} 1.4885. The IR and NMR spectra revealed it to be a mixture of geranic acid and citral. Distillation of the extract from the acidic layer gave 391 g (2.33 mol, 93%) of geranic acid, bp. 88-92°/0.1 torr (lit.[11] bp. 90-92°/2 torr), n_D^{25} 1.4851 (lit.[12] n_D^{25} 1.4839). IR and NMR showed it to be a mixture of *E* and *Z* isomers.

The recovered metallic silver was dissolved in concentrated nitric acid and the solution was then filtered through Celite. The silver oxide was precipitated with 10% aqueous sodium hydroxide solution and collected by filtration. The silver oxide thus obtained was washed with water until it became nitrate-free. It was dried and used again. The loss was generally in the range of 2-4%.

α-Cyclogeranic Acid (9).- Freshly distilled geranic acid (**8**) (*E* and *Z* mixture, 378.6 g, 2.25 mol) was added in 15 min into vigorously stirred boiling 99% formic acid (103.5 g, 2.25 mol). Reflux with vigorous stirring was continued for a further 20 min. The formic acid was carefully distilled from the stirred solution under reduced pressure and the hot stirred residue was treated in the same flask with 75% aqueous ethanol (250 mL). The solution was then allowed to crystallize. The crystals were removed at 0° by filtration, washed with 75% aqueous ethanol (2 x 250 mL) and dried. A further crop was obtained after evaporation of the mother liquor. The crude product thus obtained was used in the next experiment only when a melting point higher then 105° was measured. The lower melting point portions were purified further by recrystallisation from 75% aqueous ethanol.

The total product obtained weighed 223.3 g (1.33 mol, 59%), mp. 105-106° (lit.[8] mp. 106°); IR (KBr): 2962, 2928, 2713, 2626, 1700, 1472, 1453, 1411, 1323, 1241, 1217, 1190, 957, 823, 754, 718 cm^{-1}. ^{1}H NMR (80 MHz, $CDCl_3$): δ 0.93 (s, 3 H, CH_3), 1.0 (s, 3 H, CH_3), 1.70 (s, 4H, CH_2CH_2), 1.99 (s, 3 H, =C-CH_3), 2.58 (s, 1H, CH-CO_2), 5.48 (m, 1H, CH=), 11.30 (s, 1H, CO_2H, D_2O exchangeable).

From the mother liquor further crops of α-cyclogeranic acid (**9**) and some β-cyclogeranic acid can be obtained (about 20-25% combined yield from these crops).

Methyl α-Cyclogeranate (10).- To suspension of freshly fused potassium carbonate (27.0 g, 1.66 mol) in anhydrous acetone (1000 mL) was added carefully crystallized α-cyclogeranic acid (252.4, 1.50 mol) with vigorous stirring and exclusion of moisture. Methyl iodide was added at room temperature during 30 min and stirring was continued for 24 h at room temperature. The acetone was removed from the resulting thick suspension by distillation, the suspension was carefully treated with water (500 mL), and the stirred reaction mixture was acidified to pH 1 with a 10% solution of hydrochloric acid. Methylene chloride (500 mL) was then added and the layers separated. The aqueous layer was extracted with methylene chloride (3 x 400 mL). The combined organic layers were dried and concentrated. The remaining oil was purified by distillation under reduced pressure (foaming!). The product was a colorless oil (185.9 g, 1.02 mol, 68%), bp. 96-104°/20 torr (lit.[18] bp. 82-84°/11 torr), n_D^{26} 1.4597 (lit.[18] $n_D^{19.5}$ 1.4626). IR (film): 1736, 1678, 1456, 1440, 1395, 1375, 1332, 1247, 1210, 1190, 1155, 1140, 1042 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.94 (s, 6H, 2 CH_3), 1.67 (s, 4H, CH_2CH_2), 2.00 (s, 3H, CH_3-C=), 2.61 (s, 1H, CH-CO_2), 3.68 (s, 3H, CO_2CH_3), 5.58 (m, 1H, CH=).

Methyl 2,3-Epoxy-2,6,6-trimethyl-cyclohexane-1-carboxylate (11).- An ice-cold and vigorously stirred solution of methyl α-cyclogeranate (**10**) (91.2 g, 0.50 mol) in methylene chloride (300 mL) was treated with a solution of 3-chloroperoxybenzoic acid (50-55% purity, 190 g, 0.55 mol) in 2.4 L of methylene chloride. The addition required 2 h. The reaction mixture was stirred at 0° for 2 h and at room temperature for 2 h. The precipitate was removed by filtration and the excess 3-chloroperoxybenzoic acid was decomposed by stirring with 750 mL of a 10% aqueous sodium pyrosulfite. The organic layer was removed and the aqueous solution was extracted with methylene chloride (2 x 500 mL), dried, and evaporated. The precipitate was filtered and the remaining oil was distilled under reduced pressure to give the product as a colorless oil (80.3 g, 0.405 mol, 81%), bp. 80-82°/0.1 torr; IR (film): 1740, 1430, 1240, 1145, 1005, 880, 750 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.91 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.39 (s, 3H, CH_3-C-O), 1.70-2.00 (m, 4H, CH_2CH_2), 2.45 (s, 1H, CH-CO_2), 3.0 (t, 1H, CH-O), 3.72 (s, 3H, CO_2CH_3) (^1H NMR spectrum showed the presence of 25% of the minor isomer).

