Stereochemically Controlled Synthesis of Unsaturated Acids by the Coupled Baeyer–Villiger and Horner–Wittig Reactions: Synthesis of (*Z*)-Oct-6-enoic Acid

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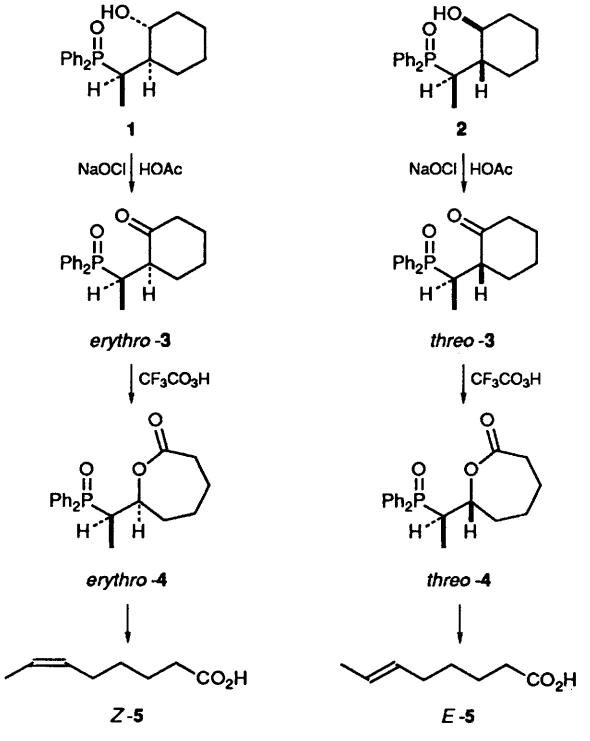
The lithium derivative of $Ph_2P(O)Et$ reacts with cyclohexene oxide to give largely one diastereoisomer of an alcohol. Oxidation to a ketone and then to a lactone followed by hydrolysis gives a Horner–Wittig intermediate and hence pure (*Z*)-oct-6-enoic acid. Complementary methods give (*E*)-oct-6-enoic acid.

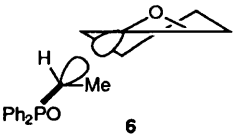
We have reported[1] a Horner–Wittig route to unsaturated acids *via* separable crystalline lactones such as **4** which, though formed with only weak *threo*-selectivity by the reduction of the corresponding keto acid, give pure *E*- or *Z*-acids, *e.g.* **5**, stereospecifically on completion of the Horner–Wittig reaction. We now report[2] an alternative approach (Scheme 1) which allows a higher material conversion into the *erythro*-lactone **4**.



Scheme 1

The lithium derivative of ethyldiphenylphosphine oxide added to cyclohexene oxide with high (*ca.* 9:1) stereoselectivity to give the crystalline alcohols **1** and **2**, separated by flash column chromatography.[3] This selectivity concerns only the chiral centre bearing the Ph_2PO group as the other two are specifically related by the *anti* attack on the epoxide. A possible explanation is that the favoured approach **6** has the large Ph_2PO group away from the ring and the Me group in the less hindered of the two remaining positions. Attempts to vary the proportions of **1** and **2** (addition of TMEDA or $Cu^{I}I$) were not successful, but treating pure **1** with 2 equiv. of BuLi and quenching with water gave a 1.5:1 mixture of **1**:**2**.†

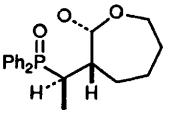
† All compounds are racemic.



The selectivity is not a consequence of a six-membered ring conformation since the lithium derivative of $Ph_2P(O)Et$ added to cyclopentene oxide to give the adducts **7** and **8** with slightly greater stereoselectivity. Similar stereoselectivities were found when epoxides of acyclic alkenes were attacked by lithium derivatives of related phosphine oxides[4] or by enolates of amides.[5] The stereochemistry of **1** and **7** is the same and was determined by X-ray crystal structure analysis.

