Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 62 (2006) 12398–12407
Tetrahedron

Stereoselective Diels–Alder reactions of 3-phosphonopropenoyl derivatives of 1,3-oxazolidin-2-ones

Eileen W. C. Cheng, Reena T. Mandalia, Majid Motevalli, Begum Mothia, Yashvant Patanwadia and Peter B. Wyatt*

Walter Besant Building, School of Biological and Chemical Sciences, Queen Mary, University of London, Mile End Road, London E1 4NS, UK

Received 21 April 2006; revised 13 September 2006; accepted 28 September 2006
Available online 27 October 2006

Abstract—Dienophiles of the general structure $(EtO)_2P(O)CH{=}CHCOX$ have been prepared, where X represents an oxazolidinone chiral auxiliary. Use of the (*S*)-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one auxiliary gave Diels–Alder adducts with several cyclic and acyclic dienes. The crystal structures of the main cyclohexa-1,3-diene and 2,3-dimethylbutadiene adducts formed during reactions in the presence of dialkylaluminium halides are consistent with a reaction, which is stereoselectively *endo* with respect to the carbonyl group and occurs on the less hindered face of the dienophile when aluminium is chelated between the two carbonyl groups.

1. Introduction

Phosphonic acids and their derivatives are of interest as analogues of functional groups such as phosphate esters and carboxylic acids and of the transition states for ester and amide hydrolysis.[1] Several synthetic methods have been devised for the stereoselective synthesis of compounds in which a phosphonic acid or ester group is attached to a chiral centre.[2] Typical approaches include the addition of $R_2P(O)H$ species to aldehydes or imines to give hydroxy- or aminophosphonates,[3] the attack of electrophiles on carbanions that are stabilised by an adjacent phosphorus atom[4] and the use of asymmetric addition reactions of unsaturated phosphonates (e.g., dihydroxylation[5] and aminohydroxylation).[6]

Despite the ability to control the formation of up to four chiral centres, the Diels–Alder reaction has seldom been used as a method for the stereoselective synthesis of phosphonic acid derivatives. Simple vinylphosphonates tend to show only limited dienophilicity and so the most promising phosphonate dienophiles are those containing an additional electron-withdrawing group.[7] Evans has shown that acryloyl derivatives of 1,3-oxazolidinone chiral auxiliaries undergo rapid and highly stereoselective Diels–Alder reactions in the presence of dialkylaluminium halides.[8] Analogous derivatives of the parent 4,5-unsubstituted, achiral 1,3-oxazolidinone system have also featured in numerous reports employing chiral Lewis acids.[9] In this paper, we discuss the preparation and Diels–Alder chemistry of 3-phosphonopropenoyl derivatives of oxazolidinones.

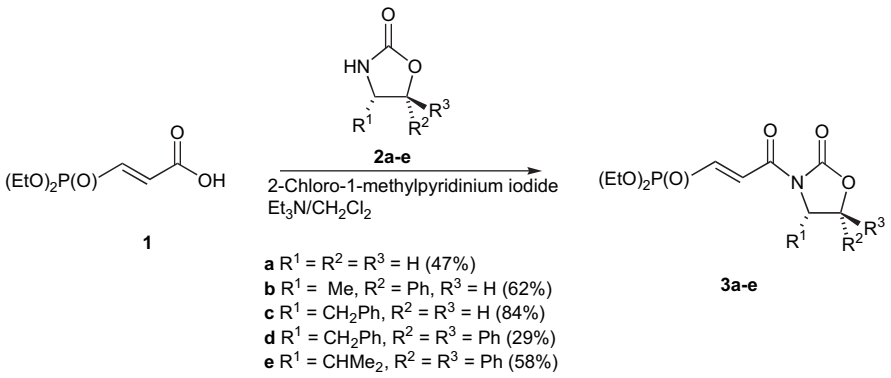
2. Results and discussion

3-(Diethoxyphosphinoyl)prop-2-enoic acid (**1**), prepared by hydrolysis of its methyl ester,[10] was coupled directly to oxazolidinones **2a**–**e** by the general approach of Knol and Feringa,[11] using 2-chloro-1-methylpyridinium iodide in the presence of triethylamine (Scheme 1). The low yield of the *N*-acyloxazolidinone **3d** is attributed to the poor solubility of the chiral auxiliary **2d** in dichloromethane. We found that *N*-acyloxazolidinone **3e** was crystalline, whereas the other oxazolidinone chiral auxiliaries that we acylated using acid **1** gave oily products.

We next examined the Diels–Alder reactions of these *N*-acyloxazolidinones with excess cyclopentadiene in dichloromethane at room temperature. ^{31}P NMR spectra of the crude products, in $CDCl_3$ solution, indicated conversion of the starting vinylphosphonate dienophiles **3** (δ_P ca. 15) into alkylphosphonates (δ_P 30–33). The reactions can generate four stereoisomeric products, but in the case of the achiral dienophile **3a** these include two pairs of enantiomers and hence ^{31}P and ^1H NMR spectra of the crude product showed only two diasteroisomeric components, with δ_P 32.0 (70%) and 31.2 (30%). The four-component mixtures were not straightforward to separate by flash chromatography, but when the reaction between **3a** and cyclopentadiene was performed at low temperature in the presence of Et_2AlCl,

* Corresponding author. Tel.: +44 20 7882 3267; fax: +44 20 7882 7427; e-mail: p.b.wyatt@qmul.ac.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.099



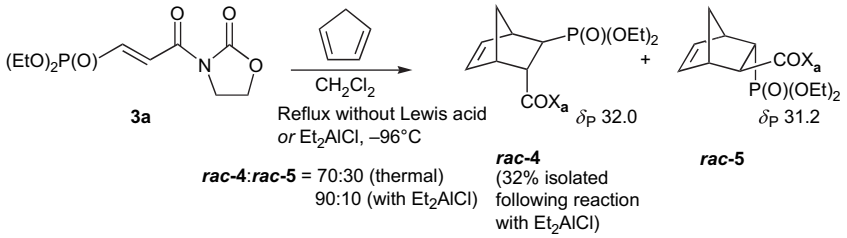
Scheme 1. Formation of 3-(3-phosphonopropenoyl)-1,3-oxazolidin-2-one derivatives **3a**–**e**.

the diastereoisomer ratio increased to 90:10 and the major diastereoisomer *rac*-**4** with δ_P 32.0 was isolated (Scheme 2). The ^{1}H NMR spectrum of *rac*-**4** included distinctive doublets of doublets of doublets for both the CHP and CHCO environments, with similar coupling constants to those of analogous esters and ketones that have *exo*-phosphonate and *endo*-carbonyl groups.[7a]

The 4-isopropyl-5,5-diphenyloxazolidin-2-one chiral auxiliary **2e** is known to be excellent at conferring crystallinity on its *N*-acyl derivatives whilst being easy to remove and recover;[12] furthermore, the crotonyl derivative of **2e** has been reported to react highly selectively in a Lewis acid-induced Diels–Alder reaction with cyclopentadiene.[13] We therefore selected the Diels–Alder reactions of dienophile **3e** for further study, using several dienes both under thermal conditions (refluxing dichloromethane) and employing dialkylaluminium chlorides as Lewis acid promoters, at low temperatures, typically −96 °C (Table 1).

^{31}P NMR spectroscopy showed that the Lewis acid-promoted Diels–Alder reactions of **3e** with cyclohexa-1,3-diene, 2,3-dimethylbutadiene and 2-methylbutadiene all occurred with high selectivity (>95% of the main stereoisomer), whereas mixtures of products were formed with cyclopenta-1,3-diene and in the thermal reactions with all four dienes. X-ray diffraction was used to confirm the structure of cycloadducts derived from three of the dienes.

The reactions of **3e** with cyclopentadiene showed relatively low stereoselectivity and gave four cycloadducts (δ_P 32.3, 32.1, 31.4 and 31.2). These were difficult to separate, but



Scheme 2. *endo* Selectivity in the reaction of dienophile **3a** with cyclopentadiene.