Methyl 3-Hydroxy-2,6,6-trimethyl-cyclohexane-1-carboxylate (12).- Sodium pieces (13.0 g, 0.56 g atom) were dissolved in anhydrous methanol (1.4 L). To this stirred solution was added epoxide **11** (99.2 g, 0.5 mol). The solution was heated to reflux temperature and reflux with stirring was continued for 10 h. The progress of the reaction was monitored by glc. The reaction mixture was cooled to room temperature and acidified to pH 1 with 10% hydrochloric acid solution. The acidified reaction mixture was diluted with water (500 mL) and extracted with diethyl ether (4 x 300 mL). The combined ethereal layer was dried and the solvent was removed in vacuum. The product **12** was a viscous oil (69.4 g, 0.35 mol, 70%), bp. 118-122°/0.4 torr (lit.[16] 100°/0.01 torr), n_D^{20} 1.4940 (lit.[16] n_D^{19} 1.4880). IR (film): 3400, 1705, 1640, 1220, 1050, 1005 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$): δ 1.07 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.75 (s, 3H, CH_3-C), 1.30-2.10 (m, 4H, CH_2CH_2), 3.49 (s, 1H, OH, D_2O exchangeable), 3.70 (s, 3H, $COOCH_3$), 3.93 (t, 1H, C*H*-OH).

Methyl 3-Oxo-2,6,6-trimethyl-cyclohexane-1-carboxylate (13).- This compound was prepared in 96% yield by the published method.[2]

Methyl 2-Bromomethyl-6,6-dimethyl-3-oxo-cyclohexane-1-carboxylate (14).- This compound was prepared in 89% yield by the published method;[2] bp. 120-140°/0.6 torr (lit.[2] bp. 122°/0.4 torr).

Methyl 7,7-Dimethyl-1,4-dioxo-2-methoxycarbonyl-4,5,6,7-tetrahydroindane-2-carboxylate (15).- This compound was obtained in 86% yield by the published method;[2] mp. 155-6° (lit.[2] mp. 156.5-8°).

Methyl 7,7-Dimethyl-1,4-dioxo-2-methoxycarbonyl-4,5,6,7-tetrahydroindane-2-yl-acetate (16).- This compound was prepared in 87% yield by the literature procedure.[2,3] An analytical sample was obtained after column chromatography (eluent: hexane-ethyl acetate, 7:3 (v/v)). IR (film): 2955, 2870, 1740, 1709, 1687, 1436, 1362, 1258, 1167 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.32 (s, 3H, 7-CH_3), 1.34 (s, 3H, 7-CH_3), 1.96 (dd, 2H, 6-H), 2.60 (dd, 2H, 5-H), 2.62 and 3.23 (AB, 2H, J_{AB} = 18.4 Hz, 3-H or 10-H), 2.89 and 3.13 (AB, 2H , J_{AB} = 17.6 Hz, 3-H or 10-H), 3.64 and 3.68 (s, 3H, CH_3O); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 198.4 (C-1), 56.0 (C-2), 34.3, 35.1, 37.8, 37.9 (C-3, C-5, C-6, C-10), 204.3 (C-4), 24.6, 25.3 (C-8, C-9), 169.6, 170.5 (C-11, C-12), 51.2, 52.9 (C-13, C-14).

Methyl 3-(7,7-Dimethyl-1,4-dioxo-2-methoxycarbonyl-4,5,6,7-tetrahydroindane-2-yl)-propionate (17).- Sodium pieces (0.2 g, 0.009 g atom) were dissolved in anhydrous methanol (50 mL). Ester **15** (23.6 g, 0.1 mol) in anhydrous tetrahydrofuran (150 mL) and methyl acrylate (12.9 g, 0.15 mol) were added and the reaction mixture was stirred and refluxed under dry nitrogen for 5 h. The progress of the reaction was monitored by tlc (eluent: hexane-diethyl ether, 1:1 (v/v)). After completion of the reaction, the mixture was acidified to pH 1 with 10% hydrochloric acid and evaporated. Water (100 mL) was added to the residue and the aqueous solution was extracted with diethyl ether (3 x 120 mL). The combined ether layer was dried, evaporated, and filtered through 50 g of Kieselgel (eluent: hexane-diethyl ether, 1:1 (v/v)). After evaporation, the residue was sufficiently pure for the next step. An analytical sample (0.5 g) was further purified by column chromatography (eluent: hexane-ethyl acetate, 7:3 (v/v)). Product **17** was isolated as a colorless oil (32.0 g, 0.99 mol, 99%). The sample collected from the column showed the following spectroscopic data: IR (film): 1720, 1700, 1680, 1610, 1420, 1245, 1150 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.32 (s, 6H, 7-CH_3), 1.96 (dd, 2H, J = 6.75, 10-H), 2.58 (dd, 2H, J = 6.75, 11-H), 2.09 and 2.42 (ddd, 2H, J = 18.0, 10.5, 2.0 Hz, 5-H and 6-H), 2.27 (m, 2H, 5-H and 6-H)), 2.54 and 3.14 (AB, 2H, J_{AB} = 18.7 Hz, 3-H), 3.66 and 3.70 (s, 6H, CH_3O). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 197.4 (C-1), 57.6 (C-2), 34.7 (C-3), 155.8, 156.0 (C-3a, C-7a), 204.5 (C-4), 28.7, 33.2 (C-5, C-6), 31.7 (C-7), 24.5 (C-8, C-9), 28.7 (C-10), 33.7 (C-11), 170.0, 172.1 (C-12, C-14), 50.8, 52.0 (C-13, C-15).