Oxidation and Epimerisation.—Of the various methods[6] for oxidising Ph_2PO-containing alcohols to ketones, NaOCl in HOAc[7] gave the highest yields and the simplest work-up. The alcohols **1** and **2** were oxidised by this reagent to give *erythro*-**3** and *threo*-**3** respectively (Scheme 1) without epimerisation, providing the reaction was worked up immediately. Prolonged exposure to HOAc, slow crystallisation (EtOAc, HOAc, 1 week), or equilibration in acid (TsOH, AcOH) converted either ketone into a 10:1 (HPLC) mixture favouring *threo*-**3** from which pure *threo*-**3** could be isolated in 81% yield. Pure *erythro*-**3** can be obtained, by isolation of pure **1** and oxidation without epimerisation, in 64% yield, and pure *threo*-**3**, by oxidation, epimerisation, and crystallisation of the mixture of **1** and **2** in 74% yield.

Baeyer–Villiger Reactions.—Pertrifluoroacetic acid[8] gave an excellent yield of the lactone *erythro*-**4** from *erythro*-**3** with complete stereospecifity and high (*ca.* 25:1 by NMR) regioselectivity. The *threo* ketone **3** gave a cleanly stereospecific but less regioselective reaction, the ratio of *threo*-**4** to *threo*-**9** being 5:3, and we were unable to separate this mixture. We assume that the poorer regioselectivity in the *threo*-series is a stereo-



threo-**9**

electronic effect: a conformationally dependent bonding interaction between the C-P LUMO and the bond from C-6 to C-7 lowering the HOMO energy and hence the migrating ability of the latter. Effects of remote electronegative groups on Baeyer–Villiger regioselectivity have been observed by others.[9]

The previous identification[1] of *erythro*- and *threo*-**4** by coupling constants in their NMR spectra is now confirmed by correlation with the X-ray structure of **1** and the known stereospecificity of the Baeyer–Villiger reaction.[10] We have already described[1] the hydrolysis of the lactones **4** and the elimination of $Ph_2PO_2^-$ from the resulting hydroxy acids. The present route provides a good yield of the acid *Z*-**5** (91% from *erythro*-**4**) and could be used to prepare *E*-**5** by hydrolysis of the mixture of *threo* **5** and **9** since only one of the resulting hydroxy acids can eliminate $Ph_2PO_2^-$. However, our previous methods provide better routes to *E*-**5**. These simple examples show the complementary nature of our two routes to unsaturated acids.

Experimental

General procedures have been described before.[11] BuLi refers to butyl-lithium and THF to dry tetrahydrofuran distilled from potassium.

2-(1-*Diphenylphosphinoylethyl*)*cyclohexanol* **1**.—BuLi (1.55 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of ethyldiphenylphosphine oxide (6 g, 26 mmol) in THF (100 cm^3) at 0 °C under nitrogen until the orange colour persisted. Further BuLi (1.55 mol dm^{-3} solution; 16.8 cm^3, 26 mmol) was added dropwise, the dark red solution was cooled to −70 °C, and cyclohexene oxide (2.85 g, 29 mmol) was added. The solution was allowed to warm to room temperature, and stirring was continued for 14 h. Saturated aqueous ammonium chloride (80 cm^3) was added, the bulk of the THF was removed by evaporation under reduced pressure, water (80 cm^3) was added, and the mixture was extracted with EtOAc (4 × 50 cm^3). The combined organic extracts were washed with water (30 cm^3) and saturated brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. HPLC analysis of the crude mixture indicated an 84:16 ratio of diastereoisomers. The minor diastereoisomer **2** was less soluble in EtOAc. Purification was achieved by flash column chromatography[3] on Merck 9385 silica gel, eluting with EtOAc and then a mixture of EtOAc and methanol (95:5) once the first diastereoisomer had been eluted. This gave the [RS-(R*,R*,R*)]-*phosphine oxide* **1** (6.08 g, 71%) as plates, m.p. 162.5–164 °C (Found: C, 73.1; H, 7.6; P, 9.3. $C_{20}H_{25}O_2P$ requires C, 73.1; H, 7.65; P, 9.4%); R_f(EtOAc) 0.38; ν_{max}/cm^{-1}($CHCl_3$) 3300br (OH), 1440 (PhP), 1175 (P=O) and 1130 (CO); δ_H($CDCl_3$) 8.0–7.2 (10 H, m, Ph_2PO), 5.6 (1 H, s, OH), 3.6–3.2 (1 H, m, *H*COH), 2.3 (1 H, quint, *J* 8, PCH), 2.2–1.8 (1 H, m, PCHC*H*CO), 1.9–0.8 [8 H, m, $(CH_2)_4$] and 1.15 (3 H, dd, J_{HH} 17, PCH*Me*); *m*/*z* 328 (4%, M^+), 230 [8, $Ph_2P(OH)CHMe^+$] and 202 (100, Ph_2POH^+). The second product to be eluted was the [RS-(R*,S*,S*)]-*phosphine oxide* **2** (1.16 g, 14%), m.p. 203.5–204 °C (Found: C, 73.0; H, 7.4; P, 9.5. $C_{20}H_{25}O_2P$ requires C, 73.15; H, 7.65; P, 9.4%); R_f (EtOAc) 0.28; ν_{max}/cm^{-1}($CHCl_3$) 3300br (OH), 1440 (PhP), 1170 (P=O) and 1120 (CO); δ($CDCl_3$) 8.0–7.2 (10 H, m, Ph_2PO), 3.6–3.2 (1 H, m, *H*COH), 3.1 (1 H, quint, *J* 8, PCH), 2.7 (1 H, s, OH), 2.15–1.7 [2 H, m, PCH*H*O and CH(*H**)COH], 2.8–1.3 [3 H, m, CHCH_2 and C*H**(H)COH], 1.4–0.8 [4 H, $CH_2(CH_2)CH_2$] and 1.1 (3 H, dd, J_{HH} 7.5 and J_{PH} 17, PCH*Me*); *m*/*z* 328 (3%, M^+), 310 (2, $M^+ - H_2O$), 230 [66, $Ph_2P(OH)CHMe$], 202 (100, Ph_2POH^+) and 201 (28, Ph_2PO^+).

