Ring Expansion by Intramolecular Acylation of Phosphine Oxides

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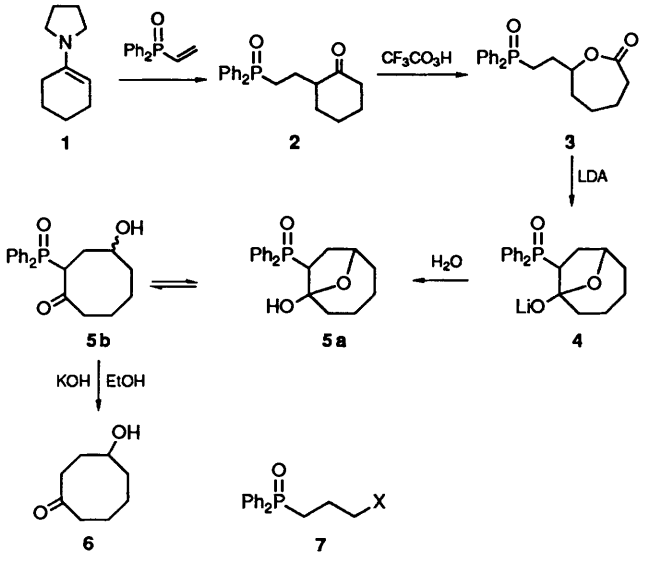
Alkylation of cyclic ketones with 2-Ph_2PO-ethyl or 3-Ph_2PO-propyl groups followed by Baeyer–Villiger oxidation and acyl transfer gives cyclic hydroxy ketones containing two or three more carbon atoms in the ring.

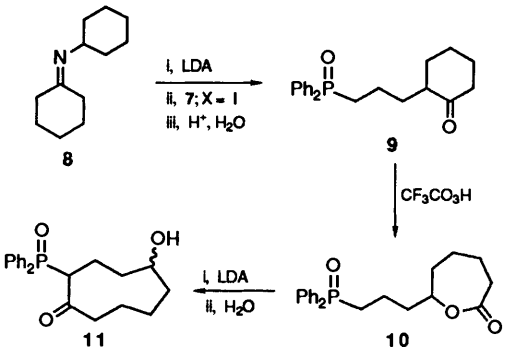
Ring expansion is an established method for the synthesis of rings of many sizes, particularly the more difficult medium rings.[1] Most frequently, cationic rearrangements are used, but examples are now known of intramolecular attack by a side chain carbanion, stabilised by carbonyl,[2] nitrile,[3] nitro,[4,5] or sulfonyl[6] groups on lactones or cyclic ketones with C–O or C–C bond cleavage. We describe a simple strategy based on phosphine oxide chemistry in which two-or three-carbon ring expansion is achieved by alkylation of a cyclic ketone with an electrophilic alkylphosphine oxide, a Baeyer–Villiger reaction, and an acyl transfer.[7]

The pyrrolidine enamine of cyclohexanone **1**, but not that of cyclooctanone, reacted with vinyldiphenylphosphine oxide to give the ketone **2**. An equivalent three-carbon chain extension to **9** was best achieved with the magnesium derivative of the cyclohexylimine[8] **8** and the iodide **7**; X = I. The corresponding sulfonate **7**; X = OTs gave no product **9**, presumably because of *N*-alkylation. The reaction with the iodide **7**; X = I was also successful with the cyclohexylimine of cyclooctanone, giving the ketone **12** in good yield.



1 **2** **3** **5b** **5a** **4** **6** **7**

Baeyer–Villiger oxidation of these ketones **2** and **9** gave the lactones **5** and **10** as the only products with complete regioselectivity in contrast to the reactions of the β-ketophosphine oxides we have used in the synthesis of unsaturated acids.[9] Acyl transfer on **3** with LDA (lithium diisopropylamide) gave the usual[7] mixture of hemiacetals **5a** and the hydroxy ketone **5b**, presumably *via* the lithium alkoxide **4**. The structure of these products **5** was confirmed by hydrolytic removal[7] of the Ph_2PO group to give 4-hydroxycyclooctanone **6**. Acyl transfer on **10** gave the hydroxyketone **11** as a mixture of disastereoisomers without any hemiacetal as is expected for the three-carbon series.[7]



8 **9** **11** **10**

Preliminary experiments[10] showed that the lactone **13** could be prepared from vinyldiphenylphosphine oxide and cyclopentanone by the same route, but in view of the superior performance of the corresponding sulfones[6] and the nitro 'zip' reaction,[4] we do not propose to develop this promising reaction sequence further.

