1,4,4-Trimethylbicyclo[3.2.0]heptane-3-one. A Key Intermediate in the Synthesis of (±)-Grandisol, a Sex Pheromone Component of the Boll Weevil *Anthonomus grandis*

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The oxidation of appropriate methylenebicyclo[3.2.0]heptanone derivatives provided the diketone 1,4,4-trimethylbicyclo[3.2.0]heptane-3,6-dione the structure of which was determined by X-ray crystallography. The selective reduction of the carbonyl group at the four-membered ring furnished the corresponding ketone which had previously been transformed to the pheromone component, grandisol. Hence, this paper formally reports a new synthesis of the latter.

The boll weevil, *Anthonomus grandis,* is a serious pest to cotton fields in North America. A four-component pheromone system was first isolated in 1969.[1] One of the components, a cyclobutane derivative termed grandisol has attracted the attention of many synthetic chemists and numerous syntheses have been reported.[2-8] The stereo and regiochemical control needed for *1* (see Scheme for this and other structures) is commonly achieved by photochemical routes. We now present a new synthesis of grandisol involving the selective reduction of one of the carbonyl groups of a bicyclic diketone.

The bicyclic ketones, *2*, are easily available by a three-step procedure from isobutyraldehyde and propargyl alcohol or 2-methyl-3-butyn-2-ol.[9] These ketones could be transformed to the diketone *3* in either of two ways. Ozonolysis of *2a* gave *3* together with a few percent of the lactone *4*. It is known[10] that ozonolysis of strained olefins can furnish hydroxy acids or lactones. The problem was minimized by performing the ozonolysis and the subsequent reduction of the ozonide at low temperature; the amount of *4* was reduced from 12 to 6 % when the reaction temperature was lowered from 25 to −78 °C. In the case of *2b*, ozonolysis yielded *3* as the sole product in quantitative yield. This was not unexpected since the tetrasubstituted double bond of *2b* should react faster with ozone.

The diketone *3* could also be synthesized by a two-step procedure starting from *2*. Oxidation of *2a* with osmium tetroxide furnished a 3:1 mixture of two isomeric diols, *5*, in quantitative yield. They were not fully characterized spectroscopically, but the absence of olefinic protons in the ^{1}H NMR spectrum and the strong hydroxyl absorption at 3450 cm^{-1} in the IR spectrum supported the assignment. Reaction of the diols with $Pb(OAc)_4$ gave the diketone *3* as the only product in 85 % yield. The structure of *3* was not secured from the IR and NMR data alone, and was therefore established by X-ray analysis (*vide infra*). We then tried to selectively reduce the carbonyl group on the four-membered ring in order to obtain the ketone *7*. However, direct reduction of *3* by the Huang-Minlon procedure gave a mixture of four products where *7* constituted only 20 %. The yield of *7* was low even when the reaction was stopped before all the starting material had reacted.

We had to look for alternative routes to *7*. The diketone *3* reacted with tosylhydrazine to give selectively the tosylhydrazone *6*. The best condi-

