The Preparation of (*R*)- and (*S*)-(*E*)-But-2-enyl-t-butylphenylphosphine Oxides and their Enantiospecific Conversion into Enantiomeric Hydrindenones related to Vitamin D

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The individual enantiomers of (*E*)-but-2-enyl-t-butylphenylphosphine oxide have been prepared, and the lithiated carbanions of each undergo completely stereoselective conjugate addition with 2-methylcyclopent-2-enone to generate enolates, which upon reaction with 4-chlorobut-3-en-2-one and subsequent reduction have been converted into the corresponding enantiomers of hydrindenones suitable for conversion into vitamin D analogues and their enantiomers.

Lithiated (*E*)-but-2-enyldiphenylphosphine oxide undergoes rapid conjugate addition to cyclopent-2-enone to give exclusively the allylically transposed *syn* adduct.[1] The regio- and stereo-chemical outcome of this reaction is rationalized in terms of a planar lithiated carbanion reacting through a *trans*-decalyl or *trans*-fused chair–chair transition state with the enone (Scheme 1). The *syn*-stereochemistry of the product has been efficiently exploited in the highly stereoselective synthesis of a racemic hydrindanol precursor of vitamin D,[2] and a bicyclo[2.2.1]heptanone.[3] Because of the need to obtain optically pure target compounds, we have turned to the preparation of enantiomerically pure allylic phosphine oxides. According to the transition-state model, it is the configuration at phosphorus that determines the face selectivity of the reactions of the lithiated carbanion with an enantiofacial enone. The non-allylic substituents attached to the stereogenic phosphorus must have substantially different steric requirements, such that the small substituent exclusively adopts a pseudoaxial, the large, a pseudoequatorial disposition in the transition state. The substituents cannot contain acidic protons. For these reasons, and because of the relative ease of preparation of the target phosphine oxide, the t-butyl group was selected as the large, and the phenyl group as the small substituent. In the context of an enantiospecific synthesis of natural vitamin D precursors, attack of the requisite lithiated (*E*)-but-2-enyl-t-butylphenylphosphine oxide must take place on the *Si*-face of the enone, 2-methylcyclopent-2-enone (Scheme 2). Providing the t-butyl group adopts a pseudoequatorial disposition in the transition state, it is the (*S*)-enantiomer of the phosphine oxide that is required.

In a preliminary study, racemic (*E*)-but-2-enyl-t-butylphenylphosphine oxide (±)-**1**, prepared from the lithium salt of t-butylphenylphosphine oxide[4] and (*E*)-1-bromobut-2-ene, was deprotonated in tetrahydrofuran (THF) with n-butyllithium, and at −70 °C was treated according to the usual conditions[1] with cyclopent-2-enone to give solely the racemic

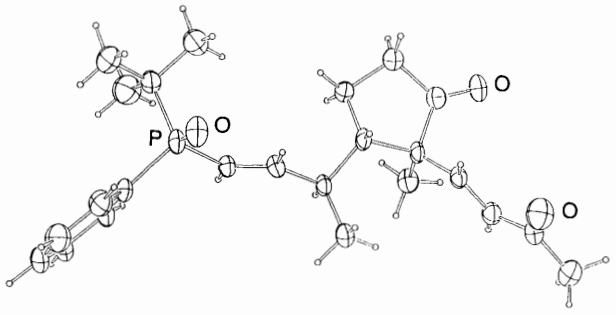
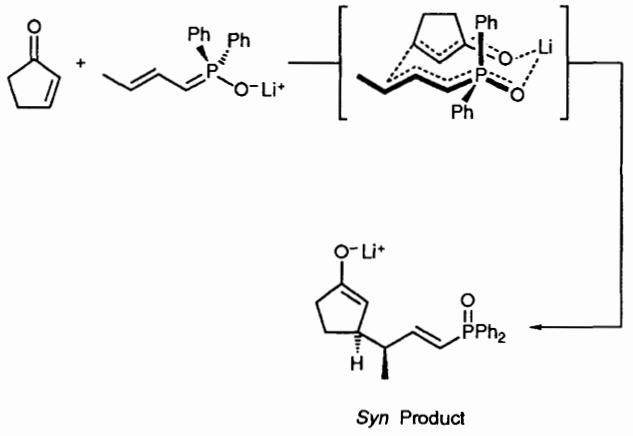


