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Synthesis and biological evaluation of A-ring analogs of the natural germination stimulant strigol

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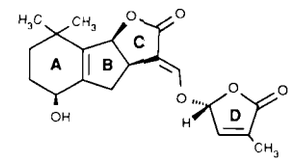
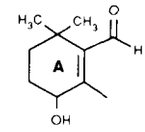
Abstract. An A-ring-derived analog of the natural germination stimulant, Strigol (**1**), has been prepared from citral in an unambiguous manner. This analog, **2**, a γ-hydroxy aldehyde for which a high stimulant activity was claimed in the literature, has been re-evaluated as a germination stimulant for seeds of parasitic weeds and was found to be inactive. It was also shown that analog **2** is rather stable in aqueous solution, in contrast to other reports.
In addition, some related A- and AB-ring-derived analogs have been prepared and biologically evaluated. The γ-hydroxy acid **12** was obtained in one step from a mixture of α- and β-cyclocitral in 58% yield. The dihydroxy analog **14** was prepared by reduction of the γ-hydroxy ester **13**. The AB-ring analog **15** has been synthesized in five steps from ester **13** following published procedures. All analogs have been evaluated using *Striga* and *Orobanche* seeds; none of the compounds induced germination. It was concluded that the actiphore of strigol does not reside in the AB part of the molecule.

Introduction

The parasitic weeds of the genera *Striga* and *Orobanche* cause serious damage to graminaceous and leguminous crops, respectively, in the tropical and semi-tropical areas of the eastern hemisphere[1-3]. The seeds of these weeds will germinate when triggered by a chemical signal which is present in the root exudate of the host plant. A natural germination stimulant was isolated from the roots of cotton and identified by *Cook* et al.[4,5]. This compound, named Strigol (**1**), can be used as a model in the design of analogs, which still have the desired biological activity and also to establish a structure–activity relationship. Suitable analogs can, in principle at least, be used as herbicides in controlling these parasitic weeds. Suicidal germination of *Striga* and *Orobanche*, *i.e.*, introduction of a germinating agent into the soil to induce germination of the parasitic seeds before planting the desired crops, is an attractive approach for reducing the number of viable seeds of these weeds[6].
From the extensive studies of *Johnson* et al.[7,8], it was tentatively concluded that the actiphore in strigol resides in the CD part of the molecule.



1 (+)-STRIGOL



2

However, other researchers claim that some A-ring-derived analogs also exhibit significant stimulatory activity[9,10]. One of these compounds, *i.e.*, compound **2**, stimulated the germination of *Striga asiatica* seeds in the same order as strigol itself, although it was noted that there were problems with the reproducibility of the bioassays[9]. Recently, *Vail* et al.[10] reported the evaluation of some A-ring analogs in a modified bioassay; compound **2** was found to be inactive, whereas other A-ring analogs were claimed to have considerable activity.
The aim of the present study was to synthesize **2** and some related A-ring analogs in an unambiguous manner and to (re-)evaluate their biological activity.

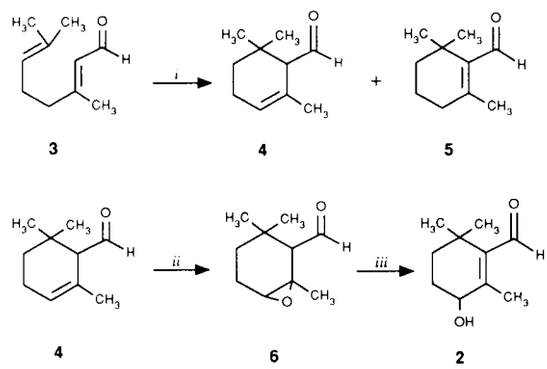
Abbreviations and synonyms:

AIBN = azobisisobutyronitrile = 2,2′-azobis(2-methylpropanenitrile)
*m*CPBA = *m*-chloroperbenzoic acid
citral = 3,7-dimethyl-2,6-octadienal
α-cyclocitral = 2,6,6-trimethyl-2-cyclohexene-1-carboxaldehyde
α-cyclocitral = 2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde
DHP = 3,4-dihydro-2*H*-pyran
DIBAL = diisobutylaluminum hydride
NBS = *N*-bromosuccinimide
NMP = *N*-methylpyrrolidone
P.A. = *pro analysi*
THP = tetrahydropyranyl
TLC = thin-layer chromatography
*p*TosOH = *p*-toluenesulfonic acid = 4-methylbenzenesulfonic acid

Results and discussion

Synthesis

The synthetic sequence to hydroxy aldehyde **2** from citral, which is depicted in Scheme 1, forms part of the total synthesis of strigol as described by *Heather* et al.[11].