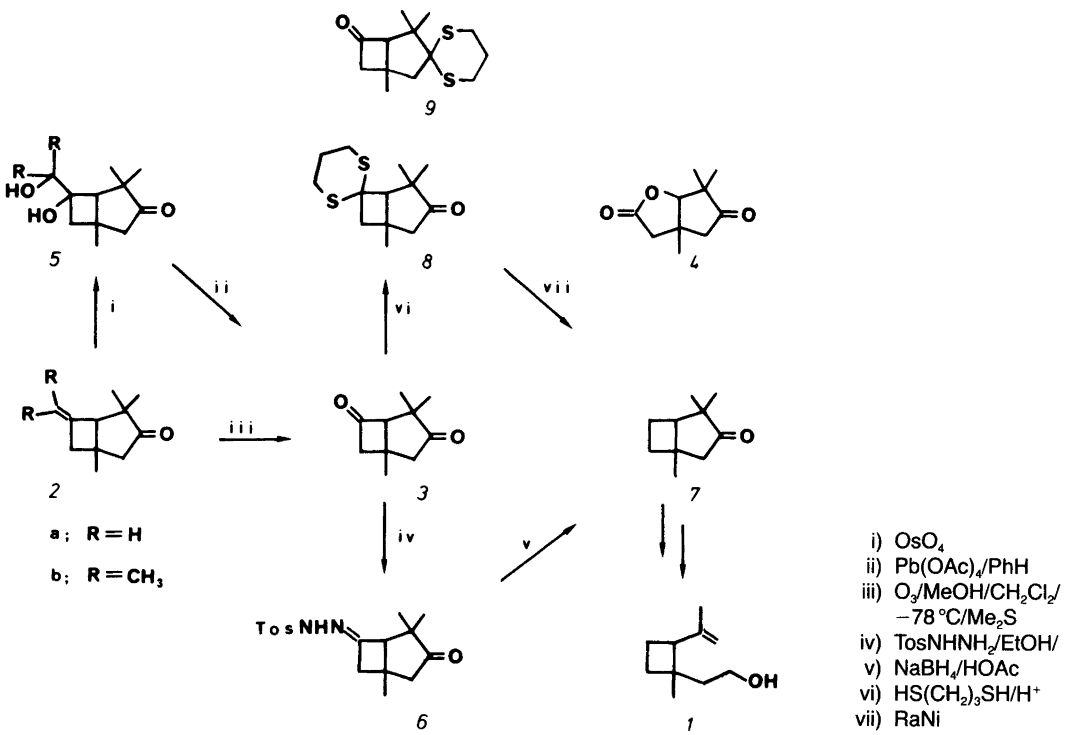
tions consisted of refluxing an ethanolic solution of stoichiometric amounts of *3* and tosylhydrazine for 7–8 h. In this way, the hydrazone *6*, which was pure by TLC, was obtained in 82 % yield. The IR spectrum of *6* gave rise to a carbonyl absorption at 1732 cm^{-1}. This was very close to that observed for the cyclopentanone moiety of *3* at 1734 cm^{-1} and confirmed that *6* was the cyclobutanone tosylhydrazone.

Several methods that will reduce a tosylhydrazone group to methylene are known.[11–13] Using sodium cyanoborohydride resulted in a mixture which contained the ketone *7* as the major product in approximately 40 %, and in an isolated yield of 25 %. Reduction with catecholborane gave four products with *7* as the major component (52 %), but the conversion was less than 25 %. Finally, we tried sodium borohydride in acetic acid. Although 90 % of the reaction mixture consisted of *7*, the conversion was only 35 %. Increasing the excess of reagent in order to improve the conversion also led to more of a by-product which probably was the corresponding alcohol. Some of the tosylhydrazone could be recovered by chromatography, but the yield of *7* based on recovered *6* was still less than 50 %.

Another route to the ketone *7* consists of the selective conversion of *3* to the thioketal *8* followed by reduction with Raney nickel. Reaction of *3* with 1,3-propanedithiol gave a 71:29 mixture of the thioketals *8* and *9*. Reaction of *3* with 1,2-ethanedithiol yielded a 66:34 mixture of the corresponding thioketals. Reduction of *8* and *9* with Raney nickel according to the procedure of Wenkert *et al.*[14] gave a mixture of bicyclic ketones which were converted to the oximes. Recrystallisation from ethanol yielded the oxime of ketone *7* in 25 % overall yield from *3*. This route actually represents a formal synthesis of grandisol since the transformation of the oxime to the pheromone component has been reported.[14,15]

The structure of 3

The X-ray analysis uniquely proved the structure of the compound to be that shown in Fig. 1. The



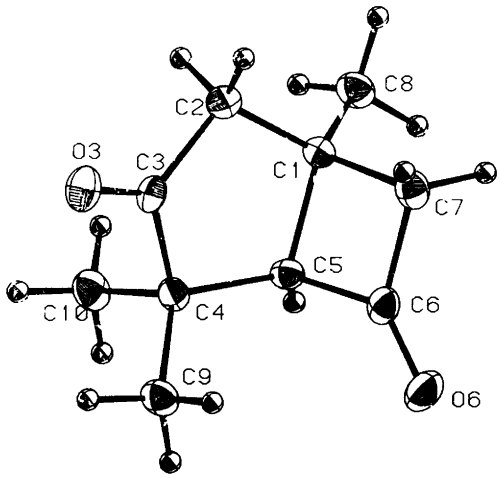


Fig. 1. ORTEP plot of the structure.

