Synthesis of (±)-Decan-9-olide (Phoracantholide I) from Cyclohexanone

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Recently, some 10-membered lactones have been isolated from the fungus culture *Diplodia pinea*[1] and the metasternal secretion of the eucalypt longicorn *Phoracantha* synonyma[2]. Phoracantholide I and its 4,5-dehydro derivative (Phoracantholide J) were isolated from the latter source[2] and have been synthesised by several workers[3-6]. Moreover, the synthetic decan-9-olide (**6**) has been transformed[3] into the racemic diplodialide A and C; (±)-diplodialide A has also been synthesised by an alternative route[7].

While most of these syntheses proceed through the cyclisation of an acyclic precursor to a 10-membered lactone, the 6-oxo-9-decanolide (**5b**) was prepared by oxidative cleavage of the isomeric 1,6-dihydroxy-3-methyl-2-oxabicyclo[4.4.0]decanes, obtained by the alkylation of the adipion dianion with 3-hydroxy-1-iodobutane[3]; this ketolactone had also been synthesised previously[8] from the same diol, prepared by the hydroxylation of the tetrahydrochroman **4**.

In the past few years, we have developed several routes to 9- to 16-membered ketolactones and ketolactams by oxidative cleavage[9] of the appropriate bicyclic precursors as well as by the intramolecular reverse Dieckmann reaction[10] of the suitably substituted cyclohexane-1,3-diones.

Recently, we described the selective reduction of 12-oxopentadecanolide and its sulphur analogue to the corresponding 16-membered lactones[11]. We here report an alternative route to the 6-oxo-9-decanolide (**5b**) and subsequent reduction of its tosylhydrazone **5c** to the title lactone **6**[12].

2-(3-Butenyl)-cyclohexanone (**2**) is obtained by the alkylation of 2-ethoxycarbonylcyclohexanone with 4-bromo-1-butene, followed by decarboxylative hydrolysis, as described previously for the preparation of 2-allylcyclohexanone[13,14]. Oxymercuration—demercuration[15] of **2** affords the hemi-acetal **3**, contaminated with a small amount of two products giving spots with higher R_f values (T.L.C.). Due to the possibility of several diastereoisomeric cyclic forms and their easy dehydration to the corresponding enol ether **4**, the hemiacetal **3** melts over a wide range (60–65 °C to 102–104 °C). Recrystallisation from benzene/petroleum ether, usually affords the first crop as silky needles, m.p. 102–104 °C, while the later fractions often melt over the wide range indicated above; however, their I.R. spectra and T.L.C. behaviour are almost identical to each other. Moreover, traces of acidic impurities easily degenerate the higher-melting (102–104 °C) product into the lower-melting mixtures.

Attempted acid-catalysed (*p*-toluenesulphonic acid) dehydration of the hemi-acetal **3** in boiling benzene[11], results in a mixture of products containing the desired enol ether **4**, the 2-(3-butenyl)-cyclohexanone (**2**), and possibly the isomeric 2-crotylcyclohexa-

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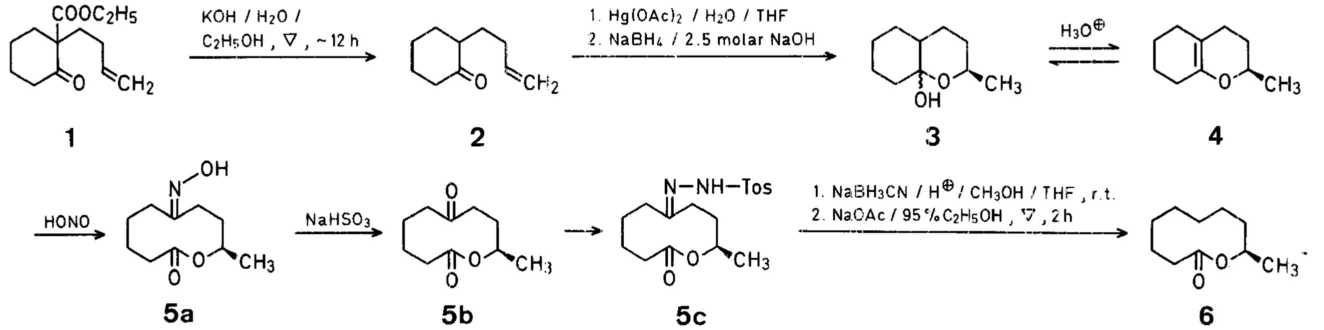

none (T.L.C.; ^{1}H-N.M.R.); the latter two products evidently arise by the acid-catalysed rearrangement of the former. Careful chromatographic separation of this mixture over silica gel, eluted with petroleum ether, affords the pure 5,6,7,8-tetrahydrochroman (**4**) in 10–20% yield; a colorless liquid; I.R. (neat): $\nu = 1695, 1156\ cm^{-1}$; ^{1}H-N.M.R. ($CCl_4$): $\delta = 1.21$ (d, $J = 6.5$ Hz, CH_3); 1.3–2.2 (m, 12H); 3.8 ppm (m, 1H). Borowitz et al. also encountered difficulties in the purification of this tetrahydropyran[8].

