Diastereoselective synthesis of ω-phosphonic acid analogues of 4-arylkainoids

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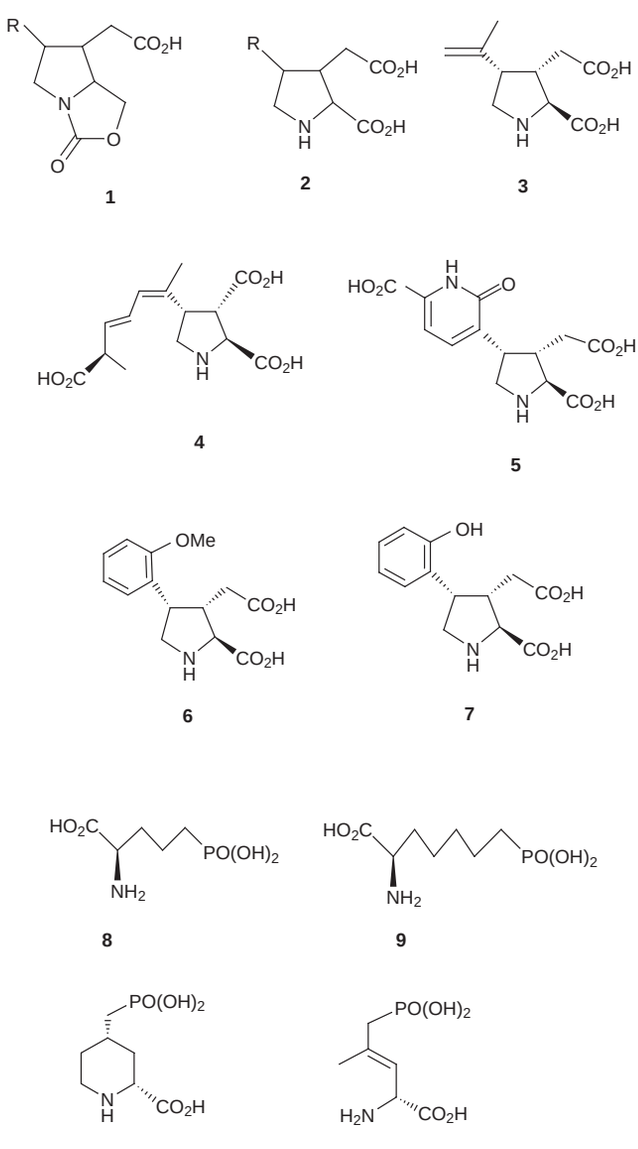
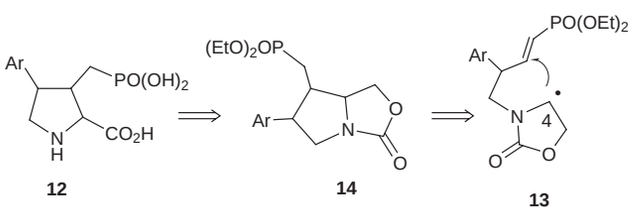
Radical cyclisation by the use of α,β-unsaturated phosphonate as a radical acceptor was applied to a synthesis of 7-phosphonomethylpyrrolo[1,2-*c*]oxazolidinones, synthetic intermediates on the route to phosphonic acid analogues of kainoids. The relative configuration at the 6;7;7a-positions was found to be highly controlled by steric effects due to the substituent at the 6-position. Thus, diethyl [{(6*S**,7*R**,7a*S**)-6-(2-methoxyphenyl)-3-oxoperhydropyrrolo[1,2-*c*]-[1,3]oxazol-7-yl}methyl]phosphonate **29a** and diethyl [{(6*S**,7*R**,7a*S**)-3-oxo-6-phenylperhydropyrrolo[1,2-*c*][1,3]-oxazol-7-yl}methyl]phosphonate **29b** were prepared with high diastereoselectivity. When the substituent at the 6-position is a 1-naphthyl group, the diethyl [{(6*S**,7*R**,7a*S**)-6-(1-naphthyl)pyrroloxazol-7-yl}methyl]phosphonate **29c** and its (6*S**,7*R**,7a*R**)-isomer **30c** were formed in the ratio **29c**:**30c** ~ 2:1. The stereostructure of compound **29a** was determined by X-ray crystallographic analysis. The 6-*o*-methoxyphenyl derivative **29a** was converted into the corresponding phosphonic acid analogue **33**.