cyclopentane ring has the envelope conformation, somewhat flattened because of the carbonyl group. C1, C2, C4 and C5 are situated in a plane with C3, 0.32 Å out of plane. The angle between this plane and that of C2, C3 and C4 is 21.6°. The four-membered ring is nearly planar with the atoms 0.02 Å out of the common plane; O6 is situated 0.12 Å out of the plane. The conformation about the C1–C7 bond is eclipsed with the torsion angles C2-C1-C7-H71 = −4.2° and C8-C1-C7-H72 = −2.8°. The same is the case for the C1–C5 bond, the torsion angle H5-C5-C1-C8 being 0.6°.

C3 is situated *cis* to the cyclobutanone moiety with respect to the planar part (C1-C2-C4-C5) of the cyclopentane ring. The hydrogen atom in equatorial position on C2 is situated quite close to a hydrogen atom on C7 (2.47 Å); a *trans* conformation could bring these hydrogen atoms closer and cause an energetically less favourable situation. The angle between the planar part of the cyclopentane moiety and the plane of the cyclobutane ring is 117.0°. There is a very long C-C bond common for these planes, C1–C5, of 1.587 Å. Long C-C bonds are often found for the two four-membered rings in bicyclo[2.2.0]butane: 1.577 Å.[16] In the latter compound, the dihedral angle of the cyclobutane rings is 113.5°. Bond lengths and angles are of expected magnitudes, as may be seen from Table 2.

Experimental

General. The instruments employed have been described elsewhere.[9]

1,4,4-Trimethylbicyclo[3.2.0]heptan-3,6-dione (*3*). A solution of 6.00 g (36.5 mmol) *2a*[9] in a mixture of 60 ml methanol and 120 ml dichloromethane was cooled to −78 °C (dry ice/methanol). Ozone was bubbled through the solution at a rate of 1.4 mmol O_3/min until the solution became pale blue. The solution was flushed with nitrogen for 10 min and 4.2 ml (3.47 g, 55.8 mmol) Me_2S was added at −78 °C. After 2 h at room temperature, 60 ml water was added. The organic layer was separated and the water phase extracted twice with petroleum ether (40–60 °C). Drying ($MgSO_4$), evaporation and distillation gave 5.47 g (90 %) of *3* together with 6 % of 1,4,4-trimethyl-6-oxabicyclo[3.3.0]octan-3,7-dione (*4*). Analytically pure samples were isolated on preparative GLC (15 % SE 52, 180 °C).

Using the same procedure, 7.00 g (26.4 mmol) of *2b*[9] yielded 6.05 g (100 %) of *3*, b.p. 57–59 °C/1.0 mmHg, m.p. 40–41 °C. IR ($CDCl_3$): 1773 (s), 1734 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.13 (s, 3H), 1.61 (s, 3H), 2.53 (d, *J* 18.62 Hz, 1H), 2.7–2.9 (complex abs., 2H), 3.00 (dd, *J* 4.42, 18.62 Hz, 1H), 3.10 (dd, *J* 3.20, 4.42 Hz, 1H). ^{13}C NMR (100.8 MHz, $CDCl_3$): δ 20.00, 27.36, 28.28 (CH_3), 30.66 (C), 49.42 (CH_2), 51.18 (C), 59.51 (CH_2), 77.18 (CH), 208.27, 220.02 (C=O). *4*, b.p. 87–88 °C/1.0 mmHg, m.p. 84–86 °C. IR($CDCl_3$): 1780 (s), 1741 (s) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.20 (s, 3H), 2.47 (broad s, 2H), 2.58 (broad s, 2H), 4.33 (s, 1H).