Table 1. Diels–Alder reactions of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e**

Diene	Conditions[a]	Selectivity (from ^{31}P NMR)	δ_P (Principal product)	Structure of principal product (isolated yield)
Cyclopenta-1,3-diene	CH_2Cl_2 reflux 60 h	66:17:9:6	32.3	**6**
	Me_2AlCl, −96 °C, 40 min	37:34:17:12	32.1	**7**
	Et_2AlCl, −96 °C, 10 min	47:32:12:9	32.3	**6** (22%)
Cyclohexa-1,3-diene	CH_2Cl_2 reflux 48 h	60:23:14:3	31.8	
	Et_2AlCl, −96 °C, 20 min	100:0:0:0	31.5	**10** (71%)
	Me_2AlCl, −78 °C, 40 min	97:3:0:0	31.5	**10** (61%)
2,3-Dimethylbuta-1,3-diene	Et_2AlCl, −96 °C, 20 min	100:0	31.0	**11** (58%)
	Me_2AlCl, −96 °C, 20 min	100:0	31.0	**11** (69%)
	CH_2Cl_2 reflux 72 h	80:20	31.4, 31.0	**12** (70%), 11 (12%)
2-Methylbuta-1,3-diene	CH_2Cl_2 reflux 48 h	57:23:20:0	31.2	
	Me_2AlCl, −96 °C, 40 min	100:0:0:0	30.9	**13** (76%)
cyclo-Octa-1,3-diene	Et_2AlCl, −70 °C, 20 min	75:15:10	33.2	**14** (59%)[b]

[a] Me_2AlCl and Et_2AlCl were used in excess (typically 3 equiv relative to **3e**).
[b] The main product **14** is formed by conjugate addition of Et_2AlCl to compound **3e**, rather than by Diels–Alder reaction.

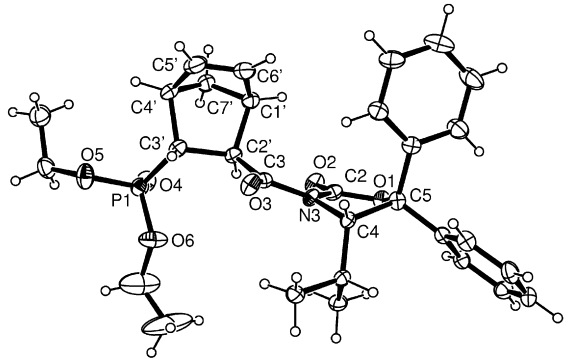


Figure 1. Molecular structure of (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **6**.

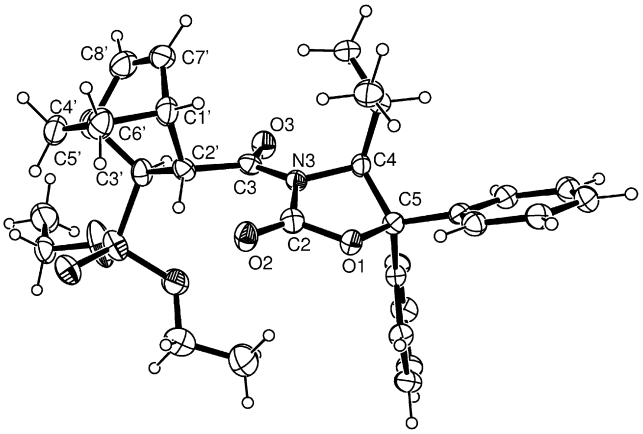
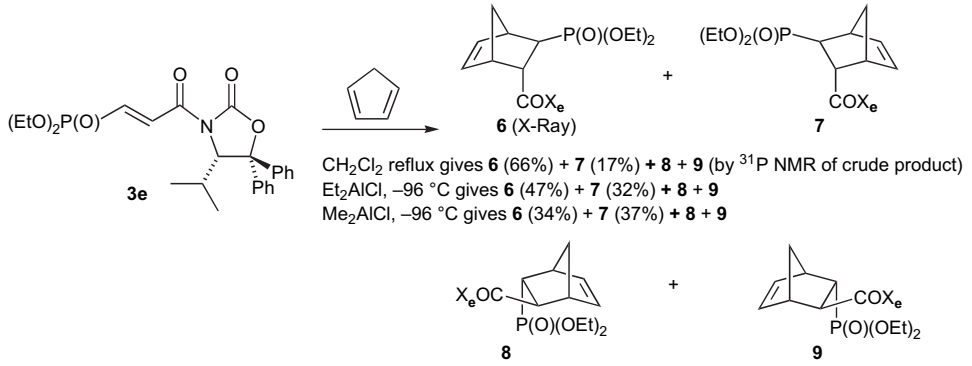


Figure 2. Molecular structure of (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **10**.

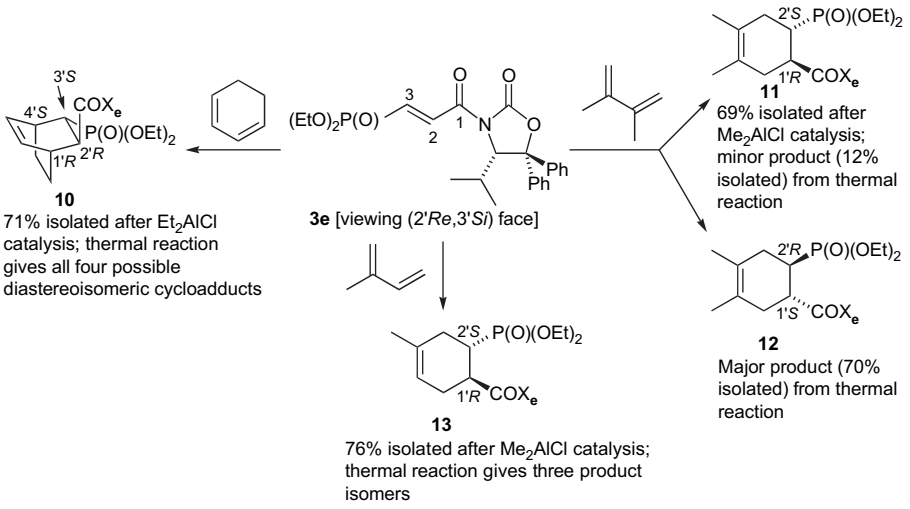
the cycloadduct with δ_P 32.3 could be obtained as a single stereoisomer following flash chromatography and recrystallisation. The ^{1}H NMR spectrum of this product resembled that of *rac*-**4**, again suggesting an *endo*-directed carbonyl and *exo*-directed P═O group, and an X-ray crystal structure (Fig. 1) showed the (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-configuration given in Scheme 3 (structure **6**). This is the favoured product of the thermal reaction and corresponds to attack on the (2′*Si*,3′*Re*)-face of the dienophile, which is the less hindered face of the conformer with the two C═O dipoles opposed to one another. The same product **6** was formed in lower proportions when Lewis acids were used; with Me_2AlCl the product with δ_P 32.1, considered to be the other C═O *endo* adduct **7**, was marginally favoured over **6**. We presume that the Lewis acids chelated between the two carbonyl groups activate the dienophile **3e** towards formation of adduct **7**, in direct analogy with Evans's proposals for simple acryloyloxazolidinones.[8] However, the formation of significant quantities of the diastereoisomer **6**, even when a large excess of Lewis acid was used, suggests that chelation of the Lewis acid is not mandatory for rapid addition of **3e** to cyclopentadiene.

An X-ray crystal structure of the cyclohexadiene adduct **10** (Fig. 2) that was isolated following the Et_2AlCl-mediated reaction established the (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-configuration shown in Scheme 4. This confirmed that the trans relationship between the phosphonate and carbonyl groups of the dienophile is preserved and that the favoured mode of addition is '*endo*' with respect to the carbonyl group and '*exo*' with respect to the phosphonate. Furthermore, the favoured product corresponds to attack on the less hindered (2′*Re*,3′*Si*)-face of the dienophile, assuming that the aluminium chelates between the two carbonyl groups as proposed by Evans.[8]

An X-ray crystal structure (Fig. 3) was also determined for the predominant Diels–Alder adduct **11** formed from 2,3-dimethylbutadiene and the dienophile **3e** when Lewis acid was used. The product has the (4*S*,1′*R*,2′*S*)-configuration; after allowing for the different numbering schemes in compounds **10** and **11** its stereochemistry is directly analogous to that of the cyclohexadiene adduct, again indicating attack on the (2′*Re*,3′*Si*) face of the dienophile. The substitution pattern of the diene does not permit '*endo*' and '*exo*' modes of attack to be distinguished in this case. The carbocyclic ring in **5a** has a half-chair conformation, similar to that of cyclohexene itself:[14] the carbonyl and phosphonate groups are trans to one another and each is pseudo-equatorial. In the ^{31}P-decoupled ^{1}H NMR spectrum of the adduct, both protons H-1′ and H-2′ appeared as triplets of doublets with triplet splittings of 10–11 Hz, consistent with involvement in axial–axial couplings with neighbours on either side, suggesting that the solution phase conformation is similar to that adopted in the crystal. One of the four OCH_2 protons is shifted upfield in this adduct and appears as a multiplet at δ 3.5; examination of the crystal structure shows that one of these hydrogen atoms is so positioned that it could be shielded by the magnetic anisotropy of a phenyl group.



Scheme 3. Possible products from the reaction of dienophile **3e** with cyclopentadiene.



Scheme 4. Stereoselective Diels–Alder reactions of the dienophile **3e**.