An oxazolidinone ring can be considered as a synthon for the synthesis of 2-amino alcohols,[1] since it can be easily cleaved under mild conditions at the two heteroatoms. It is well known that 2-amino alcohols are preparatively useful precursors for α-amino acids. Thus, the pyrrolooxazolidinones can be recognized as useful synthetic intermediates for pyrrolidine-2-carboxylic acids. The development of new methodologies for achieving stereocontrolled construction of 6,7-disubstituted pyrrolooxazolidinones **1** is of particular relevance to 3,4-disubstituted pyrrolidine-2-carboxylic acids **2**,[2] which provide the definitive structural feature of kainoids **3** and related compounds. The pronounced neuroexcitatory properties of the kainoids such as (−)-α-kainic acid **3**,[3] domoic acid **4**[4] and acromeric acid **5**[4] have been well investigated to evaluate their excitatory action on mammalian central neurons.[5] These excitatory amino acids interact with the kainate receptor to cause strong depolarisation. Therefore, several kinds of 4-arylkainoids possessing strong neurophysiological activity such as MFPA **6**[4] and HFPA **7**[6] have been prepared to obtain potential agonists to the kainate receptor.

On the other hand, it is also important to find potent glutamate receptor antagonists as well as agonists, since they would be useful lead compounds to finding potent therapeutic drugs for neuronal diseases such as epilepsy, Huntington's chorea and Parkinson's disease.[7] Discovery of antagonists to the *N*-methyl-D-aspartate (NMDA) receptor, a sub-type receptor of the glutamate receptor, have been developed based on the structural modification of NMDA receptor agonists. A successful modification for this purpose is the replacement of the ω-carboxylic acid with a phosphonic acid group as illustrated by compounds AP-5 **8**,[8] AP-7 **9**,[8] CGS **10**[8] and CGP **11**,[8] which are known potent antagonists with affinity constants in the nanomolar range. Indeed, the structure–activity relationship[9] showed that good competitive NMDA antagonists were obtained by replacement of the distal acidic function at the ω-position with a phosphonic acid. It is important to search for useful probes in an analysis of physiological functions of excitatory amino acids. Among sub-type receptor antagonists for the glutamate receptor, NMDA receptor antagonists have been well studied. However, kainate receptor antagonists,[10] which also would be important molecules is for a study of neuronal disease, have been relatively unexplored.



We became interested in a synthesis of kainate receptor antagonists by the structural modification of synthetic kainoids having potent neurophysiological activity. Thus we planned to prepare phosphonic acid analogues **12** in which the carboxylic acid at the 3-position of MFPA **6** was replaced by a phosphonic one. Herein we describe the highly diastereoselective synthesis of phosphonic acid analogues[11] of kainoids *via* radical cyclisation which has been widely studied as an extremely elegant method for the preparation of carbocyclic as well as heterocyclic compounds.[12] The key characteristic features of our strategy for the synthesis of phosphonic acid analogues of 4-arylkainoids is based on the following items: i. The use of unsaturated phosphonates as a radical acceptor[11] (structure **13**) for the introduction of a phosphonomethyl group at the desired position. ii. A short-step synthesis of the (6-arylpyrrolo[1,2-*c*]-oxazol-7-yl)methylphosphonate **14**, a synthon for 4-aryl-2-carboxy-3-(phosphonomethyl)pyrrolidine **12**, with high diastereoselectivity (Scheme 1). The radical cyclisation was found



12 **14** **13**

Scheme 1

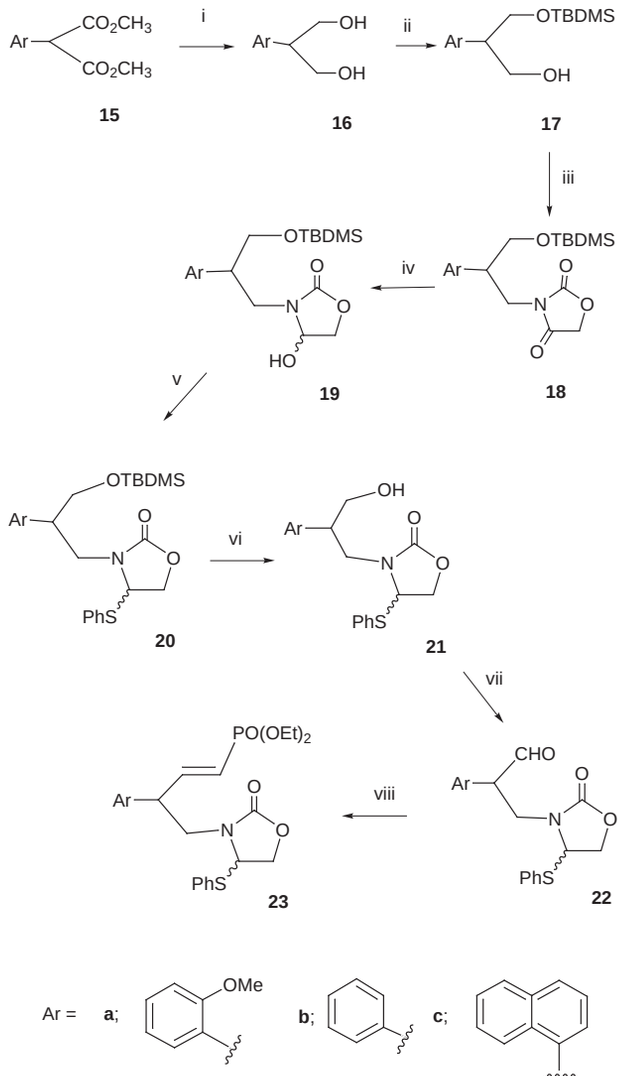
to give rise to the formation of allo-type kainoids, not natural-type ones. We now describe herein the results of our studies.