Fig. 1 ORTEP drawing of (±)-3-{3′-[(*RS*)-t-butylphenylphosphinoyl]-1′-methylprop-2′-enyl}-2-methyl-2-(3″-oxobut-1″-enyl)cyclopentan-1-one (±)-**4**. Ellipsoids are shown at the 30% probability level. The (1′*R*,2*R*,3*S*,R_p)-enantiomer is shown, but both enantiomers are present in the unit cell.



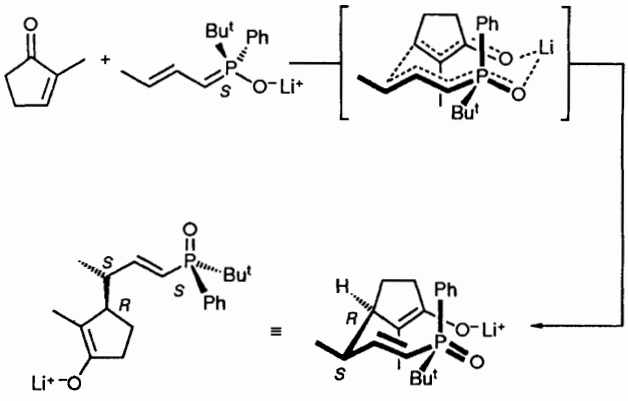
Scheme 1

adduct (±)-**2**† (92%), an oil, as a single diastereoisomer. Thus, the t-butyl and phenyl groups are sufficiently dissimilar to ensure that enantiofacial differentiation is complete. In order to ensure that the t-butyl group does indeed adopt a pseudoequatorial disposition in the transition state, and hence, to validate the prediction of Scheme 2, the relative configuration at phosphorus in the (racemic) product had to be secured. This could not be done with compound (±)-**2**. However, a crystalline product suitable for X-ray analysis was obtained by treatment of the lithiated (*E*)-but-2-enyl-t-butylphenylphosphine oxide (1 mmol) in THF (15 ml) first at −70 °C with 2-methylcyclopent-2-enone (1.0 equiv.) and then at −30 °C with 4-chlorobut-3-en-2-one **3** (1.0 equiv.). After immediate quenching with aqueous ammonium chloride, the unsaturated diketone (±)-**4**, colourless cubes (decomposing at *ca.* 120 °C), was obtained in 86% isolated yield from the phosphine oxide (±)-**1**. The relative configuration at stereogenic phosphorus as depicted in (±)-**4** and revealed by the X-ray diffraction analysis (Fig. 1)‡ indicates that the t-butyl group must be pseudoequatorial in the transition state. It is thus clear that the (*S*)-enantiomer of the phosphine oxide reacts through the *Si*-face of the enone.

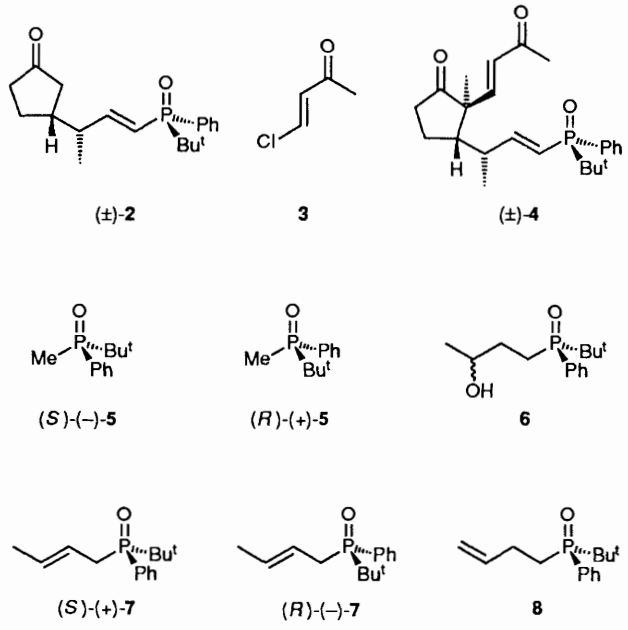
† For structures (±)-**2** and (±)-**4**, single enantiomers only are shown.