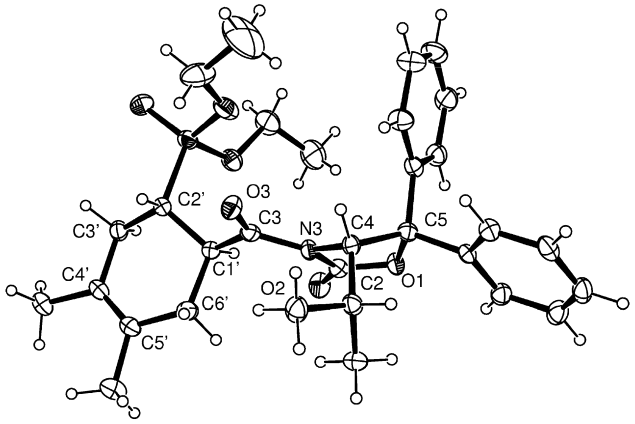


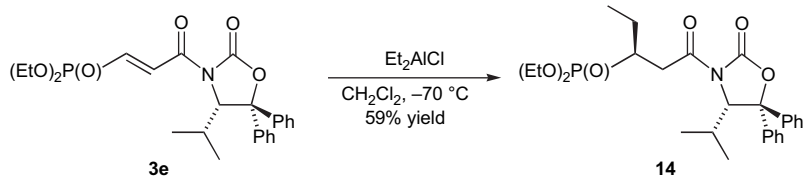
Figure 3. Molecular structure of (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11**.

When the Diels–Alder reaction between **3e** and 2,3-dimethylbutadiene was performed under thermal conditions, the above product **11** could again be isolated, but the main product was the (4*S*,1′*S*,2′*R*) diastereoisomer **12**; the NMR spectra of the two isomers were rather similar, but in the ^{1}H NMR spectrum of **12** all four OCH_2 protons appeared together as a multiplet near δ 4.0. Neither of the two diastereoisomeric adducts **11** and **12** underwent any isomerisation when heated in the presence of excess 2,3-dimethylbutadiene under the conditions employed for the thermal reaction. Thus the opposite selectivity observed in the Lewis-acid and thermal reactions was not a consequence of a switch to thermodynamic control in the latter case. The thermal reaction occurs on a non-chelated acyloxazolidinone and may take place by preferential, kinetically controlled attack on the (2*Si*,3*Re*) face of the dienophile, through a transition state in which the two carbonyl groups are antiparallel. Comparison of the ^{31}P NMR spectra of the crude cycloadduct mixtures indicate that the preferred products formed in the reactions of cyclohexa-1,3-diene and isoprene also change on switching from Lewis acid to thermal conditions.

Lewis acid-induced reaction of the dienophile **3e** with 2-methylbuta-1,3-diene (isoprene) gave a single Diels–Alder adduct **13**. From the ^{13}C and HSQC spectra the two olefinic carbons could be identified. The one with δ_C 118.3 had one attached hydrogen atom and was not coupled to ^{31}P, whereas the one with δ_C 132.7 had no attached hydrogen and had a 12 Hz coupling to ^{31}P. This implies a 1,4-relationship between the methyl and carbonyl substituents on the cyclohexene ring: thus the regiochemical preference is analogous to that seen in reactions of isoprene with simple acryloyloxazolidinones,[8] demonstrating the dominance of the electron-withdrawing effect of carbonyl group over that of the phosphinoyl group.

It is likely that the isoprene adduct **13** that is formed under Lewis acidic conditions has the (1′*R*,2′*S*)-configuration analogous to that seen in the crystal structure of the closely related 2,3-dimethylbutadiene adduct **11**. Support for this proposal is provided by the similar ^{1}H NMR spectra of the two compounds, each of which has one of the OCH_2 protons shifted ca. 0.3 ppm upfield of the other three.

A Diels–Alder reaction with *cyclo*-octa-1,3-diene was attempted in the presence of diethylaluminium chloride, but it was found that this particular diene was much less reactive than cyclohexa-1,3-diene and at −96 °C most of the dienophile remained unchanged. Upon increasing the reaction temperature to −70 °C it was possible to observe the complete consumption of starting material and the formation of new phosphorus-containing products, of which the main components, with δ_P 33.2, 33.3 and 30.0, were formed in a 75:15:10 ratio. The principal product **14** (Scheme 5) was crystallised and was shown by NMR spectroscopy, mass spectrometry and X-ray diffraction (Fig. 4) to have arisen by conjugate addition of an ethyl group at the β-position with respect to the carbonyl group. The observed (*S*)-configuration of the newly formed chiral centre in **14** indicates that ethyl group is preferentially transferred to the (2*Re*,3*Si*) face of the C=C double bond. The same three products were produced when the dienophile **3e** was treated with diethylaluminium chloride at −70 °C in the absence of any diene. Conjugate additions of diethylaluminium chloride to alk-2-enoyloxazolidinones without phosphinoyl substituents have been observed by Evans and co-workers;[8] synthetic applications were later developed by Rück and Kunz, who



Scheme 5. Conjugate addition of Et_2AlCl to **3e**.

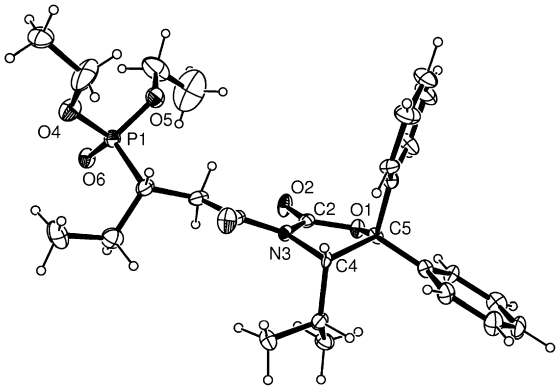
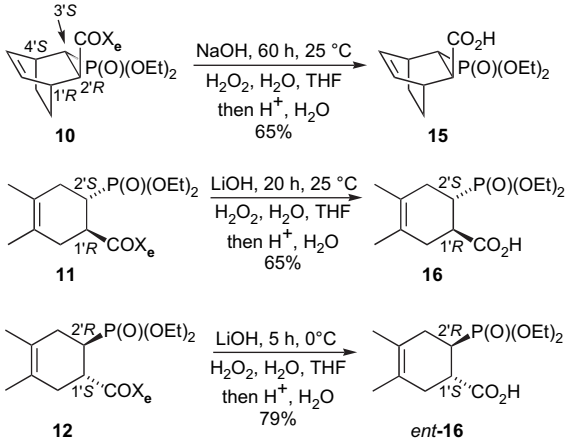


Figure 4. Molecular structure of (4*S*,3′*S*)-3-[3-(diethoxyphosphinoyl)pentanoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **14**.

found that such reactions typically generate significant amounts of minor stereoisomers.[15]

We have examined the removal of the 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one chiral auxiliary from adducts **10**, **11** and **12** (Scheme 6), using similar conditions to those described by Seebach for the cleavage of the 2-methyl-3-propanoyl derivatives of oxazolidinone **2e**.[13] The hydrolysis reactions were monitored by TLC and were found to be slow compared to Seebach's compounds, probably as a consequence of greater steric hindrance in the cycloadducts. Simple aqueous work up procedures provided the corresponding carboxylic acids **15**, **16** and *ent*-**16**, thus confirming the diastereoisomeric relationship between cycloadducts **11** and **12**.



Scheme 6. Removal of chiral auxiliaries from Diels–Alder adducts **10**, **11** and **12**.

3. Conclusions

(*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** has been found to participate in Diels–Alder reactions with a selection of dienes, giving adducts, which are often highly crystalline and easy to obtain in isomerically pure form, thus providing a new approach to the production of highly functionalised phosphonic acid derivatives of defined configuration. The dialkylaluminium chloride-accelerated reactions typically show similar facial preferences to those seen in the reactions of simple *N*-alkenoyloxazolidinones, but reactions with cyclopentadiene are rather unselective.

4. Experimental

4.1. Materials and general procedures

'Petrol' refers to the fraction of petroleum spirit with bp 40–60 °C. Dichloromethane was distilled from calcium hydride before use. The temperature of −96 °C was obtained using methanol and liquid nitrogen. Flash chromatography was performed on BDH silica gel (33–70 μm). All new compounds were >95% pure as assessed by TLC and high field NMR. Melting points were determined using a Reichert hot stage microscope and are uncorrected. Specific rotations were determined on an Optical Activity Ltd AA-1000 or Jasco P-1010 polarimeter with a path length of 0.5 dm. IR spectra were recorded using a Shimadzu FTIR 8300; samples were prepared as films by evaporation of CH_2Cl_2 solutions on NaCl plates. NMR spectra were recorded on Jeol EX270 and Bruker AM250, AMX400 or AMX600 spectrometers. FAB mass spectra were recorded on a ZAB-SE4F machine at the School of Pharmacy, University of London; other mass spectra were obtained by the EPSRC National Service in Swansea.