Results and discussion

Synthesis of the precursors for the radical cyclisation

The synthetic utility of α-acylamino radical cyclisations for the synthesis of heterocyclic systems has been widely reported. 4-(Phenylthio)oxazolidinones were shown to be useful precursors for the generation of a radical carbon at the 4-position of oxazolidin-2-ones by homolytic cleavage of the C–S bond.[2] Nucleophilic attack of an α-acylamino radical onto a carbon–carbon double bond has achieved remarkable stereocontrolled construction of polysubstituted bicyclic systems.[2] In view of the interest in the application of radical cyclisation to polysubstituted pyrrolooxazolidinone derivatives, the creation of two stereogenic centres at the 7- and 7a-position of 6,7-disubstituted pyrrolo[1,2-*c*]oxazolidinones *via* diastereoselective cyclisation at the alkene has been studied. Radical cyclisation with olefins are usually dominated by SOMO–LUMO † mixing;[12] that is the carbon radical acts as nucleophile and the olefin as an electrophile. Since the electron-withdrawing phosphonyl substituent lowers the LUMO of the olefin and accelerates the radical addition, radical reaction with species **13** can be expected to proceed faster. For the synthesis of 6-aryl-7-(phosphonomethyl)pyrrolo[1,2-*c*]oxazolidinone derivatives **14**, the new method for the creation of the stereogenic centre at the 7,7a-positions has been studied.

As the first step to the N-substituted oxazolidinones **23a**–**c** which contain a latent radical centre, we synthesized the 3-[3-hydroxy-2-(aryl)propyl]-4-(phenylsulfanyl)-1,3-oxazolan-2-one **21a**–**c** through the conventional method by starting with 2-arylpropane-1,3-diols **16** as outlined in Scheme 2. Synthesis of 3-silyloxy-2-arylpropan-1-ols **17a**–**c** was successfully achieved by treatment of 2-arylpropane-1,3-diols **16a** and **16b**,**c**,[13] obtained by reduction of dimethyl arylmalonates **15a**–**c** with $LiAlH_4$, with TBDMSCl in the presence of NaH. Coupling of alcohols **17a**–**c** with oxazolidine-2,4-dione by application of the Mitsunobu reaction[14] {Ph_3P, [$Pr^iOC(O)N{=}]_2$ in THF} afforded oxazolidinediones **18a**–**c** (70–79%). Reduction of compounds **18a**–**c** with $NaBH_4$, followed by treatment of the reduction products **19a**–**c** with diphenyl disulfide in the presence of tri-*n*-butylphosphine afforded the corresponding 4-(phenylsulfanyl)oxazolidinones **20a**–**c** as a 1:1 mixture of diastereomers. Upon exposure of siloxanes **20a**–**c** to acidic conditions (Amberlyst methanol), the silyl group could be removed to give the desired alcohols **21a**–**c**. For the preparation of the 3-arylbut-1-enephosphonates **23a**–**c**, alcohols **21a**–**c** were converted into the aldehydes **22a**–**c** by Swern oxidation. Treatment of aldehydes **22a**–**c** with tetraethyl methylenediphosphonate afforded the desired phosphonates **23a**–**c** in ~72% yield in each case.



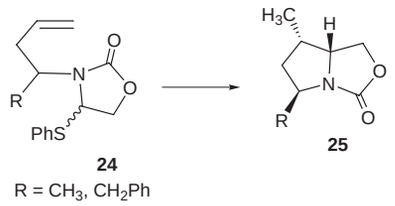
15 **16** **17** **19** **18** **20** **21** **22** **23**

Scheme 2 *Reagents and conditions*: i) $LiAlH_4$, Et_2O; ii) NaH, TBDMSCl, THF; iii) oxazolidine-2,4-dione, Ph_3P, diisopropyl azodicarboxylate, THF; iv) $NaBH_4$, MeOH; v) diphenyl disulfide, tri-*n*-butylphosphine, THF; vi) Amberlyst, MeOH; vii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; viii) $CH_2[P(O)(OEt)_2]_2$, *n*-BuLi, THF.