2-(1-*Diphenylphosphinoylethyl*)*cyclopentanol* **7**.—In the same way ethyldiphenylphosphine oxide (4.6 g, 20 mmol), BuLi (155 mol dm^{-3} solution in hexane; 13 cm^3, 20 mmol), and cyclopentene oxide (1.68 g, 20 mmol) gave [after 24 h at 50 °C, followed by extraction and purification by flash column chromatography[3] on Merck 9385 silica gel (4.5 cm diam. × 15.2 cm), eluting with EtOAc] the [RS-(R*,R*,R*)]-*phosphine oxide* **7** (4.44 g, 71%), m.p. 172.5–173 °C (Found: C, 72.6; H, 7.55; P, 9.7, M^+, 314.1431. $C_{19}H_{23}O_2P$ requires C, 72.6; H, 7.35; P, 9.85%, M, 314.1435); R_f (EtOAc) 0.31; ν_{max}/cm^{-1} ($CHCl_3$) 3330br (OH), 1440 (PhP), 1160 (P=O) and 1120 (CO); δ($CDCl_3$) 8.1–7.3 (10 H, m, Ph_2PO), 5.1 (1 H, br s, OH), 4.25–3.9 (1 H, m, *H*COH), 2.6 (1 H, quint, *J* 7.5, PCH), 2.3–1.3 [7 H, m, $OC(CH_2)_3CH$] and 1.1 (3 H, dd, J_{HH} 7.5 and J_{PH} 17, PCH*Me*); *m*/*z* 314 (4%, M^+), 286 (4), 230 [7, $Ph_2P(OH)$-$CHMe^+$] and 202 (100, Ph_2POH^+), and the [RS-(R*,S*,S*)]-*phosphine oxide* **8** (0.5 g, 8%), m.p. 167–168 °C (Found: C, 72.2; H, 7.65; P, 9.8. $C_{19}H_{23}O_2P$ requires C, 72.6; H, 7.35; P, 9.85%); R_f (EtOAc) 0.23; ν_{max}/cm^{-1}($CHCl_3$) 3300br (OH), 1440 (PhP), 1160 (P=O) and 1120 (CO); δ($CDCl_3$) 8.1–7.3 (10 H, m, Ph_2PO), 4.05 (1 H, q, *J* 7, HOCH), 2.65 (1 H, sextet, J_{HH} and J_{PH} 7, PCH), 2.2–1.1 [7 H, m, $OC(CH_2)_3CH$] and 1.0 (3 H, dd, J_{HH} 7 and J_{PH} 18, PCH*Me*); *m*/*z* 314 (2%, M^+), 230 [20, $Ph_2P(OH)CHMe^+$] and 202 (100, Ph_2POH^+).