12 **13**

Experimental

2-(2-*Diphenylphosphinoylethyl*)*cyclohexanone* **2**.—A solution of vinyldiphenylphosphine oxide[11] (2.71 g) and 1-pyrrolidinylcyclohex-1-ene[12] **1** (1.80 g) in dry 1,4-dioxane (20 cm^3) was heated under reflux for 120 h. The solution was cooled, acidified with dilute hydrochloric acid and extracted with dichloromethane. The extract was washed with water and with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to give an orange oil. Flash chromatography on silica, eluting with acetone, and two recrystallisations from ethyl acetate gave the *ketone* (2.71 g, 70%) as prisms, m.p. 109–110 °C (from ethyl acetate) (Found: C, 73.6; H, 7.05; P, 9.2%; M^+, 326.1421. $C_{20}H_{23}O_2P$ requires C, 73.6; H, 7.05; P. 9.5%; *M*, 326.1435); ν_{max}/cm^{-1} ($CDCl_3$) 1700 (C=O), 1440 (Ph–P) and 1180 (P=O); $\delta_H(CDCl_3)$ 8.0–7.3 (10 H, m, Ph_2PO) and 2.8–1.1 (13 H, m, remaining Hs); *m/z* 326 (24%, M^+), 215 (100, Ph_2POCH_2) and 202 (46, Ph_2POH).

3-*Diphenylphosphinoylpropyl Toluene*-p-*sulfonate* **7**; X = OTs.—Butyllithium (4.7 cm^3 of a 1.6 mol dm^{-3} solution in hexane) was added to a stirred solution of 3-diphenylphosphinoylpropanol[7] (1.83 g) in THF (50 cm^3) cooled to −5 °C in an ice–salt bath. A solution of toluene-*p*-sulfonyl chloride (1.47 g) in THF (10 cm^3) was added and the mixture stirred for 30 min. Water (100 cm^3) was added and the mixture extracted with dichloromethane. The combined extracts were washed

with water, dried ($MgSO_4$) and concentrated under reduced pressure to give the sulfonate (2.9 g, 99%) as a waxy solid; $\delta_H(CDCl_3)$ 7.8–7.2 (14 H, m, Ph_2PO and Ph), 4.1 (2 H, t, *J* 6, CH_2O), 2.4 (3 H, s, Me) and 2.4–1.8 (4 H, m, remaining CH_2s).

1-*Diphenylphosphinoyl*-3-*iodopropane* **7**; X = I.—A solution of 3-diphenylphosphinoylpropanol[7] (5 g) in concentrated hydriodic acid (5 cm^3) was heated under reflux for 19 h. The mixture was cooled, poured into excess water and extracted with dichloromethane. The extract was washed with water and with saturated sodium thiosulfate solution, dried (Na_2SO_4) and evaporated under reduced pressure to give the *iodide* (7.0 g, 98%) as a white solid turning yellow on exposure to air, m.p. 138–140 °C, R_F (ethyl acetate) 0.3; $\delta_H(CDCl_3)$ 7.9–7.3 (10 H, m, Ph_2PO), 3.3–3.1 (2 H, t, *J* 6, CH_2I) and 2.6–1.1 (4 H, m, CH_2CH_2P) (Found: M^+, 369.9959. $C_{15}H_{16}IOP$ requires *M*, 369.9983); *m/z* 370 (0.3%, M^+), 243 (100, $M^+ - I$), 215 (66) and 201 (73, Ph_2PO).