Radical cyclisation of compounds 23a–c

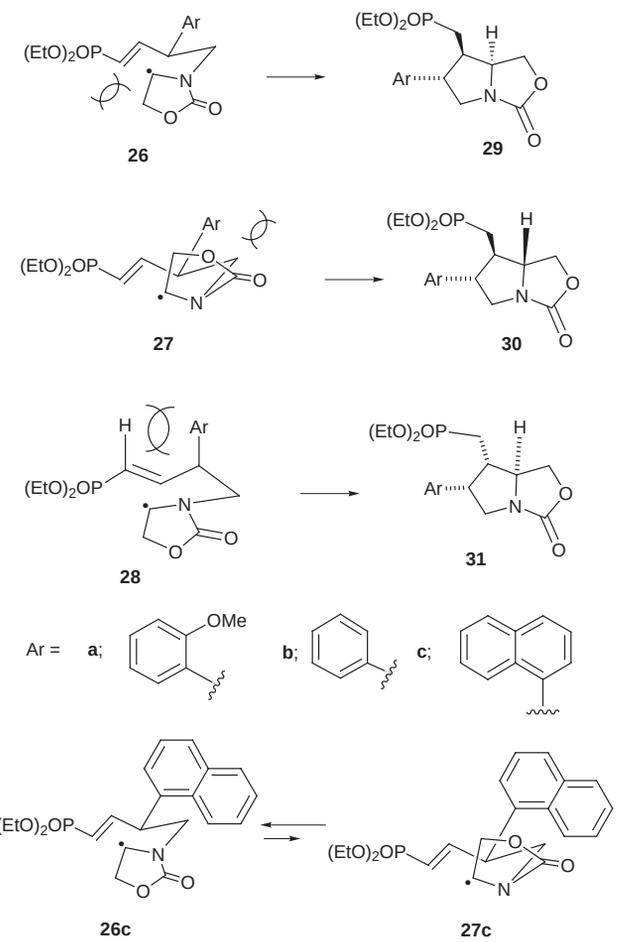
The radical cyclisation of 2-(α)-substituted 4-phenylsulfanyl-3-(but-3-enyl)oxazolidines such as compounds **24** has been thoroughly investigated.[2] Radical cyclisation of compounds **24** resulted in predominant formation of products **25** with high diastereoselectivity without formation of the alternative diastereomer (Scheme 3). However, the diastereoselectivity in the radical cyclisation has not been studied for those com-

† Singly occupied molecular orbital–lowest unoccupied molecular orbital.



Scheme 3

pounds in which the substituent was located at a β-position to the nitrogen atom. In the course of radical cyclisation, three kinds of possible transition states **26**, **27** and **28** should be considered (Scheme 4).



Scheme 4 Products **29**–**31** are equivalent to compound **14** in Scheme 1.

The reaction proceeds *via* these transition states, competitively. The probability of the transition states' being formed predominantly during the reaction course determines which product is obtained. Taking the transition state **26**, the formation of product **29**, thermodynamically the most stable isomer, can be expected. The transition state **27** would form product **30**. The difference in stability of the transition states **26** and **27** is based on the steric hindrance between the double bond and the oxazolidinone ring, or the aryl group and the oxazolidinone ring. The alternative transition state **28** is not favoured owing to the significant severe allylic strain. Thus one cannot expect the formation of products **31**. The C–C bond-formation energy giving the corresponding product would also be an important factor in the reaction pathway.

At first, radical cyclisation of compound **23a** was examined. Heating of a benzene solution of compound **23a** with 1.5 equiv. of Bu_3SnH in the presence of AIBN under reflux gave diethyl [{(6*S**,7*R**,7a*S**)-6-(2-methoxyphenyl)-3-oxoperhydropyrrolo-[1,2-*c*]oxazol-7-yl}methyl]phosphonate **29a** as a single product