(7,7-Dimethyl-1,4-dioxo-2-methoxycarbonyl-2,3,4,5,6,7-hexahydro-inden-2-yl)-acetic Acid (1a).- This compound was prepared in 51% yield following the literature procedure.[3] The product was obtained as a white crystalline solid, mp. 131-134° (lit.[3] 136-138°). Its spectroscopic data were identical to those of an authentic specimen synthesized earlier by a different method.[1]

3-(7,7-Dimethyl-1,4-dioxo-2-methoxycarbonyl-2,3,4,5,6,7-hexahydro-inden-2-yl)-propionic Acid (1b).- The corresponding diester (**17**) (32.23 g, 0.1 mol) was dissolved in a mixture of glacial acetic

acid (250 mL) and hydrochloric acid (6 M, 250 mL). This solution was then stirred and refluxed for 5 h under an atmosphere of nitrogen. During this period, 15% of the acidic solution was distilled out of the reaction flask. The progress of the reaction was monitored by tlc (eluent: toluene-methanol, 6:1 (v/v)). After completion of the reaction, the mixture was diluted to five times its volume with water and the mixture was extracted with ethyl acetate (5 x 200mL). The combined organic layers were washed with water (2 x 250 mL), brine (200 mL), then dried and evaporated. The product was a viscous oil that crystallized upon standing. Addition of ether furnished a mass of pale yellow crystals that were collected and dried.

The final product was a pale yellow crystalline solid (13.01 g, 0.052 mol, 52%), mp. 100-102° (lit.[1] mp. 101°). Its spectroscopic data were identical to those of an authentic specimen synthesized earlier by a different method.[1]

Acknowledgment.- The authors thank the financial support of the Hungarian National Fund for Science and Research (OTKA project No. 5-355 and 5-349), the interest of Professor L. Tõke and the technical assistance of A. Susztek and Z. Kapui.

REFERENCES

1. a) I. Kádas, G. Árvai, L. Tõke, G. Tóth, Á. Szöllõsy, M. Bihari, *Tetrahedron,* **50**, 2895 (1994); b) I. Kádas, V. Morvai, G. Árvai, L. Tõke, Á. Szöllõsy, G. Tóth, M. Bihari, *Monatsh. Chem.*, **126**, 107 (1995).

2. J. B. Heather, R. S. D. Mittal, C. J. Sih, *J. Am. Chem. Soc.*, **98**, 3661 (1976).

3. G. MacAlpine, R. A. Raphael, A. Shaw, A.W. Taylor, H.-J. Wild, *J. Chem. Soc. Perkin Trans. 1,* 410, (**1976**).

4. D. W. Brooks, E. Kennedy, *J. Org. Chem.*, **48**, 277 (1983).

5. D. W. Brooks, H. S. Bevinakatti, E. Kennedy, J. Hathaway, *ibid.*, **50**, 628 (1985).

6. D. W. Brooks, E. Kennedy, H. S. Bevinakatti, in *"The Chemistry of Allelopathy. Biochemical Interactions Among Plants"*. ACS Symposium Series 268, (A. C. Thompson, Ed.), American Chemical Society, Washington, D. C. **1985**, p. 437.

7. O. D. Dailey Jr., S. L. Vail, in *"The Chemistry of Allelopathy. Biochemical Interactions Among Plants"*. ACS Symposium Series 268, (A. C. Thompson, Ed.), American Chemical Society, Washington, D. C., p. 427 (**1985**).

8. O. D. Dailey Jr., *J. Org. Chem.*, **52**, 1984 (1987).

9. K. Bernhauer, R. Forster, *J. prakt. Chem.*, **147**, 199 (1936).

10. I. Kádas, unpublished results.

11. A. G. Caldwell, E. R. H. Jones, *J. Chem. Soc.*, 599 (**1946**).

12. D. J. Bennet, G. R. Ramage, J. L. Simonsen, *ibid.*, 418 (**1940**).

13. P. A. Stadler, P. Oberhänsli, *Helv. Chim. Acta*, **42**, 2597 (1959).

14. G. Wendt, *Ber.*, **74**, 1242 (1941).

(Received January 23, 1996; in revised form September 13, 1997)