Chiral 2-VinyI-1,3,2-oxazaphospholidin-2-ones: New Dienophiles for Asymmetric Diels–Alder Reactions

Nobuya Katagiri,* a Mitsuo Yamamoto, a Tomoyasu Iwaoka b and Chikara Kaneko* a

^a Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan ^b Production Technology Research Laboratory, Chugai Pharmaceutical Co. Ltd., 5-1, 5-Chome, Ukima, Kita-ku, Tokyo 115, Japan

Diels–Alder reactions of chiral dienophiles: (2R,4S)- and (2S,4S)-2-vinyl-1,3,2-oxazaphospholidin-2-ones (3 and 4) derived from (S)-valinol with cyclopentadiene led to mixtures of *endo*- and *exo*-adducts with high diastereofacial selectivity (>90% for 3 and 80 and 88% respectively for 4); an explanation is proposed based on X-ray crystallographic structures for the dienophile and the derived *endo*-cycloadduct 5.

Despite the enormous amount of work on vinyl sulphoxides,¹ relatively few studies have been concerned with asymmetric induction reactions involving chiral substrates of the phosphine oxide type.² Because high asymmetric induction has been observed in the 1,3-dipolar cycloaddition of chiral vinyl sulphoxides with acyclic nitrones and in Diels–Alder reactions with cyclopentadiene or furan,³ we have been interested in investigating the Diels–Alder reaction using chiral vinylphosphonates as the dienophiles.⁴ We have chosen vinylphospholidines **3** and **4** as our initial substrates.

Treatment of vinylphosphonic dichloride[†] with 1 equiv. of (S)-N-benzylvalinol[‡] **2** and 9 equiv. Et₃N in toluene at -78 °C for 1 h and at 20 °C for 12 h gave an 82% yield of (2R,4S)-2-vinyl-1,3,2-oxazaphospholidin-2-one 3§ {m.p. 94-96 °C, $[\alpha]_D - 44.2^\circ$ (c 1.25)}¶ and the diastereoisomeric (2S,4S)-4 {m.p. 33-34 °C, $[\alpha]_D - 29.8^\circ$ (c 1.25)} in a ca. 1:1 ratio (Scheme 1). Phospholidines **3** and **4** were separated readily by silica gel column chromatography (AcOEt-hexane). The assignment of the relative and absolute configuration of the more polar oxazaphospholidine **3** follows from X-ray crystallographic analysis (Fig. 1; see later). Accordingly, the less polar isomer has to possess the absolute structure **4**.

When 3 was treated with cyclopentadiene (neat, room temp., 3 days), a mixture of *endo*- and *exo*-adducts (*ca.* 10:19) was formed in 96% yield. Two adducts were separated readily

¶ Specific rotations were determined in CHCl₃ at room temperature.

by silica gel column chromatography and the optical purity of each adduct was determined by 500 MHz ¹H NMR spectroscopy or HPLC (μ -Porasil, n-hexane–1,4-dioxane, 88:12) to



Scheme 1 Reagent and conditions: i, Bu^tMe₂SiCl, Et₃N, tetrahydrofuran (THF); ii, PhCHO, benzene, MgSO₄; iii, NaBH₄, MeOH; iv, Buⁿ₄NF, THF; v, CH₂=CHPOCl₂, Et₃N, toluene, initially at -78 °C and then at room temp.



Fig. 1 ORTEP diagrams of (a) (2R,4S)-vinyl-1,3,2-oxazaphospholidin-2-one 3; (b) the endo-adduct 5

^{\dagger} This compound was prepared *in situ* from 2-chloroethylphosphonic dichloride and Et₃N in toluene (-78 °C to room temp.).

 $[\]ddagger$ This compound was synthesized by silulation of (S)-valinol with Bu^tMe₂SiCl, benzylation and desilulation.

[§] All enantiomers are depicted with absolute stereochemistry indicated. All new compounds displayed satisfactory ¹H NMR spectra (500 MHz) and elemental analyses (for crystalline compounds) or high-resolution mass spectra (for oil).



Scheme 2 Si-face attack

be >90% for both adducts. Because of the highly crystalline nature of the adducts, the diastereoisomeric purity of each adduct {*endo*: m.p. 91–93 °C, $[\alpha]_D$ +28.0° (*c* 0.32) and *exo*: m.p. 125–126 °C, $[\alpha]_D$ -17.0° (*c* 0.18)} can be conveniently raised to >99% by simple recrystallization from hexane-diethyl ether.

The absolute structure of the *endo*-adduct **5** thus obtained was determined by X-ray crystallographic analysis shown in Fig. 1.|| This shows that cyclopentadiene approaches from *Si*-face of **3** with high preference (Scheme 2).