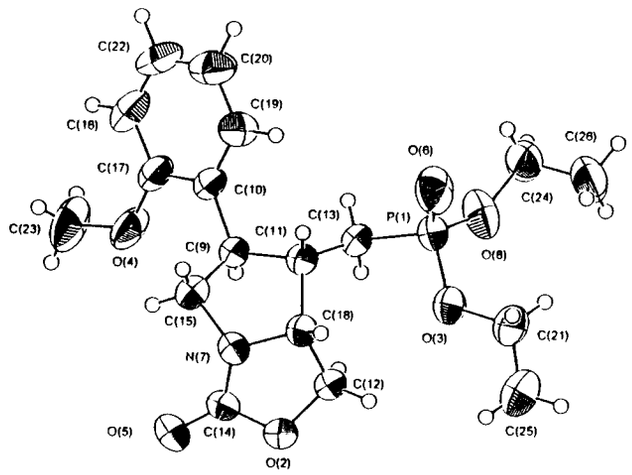
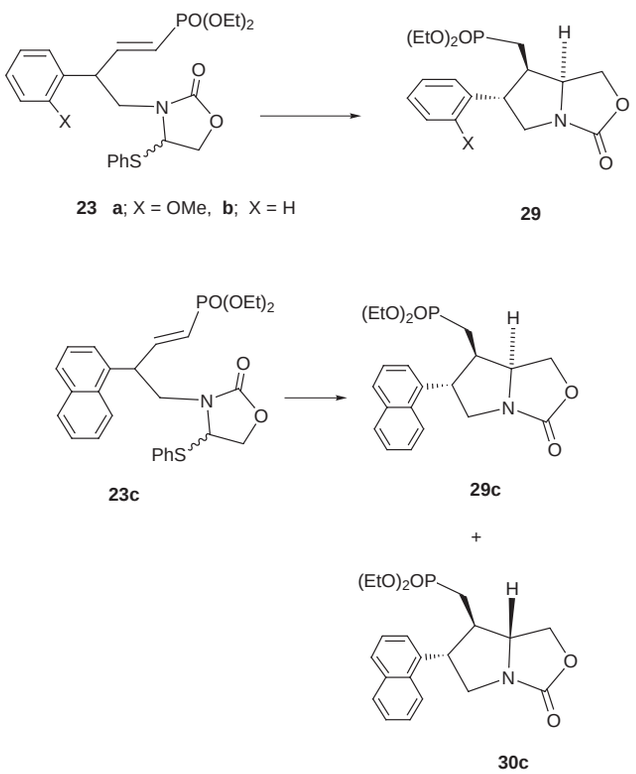


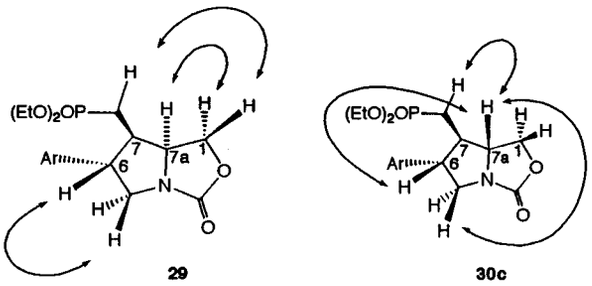
Fig. 1 Single-crystal X-ray structure of compound **29a** with crystallographic numbering scheme.



Scheme 5

in 81% yield (see Scheme 5). The reaction was, surprisingly, found to proceed with high diastereoselectivity and the formation of either alternative diastereomer **30a** or **31a** was not observed. A particularly noteworthy feature was that the radical cyclisation proceeded through the transition state **26** exclusively with complete selectivity with respect to the relative configuration at the 6-position. The method would be widely applicable to a synthesis of the (2*S**,3*R**,4*S**)-isomer of (2*S*,3*S*,4*S*)-MFPA **6**, though it would not be applicable to a synthesis of kainoids possessing the same stereochemistry as that of MFPA. The stereostructure of product **29a** was established by X-ray crystallography analysis.[15] A single-crystal X-ray structure of **29a** is shown in Fig. 1. A NOESY study of compound **29a** also clearly supported the correlation as shown in Fig. 2.

Radical cyclisation of compound **23b** in benzene solution under reflux failed to give any cyclisation product and resulted only in recovery of the staring material. Higher temperatures were required to achieve the reaction. When a toluene solution was heated, the expected product **29b** was obtained in 86% yield



a: Ar = *o*-methoxyphenyl, b: Ar = Phenyl,
c: Ar = 1-naphthyl

Fig. 2 NOESY correlation of compounds **29a**, **b**, **c** and **30c**.