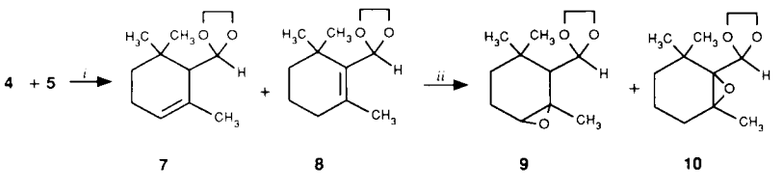


i. a. Aniline, Et_2O; b. cond. H_2SO_4. ii. mCPBA, CH_2Cl_2. iii. Pyrrolidine.

Scheme 1

Pepperman and *Blanchard*[12] reinvestigated and optimized the steps of this sequence and reported that hydroxy aldehyde **2** is very unstable. On repeating the cyclization of citral **3**, we found different ratios of α- and β-cyclocitral (**4** and **5**, respectively). Separation of **4** and **5** by distillation was not complete and, during distillation, the ratio of **4** and **5** shifted in favor of the unwanted isomer **5**. The opening of epoxide **6** with pyrrolidine and subsequent distillation of the product **2** also caused serious problems. *Pepperman* and *Blanchard*[12] reported that this conversion of **6** into **2** proceeds in lower yields than suggested by *Heather* et al.[11]. A modified procedure to prepare **2** is based on *Frank*'s observation[13] that acetalization of β-cyclocitral (**5**) with 1,2-ethanediol leads almost exclusively to the acetal **7** derived from α-cyclocitral (**4**).

By applying this acetalization procedure to a mixture of α- and β-cyclocitral (**4** + **5**), the predominant product was acetal **7**. In a typical experiment, a mixture of **4** and **5** in a ratio of 31 : 69 gave acetal **7** in 62% yield along with 31% of **8**. This mixture of acetals was then subjected to epoxidation using *m*-chloroperbenzoic acid (*m*CPBA). The resulting epoxy acetals **9** and **10** were readily separable, giving analytically pure epoxide **9**, in an acceptable yield of 50% based on the mixture of **4** and **5** (Scheme 2). Hydrolysis of

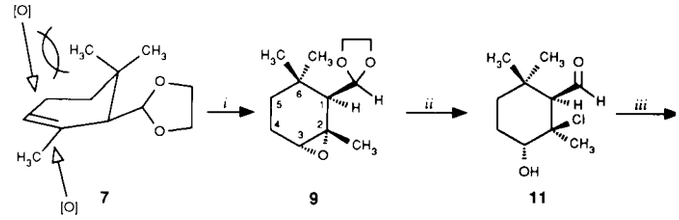


i. $HOCH_2CH_2OH$, pTosOH, C_6H_6, reflux. ii. mCPBA, CH_2Cl_2.

Scheme 2

9 with aqueous hydrogen chloride in tetrahydrofuran gave the chlorohydrin **11** which, in a subsequent treatment with potassium *tert*-butoxide, gave the desired hydroxy aldehyde **2** (Scheme 3).

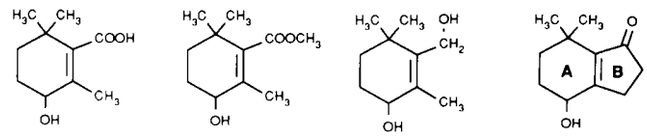
The stereochemistry of the conversion of **7** into **2** is depicted in Scheme 3. It is expected that the epoxidation of **7** takes place *anti* to the acetal group, because *syn* attack is hindered



i. mCPBA, CH_2Cl_2. ii. 1N HCl (aq.), THF. iii. KOtBu, THF.