In face of these difficulties associated with the enol ether **4**, we explored the direct hydrolytic nitrosation[11] of the parent hemiacetal **3**, expecting that it would be in equilibrium with the corresponding enol ether, in the acidic reaction medium. Fortunately, the strategy worked excellently and the desired keto-lactone **5b** and its oxime **5a** were obtained in 70–75% yield. Attempted direct deoxygenation[11,16] of the ketolactone **5b** gave poor results. However, a slight modification of the step-wise procedure[17] involving the reduction of the tosylhydrazone **5c**, followed by elimination-rearrangement of the intermediate tosylhydrazine, yielded the title phoracantholide I (**6**) in 40–45% yield.

4-Bromo-1-butene and sodium cyanoborohydride were used as received from Fluka AG. Instruments for the physical measurements and other routine experimental procedures have been described in our recent publication[11].

2-(3-Butenyl)-cyclohexanone (2):
To a stirred solution of 2-ethoxycarbonylcyclohexanone[13] (17.0 g, 0.10 mol) in 1 molar potassium *t*-butoxide in *t*-butanol (110 ml) is added potassium iodide (1.0 g) and 4-bromo-1-butene (16.2 g, 12.3 ml, 0.12 mol). After being stirred under nitrogen at room temperature for 1–2 h, the reaction mixture is gently refluxed on a water bath for 22–24 h, until a test portion gives a negative colour reaction with 1% ethanolic iron(III) chloride. The cooled reaction mixture is treated with water (30 ml), extracted with ether (3 × 50 ml), and *2-(3-butenyl)-2-ethoxycarbonylcyclohexanone* (**1**) purified by distillation, affording a mobile colourless liquid; yield: 17.5 g (78%); b.p. 108–112 °C/3 torr.

I.R. (neat): $\nu = 1730, 1712, 1645\ cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 1.28$ (t, $J = 7$ Hz, 3H, CH_3); 1.4–2.7 (m, 12H, 6CH_2); 4.20 (q, $J = 7$ Hz, 2H, H_2C-OCO); 4.7–5.3 (m, 2H, olefinic CH_2); 5.4–6.2 ppm (m, 1H olefinic).

Compound **1** is decarboxylated by refluxing under nitrogen for 10–12 h in ~7% aqueous ethanolic (2:1) potassium hydroxide (3 equivalents), as already described for the corresponding 2-allylcycloalkanones[13], to give *2-(3-butenyl)-cyclohexanone* (**2**); yield: 60–65%; colourless liquid; b.p. 68–70 °C/5 torr (Lit.[14] b.p. 82–86 °C/2.5 torr).

I.R. (neat): $\nu = 1715, 1642\ cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 0.9$–2.6 (m, 13H); 4.7–5.2 (m, 2H olefinic CH_2); 5.4–6.2 ppm (m, 1H olefinic).

2-Hydroxy-6-methyl-2,3-tetramethylene-3,4,5,6-tetrahydro-2*H*-pyran (3):
A solution of 2-(3-butenyl)-cyclohexanone (**2**; 3.04 g, 20 mmol) in tetrahydrofuran (20 ml) is added at room temperature to a stirred solution of mercury(II) acetate (6.4 g, 20 mmol) in water (20 ml). After stirring for 10 min, sodium hydroxide (2.5 molar, 10 ml) is added, *the reaction mixture* is cooled in ice/water bath, and treated with a solution of sodium borohydride (400 mg, 10.5 mmol) in sodium hydroxide (2.5 molar, 10 ml). After further stirring for 10 min, the reaction mixture is diluted with brine (10–20 ml), filtered through a cotton plug, and extracted with ether (3 × 50 ml), the extracts being washed with water (20 ml) and brine (30 ml). Drying with sodium sulfate and evaporation affords the crude product usually retaining some metallic mercury, which is removed by passing through a small bed of alumina (activity III). The resulting semi-solid is crystallised from petroleum ether (b.p. 40–60 °C) containing a small amount of benzene. Several successive solid crops melt from 60–65 °C to 100–104 °C; total yield: 75–85%. Recrystallisation of the higher-melting fractions from the same solvent mixture furnishes white silky needles, m.p. 102–104 °C.

$C_{10}H_{18}O_2$	calc.	C 70.55	H 10.66
(170.3)	found	70.48	10.64

I.R. (KBr): $\nu = 3472, 3350\ cm^{-1}$; no absorption in the carbonyl region.

The mother-liquor contains the hemi-acetal **3**, the enol ether **4**, and some impurities (T.L.C.). Its hydrolytic nitrosation, in the manner described below for compound **3**, affords the oximino-lactone **5a** and ketolactone **5b** in a total yield of ~40%.