‡ The products obtained from the optically active phosphine oxides described did not provide crystals suitable for analysis.

Crystal data for (±)-**4**: $C_{24}H_{33}O_3P$, M = 400.42, monoclinic space group $P2_1/n$, a = 7.560(1), b = 29.515(6), c = 10.710(3) Å; β = 105.33(2)°, U = 2304.7 Å^3, D_c (Z = 4) = 1.154 g cm^{-3}, F(000) = 864, μ 1.03 cm^{-1}, λ(Mo-$K\alpha$) = 0.71069 Å. Reflections were measured with an Enraf-Nonius CAD-4 four-circle diffractometer. The structure was solved by heavy-atom methods, and refined by full-matrix least-squares analysis to an R of 0.044 on 1373 F [$I > 2.5\ \sigma(I)$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

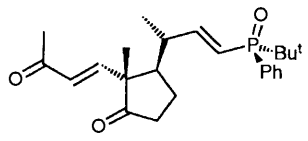


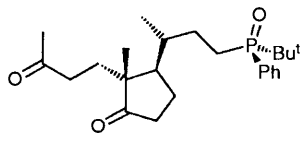
Scheme 2



Next, the optically active phosphine oxides were prepared.‡ (*S*)-t-Butylmethylphenylphosphine oxide (*S*)-(−)-**5**, needles, m.p. 99–100 °C, $[\alpha]_D^{22}$ −21.6° (*c* 0.78, $CHCl_3$) and the (*R*)-enantiomer (*R*)-(+)-**5**, $[\alpha]_D^{22}$ +23.1° (*c* 1.0, $CHCl_3$) were prepared from t-butylphenylphosphine oxide and (−)-menthyl chloroacetate according to a literature procedure.[5] Compound (*S*)-(−)-**5** (1 mmol) in THF (15 ml) at −50 °C was lithiated with butyllithium, and then treated first with propylene oxide (1.1 equiv.) and next with BF_3–ether (1 equiv.). Quenching at 0 °C for 2 h provided a 1:2 mixture of diastereoisomers of the γ-hydroxyphosphine oxide **6** (93%). The mixture was heated under reflux with camphorsulphonic acid (0.01 equiv.) in xylene with azeotropic removal of water for 36 h to give the (*S*)-but-2-enylphosphine oxide (*S*)-(+)-**7** (63%) as solely the (*E*)-isomer, colourless hygroscopic needles, m.p. 52–54 °C, $[\alpha]_D^{25}$ +16.0° (*c* 0.79, $CHCl_3$) and the regioisomeric but-3-enylphosphine oxide **8** (27%). Similarly, the (*R*)-but-2-enylphosphine oxide (*R*)-(−)-**7**, $[\alpha]_D^{25}$ −16.1° (*c* 1.05) was obtained from the (*R*)-t-butylmethylphenylphosphine oxide (*R*)-(+)-**5**.