Scheme 3

by one of the methyl groups at C6 (it is assumed that **7** adopts a conformation in which the large acetal group is positioned equatorially). The subsequent acid-catalyzed epoxide opening will take place with inversion of configuration at C2, to give **11**. The compound thus obtained will have the desired *anti*-periplanar configuration for the elimination of HCl. As a consequence of this mechanism, one expects only one diastereomer (racemic) of the intermediates **9** and **11**, as was confirmed by chromatography and ^{1}H NMR spectra.

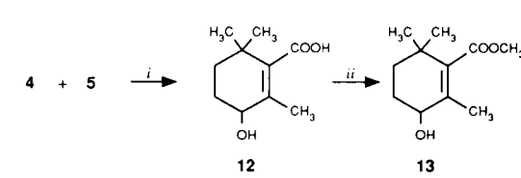


12 **13** **14** **15**

Pepperman et al.[9] reported that **2** readily oxidizes during storage to the corresponding, inactive acid **12**. To study the biological activity of related analogs, the corresponding acid **12**, its methyl ester **13**, the diol **14** and the hydroxy ketone **15** were also prepared. The latter compound is actually an AB-ring analog of strigol.

Carboxylic acid **12** could easily be obtained from an mixture of α- and β-cyclocitral by a procedure based on work by *Sierra* et al.[14]. These authors treated a mixture of α- and β-cyclocitral with 5 equivalents of *N*-bromosuccinimide (NBS) in dioxane in the presence of water and calcium carbonate and obtained 2,6,6-trimethyl-3-oxo-1-cyclohexene-1-carboxylic acid after aqueous work-up. By using NBS in carbon tetrachloride and 2 instead 5 equivalents NBS, bromination followed by aqueous work-up gave the desired 3-hydroxy-2,6,6-trimethyl-1-cyclohexene-1-carboxylic acid **12** in 58% yield (Scheme 4). This is a considerable improvement of the published procedure of *Wendt*[15], who prepared acid **12** from pure β-cyclocitral in three steps and an overall yield of 37–40% (see also *Heather* et al.[11]).

The corresponding methyl ester **13** was obtained in quantitative yield by treatment of the acid **12** with diazomethane.



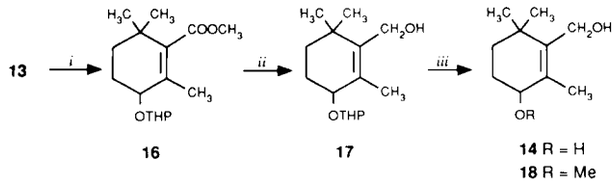
i. a. NBS, CCl_4, AIBN, hν; b. $NaHCO_3$ (aq.). ii. CH_2N_2, MeOH.

Scheme 4

This ester has previously been described as an intermediate in two total syntheses of strigol[11,16].

For reduction of methyl ester **13** to the dihydroxy analog **14**, the 3-hydroxyl function must be protected. The tetrahydropyranyl function (THP) was used. THP ether **16** was then reduced with diisobutyl aluminum hydride (DIBAL) to give the corresponding alcohol **17** in quantitative yield

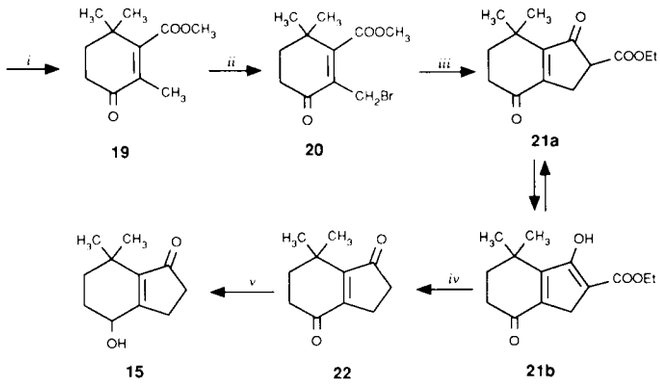
(Scheme 5). For the deprotection, **17** was treated with a mixture of acetic acid, water and tetrahydrofuran (4 : 2 : 1) at 40 °C to give the desired compound **14** in moderate yield (34%). Attempts to improve this result by using the standard procedure for deprotection of THP ethers, *i.e.*, *p*-toluenesulfonic acid in methanol, gave only the corresponding methyl ether **18**.



i. DHP, H⁺, CH_2Cl_2. ii. DIBAL, Et_2O. iii. HOAc/H_2O/THF 4:2:1.