4.2. Typical procedure for oxazolidinone acylation: preparation of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 3e

(*S*)-4-Isopropyl-5,5-diphenyloxazolidin-2-one (2.00 g, 7.11 mmol) was added to a solution of (*E*)-3-(diethoxyphosphinoyl)prop-2-enoic acid[10] (1.85 g, 8.89 mmol) in dry dichloromethane (5 mL). Triethylamine (2.96 mL, 21.2 mmol) and 2-chloro-1-methylpyridinium iodide (2.72 g, 10.6 mmol) were added to the mixture, which was stirred for 72 h at room temperature. Dichloromethane (80 mL) was then added to the mixture before it was washed with aqueous $NaHCO_3$ (4×40 mL), dried ($MgSO_4$) and the solvent was evaporated to leave a yellow solid. Flash chromatography (CH_2Cl_2–EtOAc, 97.5:2.5) afforded the *title compound* **3e** (1.93 g, 58%) as a white crystalline solid, mp 178–180 °C (from EtOAc–petrol); $[\alpha]_D$ −188 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1} (film) 1690 (C═O) and 1782 (C═O); δ_H (270 MHz, $CDCl_3$) 0.77 (d, 3H, *J* 7 Hz, CH_3CHMe),

0.90 (d, 3H, *J* 7 Hz, CH_3CHMe), 1.34 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$O), 1.95–2.07 (m, 1H, Me$_2$C*H*), 4.14 (quintet, 4H, *J* 7 Hz, 2×CH$_3$CH_2O), 5.44 (d, 1H, *J* 3 Hz, NCH), 6.96 (dd, 1H, *J* 19, 17 Hz, CH=), 7.24–7.46 (m, 10H, 2×Ph), 7.90 (dd, 1H, *J* 21, 19 Hz, CH=); δ_P (109 MHz, $CDCl_3$) 15.2; δ_C (101 MHz, $CDCl_3$) 16.70 (CH_3), 16.76 (2×CH_3), 22.18 (CH_3), 30.49 (*C*Me$_2$), 63.06 (d, $^2J_{C-P}$ 6 Hz, 2×CH_2O), 65.27 (CHN), 90.20 (C–O) [125.92, 126.23, 128.49, 128.85, 129.17, 129.43, together aromatic C], 133.28 (d, $^1J_{C-P}$ 186 Hz, PC=), 135.35 (d, $^2J_{C-P}$ 10 Hz, CO*C*=), 138.27 (C-1 of Ph), 142.31 (C-1 of Ph), 152.88 (OCON), 163.44 (d, $^3J_{C-P}$ 28 Hz, C–*C*=O); *m*/*z* (ESI) found: $[M+NH_4]^+$ 489.2146. $C_{25}H_{34}N_2O_6P$ requires 489.2149.

4.2.1. 3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-1,3-oxazolidin-2-one 3a. Flash chromatography [gradient from CH_2Cl_2–Et_2O (3:1) to (3:2)] gave **3a** (47% yield) as a colourless oil; ν_{max}/cm^{-1} (film) 1686 (C=O) and 1779 (C=O); δ_H (250 MHz, $CDCl_3$) 1.38 (t, 6H, *J* 7 Hz, 2×CH_3), 4.07–4.23 (m, 6H, 2×CH_2OP+CH_2N), 4.49 (t, 2H, *J* 8 Hz, CH_2OCO), 7.02 (dd, 1H, *J* 19, 17 Hz, C=C*H*CO), 7.98 (dd, 1H, *J* 21, 17 Hz, C=C*H*P); δ_P (101 MHz, $CDCl_3$) 15.0; δ_C (101 MHz, $CDCl_3$) 16.66 (d, $^3J_{C-P}$ 6 Hz, *C*H_3CH$_2$O), 42.97 (CH_2N) [62.90, 63.08, 63.14, together 3×CH_2], 132.71 (d, *J* 186 Hz, PC=), 135.49 (d, *J* 10 Hz, CO*C*=), 153.56 (O–CO–N), 163.59 (d, *J* 28 Hz, C–*C*O–N); *m*/*z* (FAB) found: $[M+H]^+$ 278.0780. $C_{10}H_{17}NO_6P$ requires 278.0794.

4.2.2. (4*S*,5*R*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 3b. Flash chromatography [CH_2Cl_2–Et_2O, gradient from (2:1) to (3:2)] gave **3b** (62% yield) as a colourless oil; $[\alpha]_D^{36}$ −20.6 (*c* 2, $CHCl_3$); ν_{max}/cm^{-1} (film) 1686 (C=O) and 1782 (C=O); δ_H (250 MHz, $CDCl_3$) 0.95 (d, 3H, *J* 7 Hz, NCH–CH_3), 1.38 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$), 4.18 (quint, 4H, *J* 7 Hz, 2×CH_2OP), 4.82 (quint, 1H, *J* 7 Hz, NC*H*–CH$_3$), 5.73 (d, 1H, *J* 7 Hz, PhC*H*O), 7.03 (dd, 1H, *J* 19 and 17 Hz, C=C*H*CO), 7.29–7.44 (m, 5H, Ph), 8.01 (dd, 1H, *J* 21 and 17 Hz, C=C*H*P); δ_P (101 MHz, $CDCl_3$) 15.1; δ_C (101 MHz, $CDCl_3$) 14.82 (4-Me), 16.72 (d, $^3J_{C-P}$ 6 Hz, *C*H_3CH$_2$O), 55.48 (C-4), 63.20 (d, $^2J_{C-P}$ 6 Hz, CH_2O), 79.78 (C-5), 126.05 (Ph), 129.17 (Ph), 129.34 (Ph), 132.84 (d, $^1J_{C-P}$ 186 Hz, PC=), 133.30 (Ph quaternary C), 136.00 (d, $^2J_{C-P}$ 9 Hz, CO*C*=), 153.02 (O–CO–N), 163.31 (d, $^3J_{C-P}$ 28 Hz, C–*C*O–N); *m*/*z* (EI) found: M^+ 367.1184. $C_{17}H_{22}NO_6P$ requires 367.1185.

4.2.3. (*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-benzyl-1,3-oxazolidin-2-one 3c. Flash chromatography [gradient from CH_2Cl_2–Et_2O (2:1) to (3:2)] gave **3c** (84% yield) as a colourless oil; $[\alpha]_D^{36}$ +52.2 (*c* 2.26, $CHCl_3$); ν_{max}/cm^{-1} (film) 1684 (C=O) and 1782 (C=O); δ_H (250 MHz, $CDCl_3$) 1.38 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$), 2.82 (dd, 1H, *J* 13 and 9 Hz, *H*CHPh), 3.35 (dd, 1H, *J* 13 and 3 Hz, HC*H*Ph), 4.12–4.30 (m, 6H, 3×CH_2O), 4.69–4.79 (m, 1H, NC*H*–CH$_2$), 7.06 (dd, 1H, *J* 19 and 17 Hz, C=C*H*CO), 7.19–7.38 (m, 5H, Ph), 7.99 (dd, 1H, *J* 21 and 17 Hz, C=C*H*P); δ_P (101 MHz, $CDCl_3$) 15.8; δ_C (101 MHz, $CDCl_3$) 16.72 (d, $^3J_{C-P}$ 6 Hz, *C*H_3CH$_2$O), 37.93 (*C*H_2Ph), 55.69 (C-4), 63.24 (d, $^2J_{C-P}$ 6 Hz, CH_2O), 66.96 (C-5), 127.86 (Ph), 129.41 (Ph), 129.79 (Ph), 132.84 (d, $^1J_{C-P}$ 186 Hz, PC=), 135.25 (Ph quaternary C), 135.93 (d, $^2J_{C-P}$ 10 Hz, CO*C*=), 153.43 (O–CO–N), 163.54 (d, $^3J_{C-P}$ 28 Hz, C–*C*O–N); *m*/*z* (FAB) found: $[M+H]^+$ 368.1268. $C_{17}H_{23}NO_6P$ requires 368.1263.