6-Oximino-9-decanolide (5a)[11]:
To a suspension of the hemi-acetal mixture **3** (1.7 g, 10 mmol) in 95% ethanol (3–4 ml), containing freshly washed *n*-butyl nitrite[18] (1.4 ml, 1.26 g, ~12 mmol), is added 1 normal hydrochloric acid (0.5 ml); complete solution is obtained and there is a slight exothermic reaction. The closed reaction mixture is surrounded by a tap-water bath and stirred for 4–6 h, occassionally releasing the excess pressure in the first 15–20 min. During this time the crystalline oxime separates from the bluish-green solution. After standing overnight in a refrigerator, the crystalline product is filtered and washed with chilled ethanol. Concentration of the mother liquor and crystallisation from ethanol furnishes further quantities of the same oxime; total yield: 1.2–1.3 g (60–65%). Recrystallisation from the same solvent affords the analytical sample as white glistening plates; m.p. 141–143 °C.

$C_{10}H_{17}NO_3$	calc.	C 60.28	H 8.60	N 7.03
(199.3)	found	60.22	8.56	6.97

I.R. (KBr): $\nu = 3300, 1721, 1672\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.26$ (d, $J = 6.5$ Hz, 3H, CH_3); 1.4–3.3 (m, 12H, 6CH_2); 5.0 (m, 1H, HC—OCO); 8.5 ppm (m, 1H, exchangeable with D_2O, C=N—OH).

6-Oxo-9-decanolide (5b):
The mother liquor (~0.6 g) from the above reaction is heated under reflux for 6 h in a mixture of ethanol (3 ml), water (5 ml), and sodium hydrogen sulphite (1.0 g)[11]. Excess of ethanol is evaporated and the cooled reaction mixture acidified with 1 normal hydrochloric acid (5 ml). Extraction with ether (3 × 30 ml), drying with sodium sulfate, and evaporation affords a pale-yellow liquid, which on crystallisation from petroleum ether yields the ketolactone **5b**; yield: 10–15%.

Deoximation of the pure oxime **5a** (1.99 g, 10 mmol) in the manner described above, using ethanol or dioxan (10 ml), water (20 ml), and sodium hydrogen sulphite (5.2 g), affords a colourless liquid, which on treatment with petroleum ether (b.p. 40–60 °C) furnishes the product **5b** as white shiny crystals; yield: 85–95% yield. Recrystallisation from the same solvent provides the analytical sample as a white shiny solid; m.p. 43–44 °C (Lit.[3] m.p. 44–44.5 °C; Lit.[8] m.p. 37–37.5 °C).

I.R. (KBr): $\nu = 1724, 1709, 1252\ \text{cm}^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.25$ (d, $J = 6.5$ Hz, 3H, CH_3); 1.4–2.9 (m, 12H, 6CH_2); 5.10 ppm (m, 1H, HC—OCO).

The tosylhydrazone **5c**, obtained in the usual manner[16], is crystallised from 95% ethanol; yield: ~100%; m.p. 149–151 °C.

(±)-Decan-9-olide (6):

To a stirred solution of the tosylhydrazone **5c** (1.76 g, 5 mmol) in tetrahydrofuran (20 ml), containing methyl orange indicator (2–3 drops of a 1% solution). is added dropwise, during 25–30 min, sodium cyanoborohydride (630 mg, 10 mmol) dissolved in methanol (10 ml). Simultaneously, a solution of concentrated hydrochloric acid in methanol (1:9) is added at such a rate as to keep the reaction mixture in the red-orange range (pH 3.0–3.8). After further stirring for 1–1.5 h, the excess of the solvents is evaporated, the concentrate diluted with water (20 ml), extracted with ether (3 × 50 ml), and the extracts washed with water (30 ml) and brine (50 ml). Ether is removed, 95% ethanol (25 ml) and sodium acetate (2.5 g) are added, and the mixture is refluxed for 1.5–2.0 h; there is a brisk reaction in the first 10–15 min and a gas is evolved. Excess of ethanol is carefully evaporated, the residue is dissolved in water (20 ml) and extracted with ether (3 × 30 ml), the combined extracts are washed successively with water (10 ml), saturated sodium hydrogen carbonate solution (15 ml), and brine (25 ml). Drying with sodium sulphate and evaporation yields a pale-yellow oil (~900 mg), having an odour similar to that of cyclohexanone. Short-path distillation (bath temperature 100–120 °C/5 torr) affords a colourless liquid; yield: 536 mg (63%), still containing some impurities (T.L.C.). Passage through a column of silica gel (30 g), eluting with 1:1 petroleum ether (b.p. 40–60 °C)/benzene, furnishes the colourless liquid homogeneous on T.L.C.; yield: 380 mg (45%); cf. Ref.[3].

I.R. (neat): $\nu = 1721, 1247\ \text{cm}^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 1.24$ (d, $J = 6.5$ Hz, 3H, CH_3); 1.0–2.6 (m, 14H, 7CH_2); 4.95 ppm (m, 1H, HC—OCO).

6-Oxo-9-decanolide (**5b**) has also been prepared by the Michael addition of 1-morpholinocyclohexane to methyl vinyl kentone, followed by lithium aluminium hydride reduction, and hydrolysis to afford a mixture of the hemi-acetal **3** and the corresponding enol ether **4**. Moreover, 7-oxo-9-decanolide has been prepared from 2-allylcycloheptanone[12].

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