X-ray crystallography of 3. Data for unit cell determination and intensity data were collected using a Syntex P1 four-circle diffractometer, Mo *Kα* radiation (λ = 0.71069 Å). The temperature at the crystal site was kept at −150 °C, specimen dimensions 0.30×0.4×0.5 mm. The θ/2Θ scan technique was employed with scan speed 3° min^{-1} (2θ, scan range 1.8°. 2124 reflections with sin θ/λ ≤ 0.65 $Å^{-1}$ were measured; of these 1896 were larger than 2.5 δ (*I*) and were used for the structure analysis.

Crystal data. 1,4,4-trimethylbicyclo[3.2.0]heptan-3,6-dione, $C_{10}H_{14}O_2$, m.p. 40–41 °C, triclinic.

Table 1. Fractional atomic coordinates

Atom	X	Y	Z
O3	.7980(1)	.4223(1)	1.0122(0)
O6	1.1646(1)	.7920(1)	.5863(0)
C1	.6899(1)	.8703(1)	.7666(1)
C2	.6391(1)	.7437(1)	.9129(1)
C3	.7592(1)	.5522(1)	.9069(1)
C4	.8156(1)	.5440(1)	.7461(1)
C5	.8047(1)	.7431(1)	.6623(1)
C6	.9980(1)	.8133(1)	.6565(1)
C7	.8962(1)	.9298(1)	.7620(1)
C8	.5032(1)	1.0244(1)	.7051(1)
C9	1.0276(1)	.4084(1)	.7302(1)
C10	.6374(1)	.4840(1)	.7016(1)
H21	.491(2)	.745(2)	.923(1)
H22	.676(2)	.770(1)	.998(1)
H5	.748(2)	.773(1)	.563(1)
H71	.967(2)	.889(2)	.854(1)
H72	.889(2)	1.058(2)	.716(1)
H81	.447(2)	1.101(2)	.773(1)
H82	.393(2)	.978(2)	.688(1)
H83	.544(2)	1.103(1)	.610(1)
H91	1.147(2)	.444(1)	.759(1)
H92	1.058(2)	.400(2)	.627(1)
H93	1.026(2)	.288(2)	.797(1)
H101	.501(2)	.571(2)	.706(1)
H102	.630(2)	.364(2)	.766(1)
H103	.665(2)	.477(2)	.599(1)

$a = 6.631(1)$ Å; $b = 7.941(1)$ Å; $C = 9.496(2)$ Å; $\alpha = 73.58(1)°$; $\beta = 82.19(2)°$; $\gamma = 73.55(1)°$; $V = 459.1(1)$ Å^3; (t = −150 °C); $M = 166.22$; $Z = 2$; $D_x = 1.202$ g cm^{-3}; $F(000) = 180$. Space group PT_1 (No. 2).

Structure determination. The structure was determined by direct methods using the program assembly MULTAN; hydrogen atomic positional parameters were calculated from stereochemical considerations. The refinement by full-matrix least-squares calculations (minimizing $\Sigma w(\Delta F)^2$) terminated with a conventional R value of 0.037, $R_w = 0.045$ and $S = [\Sigma w(\Delta F)^2/(n-m)]^{\frac{1}{2}} = 2.52$. Final positional parameters are given in Table 1, the thermal parameters and the structural factor listing may be obtained from the authors.

The thermal parameters for the oxygen and carbon atoms were analysed in terms of rigid-body motion. The r.m.s. ΔU was found to be $1.4 \cdot 10^{-4}$ Å^2, and the results were used for correction of the bond lengths for libration. Structural data are listed in Table 2. Estimated standard deviation as calculated from the variance-covariance matrix are 0.001 Å in bond lengths and 0.1° in bond angles and torsion angles not involving hydrogen atoms.

An ORTEP plot of the molecule is presented in Fig. 1.