Scheme 5

The preparation of AB-ring analog **15**, depicted in Scheme 6, has been described by *Brooks* et al.[16,17]. The first three steps are part of several total syntheses of strigol and have been described in detail. The decarboxylation and selective reduction of **21** have only been mentioned by *Brooks* et al. in a symposium report[17] and, therefore, a detailed description of these steps is included in the experimental section.



Jones ox. ii. NBS, CCl_4, AIBN, hv. iii. NaH, $CH_2(COOEt)_2$, THF. iv. LiCl, NMP, 100 °C. v. $NaBH_4$, MeOH.

Scheme 6

Decarboxylation of **21** with lithium chloride in *N*-methylpyrrolidone (NMP) gave the diketone **22** in quantitative yield. Subsequent treatment of **22** with sodium borohydride in methanol gave selective reduction of the less hindered carbonyl function and **15** was obtained in good yield (75%).

Biological activity

Aqueous solutions of A-ring analogs **2**, **12–15** (concentrations varying between 10 and 0.01 mg/l) were evaluated for stimulating activity on seeds of *Striga Asiatica* (L.) Kuntze, *Striga hermonthica* (Del.) Benth., *Orobanche aegyptiaca* Pers. and *Orobanche crenata* Forsk.[18]. The germination percentages obtained were not above the results of the control. It was concluded that these A-ring analogs are not germination stimulants. This means that *Pepperman*'s claim[9] of a high activiy for analog **2** is incorrect. *Pepperman* attributed problems with the reproducibility of the bioassay to the poor stability of analog **2**. By extracting an aqueous test solution of **2** with diethyl ether, 4 days after its preparation, pure compound **2** was recovered, which suggests that the aldehyde **2** is rather stable, at least in solution. The other A-ring analogs have not been evaluated previously, but *Vail* et al.[10] found some activity for the ethyl ester of acid **12**. In the present bioassay, the corresponding methyl ester **13** was inactive.

The results presented in this paper strongly suggest that A- and AB-ring analogs cannot act as germination stimulants and support the tentative conclusion (based on work of *Johnson* et al.[8,19]) that the actiphore of strigol resides in the CD part of the molecule.

Experimental

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer 298 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM390 (90 Mhz) spectrometer with TMS as internal standard. For mass spectroscopy, a double-focussing VG 7070E was used. "Flash" chromatography was carried out at a pressure of *ca.* 1.5 bar using silica gel 60H (Merck art. No. 7719). Thin-layer chromatograms (TLC) were run on plastic-supported silica gel 60 plates (0.2-mm layer, F_{254}, Merck art. No. 5735) or glass-supported silica gel 60 plates (0.25-mm layer, F_{254}, Merck art. No. 5715).

Solvents were dried using the following methods: Dimethylformamide P.A. was dried on molecular sieves 4 Å. Tetrahydrofuran was distilled from lithium aluminum hydride just before use. Petroleum ether 60–80 and hexane were distilled from calcium hydride. Diethyl ether was pre-dried over calcium chloride and then distilled from sodium hydride. Dichloromethane was distilled from phosphorus pentoxide. All other solvents used were of either P.A. or analytical grade.

Pure sodium hydride was obtained from a 60% dispersion in mineral oil by washing the dispersion several times with anhydrous hexane to remove the oil. To exclude contact of the sodium hydride with wet air, the washings were carried out in a continuous stream of dry nitrogen.

2,3-Epoxy-2,6,6-trimethyl-1-cyclohexanecarboxaldehyde ethylene acetal (**9**)

