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Synthetic Pathways to 2,2-Dimethyl-6-oxo-1-cyclohexaneacetic Acid, a Useful Isoprenoid Building Block

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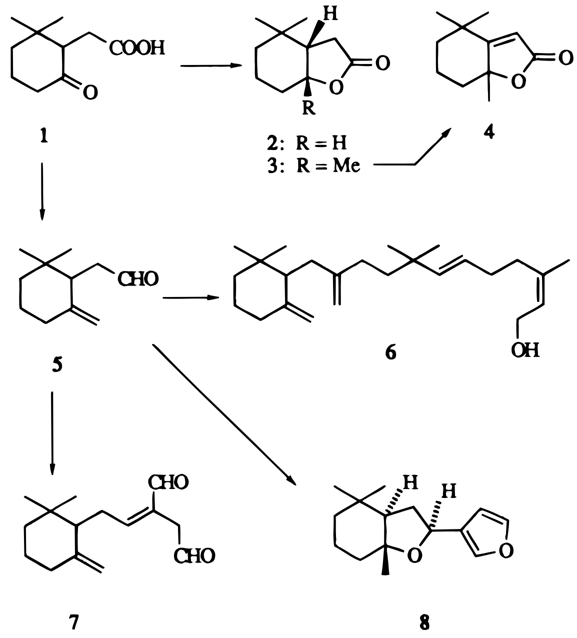
Abstract:

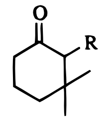
Six new synthetic routes to 2,2-dimethyl-6-oxo-1-cyclohexaneacetic acid (1) from readily available starting materials have been evaluated. The most efficient method (yield 35%) involves alkylation of Hagemann's ester with ethyl bromoacetate followed by hydrolysis of the resultant ethyl 3-(ethoxycarbonyl)-2-methyl-6-oxo-1-cyclohexeneacetate to unsaturated keto acid 2-methyl-6-oxo-1-cyclohexeneacetic acid (19) and then treatment of 19 with Me_2CuLi. A method from mesityl oxide is longer and slightly less efficient (30%). These two methods are suitable for a large-scale preparation of 1.

Scheme 1



Shown in Scheme 1 are important compounds that, most conveniently, can be prepared from keto acid **1**. Lactone **2** has been obtained by reductive lactonization of **1**.[1] *cis*-Tetrahydroactinidiolide (**3**) has been synthesized by the addition reaction of methylmagnesium bromide with **1** and, subsequently, has served as an inexpensive precursor to dihydroactinidiolide (**4**).[2] A short and efficient preparation of γ-cyclohomocitral (**5**) has been reported.[3] Compound **5** is the only starting material described to date for the synthesis of diumycinol (**6**),[3] the lipidic moiety of the antibiotic diumycin,[4] and ancistrodial (**7**)[5] and ancistrofuran (**8**),[6] the two principal components of the defensive secretion from the soldiers of the termite *Ancistrotermes cavithorax*.[7]

Several inefficient and tedious syntheses of keto acid **1** have been reported, but no single method described to date is suitable for a large-scale preparation. For example, the most efficient synthesis of **1** in a 26% yield starts with 3-methylcyclohex-2-en-1-one, a moderately expensive substrate, and requires difficult chromatographic separations.[3] A conceptually simple approach to **1** is by alkylation of a metal enolate of 3,3-dimethylcyclohexanone (**9**) with an alkyl haloacetate. Although lithium 3,3-dimethylcyclohex-1-en-1-olate, the required regioisomer, can be efficiently and selectively generated, its subsequent alkylation with a haloacetate ester produces mainly (>90%) an *O*-alkylated derivative.[3] The undesired *O*-alkylation is also a major problem in the short albeit highly inefficient (4%) preparation of **1** by the reaction of an enolate of keto ester **10** with ethyl bromoacetate followed by hydrolysis of the resultant keto diester and decarboxylation.[8] A five-step sequence for transformation of the ethoxycarbonyl function of **10** into a carboxymethyl moiety gave **1** in an overall yield of 13%.[4]