6-Hydroxy-6-hydroxymethyl-1,4,4-trimethylbicyclo[3.2.0]heptan-3-one (*5*). To a mixture of 0.81 g (6.0 mmol) *N*-methyl-morpholine-*N*-oxide · H_2O,[17] 8.2 mg (0.03 mmol) OsO_4, 9.5 ml *t*-butyl alcohol, 3 ml water and 1.5 ml acetone was added 0.82 g (5.0 mmol) of *2a*. The solution was stirred for 100 h when volatile components were evaporated. The residue was acidified with 10 % HCl (aq.) to pH 1–2 and 0.6 ml 15 % $NaHSO_3$ (aq.) was added. The water layer was saturated

Table 2. Structural data. Estimated standard deviations are 0.001 Å in bond lengths and 0.1° in angles

Bond lengths (Å)		Corr.	Bond angles (°)	
C3 O3	1.211	1.213	C8 C1 C2	114.2
C6 O6	1.204	1.207	C8 C1 C5	115.9
C1 C5	1.583	1.587	C8 C1 C7	114.3
C1 C8	1.518	1.521	C2 C1 C5	105.9
C1 C7	1.560	1.564	C2 C1 C7	114.1
C1 C2	1.526	1.530	C5 C1 C7	89.8
C2 C3	1.517	1.520	C1 C2 C3	106.9
C3 C4	1.537	1.541	C2 C3 O3	125.5
C4 C5	1.542	1.545	C2 C3 C4	110.0
C4 C9	1.528	1.531	O3 C3 C4	124.4
C4 C10	1.540	1.544	C3 C4 C9	111.3
C5 C6	1.525	1.528	C3 C4 C10	105.8
C6 C7	1.517	1.521	C3 C4 C5	103.7
			C9 C4 C10	110.4
C-H (mean)	0.98 (1)		C9 C4 C5	115.4
			C5 C4 C10	109.7
Torsion angles		(°)	C4 C5 C1	108.9
			C4 C5 C6	118.1
C1 C2 C3 C4		−21.3	C1 C5 C6	87.7
C2 C3 C4 C5		21.5	C5 C6 O6	132.7
C3 C4 C5 C1		−13.6	C5 C6 C7	93.6
C4 C5 C1 C2		1.4	O6 C6 C7	133.5
C5 C1 C2 C3		11.7	C6 C7 C1	88.8
C1 C5 C6 C7		2.5		
C5 C6 C7 C1		−2.6		
C4 C5 C1 C7		116.5		
C6 C5 C1 C2		−117.5		

with NaCl and extracted with ethyl acetate (5–15 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 1.02 g (100 %) of *5* as a sticky oil, which by GLC was composed of a 76:24 mixture of stereoisomeric diols. IR (film): 3450 (s), 1745 (s) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 1.07 (s, 3H), 1.13 (s, 3H), 1.47 (s, 3H), 1.8–2.6 (complex abs., 5H), 3.3–4.0 (complex abs., 4H).

1,4,4-Trimethylbicyclo[3.2.0]heptan-3,6-dione (*3*). To a stirred solution of 1.02 g (5 mmol) of *5* in 15 ml of dry benzene kept at room temperature, was added 4.75 g (6 mmol) 85 % $Pb(OAc)_4$. The solution was filtered through Celite. Distillation produced 0.71 g (85 % of *2a*) of *3* (b.p. 57–59 °C/1.0 mmHg).

Tosylhydrazone of 3 (*6*). A solution of 2.93 g (17.6 mmol) of *3* and 3.42 g (18.2 mmol) of *p*-tosylhydrazine in 25 ml 95 % ethanol was refluxed for 7 h, cooled and filtered to give 4.81 g (82 %) of *6*, m.p. 209–210 °C (decomp). IR (KBr): 3193 (s), 1732 (s), 1337 (s), 1170 (s) cm^{-1}. ^1H NMR (60 MHz, DMSO-d_6): δ 0.72 (s, 3H), 0.98 (s, 3H), 1.40 (s, 3H), 2.40 (s, 3H), 2.60 (broad s, 3H), 2.93 (broad s, 1H), 3.33 (broad s, 1H), 7.42 (d, *J* 9 Hz, 2H), 7.77 (d, *J* 9 Hz, 2H), 10.37 (broad s, 1H).