4.2.4. (*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-benzyl-5,5-diphenyl-1,3-oxazolidin-2-one 3d. Flash chromatography in CH_2Cl_2–EtOAc (85:15) gave **3d** (29% yield) as a colourless oil; $[\alpha]_D^{36}$ −218 (*c* 1.2, CH_2Cl_2); ν_{max}/cm^{-1} (film) 1786 (C=O) and 1688 (C=O); δ_H (270 MHz, $CDCl_3$) 1.32 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$), 2.76 (dd, 1H, *J* 14 and 8 Hz, *H*CHPh), 2.87 (dd, 1H, *J* 14 and 5 Hz, HC*H*Ph), 4.12 (quintet, 4H, *J* 7 Hz, 2×CH_2O), 4.65 (dd, 1H, *J* 8 and 5 Hz, NC*H*–CH$_2$), 6.70–6.75 (m, 2H, Ar–H), 6.86 (dd, 1H, *J* 19 and 17 Hz, C=C*H*CO), 7.07–7.44 (m, 13H, Ar–H), 7.85 (dd, 1H, *J* 21 and 17 Hz, C=C*H*P); δ_P (109 MHz, $CDCl_3$) 15.1; *m*/*z* (ESI) found: $[M+NH_4]^+$ 537.2155. $C_{29}H_{34}N_2O_6P$ requires 537.2149.

4.3. Typical procedure for Lewis acid-promoted Diels–Alder reaction: preparation of (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 10

(*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.200 g, 0.424 mmol) was dissolved in dry dichloromethane (2 mL). The solution was cooled to −96 °C under nitrogen. Cyclohexa-1,3-diene (1.0 mL, 10.5 mmol) and 1.8 M diethylaluminium chloride in toluene (0.37 mL, 0.66 mmol) were added to the solution, which was stirred for 20 min at −96 °C. The reaction mixture was then poured into 2 M HCl (90 mL). It was extracted with dichloromethane (40 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (4×20 mL), followed by 0.4 M aqueous potassium sodium (+)-tartrate (40 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. Analysis of the residue by ^{31}P NMR showed complete conversion of dienophile into a single product. Flash chromatography (EtOAc–petrol, 7:3) yielded the *title compound* **10** (0.166 g, 71%) as a white solid. Recrystallisation from dichloromethane–petrol gave colourless needles, mp 201–202 °C, $[\alpha]_D$ −73.7 (*c* 0.93, $CHCl_3$); ν_{max}/cm^{-1} (film) 1706 (C=O) and 1779 (C=O); δ_H (400 MHz, CD_2Cl_2, assignments supported by COSY) 0.67 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.75 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.81 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 0.96–1.08 (m, 4H, CH_3CH$_2$O+H-8′$_a$), 1.2–1.3 (m, 1H, H-7′$_a$), 1.69–1.77 (m, 1H, H-7′$_b$), 1.89–1.96 (m, 1H, C*H*Me$_2$), 2.00–2.08 (1H, m, H-8′$_b$), 2.37 (ddt, 1H, *J* 19, 7, 2 Hz, CHP), 2.78–2.80 (m, 1H, H-1′), 3.00–3.02 (m, 1H, H-4′), 3.40–3.50 (m, 1H, CH–O), 3.56–3.66 (m, 1H, CH–O), 3.7–3.8 (m, 3H, CH_2O+CHC=O), 5.37 (d, 1H, *J* 3 Hz, NCH), 5.93 (t, 1H, *J* 7 Hz, H-6′), 6.41 (tt, 1H, *J* 7, 1 Hz, H-5′), 7.17–7.45 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 31.5; δ_C (101 MHz, CD_2Cl_2, assignments supported by HSQC) 16.18 (*C*H_3CHMe), 16.58 (2×*C*H_3CH$_2$O), 20.59 (C-8′), 22.01 (*C*H_3CHMe), 25.59 (C-7′), 30.03 (C-1′), 30.74 (*C*HMe$_2$), 35.31 (d, $^1J_{C-P}$ 141 Hz, *C*P), 35.45 (d, $^2J_{C-P}$ 5 Hz, C-4′), 43.32 (d, $^2J_{C-P}$ 4 Hz, *C*H–C=O), 61.62 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 61.92 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 64.68 (*C*HN), 89.29 (O–*C*Ph$_2$), 125.71 (Ph), 126.12 (Ph), 128.25 (Ph), 128.79 (Ph), 128.91 (Ph), 129.28 (Ph), 129.88 (C-6′), 137.54 (d, $^3J_{C-P}$ 18 Hz, C-5′), 138.77 (Ph quaternary C), 143.12 (Ph

quaternary C), 152.62 (O–*C*=O–N), 173.25 (d, $^3J_{C-P}$ 4 Hz, C–*C*O–N); *m*/*z* (ESI) found: [M+H$^+$] 552.2517. $C_{31}H_{39}NO_6P$ requires 552.2510.

4.3.1. (1′*R,2′*R**,3′*S**,4′*S**)-[3-(Diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-oxazolidin-2-one *rac*-4.** 3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-1,3-oxazolidin-2-one **3a** (228 mg, 0.822 mmol) was dissolved in CH_2Cl_2 (2 mL) under nitrogen and cooled to −96 °C before being treated with excess cyclopenta-1,3-diene (2 mL) followed by 1.8 M Et_2AlCl in toluene (0.64 mL, 1.15 mmol). The reaction mixture was stirred at −96 °C for 20 min, then 10% aqueous sodium potassium tartrate solution (20 mL) was added to the reaction mixture, which was allowed to attain room temperature. The mixture was extracted with CH_2Cl_2 (20 mL) and the organic layer was washed with 2 M hydrochloric acid (30 mL) followed by saturated aqueous $NaHCO_3$ (30 mL). Drying ($MgSO_4$) and evaporation of the organic phase gave the crude product (190 mg). Flash chromatography with CH_2Cl_2–EtOAc (1:3) gave the major Diels–Alder product *rac*-**4** (86.5 mg, 31%) as a colourless oil with the following properties; ν_{max}/cm^{-1} (film) 1696 (C=O) and 1777 (C=O); δ_H (250 MHz, $CDCl_3$) 1.30 (t, 6H, *J* 7 Hz, 2×C*H*$_3$CH$_2$O), 1.43 (d, 1H, *J* 9 Hz, H-7′), 1.93 (d, 1H, *J* 9 Hz, H-7′), 2.36 (ddd, 1H, *J* 15.5, 6.0 and 1.8 Hz, H-3′), 3.18–3.22 (m, 1H, H-4′), 3.49 (br s, 1H, H-1′), 3.88–4.16 (m, 6H, C*H*$_2$N+2×C*H*$_2$O), 4.30 (ddd, 1H, *J* 18, 6 and 3.4 Hz, H-2′), 4.43 (t, 2H, *J* 8 Hz, C*H*$_2$OCO), 5.81 (dd, 1H, *J* 5 and 3 Hz, H-5), 6.41 ('t', 1H, *J* 5 Hz, H-6′) and 6.43 (t, 1H, *J* 5 Hz, H-5′); δ_P (101 MHz, $CDCl_3$) 32.0; δ_C (63 MHz, $CDCl_3$, assignments by ^{1}H–^{13}C correlation) 16.5 (*C*H$_3$CH$_2$O), 16.6 (*C*H$_3$CH$_2$O), 38.1 (d, $^1J_{C-P}$ 142 Hz, C-3′), 43.0 (C-4), 44.9–45.1 (m, C-2′ and C-4′), 47.3 (C-1′), 48.7 (C-7′), 61.7–62.1 (m, 3×OCH$_2$), 132.0 (C-6′), 139.7 (d, $^3J_{C-P}$ 15 Hz, C-5′), 153.3 (O–*C*O–N), 172.6 (C–*C*O–N); *m*/*z* (FAB) found: [M+H$^+$] 344.1250. $C_{15}H_{23}NO_6P$ requires 344.1263.

4.3.2. (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-[3-(Diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 6. (*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl) prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.060 g, 0.089 mmol) was dissolved in dry dichloromethane (1.0 mL). The solution was cooled to −96 °C under nitrogen. Cyclopentadiene (1.0 mL) and 1.8 M diethylaluminium chloride in toluene (0.343 mL, 0.617 mmol) were added to the solution, which was stirred for 10 min. The reaction mixture was then poured into 2 M HCl (75 mL). It was extracted with dichloromethane (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (2× 20 mL) followed by 0.4 M aqueous potassium sodium (+)-tartrate (20 mL). The organic phase was dried ($MgSO_4$) and the solvent was then removed by rotary evaporation. The residue was then subjected to flash chromatography using ethyl acetate–petrol (70:30), followed by recrystallisation from dichloromethane–petrol to give the cycloadduct **6** (0.015 g, 22%) as a white solid, mp 151–155 °C, $[\alpha]_D$ −199 (*c* 0.18, $CHCl_3$); following further recrystallisation the product was obtained as colourless, orthorhombic plates, mp 165–167 °C; ν_{max}/cm^{-1} (film) 1697 (C=O) and 1771 (C=O); δ_H (400 MHz, $CDCl_3$) 0.78 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 0.85 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 1.22–1.32 (m, 7H, 2×C*H*$_3$CH$_2$O+H-7′$_a$), 1.82 (d, 1H, *J* 9 Hz, H-7′$_b$), 1.98–2.04 (m, 1H, C*H*Me$_2$), 2.30 (ddd, 1H, *J* 16, 6, 1.6 Hz, H-3′, on decoupling ^{31}P simplifies to dd, *J* 6, 1.3 Hz), 2.75–2.79 (m, 1H, HCC=), 3.09–3.13 (m, 1H, HCC=), 4.03–4.19 (m, 4H, 2×CH$_2$O), 4.30 (ddd, 1H, *J* 18, 6, 3 Hz, H-2′, on decoupling ^{31}P simplifies to dd, *J* 6, 3 Hz), 4.84 (dd, 1H, *J* 5, 3 Hz, HC=), 5.19 (d, 1H, *J* 4 Hz, NC*H*), 6.22 (dd, 1H, *J* 5, 3 Hz, HC=), 7.24–7.57 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 32.3; *m*/*z* (ESI) found: [M+H]$^+$ 538.2345. $C_{30}H_{37}NO_6P$ requires 538.2353.