In order to clarify the origin of this diastereoselectivity,^{5,6} the X-ray crystallographic analysis of **3** was undertaken and revealed two interesting structural features: (*i*) the carbon–

Crystal data for 3: C₁₄H₂₀NO₂P, M = 265.30, orthorhombic, space group P2₁₂₁₂₁, a = 8.3324(8), b = 9.0550(4), c = 18.951(1) Å, U = 1429.8 Å³, D_c (Z = 4) = 1.232 g cm⁻³, F(000) = 568, $\mu = 16.56$ cm⁻¹, λ (Cu-Kα) = 1.5418 Å. The structure was solved and refined as for 5; R = 0.057 for 1680 F [$I > 2\sigma(I)$].

R = 0.057 for 1680 F [$I > 2\sigma(I)$]. 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.

J. CHEM. SOC., CHEM. COMMUN., 1991

carbon double bond and the P=O group are syn planar (s-cis) and (ii) the oxazaphospholidine ring is almost flat and its nitrogen atom is in sp² hybridization.|| It is obvious that the *Re*-face is shielded by the benzyl group. This conformation (Fig. 1) of the isomer 3, having the phosphonyl oxygen *anti* to the phenyl group though *cis* to the isopropyl group, might also explain why 3 is more polar than 4. High diastereofacial selectivity was also observed in the Diels-Alder reaction of (2S,4S)-4 with cyclopentadiene to give two adducts (*endolexo* = 0.67, diastereoisomeric excess 80% for *endo*- and 88% for *exo*-adducts).

This remarkable Diels–Alder reaction of the vinyl phospholidine **3** with cyclopentadiene (without addition of chelating agents) complements and advances the related chemistry explored with vinyl sulphoxides.¹ The potential utility of these reactions in natural product synthesis is clear, since the resulting phospholidine derivatives can be manipulated by the Horner–Emmons reaction. A wide range of application for asymmetric synthesis seems to be possible and is now being intensively pursued in this laboratory.

We are grateful to Dr Yasuji Nawata, Analytical Chemistry Research Laboratory, Chugai Pharmaceutical Co. Ltd., for the X-ray crystallographic analysis.

Received, 28th May 1991; Com. 1/02489B

References

- 1 Asymmetric Synthesis, ed. J. D. Morrison and J. W. Scott, Academic Press, New York, 1984, vol. 4, p. 241.
- 2 Ref. 1, p. 263.
- 3 The work was carried out mostly by two groups headed by T. Koizumi and C. Maignan. See review: M. J. Taschner in *Organic Synthesis, Theory and Applications*, ed. T. Hudlicky, JAI Press, London, 1989; vol. 1, p. 1.
- 4 Use of achiral dialkyl vinylphosphonates and related compounds in Diels-Alder reactions has ample precedent: W. M. Daniewski and C. E. Griffin, J. Org. Chem., 1966, 31, 3232; H. J. Callot and C. Benezra, Can. J. Chem., 1970, 48, 3382; O. Elisabeth, H. Ernst and Z. Erich, Chem. Ber., 1982, 115, 1028; N. Katagiri, M. Yamamoto and C. Kaneko, Chem. Lett., 1990, 1855.
- 5 The first use of chiral vinylphosphine oxides in Diels-Alder reactions was reported by R. Badalski, J. Koszuk, H. Krawczyk and K. M. Pietrusiewicz, J. Org. Chem., 1982, **47**, 2219.
- 6 Highly enantioselective base-catalysed 1,4-additions of chiral allyl phospholidines with cyclic enones have been reported: D. H. Hua, R. Chan-Yu-King, J. A. McKie and L. Myer, J. Am. Chem. Soc., 1987, 109, 5026.

^{||} Crystal data for 5: C₁₉H₂₆NO₂P, M = 331.40, monoclinic, space group P2₁, a = 16.669(1), b = 17.590(2), c = 6.144(1) Å, $\beta = 97.89(1)^\circ$, U = 1784.4 Å³, $D_c(Z = 4) = 1.234$ g cm⁻³, F(000) = 712, $\mu = 14.22$ cm⁻¹, λ (Cu-K α) = 1.5418 Å. Reflections were measured with an Enraf-Nonius CAD-4 four-circle diffractometer. The structure was solved by direct methods (MULTAN) and refined by full-matrix least-squares analysis to R = 0.065 for 3068 F [$I > 2\sigma(I)$]. The positional parameters of hydrogen atoms were calculated stereochemically and added in the calculation of structure factors. All nonhydrogen atoms were refined anisotropically.