A mixture of α- and β-cyclocitral[20] (3.04 g, 20 mmole), (GLC: 69% β, 31% α isomer), 1,2-ethanediol (1.67 g, 27 mmole), pyridinium *p*-toluenesulfonate (0.025 g) and benzene (50 ml) was heated at reflux in an apparatus fitted with a Dean–Stark trap for azeotropic removal of the water, until the evolution of water subsided (16 h). The solution was cooled to room temperature and benzene was removed *in vacuo*. The residue was diluted with diethyl ether (50 ml), extracted with 5% aqueous sodium bicarbonate (2 ×), washed with water, dried over $MgSO_4$, filtered and concentrated. The crude mixture of α- and β-cyclocitral ethylene acetal **7** and **8** (62% and 31%, respectively) was used in the subsequent reaction without purification. ^{1}H NMR ($CDCl_3$) δ: 0.90 (s, 3H, CH_3 at C6), 1.06 (s, 3H, CH_3 at C6), 1.78 (d, *J* 2 Hz, 3H, CH_3 at C2), 0.89–2.15 (m, 4H, 2H4 + 2H5), 3.66–4.13 (m, 4H, OCH_2CH_2O), 4.87 (d, *J* 3 Hz, 1H, OCHO), 5.43 (broad s, 1H, H3) ppm; [δ: 0.99 (s, CH_3 at C6) and 5.25 (s, OCHO) ppm were assigned to the β-isomer **8**]. A solution of *m*-chloroperoxybenzoic acid (*m*CPBA, 4.68 g, 70–75%, *ca.* 19 mmole) in dichloromethane (50 ml) was gradually added to a stirred solution of the crude mixture of α- and β-cyclocitral ethylene acetal (**7** + **8**) (3.68 g, 18.8 mmole) in dichloromethane (20 ml). During addition, the temperature of the reaction mixture was maintained below 10 °C. Stirring was continued for 2 h at room temperature. Excess of *m*CPBA was neutralized with 10% aqueous sodium thiosulfate solution and the mixture was made basic by the addition of sodium carbonate. The aqueous layer was extracted with dichloromethane (1 ×). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated to give a mixture of **9** and **10** as a colorless oil (3.87 g). Purification of the crude product by flash chromatography (silica gel; hexane/ethyl-acetate 9/1) gave pure **9** and 1,2-epoxy-2,6,6-trimethyl-1-cyclohexanecarboxaldehyde ethylene acetal **10**).

Compound **9**: white solid (2.14 g, 50%, based on the mixture of cyclocitrals **4** + **5**), m.p. 123–125 °C. ^{1}H NMR ($CDCl_3$) δ: 0.92 (s, 3H, CH_3 at C6), 0.95 (s, 3H, CH_3 at C6), 1.40 (s, 3H, CH_3 at C2),

1.40–2.00 (m, 5H, H1 + 2H4 + 2H5), 2.56 (br.s, 1H, H3), 3.69–4.07 (m, 4H, OCH_2CH_2O), 4.88 (d, *J* 6 Hz, 1H, OCHO) ppm. MS (CI$^+$): 213 $(M + 1)^+$, 197 $(M - CH_3)^+$, 139 $(M - C_3H_5O_2)^+$, 73 [100%, $(C_3H_5O_2)^+$]. Anal calcd. for $C_{12}H_{20}O_3$: C 67.89, H 9.50; found: C 68.12, H 9.67%.

Compound **10**: colorless oil (0.93 g, 23%, based on the mixture of cyclocitrals **4** + **5**). ^{1}H NMR ($CDCl_3$) δ: 1.09 (s, 6H, 2 CH_3 at C6), 1.33 (s, 3H, CH_3 at C2), 0.71–1.90 (m, 6H, 2H3 + 2H4 + 2H5), 3.65–4.13 (m, 4H, OCH_2CH_2O), 4.73 (s, 1H, OCHO) ppm. MS (CI$^+$): 213 $(M + 1)^+$, 211 $(M - H)^+$, 139 $(M - C_3H_5O_2)^+$, 73 [100%, $(C_3H_5O_2)^+$].

2-Chloro-3-hydroxy-2,6,6-trimethyl-1-cyclohexanecarboxaldehyde (**11**)