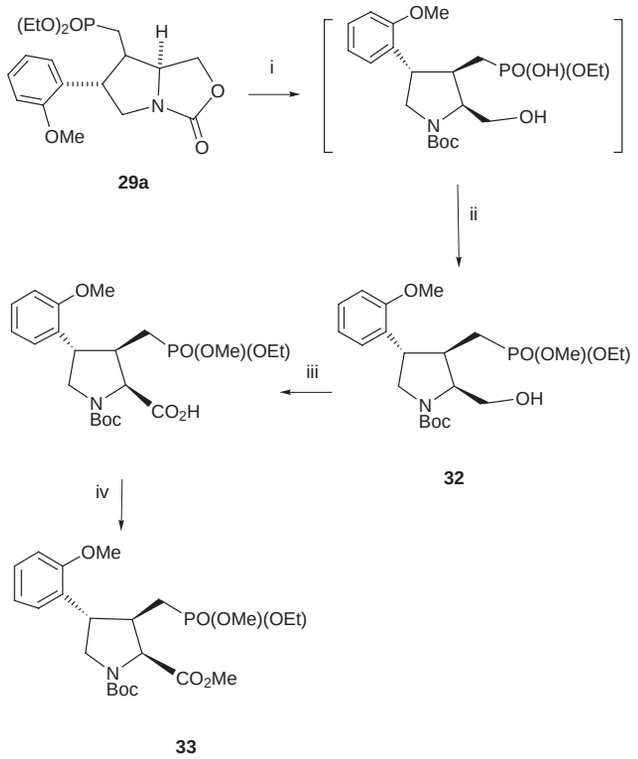
as a single product as expected. In the case of substrate **23c**, a different mode of reaction was observed from that of analogues **23a**,**b**. The reaction proceeded in benzene solution to give the expected product **29c** in 40% yield accompanied by the formation of (6*S**,7*R**,7a*R**)-isomer **30c**, in 22% yield. In the radical cyclisation of compounds **23a**,**b**, the reaction proceeded through the transition states **26a**,**b** predominantly rather than **27a**,**b** because of the presence of steric hindrance between the aromatic ring and the oxazolidinone in radicals **27a**,**b**. Therefore compounds **23a**,**b** afforded only one kind of product, the stereochemistry of which was shown in products **29a**,**b**. However, in the radical cyclisation of compound **23c**, the reaction proceeds *via* two transition states, **26c** and **27c**, since the naphthyl ring is so bulky as to partly inhibit its free rotation. It is easily predicted that radical **27c** is less stable than radical **26c**, because of the steric hindrance produced by the aromatic ring and the oxazolidinone, from their stereo-model study as above (see Scheme 4). The cyclisation products **29c** and **30c** were easily separated by preparative HPLC as described in the Experimental section. The stereochemistry of products **29a**–**c** and **30c** was determined by ^{1}H, ^{13}C NMR and NOESY experiments as in the case of compound **29a**. All of the proton and carbon signals of the cyclisation products **29b**,**c** and **30c** could be assigned satisfactorily. In these radical cyclisations, the formation of the all-*cis* product **31** was not observed.

Synthesis of 1-*tert*-butyl-2-methyl (2*S**,3*R**,4*S**)-3-{[ethoxy(methoxy)phosphoryl]methyl}-4-(2-methoxyphenyl)tetrahydropyrrole-1,2-dicarboxylate 33

At the next stage, it is required to convert the cyclisation product into the corresponding phosphonic acid analogue of kainoids. Ring cleavage of the oxazolidinone ring of compound **29a** was effected with aqueous base, and subsequent protection of the nitrogen atom with a *tert*-butoxycarbonyl group to yield compound **32** (Scheme 6). Oxidation of the primary hydroxy group with $RuCl_3$–$NaIO_4$ followed, without purification, by esterification with diazomethane gave fully protected ester **33** in 19.7% yield. Thus, the method of synthesis of a phosphonic analogue of the (6*S**,7*R**,7a*S**)-isomers of 6-arylkainoids was established.

Experimental

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under nitrogen. THF and diethyl ether were distilled from sodium benzophenone ketyl; methylene dichloride (CH_2CH_2) was distilled from CaH_2. All reactions were monitored by TLC using commercially available glass-backed plates. For column chromatography, silica gel 60 (0.043–0.063 mm) was used and the columns were eluted in the flash mode. ^{1}H NMR spectra were recorded on a Bruker AM 400 or a Varian Gemini 300 spectrometer operating at 400 MHz and 300 MHz, respectively, for solution in $CDCl_3$. The chemical shifts, relative to tetramethylsilane (TMS) where δ(TMS) = 0,



Scheme 6 *Reagents and conditions*: i) NaOH, Boc_2O, aq. 1,4-dioxane; ii) CH_2N_2, Et_2O; iii) $RuCl_3$, $NaIO_4$, CCl_4, aq. CH_3CN.

and coupling constants (J) are given as δ-values (ppm) and in Hz, respectively. The multiplicity of the signal is indicated as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad signal. ^{13}C NMR spectra were recorded in $CDCl_3$ on the Bruker AM-400 (100 MHz). Chemical shifts are recorded relative to $CDCl_3$ (central line of triplet, δ_C 77.0) unless otherwise stated. IR spectra were recorded by using a Perkin-Elmer FT-IR 1710 spectrometer. Mass spectra (MS) were measured on a TSQ 700 or a VG Auto Spec instrument. Light petroleum refers to the fraction with distillation range 30–60 °C.