[R-(R*,R*)]-2-(1-*Diphenylphosphinoylethyl*)*cyclohexane*.—This compound was prepared following the method of Stevens *et al.*,[7]. Aqueous sodium hypochlorite (10–14% available Cl; 12.5 cm^3) was added dropwise over 20 min to a vigorously stirred solution of the phosphine oxide **1** (1 g, 3.05 mmol) in glacial acetic acid (25 cm^3) at 16 °C. The mixture was warmed to 20 °C and further aqueous sodium hypochlorite (10 cm^3) was added dropwise over 1 h, with vigorous stirring, at such a rate as to maintain the yellow colouration in the flask. The mixture was cooled to 0 °C, water (100 cm^3) was added, and the resulting mixture was extracted with EtOAc (3 × 30 cm^3). The combined organic extracts were washed with saturated aqueous sodium metabisulfite (20 cm^3) at *ca.* 0 °C. The organic extracts were dried ($NaSO_4$) and evaporated under reduced pressure (2 mmHg, solid CO_2 cooled condenser) at *ca.* 0 °C. EtOAc (75 cm^3) was added to dissolve the residue and the solution was washed at 0 °C with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), water (20 cm^3) and saturated brine (20 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was immediately purified by flash column chromatography[3] on Merck 9385 silica gel (3.5 cm diam. × 16.5 cm), eluting with EtOAc and then EtOAc–methanol (95:5) to give the *phosphine oxide erythro*-**3** (0.89 g, 89.5%), m.p. 159–160 °C (Found: C, 73.4; H, 7.1; P, 9.6. $C_{20}H_{23}O_2P$ requires C, 73.6; H, 7.1; P, 9.5%); R_f (EtOAc) 0.16; ν_{max}/cm^{-1}($CHCl_3$) 3350br (ketone hydrate OH), 1700 (C=O), 1440 (PhP) and 1170 (P=O); δ_H($CDCl_3$) 8.0–7.3 (10 H, m, Ph_2PO), 3.17 (1 H, dq, J_{PH} 13.3 and J_{HH} 7, PC*H*CHCO), 2.95–2.5 (1 H, m, CHCO), 2.5–2.1 (2 H, m, CH_2CO), 2.1–1.1 [8 H, m, $(CH_2)_4$] and 1.08 (3 H, dd, J_{HH} 7 and J_{PH} 16.6, PCH*Me*); *m*/*z* 326 (7%, M^+), 281 (40), 230 (33, $Ph_2POC_2H_5^+$) and 202 (100, Ph_2POH^+).

[R-(R*,S*)]-2-(1-*Diphenylphosphinoylethyl*)*cyclohexanone* **3**.—This compound was obtained from the phosphine oxide **1**, following the Method of Stevens *et al.*,[7] but with subsequent epimerisation. In the same way, aqueous sodium hypochlorite and the phosphine oxide **1** (2 g, 6.1 mmol) in glacial acetic acid (50 cm^3) at 20 °C gave a white foam (2.07 g). This was left to crystallise at room temperature for 1 week and resulted in almost complete conversion of *erythro*-**3** into *threo*-**3** by epimerisation and selective crystallation. A proportion of the residue (2 g) was purified by flash column chromatography[3] on Merck 9385 silica gel (3.5 cm diam. × 15.2 cm column per 1 g residue), eluting with EtOAc–methanol (97:3) to give the *phosphine oxide threo*-**3** (1.67 g, 87%), m.p. 139–140 °C (Found:

73.3; H, 7.2; P, 9.7. $C_{20}H_{23}O_2P$ requires C, 73.6; H, 7.1; P, 9.5%); R_f (EtOAc) 0.23; ν_{max}/cm^{-1}($CHCl_3$) 3360br (ketone hydrate OH), 1700 (C=O), 1440 (PhP) and 1170 (P=O); δ_H($CDCl_3$) 7.95–7.3 (10 H, m, Ph_2PO), 3.34 (1 H, dquint, J 1.4 and 7.3, PCH), 2.9–1.3 [9 H, m, $(CH_2)_4$], 2.5–2.1 (2 H, m, CH_2CO), 2.1–1.1 [8 H, m, $(CH_2)_4$] and 1.08 (3 H, dd, J_{HH} 7 and J_{PH} 16.6 PCH*Me*); *m/z* 326 (7%, M^+), 281 (40) 230 (33, $Ph_2POC_2H_5^+$) and 202 (100, Ph_2POH^+).