A mixture of epoxyacetal **9** (2.20 g, 0.010 mole) in tetrahydrofuran (25 ml) and 1N aqueous hydrogen chloride solution (12 ml) was stirred at room temperature for 72 h. The aqueous layers were saturated with sodium chloride and extracted with diethyl ether (3 ×). The combined organic layers were extracted with saturated aqueous sodium bicarbonate solution, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel; petroleum-ether/ethyl-acetate 9 : 1) to give **11** as a white solid (1.38 g, 65%). An analytical sample was recrystallized from petroleum ether. (The product is rather unstable and can best be stored under argon at -20°C); m.p. 89–91°C. ^{1}H NMR ($CDCl_3$) δ: 1.13 (s, 3H, CH_3 at C6), 1.16 (s, 3H, CH_3 at C6), 1.33 (s, 3H, CH_3 at C2), 1.57–2.60 (m, 4H, 2H4 + 2H5), 2.65 (d, *J* 3 Hz, 1H, H1), 3.06 (s, OH), 3.91 (t, *J*3 Hz, 1H, H3), 10.07 (d, *J* 3 Hz, 1H, CHO) ppm. IR (CCl_4) ν: 3540 (OH), 2740 (CHO), 1710 (CHO) cm^{-1}. MS (CI$^+$): 205/207 $(M + 1)^+$, 187/189 $(M - OH)^+$, 158/160, 85/87 (100%/47%). Anal. calcd. for $C_{10}H_{17}ClO_2$: C 58.68, H 8.37; found: C 58.74, H 8.49%.

3-Hydroxy-2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde (**2**)

A solution of chlorohydrin **11** (0.41 g, 2.0 mmole) in anhydrous tetrahydrofuran (5 ml) was added to a stirred mixture of potassium *tert*-butoxide (0.25 g, 2.0 mmole) in tetrahydrofuran (20 ml). After stirring for 1 h at room temperature, the reaction was complete as monitored by TLC using petroleum-ether/ethyl-acetate 4/6; R_f 0.24. Tetrahydrofuran was removed *in vacuo* and the residue was dissolved in a mixture of diethyl ether and 1N aqueous hydrogen chloride and then extracted with diethyl ether (2x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give pure **2** (0.33 g, 96%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.07 (s, 3H, CH_3 at C6), 1.12 (s, 3H, CH_3 at C6), 2.20 (s, 3H, CH_3 at C2), 0.80–2.26 (m, 4H, 2H4 + 2H5), 4.03 (t, *J* 5 Hz, 1H, H3), 10.07 (s, 1H, CHO) ppm. IR (NaCl) ν: 3610–3140 (OH), 1680 (CHO), 1605 (C=C), 1460 cm^{-1}. MS (CI$^+$): 169 $(M + 1)^+$, 168 $(M)^+$, 153 $(M - CH_3)^+$, 139 [100%, $(M - CHO)^+$]; peak match calcd. for $C_{10}H_{16}O_2$: 168.1150; found: 168.1147.

3-Hydroxy-2,6,6-trimethyl-1-cyclohexene-1-carboxylic acid (**12**)

A stirred mixture of α- and β-cyclocitral (15.2 g, 0.10 mole; 61% β-citral), *N*-bromosuccinimide (NBS, 17.5 g, 0.10 mole) and a catalytic amount of AIBN in carbon tetrachloride (200 ml) was heated at 60°C. When the initial color faded away, a second equivalent of NBS (17.5 g, 0.10 mole) was added and stirring was continued for 1 h at 60°C. The mixture was allowed to cool to room temperature and floating succinimide was filtered off. The resulting solution was concentrated *in vacuo*. The residue was taken up in saturated aqueous sodium bicarbonate (300 ml) and diethyl ether (100 ml), stirred at room temperature for 16 h and then the aqueous layer was extracted with diethyl ether (3x). The aqueous layer was cooled to 0°C, brought to pH 3 by addition of cold (0°C) 50% aqueous hydrogen chloride and extracted with a mixture of diethyl-ether/tetrahydrofuran (1 : 1) (5x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude, white solid was washed with small amounts of cold diethyl ether and dried over phosphorus pentoxide in a dessicator to give pure **12**. Yield 10.63 g (58%), m.p. 183–184°C (lit.[15] 184°C). ^{1}H NMR (acetone-d_6) δ: 1.08 (s, 3H, CH_3 at C6), 1.11 (s, 3H, CH_3 at C6), 1.77 (s, 3H, CH_3 at C2), 1.22–2.00 (m, 4H, 2H4 + 2H5), 3.91 (t, *J* 5 Hz, 1H, H3) ppm. IR (KBr) ν: 3600–3200 (OH), 3200–2500 (COOH), 1690 (COOH), 1652 (C=C) cm^{-1}. MS (CI$^+$): 185 $(M + 1)^+$, 184 $(M)^+$, 167 $(M - OH)^+$, 139 [100%, $(M - COOH)^+$]. Anal. calcd. for $C_{10}H_{16}O_3$: C 65.19, H 18.75; found: C 64.79, H 18.80%.