2-(3-*Diphenylphosphinoylpropyl*)*cyclohexanone* **9**.—Butyllithium (5.83 cm^3 of a 1.6 mol dm^{-3} solution in hexane) was added to a stirred solution of diisopropylamine (1.46 cm^3) in THF (20 cm^3) at 0 °C in an ice–salt bath. The mixture was stirred for 15 min and cyclohexanone cyclohexylimine[8,13] **8** (1.56 g) in THF (2 cm^3) was added dropwise *via* a syringe. Stirring was continued for 20 min and the solution added *via* a double ended cannula to a stirred solution of 1-diphenylphosphinoyl-3-iodopropane **7**; X = I (3.22 g) in THF (25 cm^3) at 0 °C. After 30 min, the reaction mixture was quenched with dilute hydrochloric acid and extracted with dichloromethane. The extract was washed with water and with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography on silica gel eluting with acetone and recrystallisation from ethyl acetate gave the *ketone* (2.04 g, 69%) as needles, m.p. 101–103 °C (Found: C, 74.0; H, 7.45; P, 9.1%; M^+, 340.1594. $C_{21}H_{25}O_2P$ requires C, 74.1; H, 7.35; P, 9.1%; *M*, 340.1592); ν_{max}/cm^{-1} ($CDCl_3$) 1700 (C=O), 1440 (Ph–P) and 1180 (P=O); $\delta_H(CDCl_3)$ 7.9–7.3 (10 H, m, Ph_2PO) and 2.4–1.0 (15 H, m, other Hs); *m/z* 340 (17%, M^+), 241 (56), 215 (95) and 202 (100, Ph_2POH).

2-(3-*Diphenylphosphinoylpropyl*)*cyclooctanone* **12**.—In the same way, butyllithium (6.06 cm^3 of a 1.6 mol dm^{-3} solution in hexane), diisopropylamine (1.52 cm^3) and cyclooctanone cyclohexylimine[8,14] (1.87 g) gave the *ketone* (2.36 g, 71%) as prisms, m.p. 133–134 °C (Found: C, 75.3; H, 8.05; P. 8.4%; M^+, 368.1913. $C_{23}H_{29}O_2P$ requires C, 75.0; H, 7.9; P, 8.4%; *M*, 368.1905); ν_{max}/cm^{-1} ($CDCl_3$) 1700 (C=O), 1440 (Ph–P) and 1180 (P=O); $\delta_H(CDCl_3)$ 7.9–7.3 (10 H, m, Ph_2PO) and 2.7–0.9 (19 H, m, other Hs); *m/z* 368 (7.1%, M^+), 215 (51, Ph_2POCH_2) and 202 (100, Ph_2POH).

7-(2-*Diphenylphosphinoylethyl*)*oxepan*-2-*one* **3**.—Trifluoroperacetic acid [3 cm^3 of a 1.3 mol dm^{-3} solution prepared[15] from hydrogen peroxide (85% pure, 1.2 g) and trifluoroacetic anhydride (6.5 cm^3)] in dichloromethane (15 cm^3) was added to a stirred solution of 2-(3-diphenylphosphinoylethyl)cyclohexanone **2** (500 mg) and disodium hydrogen phosphate (1 g) in dichloromethane (2.5 cm^3) at 0 °C in an ice–salt bath. Stirring was continued at this temperature for 15 min and for a further 18 h at room temperature. The organic layer was washed with sodium hydrogen carbonate solution, with sodium sulfite solution and with water, dried ($MgSO_4$) and the solvent removed under reduced pressure. Recrystallisation from ethyl acetate gave the *lactone* (425 mg, 81%) as a waxy solid; ν_{max}/cm^{-1} ($CDCl_3$) 1720 (C=O), 1440 (Ph–P) and 1180 (P=O); $\delta_H(CDCl_3)$ 8.1–7.3 (10 H, m, Ph_2PO), 4.5–4.1 (1 H, m, CH–O), 2.8–2.2 (4 H, m, $COCH_2$ and CH_2P) and 2.2–1.1 (8 H, m, other CH_2s) (Found: M^+, 342.1356. $C_{20}H_{23}O_3P$ requires *M*, 342.1385); *m/z* 342 (0.68%, M^+), 285 (30), 272 (32), 215 (52, Ph_2POCH_2) and 202 (100, Ph_2POH).