Reduction of 6

(a) *With $NaCNBH_3$.*[11] To a solution of 0.33 g (1.0 mmol) of *6* in 2 ml DMF, 2 ml sulfolane and 50 mg *p*-toluenesulfonic acid, was added 0.25 g (4.0 mmol) of $NaCNBH_3$. The mixture was heated to 110 °C for 2 h, cooled, and 5 ml cyclohexane and 10 ml water were added successively. The organic phase was separated and the water phase extracted with cyclohexane. The collected extracts were washed once with water, dried ($MgSO_4$) and evaporated to yield a mixture which contained 40 % of *7* as shown by GLC. Short path distillation gave 38 mg (25 %) of *7*. An analytical sample was obtained by preparative GLC (10 % SP2100. 120 °C), and the spectroscopic data were in accordance with those reported in the literature.[14,15]

(b) *With catecholborane.*[12] To a suspension of 1.00 g (3.0 mmol) of *6* in 25 ml $CHCl_3$ kept at 0 °C, was added 0.36 ml (3.4 mmol) of catecholborane. After 7 h, 1.25 g (9.4 mmol) of $NaOAc \cdot 3H_2O$ were added and the mixture refluxed for 1 h. Distillation gave 54 mg (12 %) of *7*. Chromatography of the residue (silica/chloroform) yielded 0.75 g of *6*. Based on recovered *6* the yield of *7* was 47 %.

(c) *With $NABH_4$ in acetic acid.*[13] A suspension of 0.88 g (2.7 mmol) of *6* in 4 ml of glacial acetic acid was cooled to 0 °C and 4 ml of a reagent made up from 945 mg (25.0 mmol) of $NaBH_4$ in 35.0 ml glacial acetic acid were added with vigorous stirring. The reaction mixture was allowed to reach room temperature and was stirred overnight. It was then diluted with CH_2Cl_2 and made basic with 15 % NaOH (aq.) The water phase was extracted with CH_2Cl_2. The collected extracts were dried ($MgSO_4$) and evaporated. Chromatography (silica/chloroform) afforded 92 mg (22 %) of *7* and 0.47 g of *6*. The yield of *7* was 65 % based on recovered *6*.

6,6-(1,5-Dithiapentylene)-1,4,4-trimethylbicyclo-[3.2.0]heptan-3-one (*8*). A mixture of 0.59 g (3.5 mmol) of *3*, 380 mg (3.5 mmol) of 1,3-propanedithiol and 318 mg *p*-toluenesulfonic acid in 17 ml glacial acetic was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2. The organic phase was separated and washed with water and brine, dried ($MgSO_4$) and the solvent evaporated to give a yellow oil. Chromatography (silica/chloroform) yielded 0.80 g of an oil consisting of two products in a ratio of 71:29. An analytical sample of the major isomer *8* was obtained by preparative GLC (20 % Apiezon L, 220 °C). IR ($CDCl_3$): 1764 (s) cm^{-1}. ^1H NMR (60 MHz, $CHCl_3$): δ 1.13 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.7–2.2 (complex abs., 2H), 2.4–3.3 (complex abs., 9H).

1,4,4-Trimethylbicyclo[3.2.0]heptan-3-one oxime (*10*). To a solution of 0.80 g of the above mixture of *8* and *9* in 70 ml ethanol, were added 20 g of Raney nickel (W-2). The mixture was stirred for 6 h at room temperature. The solution was decanted from the solid and passed through Celite. The solid and Celite were washed repeatedly with ether. The combined organic solutions were concentrated to approximately 10 ml by distillation and 400 mg hydroxylamine hydrochloride and 400 mg finely powdered KOH were added. After 2 h of reflux the solution was poured into 30 ml of

brine and extracted with CH_2Cl_2. Drying ($MgSO_4$) and evaporation afforded an oil which crystallized at −10 °C. Recrystallization from ethanol yielded 146 mg (25 %) of *10*, m.p. 116–118 °C (m.p. lit.[14] 117–119 °C), with spectroscopic data according to the literature.[14]

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