Methyl 3-hydroxy-2,6,6-trimethyl-1-cyclohexene-1-carboxylate (**13**)

A solution of diazomethane in diethyl ether (25 ml; *ca.* 0.3M) was added to a solution of carboxylic acid **12** (0.55 g, 3.0 mmole) in absolute methanol (40 ml) with stirring at room temperature until a yellow color remained. After stirring for 30 min gaseous nitrogen was bubbled through the solution to remove excess diazomethane. The solution was concentrated *in vacuo* to give **13** as a pale yellow liquid. ^{1}H NMR ($CDCl_3$) δ: 1.05 (s, 3H, CH_3 at C6), 1.07 (s, 3H, CH_3 at C6), 1.70 (s, 3H, CH_3 at C2), 1.28–2.10 (m, 4H, 2H4 + 2H5), 3.71 (s, 3H, OCH_3), 3.93 (t, *J* 5 Hz, 1H, H3) ppm. IR (NaCl) ν: 3700–3060 (OH), 1720 (COOMe), 1650 (C=C) cm^{-1}. MS (CI$^+$): 199 $(M + 1)^+$, 198 $(M)^+$, 197 [100%, $(M - H)^+$], 168 $(M - CH_2O)^+$; peak match calcd. for $C_{11}H_{18}O_3$: 198.1256; found: 198.1252.

1-(Hydroxymethyl)-2,6,6-trimethyl-1-cyclohexene-3-ol (**14**)

A solution of ester **13** (0.60 g, 3.0 mmole), freshly distilled 3,4-dihydro-2H-pyran (DHP, 0.3 ml, 3.3 mmole) and a catalytic amount of pyridinium *p*-toluenesulfonate (0.1 g) in dichloromethane (25 ml) was stirred for 72 h at room temperature. The solution was washed with saturated aqueous sodium bicarbonate and brine, dried over Na_2SO_4, filtered and concentrated. The crude oil (0.89 g) was purified by flash chromatography (silica gel; petroleum-ether/ethyl-acetate 9 : 1) to give THP ether **16** (mixture of diastereomers; 0.81 g, 96%) as a colorless oil. ^{1}H NMR (CCl_4) δ: 1.02, 1.04, 1.07, 1.09 (4 s, 6H, 2 CH_3 at C6), 1.57, 1.68 (2 s, 3H, CH_3 at C2), 1.68–2.06 [m, 10H, 2H4 + 2H5 + 3CH_2(THP)], 3.64 (s, 3H, OCH_3), 3.24–4.06 [m, 3H, H_3 + OCH_2(THP)], 4.65 (broad s, OCHO) ppm. IR (NaCl) ν: 1725 (COOMe), 1655 (C=C) cm^{-1}. MS (CI$^+$): 283 $(M + 1)^+$, 181 [100%, $(M - OTHP)^+$], 85 [100%, $(THP)^+$].

DIBAL (5 ml, 1M in diethyl ether) was gradually added to a solution of THP-protected ester **16** (0.425 g, 1.5 mmole) in anhydrous diethyl ether (15 ml) with stirring at 0°C under nitrogen. The cooling bath was removed and stirring was continued at room temperature for 30 min. Aqueous hydrogen chloride (15 ml) was then added and the ether layer was separated. The aqueous layer was extracted with diethyl ether (2x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Crude **17** (0.38 g, 100%) was obtained as a pale yellow oil and was sufficiently pure for further use. ^{1}H NMR ($CDCl_3$) δ: 0.98 (s, 3H, CH_3 at C6), 1.06 (s, 3H, CH_3 at C6), 1.76, 1.88 (2 s, 3H, CH_3 at C2), 0.90–1.98 [m, 10H, 2H4 + 2H5 + 3 CH_2(THP)], 4.08 (s, 2H, CH_2O at C1), 3.27–4.18 [m, 3H, H3 + OCH_2(THP)], 4.72 (broad s, OCHO) ppm. IR (NaCl) ν: 3700–3100 (OH), 1640 (C=C) cm^{-1}.