4.3.3. (4*S*,1′*R*,2′*S*)-[2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 11. A solution of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.200 g, 0.414 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −96 °C under nitrogen. 2,3-Dimethylbuta-1,3-diene (0.5 mL, 4.4 mmol) and 1.0 M dimethylaluminium chloride in hexane (1.32 mL, 1.32 mmol) were added to the solution, which was stirred for 20 min. The reaction mixture was then poured into 2 M HCl (45 mL). It was extracted with $CHCl_3$ (50 mL). The organic phase was washed with brine, dried ($MgSO_4$) and the solvent was then evaporated to leave the crude product (0.27 g). ^{31}P NMR showed the consumption of the starting dienophile **3e** and the formation of a single product, δ_P 31.0. Flash chromatography (CH_2Cl_2–EtOAc, 85:15) yielded the *title compound* **11** (163 mg, 69%) as a white foam. Slow evaporation of a solution of **11** in ethyl acetate–petrol (1:4) gave colourless, monoclinic crystals, mp 135–139 °C, $[\alpha]_D^{25}$ −62.1 (*c* 0.98, $CHCl_3$); ν_{max}/cm^{-1} (film) 1716 (C=O) and 1782 (C=O); δ_H (400 MHz, $CDCl_3$, assignments supported by COSY) 0.76 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 0.91 (d, 3H, *J* 7 Hz, C*H*$_3$CHMe), 0.97 (t, 3H, *J* 7 Hz, C*H*$_3$CH$_2$O), 1.21 (t, 3H, *J* 7 Hz, C*H*$_3$CH$_2$O), 1.62 (s, 6H, 2×C*H*$_3$C=C), 1.92–2.00 (m, 1H, C*H*Me$_2$), 2.07–2.43 (m, 4H, 2×CH$_2$C=C), 2.47 (m, 1H, simplifies to td, *J* 11, 6 Hz upon decoupling ^{31}P, C*H*P=O), 3.45–3.52 (m, 1H, OCH), 3.74–3.87 (m, 3H, 3×OCH), 4.11 (tt, 1H, *J* 10, 6 Hz, simplifies to td, *J* 10, 6 Hz upon decoupling ^{31}P, C*H*–C=O), 5.45 (d, 1H, *J* 3 Hz, NCH), 7.25–7.53 (m, 10H, 2×Ph), δ_P (109 MHz, $CDCl_3$) 31.0; δ_C (101 MHz, $CDCl_3$, assignments supported by DEPT and HSQC) 16.11 (d, *J* 6 Hz, *C*H$_3$CH$_2$O), 16.30 (*C*H$_3$CH), 16.40 (d, *J* 6 Hz, *C*H$_3$CH$_2$O), 18.62 (2×*C*H$_3$C=C), 22.09 (*C*H$_3$CH), 30.21 (*C*HMe$_2$), 30.51 (d, $^2J_{C-P}$ 5 Hz, *C*H$_2$CHP=O), 31.94 (d, $^1J_{C-P}$ 140 Hz, *C*H–P=O), 35.76 (d, $^3J_{C-P}$ 6 Hz, *C*H$_2$–CHC=O), 38.76 (d, $^2J_{C-P}$ 4 Hz, *C*H–C=O), 61.08 (d, $^2J_{C-P}$ 7 Hz, *C*H$_2$O), 61.63 (d, $^2J_{C-P}$ 6 Hz, *C*H$_2$O), 64.18 (*C*H–N), 88.96 (Ph$_2$*C*–O), 123.15 (CH$_3$*C*=C), 124.31 (d, $^3J_{C-P}$ 13 Hz, CH$_3$*C*=C), 125.98 (Ph), 126.08 (Ph), 127.89 (Ph), 128.34 (Ph), 128.40 (Ph), 128.78 (Ph), 138.57 (quaternary C of Ph), 142.32 (quaternary C of Ph), 152.33 (O*C*ON), 174.62 (d, $^3J_{C-P}$ 5 Hz, CH–*C*O–N); *m*/*z* (ESI) found: [M+H]$^+$ 554.2669. $C_{31}H_{41}NO_6P$ requires 554.2666.

4.3.4. Reaction of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)-prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 3e with 2,3-dimethylbuta-1,3-diene in the absence of Lewis acid. A mixture of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.050 g, 0.11 mmol), 2,3-dimethylbuta-1,3-diene (0.50 mL, 4.4 mmol) and CH_2Cl_2 (0.5 mL) was heated

under reflux for 72 h. The solvent was evaporated and the residue was separated by flash chromatography with EtOAc–petrol (3:7) to give first (4*S*,1′*S*,2′*R*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **12** (0.041 g, 70%) as a white foam and then (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11** (0.007 g, 12%) as a white foam.

(4*S*,1′*S*,2′*R*)-[2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **12** had mp 47–49 °C, $[\alpha]_D$ −143 (*c* 1.17, $CHCl_3$); ν_{max}/cm^{-1} (film) 1714 (C=O) and 1786 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 (d, 3H, *J* 7 Hz, CH_3CHMe), 1.02 (d, 3H, *J* 7 Hz, CH_3CHMe), 1.24–1.47 (m, 11H, 2×CH_3CH$_2$O+CH_3C=C+2×CHC=), 1.57 (s, 3H, CH_3C=C), 1.97–2.05 (m, 1H, C*H*Me$_2$), 2.22–2.24 (m, 2H, CH$_2$C=C), 2.47–2.54 (m, 1H, C*H*P=O), 4.05–4.15 (m, 5H, 2×OCH$_2$+C*H*CO), 5.33 (d, 1H, *J* 3 Hz, NCH), 7.27–7.50 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 31.4; δ_C (101 MHz, $CDCl_3$) 16.70, 16.81 (d, *J* 6 Hz), 18.70, 18.96, 21.70, 30.14, 31.06 (d, *J* 4 Hz), 33.11 (d, *J* 142 Hz), 35.30 (d, *J* 12 Hz), 38.34, 61.84 (d, *J* 7 Hz), 62.30 (d, *J* 6 Hz), 66.04, 89.92, 123.35, 124.33 (d, *J* 13 Hz), 126.02, 126.16, 128.36, 128.85, 128.92, 129.21, 138.32, 143.03, 153.53, 175.18 (d, *J* 5 Hz); *m*/*z* (ESI) found: $[M+H]^+$ 554.2670. $C_{31}H_{41}NO_6P$ requires 554.2666.

(4*S*,1′*R*,2′*S*)-[2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11** was identical by ^1H and ^{31}P NMR to the major product of the Lewis acid-induced Diels–Alder reaction described in the previous experiment.