9: R = H
10: R = CO_2Et

In this paper we report six new synthetic routes to keto acid **1** from readily available starting materials, namely, cyclohexane-1,3-dione (**11**) and Hagemann's ester (**17**) (Scheme 2) and mesityl oxide (Scheme 3). Our initial attempts focused on alkylation of **11** by ethyl bromoacetate to give diketo ester **12**, which subsequently could be transformed into **1** by three independent approaches, shown in Scheme 2. Although the reported modest yield of **12**[9] could not be improved (Scheme 2), this yield of 32% is

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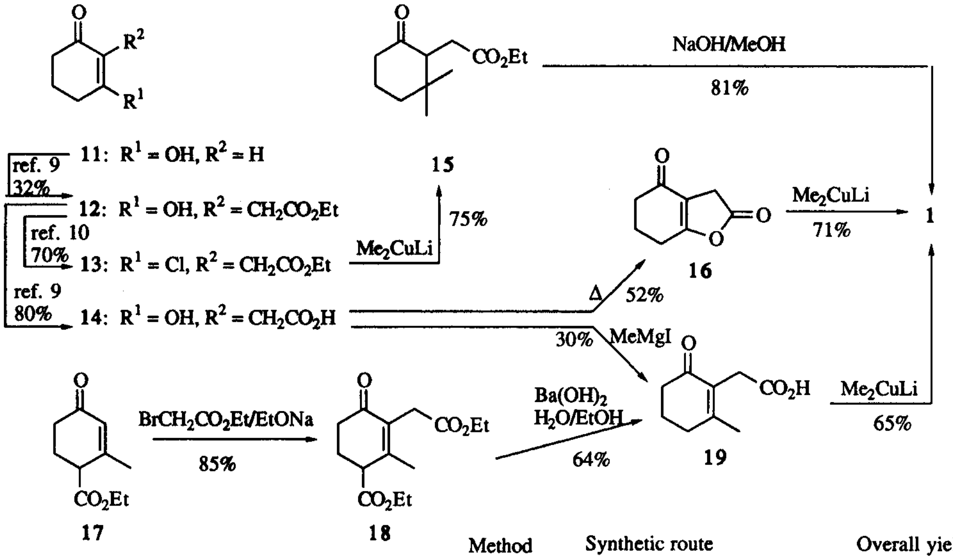
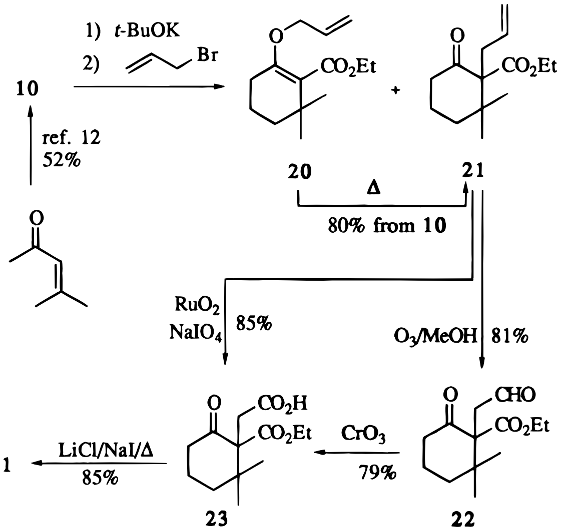
Scheme 2



Method	Synthetic route	Overall yield
A	11→12→13→15→1	14%
B	11→12→14→16→1	9%
C	11→12→14→19→1	5%
D	17→18→19→1	35%

Scheme 3



Method	Synthetic route	Overall yield from mesityl oxide
E	10→21→22→23→1	23%
F	10→21→23→1	30%

relatively high compared to the yields produced in related alkylation reactions with haloacetate esters. Furthermore, the experimental conditions and workup are simple and suited for large-scale preparation. The first synthetic route to **1** involved the reaction of **12** with phosphorus oxychloride to give a chloro derivative **13**[10] followed by a conjugate addition of lithium dimethylcuprate with **13** and then hydrolysis of the resultant keto ester **15** (method A). Two additional routes utilized diketo acid **14**[9] derived from **12**. Sublimation of **14** gave unsaturated lactone **16**, which was treated with lithium dimethylcuprate to yield **1** (method B). A modified procedure involved the reaction of **14** with methylmagnesium iodide followed by a conjugate addition of lithium dimethylcuprate with the resultant unsaturated keto acid **19** (method C). Unfortunately, all three methods (A−C) gave keto acid **1** in quite low overall yields.