THP alcohol **17** (100 mg, 0.4 mmole) was added to a mixture of acetic-acid/tetrahydrofuran/water 4 : 2 : 1 (7 ml) and stirred for 45 min at room temperature and for 5 h at 40°C. The mixture was diluted with water (10 ml), made alkaline by the addition of saturated aqueous sodium bicarbonate and extracted with diethyl ether (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was further purified by flash chromatography (silica gel; petroleum-ether/ethyl-acetate 1 : 1), followed by crystallization from petroleum-ether/ethyl-acetate to give **14** as a white solid (23 mg, 34%), m.p. 106–108°C. ^{1}H NMR ($CDCl_3$) δ: 1.00 (s, 3H, CH_3 at C6), 1.07 (s, 3H, CH_3 at C6), 1.86 (s, 3H, CH_3 at C2), 1.31–1.97 (m, 4H, 2H4 + 2H5), 3.94 (t, *J* 5 Hz, 1H, H3), 4.12 (s, 1H, CH_2O at C1) ppm. IR (KBr) ν: 3600–3020 (OH) cm^{-1}. MS (CI$^+$): 152 $(M - H_2O)^+$, 139 [100%, $(M - CH_2OH)^+$]. Anal calcd. for $C_{10}H_{18}O_2$: C 70.55, H 10.66; found: C 70.63, H 10.68%.

*4-Hydroxy-7,7-dimethyl-2,3,4,5,6,7-hexahydro-1*H*-indene-1-one* (**15**)

A solution of enol ester **21** (125 mg, 0.5 mmole) in *N*-methylpyrrolidone (NMP, 5 ml) was added to a solution of lithium chloride (55 mg, 25 mmole) in NMP (30 ml) while stirring at room temperature under nitrogen. Then the mixture was stirred for 6 h at 100°C. After cooling, 2N aqueous hydrogen chloride (30 ml) was added and the mixture was extracted with diethyl ether (4x). The combined organic layers were washed with water (3x), dried

over $MgSO_4$, filtered and concentrated. 7,7-Dimethyl-2,3,6,7-tetrahydro-1*H*-indene-1,4(5*H*)-dione (**22**) was obtained as a pale yellow liquid (97 mg, >100%) and was used in subsequent reactions without further purification. ^{1}HN MR ($CDCl_3$) δ: 1.33 (s, 6H, 2 CH_3 at C7), 1.90 (t, *J* 7 Hz, 2H, 2H3), 2.33–2.69 (m, 6H, 2H2 + 2H4 + 2H5) ppm. IR (CCl_4) v: 1710, 1685 (C=O) cm $^{-1}$. MS (EI$^+$): 178 $(M)^+$, 163 $(M - CH_3)^+$, 150 $(M - CO)^+$, 135 [100%, $(M - CH_3 - CO)^+$].

Sodium borohydride (0.025 g, 0.7 mmole) in methanol (5 ml) was added to a solution of diketone **22** (90 mg, 0.5 mmole) in methanol (5 ml) with stirring at room temperature. After 30 min, the mixture was quenched by dropwise addition of 1N aqueous hydrogen chloride to pH ~2 and methanol was removed *in vacuo*. The aqueous residue was diluted with water (10 ml) and extracted with diethyl ether (2x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The partially solidified residue was purified by flash chromatography (silica gel; petroleum-ether/ethyl-acetate 1:1) to give **15** as a white solid (70 mg, 75%). An analytical sample was recrystallized from petroleum-ether/ethyl-acetate; m.p. 112–114°C. ^{1}H NMR ($CDCl_3$) δ: 1.17 (s, 6H, 2 CH_3 at C6), 1.40–2.99 (m, 8H, 2H2 + 2H3 + 2H4 + 2H5), 4.39 (t, *J* 6 Hz, 1H, H4) ppm. IR (KBr) v: 3550–3100 (OH), 1665 (C=O), 1620 (C=C) cm $^{-1}$. MS (CI$^+$): 181 [100%, $(M + 1)^+$], 180 $(M)^+$, 163 $(M-H_2O)^+$, 138 $(M - CH_2CO)^+$. Anal. calcd. for $C_{11}H_{16}O_2$: C 72.77, H 8.96; found: C 73.30, H 8.95.

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