4.3.5. (4*S*,1′*R*,2′*S*)-[2-(Diethoxyphosphinoyl)-4-methylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 13. A solution of (*S*)-3-[(*E*)-3-(diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.200 g, 0.424 mmol in dry CH_2Cl_2 (2 mL) was cooled to −96 °C under nitrogen. Isoprene (1.0 mL, 10.0 mmol) and 1.0 M dimethylaluminium chloride in hexane (1.32 mL, 1.32 mmol) were added to the solution, which was stirred for 40 min. The reaction mixture was then poured into 2 M HCl (45 mL). It was extracted with $CHCl_3$ (50 mL) and the organic layer was washed with brine (40 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated to leave the crude product (0.23 g). ^{31}P NMR showed only two peaks δ_P ($CDCl_3$) 15.2 (5%, unreacted dienophile) and 30.9 (95%, product). Flash chromatography (EtOAc–CH_2Cl_2, 96:4) gave the *title compound* **13** (0.174 g, 76%) as a white solid, mp 73–75 °C, $[\alpha]_D^{25}$ −21.7 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 1703 (C=O) and 1772 (C=O); δ_H (400 MHz, $CDCl_3$) 0.74 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.89 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.98 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.21 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.67 (s, 3H, CH_3C=C), 1.93–1.97 (m, 1H, C*H*Me$_2$), 2.13–2.55 (m, 5H, 2×CH_2–C=C+CHP), 3.48–3.54 (m, 1H, OCH), 3.77–3.86 (m, 3H, 3×OCH), 4.01–4.10 (m, 1H, CHC=O), 5.37–5.39 (m, 1H, CH=C), 5.44 (d, 1H, *J* 3 Hz, NCH), 7.25–7.53 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 30.9; δ_C (101 MHz, $CDCl_3$) 16.13 (d, $^3J_{C-P}$ 6 Hz, *C*H$_3$CH$_2$O), 16.23 (*C*H$_3$CHMe), 16.39 (d, $^3J_{C-P}$ 6 Hz, *C*H$_3$CH$_2$O), 22.05 (*C*H$_3$CHMe), 23.15 (*C*H$_3$C=), 28.92 (d, J_{C-P} 5 Hz, *C*H$_2$–C=), 30.06 (d, J_{C-P} 12 Hz, *C*H$_2$–C=), 30.21 (*C*Me$_2$), 31.67 (d, $^1J_{C-P}$ 141 Hz, *C*H–P=O), 37.83 (d, J_{C-P} 5 Hz, *C*H–C=O), 61.17 (d, $^2J_{C-P}$ 7 Hz, CH$_2$O), 61.70 (d, $^2J_{C-P}$ 6 Hz, CH$_2$O), 64.21 (N*C*H–CO), 88.97 (CO–*C*Ph$_2$), 118.30 (H*C*=C) [125.51, 125.90, 125.98, 126.06, 127.89, 128.35, 128.41, 128.78, together aromatic *C*H], 132.47 (d, $^3J_{C-P}$ 12 Hz, Me*C*=C), 138.55 (quaternary C of Ph), 142.36 (quaternary C of Ph), 152.31 (N–*C*O–O), 174.74 (d, $^3J_{C-P}$ 6 Hz, C–*C*O–N); *m*/*z* (ESI) found: $[M+H]^+$ 540.2506. $C_{30}H_{39}NO_6P$ requires 540.2510.

4.4. (4*S*,3′*S*)-3-[3-(Diethoxyphosphinoyl)pentanoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 14

(*S*)-3-[(*E*)-3-(Diethoxyphosphinoyl)prop-2-enoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3e** (0.100 g, 0.212 mmol) was dissolved in dry dichloromethane (2 mL). The solution was cooled to −70 °C under nitrogen. Diethylaluminium chloride 1.8 M in toluene (1.0 mL) was added to the solution, which was stirred for 20 min at −70 °C. The reaction mixture was then poured into 2 M HCl (45 mL), then extracted with dichloromethane (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (2×20 mL) followed by 0.4 M aqueous potassium sodium (+)-tartrate (20 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated. ^{31}P NMR on the residue indicated that the starting material had been converted into three products δ_P (109 MHz, $CDCl_3$) 33.2 (72%), 33.3 (21%) and 30.0 (7%). Flash chromatography (EtOAc–petrol, 7:3) afforded a white solid, which was recrystallised from EtOAc–petrol to give the *title compound* **14** (0.066 g, 59%), mp 145–149 °C; repeated recrystallisation from EtOAc–petrol gave colourless, orthorhombic crystals, mp 149–151 °C, $[\alpha]_D^{25}$ −144 (*c* 0.36, $CHCl_3$); ν_{max}/cm^{-1} (film) 1705 (C=O) and 1784 (C=O); δ_H (400 MHz, $CDCl_3$) 0.76 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.89 (d, 3H, *J* 7 Hz, CH_3CHMe), 0.97 (t, 3H, *J* 7 Hz, CH_3CH$_2$CHP), 1.22 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.23 (t, 3H, *J* 7 Hz, CH_3CH$_2$O), 1.44–1.56 (m, 1H, CH_2CHP), 1.70–2.04 (m, 1H, CH_2CHP), 1.95–2.03 (m, 1H, C*H*Me$_2$), 2.34–2.45 (m, 1H, CHP), 3.07–3.18 (m, 2H, CH_2CO), 3.97–4.04 (m, 4H, 2×CH_2O), 5.37 (d, 1H, *J* 3 Hz, NC*H*), 7.26–7.49 (m, 10H, 2×Ph); δ_P (109 MHz, $CDCl_3$) 33.2; δ_C (101 MHz, $CDCl_3$, assignment by DEPT and ^1H–^{13}C correlation) 12.07 (d, $^3J_{C-P}$ 8 Hz, *C*H$_3$CH$_2$CHP), 16.38 (*C*H$_3$CH), 16.41 (*C*H$_3$CH$_2$O), 16.43 (*C*H$_3$CH$_2$O), 21.82 (*C*H$_3$CHMe), 22.10 ($^2J_{C-P}$ 4 Hz, *C*H$_2$CHP), 29.91 (*C*HMe$_2$), 32.67 (d, $^1J_{C-P}$ 142 Hz, *C*HP), 34.29 (*C*H$_2$CO), 61.51 (d, $^2J_{C-P}$ 7 Hz, *C*H$_2$O), 61.73 (d, $^2J_{C-P}$ 6 Hz, *C*H$_2$O), 64.90 (*C*HN), 89.37 (O–*C*Ph$_2$), 125.49 (Ph), 125.88 (Ph), 127.98 (Ph), 128.39 (Ph), 128.63 (Ph), 128.88 (Ph), 128.95 (Ph), 138.07 (quaternary C of Ph), 142.26 (quaternary C of Ph), 152.84 (O*C*=O), 171.08 (d, $^3J_{C-P}$ 16 Hz, C*C*=O); *m*/*z* (ESI) found: $[M+H]^+$ 502.2351. $C_{27}H_{37}NO_6P$ requires 502.2353.

4.4.1. (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-(Diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid 15. (4*S*,1′*R*,2′*R*,-3′*S*,4′*S*)-[3-(Diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **10** (19.8 mg, 0.0359 mmol) was dissolved in a mixture of THF (0.2 mL) and EtOH (0.2 mL). NaOH 1 M (0.05 mL) was added followed by 35% aqueous H_2O_2 (0.05 mL) and

the mixture was stirred for 60 h at 25 °C. Na_2SO_3 (50 mg) was then added, the organic solvents were removed by rotary evaporation and the residue was diluted with 1 M NaOH (10 mL) and filtered. The filtrate was washed with Et_2O (2×10 mL); the aqueous phase was acidified to pH 2 using 2 M HCl, then saturated with NaCl and extracted with $CHCl_3$ (5×20 mL). Drying ($MgSO_4$) and evaporation of the $CHCl_3$ extracts gave the *title compound* **15** (6.7 mg, 65%) as a white crystalline mass, mp 120–122 °C, $[\alpha]_D^{25}$ +20.1 (*c* 0.38, CH_2Cl_2); ν_{max}/cm^{-1} (film) 1728 (C=O) and 2400–3600 (O–H); δ_H (400 MHz, $CDCl_3$) 1.07–1.15 (m, 1H, H-7 or H-8), 1.25–1.38 (m, 7H, 2×CH_3 and H-7 or H-8), 1.59–1.68 (m, 1H, H-7 or H-8), 2.01–2.09 (m, 1H, H-7 or H-8), 2.29 (ddt, 1H, *J* 19, 7, 2 Hz, H-3), 2.86–2.93 (m, 2H), 3.06–3.10 (m, 1H), 4.05–4.19 (m, 4H, 2×OCH_2), 6.18 ('t', 1H, *J* 7 Hz, H-5 or H-6), 6.44 ('t', *J* 7 Hz, H-6 or H-5); δ_P (162 MHz, $CDCl_3$) 32.4; *m/z* (ESI) found: $[M+H]^+$ 289.1202. $C_{13}H_{22}O_5P$ requires 289.1199.

4.4.2. (1*R*,2*S*)-2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carboxylic acid 16. A solution of (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4-methylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **11** (142 mg, 0.257 mmol) in THF (1.4 mL) was stirred at 25 °C for 20 h with $LiOH\cdot H_2O$ (17.2 mg, 0.410 mmol) in H_2O (0.3 mL) and 35% aqueous H_2O_2 (0.1 mL). Addition of Na_2SO_3 (120 mg) and work up by analogy with the preceding experiment gave the *title compound* **16** (48.5 mg, 65%) as a colourless oil; $[\alpha]_D^{23}$ +78.2 (*c* 2.2, CH_2Cl_2); *m/z* (ESI) found: $[M+H]^+$ 291.1356. $C_{13}H_{24}O_5P$ requires 291.1356. Compound **16** was identical by ^1H NMR, ^{31}P NMR, IR and TLC (EtOAc) to the (1*S*,2*R*)-enantiomer *ent*-**16**, which is described below.