The same keto acid **19** has been prepared previously[11] in an overall yield of 40% by alkylation of Hagemann's ester **17** with ethyl chloroacetate followed by hydrolysis and decarboxylation of the resultant keto diester **18**. We found that substitution of ethyl bromoacetate for the chloroacetate ester increases efficiency of the *C*-alkylation of **17** from the reported yield of 62% to 85%. More importantly, the reaction with the bromoacetate is fast at room temperature and we did not notice any induction period in the preparation of several hundred grams of **19**. The efficiencies of small- and large-scale preparations were virtually identical. Following the last step of conjugate addition of **19** with lithium dimethylcuprate, this short and simple method (D) furnishes keto acid **1** in an overall yield of 35%. Chromatography is not required.

The fifth method (E) (Scheme 3) is a longer reaction sequence, but it utilizes quite inexpensive starting materials, and workup is simple at all steps. The major problem of *O*-alkylation of keto ester **10** with haloacetate esters, as already discussed, was overcome by alkylation with allyl bromide followed by thermal rearrangement of the *O*-allyl derivative **20**, in a mixture with the desired *C*-allyl product **21**, to the single isomer **21**. The allyl group in **21** was transformed into the acetic acid function of **23** by ozonolysis and then oxidation of the intermediate aldehyde **22**. Removal of the ethoxycarbonyl group in **23** to give **1** was best conducted under the nonhydrolytic conditions shown in Scheme 3. The overall yield of **1** was 44% from **10** or 23% from mesityl oxide.

The sixth method (F) (Scheme 3) is a modification of route E. Specifically, catalytic oxidation of the allyl group

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in **21** furnished acid **23** directly and in an improved yield of 85%. The overall yield of **1** obtained by method F was 58% from **10** or 30% from mesityl oxide.

In summary, two methods which utilize Hagemann's ester (D) and mesityl oxide (F) as commercially available substrates can be recommended for a practical synthesis of keto acid **1**. The Hagemann's ester method is experimentally simpler.

Experimental Section

All reagents were obtained from Aldrich. Ethyl 2,6-dioxo-1-cyclohexaneacetate (**12**),[9] ethyl 2-chloro-6-oxo-1-cyclohexeneacetate (**13**),[10] 2,6-dioxo-1-cyclohexaneacetic acid (**14**),[9] and ethyl 2,2-dimethyl-6-oxo-1-cyclohexanecarboxylate (**10**)[12] were synthesized as described previously in yields similar to those reported. Melting points are not corrected. ^{1}H NMR spectra were recorded at 200 MHz in $CDCl_3$ with TMS as an internal reference. Mass spectra were taken at 70 eV.

Synthesis of 2,2-Dimethyl-6-oxo-1-cyclohexaneacetic acid (1) from 13: Method A. A standard solution of lithium dimethylcuprate[3] (0.1 mol) in ether (200 mL) was treated dropwise at −10 °C with a solution of **13** (6.5 g, 0.03 mol) in ether (50 mL). The resultant heterogeneous mixture was stirred at 0 °C for 30 min and then poured into aqueous ammonium chloride (10%, 500 mL). Extraction with ether was followed by drying over magnesium sulfate, concentration, and distillation of the oily residue (111−116 °C/0.3 mmHg) to afford 5.0 g (75%) of ethyl 2,2-dimethyl-6-oxo-1-cyclohexaneacetate (**15**).

A solution of **15** (4.2 g, 0.02 mol) and sodium hydroxide (1.2 g, 0.03 mol) in methanol (50 mL) was heated to 60 °C for 1 h. Concentration on a rotary evaporator was followed by addition of water (25 mL) to the residue, acidification with hydrochloric acid, and extraction with chloroform. Keto acid **1** (3.0 g, 81%) was obtained by concentration of the extract followed by crystallization of the residue from cyclohexane/acetone, mp 129−131 °C (lit.[4,8] mp 131−132 °C).