[RS-(R*,S*)]-2-(1-*Diphenylphosphinoylethyl*)*cyclohexanone*.—This compound was prepared from the phosphine oxide **2**. In a manner similar to that described above aqueous sodium hypochlorite and the phosphine oxide **2** (150 mg, 0.46 mmol) in glacial acetic acid (3 cm^3) gave the phosphine oxide *threo*-**3** (124 mg 83%).

Acid-catalysed Epimerisation of the Phosphine Oxide erythro-**3**.—Toluene-*p*-sulfonic acid (*ca.* 5 mg) and the phosphine oxide *erythro*-**3** (25 mg) in glacial acetic acid (3 cm^3) were stirred at room temperature for 7 days. Water (15 cm^3) was added, and the mixture was extracted with chloroform (3 × 5 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 5 cm^3) and water (5 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. Deuteriochloroform was immediately added to the residue and NMR and HPLC showed the equilibrium ratio of diastereoisomers *threo*:*erythro* in solution was 10:1.

Pertrifluoroacetic Acid Oxidation of the Ketone erythro-**3**.—Following the method of Emmons and Lucas,[8] pertrifluoroacetic acid (1.34 mol dm^{-3} solution in dichloromethane; 1.5 cm^3, 2 mmol) was added dropwise by glass pipette to a vigorously stirred mixture of the phosphine oxide *erythro*-**3** (0.32 g, 0.96 mmol) and disodium hydrogen phosphate (420 mg, 3 mmol) in distilled dichloromethane (5 cm^3) at 0 °C. Stirring was continued at room temperature for 1.5 h, after which the mixture was cooled to 0 °C, and anhydrous sodium sulfite (0.8 g) was added, followed by dichloromethane (15 cm^3). The mixture was filtered through Celite, which was washed through with further dichloromethane (3 × 20 cm^3), and the combined filtrate and washings were evaporated under reduced pressure. The residue was purified by flash column chromatography[3] on Merck 9385 silica gel (27 g; 2 cm diam. × 15.2 cm), eluting with EtOAc (250 cm^3) and then ethyl acetate–methanol (97:3; 500 cm^3) to give *erythro*-**4** [*RS*-(**R*,S**)]-7-(1-diphenylphosphinoylethyl)-oxepan-2-one[1] (0.30 g, 89%).

Pertrifluoroacetic Acid Oxidation of the Ketone threo-**3**.—Following the method of Emmons and Lucas, pertrifluoroacetic acid and the phosphine oxide *threo*-**3** (100 mg, 0.31 mmol) gave a mixture of *threo*-**4** [*RS*-(*R*,*R**)]-7-(1-diphenylphosphinoylethyl)oxepan-2-one and [*RS*-(*R**,*S**)]-3-(1-diphenylphosphinoylethyl)oxepan-2-one **9** in the ratio 5:3 by NMR: δ($CDCl_3$) 7.84–7.74 (4 H, m, Ph_2PO *ortho* protons), 7.56–7.47 (6 H, m, Ph_2PO *meta* and *para* protons), 4.41 [5/8 H, ddd, J 9, 6 and 2.4, **4** OCH], 4.18–4.11 [3/8 H, dm, $J_{geminal}$ 12, **9** OCH (*H**)], 3.79 [3/8 H, t, J 12, **9** OC*H**(H)], 3.05 [3/8 H, quintet, J 7.4, **9** PCH], 2.97–2.85 [3/8 H + 5/8 H, m, **9** CHC=O and **4** PCH], and 2.6–1.2 [27/8 H + 55/8 H, m, **9** $OCH_2(CH_2)_3$ and Me, and **4** $(CH_2)_4$ and Me].

Acknowledgements

We thank SERC and Glaxo Group Research (Ware) for a CASE award, Drs. M. P. Gomez-Sal and P. R. Raithby[12] for the X-ray crystal structure determination of **1**, Dr. W. B. Cruse[13] for that of **7**, and Dr. Eric Collington for many helpful discussions

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Paper 2/02865D
Received 1*st June* 1992
Accepted 16*th June* 1992