2-(2-Methoxyphenyl)propane-1,3-diol 16a

To a suspension of $LiAlH_4$ (0.76 g, 20.0 mmol) in diethyl ether (40 cm^3) was added a solution of malonate **15a** (2.38 g, 10.0 mmol) in diethyl ether (20 cm^3) at 0 °C. After being stirred for 10 h, the mixture was heated under reflux for 1.5 h. The mixture was quenched with 20% aq. sodium hydroxide under ice-cooling. Inorganic substances were removed by filtration. The organic layer was dried ($MgSO_4$), and evaporated *in vacuo*. The resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (4 : 1) gave *title diol* **16a** (1.18 g, 65%) as crystals, mp 75–77 °C; δ_H 7.30–7.20 (m, 1H), 7.20–7.15 (m, 1H), 6.99–6.85 (m, 2H), 4.08–3.97 (m, 2H), 3.97–3.85 (m, 2H), 3.82 (s, 3H) and 3.60–3.50 (m, 1H); δ_C 157.1, 128.1, 127.8, 127.6, 120.6, 110.6, 64.9 (2 carbons), 55.2 and 42.7; ν_{max}(KBr)/cm^{-1} 3294, 1494, 1242, 965 and 758; *m*/*z* (EI) 182.1 (M^+) (Found: C, 65.8; H, 7.75. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%).

3-(*tert*-Butyldimethylsilyloxy)-2-(2-methoxyphenyl)propan-1-ol 17a

To an ice-cooled, stirred suspension of 60% NaH (4.40 g, 110.0 mmol: used after removal of oil by washing with light petroleum) in THF (40 cm^3) was added dropwise a solution of diol **16a** (18.20 g, 100.0 mmol) in THF (40 cm^3). After being stirred at rt for 1 h, the mixture was treated with a solution of TBDMSCl (16.58 g, 110.90 mmol) in THF (100 cm^3) under ice-cooling.

After having been stirred at rt for 8 h, the mixture was quenched with ammonium chloride, then was extracted with ethyl acetate. The solution was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel [hexane–ethyl acetate (50:1)] to give *title compound* **17a** (26.02 g, 88%) as an oil; δ_H 7.21–7.11 (m, 1H), 7.11–7.01 (m, 1H), 6.87–6.77 (m, 2H), 4.09–3.99 (m, 1H), 3.89–3.79 (m, 2H), 3.79 (s, 3H), 3.53–3.45 (m, 1H), 2.85–2.79 (m, 1H), 0.84 (s, 9H) and 0.00 (s, 6H); δ_C 157.2, 128.0, 127.9, 127.8, 120.5, 110.5, 66.6, 66.0, 55.3, 42.4, 25.8 (3 carbons), 18.1 and −5.6 (2 carbons); ν_{max}(neat)/cm^{-1} 3446, 2954, 1494, 1243, 1103, 1055, 837 and 753; *m*/*z* (EI) 239.1 (M^+ − Bu) (Found: C, 64.5; 9.5. $C_{16}H_{28}O_3Si$ requires C, 64.82; H, 9.52%).

3-(*tert*-Butyldimethylsilyloxy)-2-phenylpropan-1-ol 17b

This compound (16.40 g, 62%) was obtained as an oil from diol **16b** (15.20 g, 100.0 mmol) according to the same conditions as above; δ_H 7.27–7.14 (m, 5H), 4.07–3.96 (m, 1H), 3.89–3.74 (m, 2H), 3.05–2.95 (m, 1H), 2.73–2.69 (m, 1H), 0.85 (s, 9H) and 0.00 (s, 6H); δ_C 1138.5, 129.6 (2 carbons), 129.0 (2 carbons), 127.7, 64.9, 64.0, 43.7, 25.8 (3 carbons), 18.2 and −5.6 (2 carbons); ν_{max}(neat)/cm^{-1} 3393, 2929, 2360, 1472, 1255, 1094, 837 and 669; *m*/*z* (EI) 267.1 (M^+ + 1) (Found: C, 67.4; H, 9.7. $C_{15}H_{26}O_2Si$ requires C, 67.61; H, 9.84%).