Synthesis of 1 from 14: Method B. Diketo acid **14** (8.5 g, 0.05 mol) was placed in a sublimator and heated (160 °C/15 mmHg) to give 4.0 g (52%) of sublimed 6,7-dihydrobenzo[*b*]furan-2(3*H*),4(5*H*)-dione (**16**): mp 65−67 °C; ^{1}H NMR δ 1.9−2.9 (m, 6 H), 3.37 (t, J = 2 Hz, 2 H); IR ν 1660, 1800 cm^{-1}; MS m/z 96 (60), 124 (70), 152 (100, M$^+$).

Anal. Calcd for $C_8H_8O_3$: C, 63.16; H, 5.31. Found: C, 62.93; H, 5.37.

A solution of lithium dimethylcuprate[3] (0.05 mol) in ether (50 mL) was treated dropwise at 0 °C with a solution of **16** (3.0 g, 0.02 mol) in ether/benzene (1:1, 30 mL). The mixture was stirred at 0 °C for 1 h and then poured into aqueous ammonium chloride (10%, 200 mL). The organic layer was discarded, and the aqueous solution was acidified with hydrochloric acid (12 N) and extracted with chloroform (4 × 50 mL). Standard workup gave 2.6 g (71%) of keto acid **1**, mp 128−130 °C (from dichloromethane/cyclohexane).

Synthesis of 1 from 14: Method C. A solution of **14** (11.9 g, 0.07 mol) in anhydrous THF (500 mL) was treated dropwise with a solution of methylmagnesium iodide (0.21 mol) in ether (65 mL), and the resultant suspension was stirred at 50 °C for 4 h. Then the mixture was poured into cold hydrochloric acid (0.4 N, 600 mL) and extracted with chloroform (4 × 200 mL). Concentration of the extract was followed by silica gel chromatography. Elution with chloroform gave 3.5 g (30%) of 2-methyl-6-oxo-1-cyclohexeneacetic acid (**19**): mp 113−114 °C (lit.[11] mp 113−114 °C).

Compound **19** was allowed to react with lithium dimethylcuprate as described above for the reaction of **16** to give **1** (65%).

Synthesis of 1 from Hagemann's Ester (17): Method D. A solution of sodium ethoxide prepared from sodium (17.5 g, 0.75 mol) and anhydrous ethanol (750 mL) was cooled to −5 °C, stirred, and treated dropwise with **17** (135 g, 0.75 mol). Then ethyl bromoacetate (142 g, 0.85 mol) was added dropwise at such a rate that the temperature of the mixture did not exceed 40 °C. The mixture was stirred for 1 h after the addition was complete. Workup as described previously[11] and distillation (140−145 °C/1 mmHg) gave 170 g (85%) of ethyl 3-(ethoxycarbonyl)-2-methyl-6-oxo-1-cyclohexeneacetate (**18**). Hydrolysis of **18** and decarboxylation of the resultant diacid to give **19** were conducted as a one-pot procedure as described previously.[11] Synthesis of **1** from **19** is described above.

Synthesis of 1 from 10: Method E. Keto ester **10** (39.6 g, 0.2 mol) was added in one portion at 22 °C to a solution of potassium *tert*-butoxide (22.8 g, 0.2 mol) in *tert*-butyl alcohol (500 mL). The mixture was stirred for 10 min, treated with allyl bromide (36.4 g, 0.3 mol), stirred at 23 °C for an additional 12 h, and then poured into ice and water (500 mL). The mixture was extracted with ether, and the extract was dried with sodium sulfate and concentrated. The ^{1}H NMR spectrum of the oily residue gave two triplets at δ 1.0−1.4 and two quartets at δ 4.0−4.4 for ethoxycarbonyl groups, indicating that both *O*- and *C*-alkylation occurred. The crude product was heated to 140 °C for 2 h under a nitrogen atmosphere and then distilled (82−87 °C/0.15 mmHg) to give 38 g (80%) of ethyl 1-allyl-2,2-dimethyl-6-oxo-1-cyclohexanecarboxylate (**21**): ^{1}H NMR δ 0.85 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H), 1.27 (s, 3 H), 2.5−3.2 (m, 8 H), 4.13 (q, J = 7 Hz, 2 H), 5.00 (m, 2 H), 5.85 (m, 1 H); IR ν 1640, 1720, 1745 cm^{-1}; MS m/z 41 (100), 43 (50), 55 (80), 69 (70), 95 (50), 123 (50), 136 (50), 238 (10, M$^+$).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.31. Found: C, 70.30; H, 9.35.