4.4.3. (1*S*,2*R*)-2-(Diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carboxylic acid *ent*-16. A solution of (4*S*,1′*S*,2′*R*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one **12** (242 mg, 0.437 mmol) in THF (2.5 mL) was stirred at 0 °C for 5 h with water (0.6 mL), 35% aqueous hydrogen peroxide (0.2 mL) and $LiOH\cdot H_2O$ (29.5 mg, 0.704 mmol). Solid Na_2SO_3 (0.5 g) was added and the THF was removed by rotary evaporation. NaOH 1 M (5 mL) was added and the mixture was filtered. The white precipitate was washed with water (20 mL) and the combined filtrates were acidified with 2 M HCl to pH 2. Extraction with $CHCl_3$ (3×20 mL), then drying ($MgSO_4$) and evaporation, gave the title compound **16** (88.4 mg, 79%) as a colourless oil; $[\alpha]_D^{24}$ −78.8 (*c* 2.9, CH_2Cl_2); ν_{max}/cm^{-1} (film) 1728 (C=O) and 2400–3600 (O–H); δ_H (400 MHz, $CDCl_3$) 1.31 (t, 6H, *J* 7 Hz, 2×CH_3CH$_2$O), 1.61 (s, 3H, CH_3C=C), 1.63 (s, 3H, CH_3C=C), 2.20–2.28 (m, 4H, 2×CH_2C=C), 2.39–2.49 (m, 1H, H-2), 2.74 ('tt', 1H, *J* 10, 6 Hz, H-1), 4.08–4.17 (m, 4H, 2×OCH_2), 8.0 (br s, 1H, CO_2H), δ_P (162 MHz, $CDCl_3$) 30.9; δ_C (101 MHz, $CDCl_3$, assignments supported by HSQC) 14.95 (d, *J* 6 Hz, *C*H_3CH$_2$O), 17.24 (*C*H_3C=), 17.30 (*C*H_3C=), 28.57 (d, J_{C-P} 4 Hz, *C*H_2), 32.10 (d, $^1J_{C-P}$ 144 Hz, *C*H–P=O), 32.82 (d, $^3J_{C-P}$ 12 Hz, *C*H_2–CHC=O), 39.02 (d, $^2J_{C-P}$ 3 Hz, *C*H–C=O), 60.74 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 60.99 (d, $^2J_{C-P}$ 7 Hz, *C*H_2O), 121.95 (d, $^3J_{C-P}$ 11 Hz, CH_3*C*=C), 122.26 (CH_3*C*=C), 176.48 (d, $^3J_{C-P}$ 7 Hz, CO_2H); *m/z* (ESI) found: $[M+H]^+$ 291.1357. $C_{13}H_{24}O_5P$ requires 291.1356.

4.5. X-ray diffraction data

4.5.1. X-ray diffraction data for (4*S*,1′*S*,2′*S*,3′*R*,4′*R*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.1]hept-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 6. Chemical formula: $C_{30}H_{36}NO_6P$; formula weight 537.57; crystal system: orthorhombic; unit cell dimensions and volume with estimated standard deviations: *a*=10.5567(3) Å; *b*=12.0318(2) Å; *c*=21.8433(6) Å; α=90°; β=90°; γ=90°; *V*=2774.45(12) Å^3; temperature 120(2) K; space group $P2_12_12_1$; *Z*=4; λ=0.71073 Å; linear absorption coefficient (μ): 0.143 mm^{-1}; number of reflections measured: 24586; number of independent reflections: 6367 [R_{int}=0.0595]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0489, wR_2=0.1089; absolute structure parameter 0.25(10).

4.5.2. X-ray diffraction data for (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-[3-(diethoxyphosphinoyl)bicyclo[2.2.2]oct-5-ene-2-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 10. Chemical formula: $C_{31}H_{38}NO_6P$; formula weight 551.59; crystal system: orthorhombic; unit cell dimensions and volume with estimated standard deviations: *a*=8.6007(4) Å; *b*=9.0921(4) Å; *c*=36.0268(16) Å; α=90°; β=90°; γ=90°; *V*=2817.2(2) Å^3; temperature 120(2) K; space group $P2_12_12_1$; *Z*=4; λ=0.71073 Å; μ=0.143 mm^{-1}; number of reflections measured: 19016; number of independent reflections: 6338 [R_{int}=0.0655]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0563, wR_2=0.1027; absolute structure parameter −0.08(13).

4.5.3. X-ray diffraction data for (4*S*,1′*R*,2′*S*)-[2-(diethoxyphosphinoyl)-4,5-dimethylcyclohex-4-ene-1-carbonyl]-5,5-diphenyl-4-isopropyloxazolidin-2-one 11. Chemical formula: $C_{31}H_{40}NO_6P$; formula weight 553.61; crystal system: monoclinic; unit cell dimensions and volume with estimated standard deviations: *a*=9.7614(5) Å; *b*=14.9366(5) Å; *c*=10.2496(6) Å; α=90°; β=91.497(2)°; γ=90°; *V*=1493.90(13) Å^3; temperature 120(2) K; space group $P2_1$; *Z*=2; λ=0.71073 Å; μ=0.135 mm^{-1}; number of reflections measured: 14558; number of independent reflections: 6686 [R_{int}=0.0464]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0524, wR_2=0.0951; absolute structure parameter 0.11(9).

4.5.4. X-ray diffraction data for (4*S*,3′*S*)-3-[3-(diethoxyphosphinoyl)pentanoyl]-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one 14. Chemical formula: $C_{27}H_{36}NO_6P$; formula weight 501.54; crystal system: orthorhombic; unit cell dimensions and volume with estimated standard deviations: *a*=9.2445(2) Å; *b*=15.3913(5) Å; *c*=18.2225(6) Å; α=90°; β=91.497(2)°; γ=90°; *V*=2600.7(18) Å^3; temperature 160(2) K; space group $P2_12_12_1$; *Z*=4; λ=0.71073 Å; μ=0.148 mm^{-1}; number of reflections measured: 19081; number of independent reflections: 5916 [R_{int}=0.0486]; final *R* indices [$I>2\sigma(I)$]: R_1=0.0451, wR_2=0.0949; absolute structure parameter 0.12(9).

Crystallographic data (excluding structure factors) for compounds **6**, **10**, **11** and **14** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 617238, 605148, 605149 and 617237, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank the EPSRC National Crystallography Service at Southampton for data collection. We are grateful to Mr. G. Coumbarides (NMR spectroscopy), Mrs. B. Stein (Mass Spectrometry at the EPSRC National Service Centre, Swansea) and to the late Mr. M. Cocksedge (FAB mass spectra at the ULIRS mass spectrometry service). We appreciate the contributions of Dr. Christine Bladon through her helpful suggestions and discussions.

References and notes

1. Naydenova, E.; Topashka-Ancheva, M.; Todorov, P.; Yordanova, T.; Troev, K. *Bioorg. Med. Chem.* **2006**, *14*, 2190–2196; DeClercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. *Nature* **1986**, *323*, 464–467; Bandini, E.; Martelli, G.; Spunta, G.; Panunzio, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2127–2130 and references cited therein.
2. For a review of the synthesis of non-racemic, chiral phosphonates see: Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609–16644.
3. Qian, C.; Huang, T.; Zhu, C.; Sun, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2097–2103; Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818–4825.
4. Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032–5034.
5. Yokomatsu, T.; Yamagishi, T.; Suemune, K.; Yoshida, Y.; Shibuya, S. *Tetrahedron* **1998**, *54*, 767–780.
6. Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379–8385; Cravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745–748.
7. (a) Öhler, E.; Haslinger, E.; Zbiral, E. *Chem. Ber.* **1982**, *115*, 1028–1034; (b) Wyatt, P. B.; Villalonga-Barber, C.; Motevalli, M. *Tetrahedron Lett.* **1999**, *40*, 149–152; (c) Robiette, R.; Marchand-Brynaert, J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2155–2158; (d) Robiette, R.; Defacqz, N.; Stofferis, J.; Marchand-Brynaert, J. *Tetrahedron* **2003**, *59*, 4167–4175.
8. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.
9. Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.
10. van der Holst, J. P. J.; van Hooidonk, C.; Kienhuis, H. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 40–43.
11. Knol, J.; Feringa, B. L. *Synth. Commun.* **1996**, *26*, 261–268.
12. Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387–398.
13. Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093–2126.
14. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994; p 726.
15. Rück, K.; Kunz, H. *Synthesis* **1993**, 1018–1028.