7-(3-*Diphenylphosphinoylpropyl*)*oxepan*-2-*one* **10**.—In the same way, trifluoroperacetic acid (5 cm^3 of a 1.3 mol dm^{-3} solution), 2-(3-diphenylphosphinoylpropyl)cyclohexanone **9** (1.0 g) and disodium hydrogen phosphate (2 g) in dichloromethane (5 cm^3) gave the *lactone* (0.95 g, 91%) as needles, m.p. 105–107 °C (from ethyl acetate) (Found: C, 70.8; H, 7.05%; M^+, 356.1541. $C_{21}H_{25}O_3P$ requires C, 70.8; H, 7.0%; *M*, 356.1541); ν_{max}/cm^{-1} ($CDCl_3$) 1720 (C=O), 1590 (Ph), 1440 (Ph–P) and 1180 (P=O); $\delta_H(CDCl_3)$ 7.9–7.3 (10 H, m, Ph_2PO), 4.4–4.0 (1 H, m, CH–O) and 1.7–0.8 (14 H, m, other Hs); *m/z* 356 (3.5%, M^+), 215 (100, Ph_2POCH_2) and 202 (96, Ph_2POH).

2-(*Diphenylphosphinoyl*)-4-*hydroxycyclooctanone* **5**.—Butyllithium (4.3 cm^3 of a 1.6 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of diisopropylamine (1.0 cm^3) in THF (18 cm^3) at 0 °C in an ice–salt bath. The solution was stirred at room temperature for 15 min, cooled to −78 °C, and added *via* a double-ended cannula to a stirred solution of 7-(2-diphenylphosphinoylethyl)oxepan-2-one **3** (2.0 g) in THF (40 cm^3) at −78 °C. Stirring was continued for 20 min, the mixture quenched with saturated ammonium chloride solution (20 cm^3) and allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue taken up in dichloromethane. The organic extract was washed with water and with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to give an oil. Recrystallisation from ethyl acetate gave the *phosphine oxide* (1.05 g, 53%) as needles, m.p. 108–110.5 °C (from ethyl acetate, softening at 95 °C) (Found: C, 70.6; H, 6.7; P, 9.1%; M^+, 342.1392. $C_{20}H_{23}O_3P$ requires C, 70.2; H, 6.75; P, 9.1%; *M*, 342.1385); ν_{max}/cm^{-1} ($CDCl_3$) 3350 (OH), 1130 and 980; $\delta_H(CDCl_3)$ 7.8–7.3 (10 H, m, Ph_2PO), 4.4 (1 H, dt, *J* 1.5 and 7.5, OCH), 3.15–3.0 (1 H, m, PCH), 2.6–2.4 (1 H, m, $PCHCH_AH_BCH_2$), 2.1–1.9 (1 H, m, $PCHCH_AH_BCH_2$) and 1.9–1.1 (9 H, m, methylene envelope and OH); *m/z* 342 (0.7%, M^+), 229 (100) and 202 (88, Ph_2POH).

2-(*Diphenylphosphinoyl*)-5-*hydroxycyclononanone* **11**.—In the same way, butyllithium (4.4 cm^3 of a 1.6 mol dm^{-3} solution in hexane), diisopropylamine (1.10 cm^3) in THF (18 cm^3), and 7-(3-*diphenylphosphinoylpropyl*)*oxepan*-2-*one* **10** (2.0 g) in THF (40 cm^3) gave the *phosphine oxide* (1.04 g, 52%) as a waxy solid; ν_{max}/cm^{-1} ($CDCl_3$) 3400 (OH), 1705 (C=O), 1440 (Ph–P) and 1175 (P=O); $\delta_H(CDCl_3)$ 7.9–7.2 (10 H, m, Ph_2PO), 4.3–3.9 (1 H, m, PCHCO), 3.9–3.4 (1 H, m, CHOH) and 2.7–1.1 (13 H, m, methylene envelope and OH) (Found: M^+, 356.1522. $C_{21}H_{25}O_3P$ requires *M*, 356.1541); *m/z* 356 (0.9%, M^+), 229 (76) and 202 (100, Ph_2POH).

4-*Hydroxycyclooctanone* **6**—Sodium hydroxide (20 cm^3 of a 4 mol dm^{-3} solution) was added to a stirred solution of 2-(diphenylphosphinoyl)-4-hydroxycyclooctanone **5** (300 mg) in ethanol (10 cm^3). The mixture was vigorously stirred at 60 °C for 3 h, and allowed to cool to room temperature. Water was added and the mixture extracted with dichloromethane. The extract was washed with water and with brine and the solvent removed under reduced pressure to give an oil. Column chromatography on silica gel eluting with ethyl acetate gave the ketone (75 mg, 60%) as a straw coloured liquid whose NMR spectrum was identical with that of an authentic sample of 4-hydroxycyclooctanone.[16]

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