A solution of **21** (23.8 g, 0.1 mol) in methanol (200 mL) was allowed to react with ozone, and then the mixture was worked up by using a general procedure.[13,14] Distillation (122−125 °C/0.3 mmHg) yielded 19.4 g (81%) of 1-(ethoxycarbonyl)-2,2-dimethyl-6-oxo-1-cyclohexaneacetaldehyde (**22**) as a colorless oil [^{1}H NMR δ 0.84 (s, 3 H), 1.04 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H), 1.5−3.6 (m, 8 H), 4.16 (q, J = 7 Hz, 2 H), 9.53 (t, J = 1.2 Hz, 1 H)]. The aldehyde **22** was oxidized to 1-(ethoxycarbonyl)-2,2-dimethyl-6-oxo-1-cyclohexaneacetic acid (**23**) by treatment with a standard Jones

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reagent under general conditions described previously.[15,16] The mixture in acetone (800 mL) was concentrated on a rotary evaporator to 100 mL, treated with brine, and then extracted with dichloromethane. The extract was washed with a solution of sodium bicarbonate (10% in water, 4 × 75 mL), and the basic aqueous solution was acidified with 50% sulfuric acid and then extracted with dichloromethane (3 × 100 mL). Concentration gave 16.2 g (79%) of crystalline acid **23**: mp 89−90 °C; ^{1}H NMR δ 0.91 (s, 3 H), 1.00 (s, 3 H), 1.26 (t, $J = 7$ Hz, 3 H), 1.5−3.6 (m, 8 H), 4.18 (q, $J = 7$ Hz, 2 H); IR ν 1725, 1750 cm^{-1}; MS *m/z* 41 (100), 55 (80), 67 (50), 69 (60), 95 (60), 123 (50), 141 (30), 169 (30), 256 (2, M$^+$).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.90; H, 7.87. Found: C, 60.88; H, 7.91.

A mixture of **23** (11.0 g, 43 mmol), lithium chloride (3 g), sodium iodide (10 g), water (7 mL), and 2,4,6-collidine (100 mL) was heated under reflux for 7 h, then concentrated on a rotary evaporator, and poured onto ice. Acidification with hydrochloric acid (12 N) was followed by extraction with dichloromethane (5 × 50 mL). The extract was shaken with a solution of sodium bicarbonate (10% in water, 200 mL), and the aqueous layer was washed with dichloromethane (2 × 50 mL) and then acidified with 50% sulfuric acid. The acidic aqueous mixture was extracted with dichloromethane (3 × 75 mL). The extract was decolorized by treatment with charcoal and concentrated. Crude keto acid **1** was crystallized from dichloromethane/cyclohexane and then from acetone/cyclohexane to afford 6.6 g (85%): mp 129−130 °C.

Synthesis of 1 from 10: Method F. Alternatively, a solution of **21**, prepared as described in method E (2.4 g, 10 mmol), in acetone (100 mL) was added dropwise to a stirred mixture of ruthenium dioxide (0.5 g) and sodium periodate (2 g) dissolved in water (40 mL) maintained in an ice bath. The resulting black suspension was allowed to warm to 23 °C, and additional sodium periodate (2 × 3 g) in water (50 mL each) was added over a 3 h period. The resulting yellow suspension was stirred at 23 °C for 15 h, and then acid **23** was isolated in two crops (2.2 g, 85%) following the above workup procedure. Removal of the ethoxycarbonyl group of **23** was also conducted as described in method E.

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