The lithiated reagent from the phosphine oxide (*S*)-(+)-**7** (1 mmol) in THF (15 ml) at −70 °C was treated with 2-methylcyclopent-2-enone and the chloroenone **3** as described above to give the unsaturated diketone (+)-**4** (80%), cubes, $[\alpha]_D^{25}$ +40.6° (*c* 0.33, CH_2Cl_2). Two methods for reduction of the unsaturated diketone to the δ-diketones required for aldol cyclisation were used. In the first the unsaturated diketone was hydrogenated in ethyl acetate containing a few drops of


(+)-4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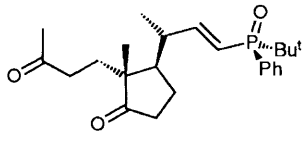
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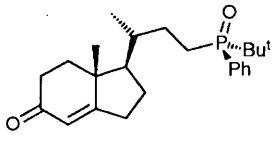
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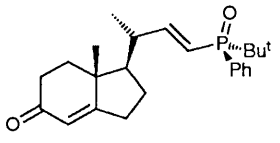
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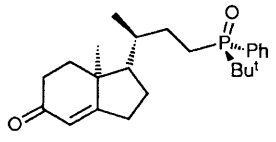
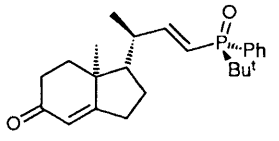

(−)-11


(−)-12

pyridine over 10% palladium on charcoal at 220 kPa to give quantitatively the diketone (+)-**9**, foam $[\alpha]_D^{26}$ −5.8° (*c* 1.78, $CHCl_3$). The presence of the pyridine prevents palladium-catalysed migration of the double bond of the vinylic phosphine oxide unit in (+)-**4** from taking place, as described in a related case.[2] The second method involved selective conjugate reduction whereby a variation of a literature method for the reduction of conjugate enones[6] was used. The enone (+)-**4** (3.5 mmol) in chloroform (25 ml) was stirred with diphenylsilane (1.2 equiv.), zinc chloride (0.1 equiv.), copper(II) chloride (0.1 equiv.) and tetrakis(triphenylphosphine)palladium (0.2 equiv.) at room temperature for 3 h to give the diketone (+)-**10** (86%), foam $[\alpha]_D^{25}$ +5.5° (*c* 0.9, $CHCl_3$). Each diketone was submitted to aldol ring closure with 2% potassium hydroxide in methanol under reflux for 2 h to give the hydrindenones (+)-**11** (70%), foam, $[\alpha]_D^{25}$ +6.25° (*c* 1.1, $CHCl_3$) and (+)-**12** (70%), foam, $[\alpha]_D^{25}$ + 21.0° (*c* 1.2, CH_2Cl_2) respectively. Commencing with the lithiated reagent from the phosphine oxide (*R*)-(−)-**7**, the hydridenones (−)-**11**, $[\alpha]_D^{25}$ −6.7° (*c* 0.5, $CHCl_3$), and (−)-**12** $[\alpha]_D^{25}$ −20.9° (*c* 1.5, CH_2Cl_2) were prepared in the same fashion.

Thus, enantiomeric hydrindenones suitable for conversion into both natural and unnatural analogues of vitamin D have been prepared from both (*S*)- and (*R*)-but-2-enyl-t-butylphenylphosphine oxides. The absolute configurations of these compounds follow from those of the starting but-2-enylphosphine oxides, which are themselves obtained from the enantiomeric t-butylmethylphenylphosphine oxides (*S*)-(−)- and (*R*)-(+)-**5** of known absolute configurations. The phosphine oxide groups in the hydrindenones **11** and **12** are nicely located for chain extension to be carried out *via* the Horner–Wittig reaction,[2] once the hydrindenones have been reduced to hydrindanones and the unsaturation in the side chains of the hydrindenones **12** has been removed. Alternatively, this unsaturation can be exploited to provide other precursors bearing somewhat more truncated side chains.

The conversions described herein illustrate the burgeoning synthetic importance of the conjugate addition reactions of stabilized lithiated allylic carbanions with cyclic enones.[1] Finally, we draw attention to the use of the β-chlorovinyl ketone **3** to enhance the efficiency of the trapping of the enolate produced by the conjugate addition of the lithiated phosphine oxides to 2-methylcyclopent-2-enone; the reagent is complementary to, but considerably more reactive than, the β-sulphonylvinyl ketones previously described by us.[2,7]

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