3-(*tert*-Butyldimethylsilyloxy)-2-(1-naphthyl)propan-1-ol 17c

This compound (22.85 g, 72%) was obtained from diol **16c** (20.20 g, 100.0 mmol) as an oil [from **15c** (20.20 g, 100.0 mmol)]; δ_H 8.11 (d, *J* 8.5, 1H), 7.80 (d, *J* 8.5, 1H), 7.69 (d, *J* 8.2, 1H), 7.49–7.40 (m, 2H), 7.38–7.33 (m, 1H), 7.23–7.20 (m, 1H), 4.19–4.14 (m, 1H), 4.01–3.87 (m, 3H), 2.90–2.87 (m, 1H), 0.86 (s, 9H) and 0.00 (s, 6H); δ_C 134.3, 133.9, 131.9, 129.0, 127.8, 126.5, 125.7, 125.3, 124.3, 122.6, 65.7, 64.9, 43.4, 25.8 (3 carbons), 18.3, −5.5 and −5.4; ν_{max}(neat)/cm^{-1} 3049, 2360, 1471, 1096, 837 and 777; *m*/*z* (EI) 259.1 (M^+ − ^{t}Bu) (Found: C, 72.0; H, 8.8. $C_{19}H_{28}O_2Si$ requires C, 72.10; H, 8.92%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-(2-methoxyphenyl)propyl]-1,3-oxazolane-2,4-dione 18a

A solution of diisopropyl azodicarboxylate (2.17 cm^3, 11.0 mmol) in THF was added dropwise to an ice-cooled, stirred solution of the alcohol **17a** (2.96 g, 10.0 mmol), oxazolidine-2,4-dione (1.11 g, 11.0 mmol) and triphenylphosphine (2.89 g, 11.0 mmol) in THF (30 cm^3). After being stirred at the same temperature for 10 min, the stirred mixture was kept at rt for 12 h. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (10:1) gave *title compound* **18a** (2.99 g, 79%); δ_H 7.25–7.13 (m, 2H), 6.94–6.91 (m, 2H), 4.51 (d, *J* 15.8, 1H), 4.45 (d, *J* 15.8, 1H), 4.05–3.84 (m, 3H), 3.84–3.73 (m, 2H), 3.79 (s, 3H), 0.86 (s, 9H) and 0.02 (s, 6H); δ_C 170.2, 157.4, 155.7, 128.7, 128.2, 126.7, 120.4, 110.5, 67.3, 64.8, 55.2, 41.7, 39.7, 25.7 (3 carbons), 18.2 and −15.7 (2 carbons); ν_{max}(neat)/cm^{-1} 2953, 2342, 1737, 1417, 1246 and 776; *m*/*z* (EI) 322.1 (M^+ − ^{t}Bu) (Found: C, 60.0; H, 7.75; N, 3.7. $C_{19}H_{29}NO_5Si$ requires C, 60.13; H, 7.70; N, 3.69%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-phenylpropyl]-1,3-oxazolane-2,4-dione 18b

This compound (2.43 g, 70%) was obtained from the alcohol **17b** (2.66 g, 10.0 mmol) as a crystalline solid according to the same conditions as above; mp 57–59 °C; δ_H 7.36–7.14 (m, 5H), 4.55–4.38 (m, 2H), 3.98–3.88 (m, 2H), 3.90–3.80 (m, 2H), 3.50–3.55 (m, 1H), 0.87 (s, 9H) and 0.00 (s, 6H); δ_C 170.2, 155.7, 138.5, 128.5 (2 carbons), 128.1 (2 carbons), 127.4, 67.5, 66.1, 45.3, 42.7, 25.8 (3 carbons), 18.3 and −5.6 (2 carbons); ν_{max}(KBr)/cm^{-1} 2926, 1808, 1703, 1456, 1423, 1255, 1156, 1050 and 790; *m*/*z* (EI) 350.1 (M^+ + 1) and 292.1 (M^+ − ^{t}Bu) (Found: C, 61.7; H, 7.8; N, 4.0. $C_{18}H_{27}NO_4Si$ requires C, 61.86; H, 7.79; N, 4.01%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-(1-naphthyl)propyl]-1,3-oxazolane-2,4-dione 18c

This compound (3.13 g, 78%) was obtained from the alcohol **17c** (3.16 g, 100.0 mmol) as a crystalline solid according to the same conditions as above; mp 76–79 °C; δ_H 8.18 (d, *J* 8.6, 1H), 7.86 (d, *J* 8.6, 1H), 7.78–7.75 (m, 1H), 7.57–7.45 (m, 4H), 4.48 (d, *J* 15.9, 1H), 4.40 (d, *J* 15.9, 1H), 4.43–4.34 (m, 1H), 4.15 (dd, *J* 7.5 and 13.8, 1H), 4.04 (dd, *J* 8.0 and 13.8, 1H), 4.02–3.92 (m, 2H), 0.88 (s, 9H), 0.01 (s, 3H) and −0.02 (s, 3H); δ_C 170.4, 155.9, 134.7, 133.9, 131.9, 129.0, 127.8, 126.5, 125.7, 125.3, 124.3, 122.6, 67.5, 66.3, 43.4, 39.2, 25.8 (3 carbons), 18.3, −5.5 and −5.6; ν_{max}(KBr)/cm^{-1} 2929, 1826, 1734, 1446, 1079, 837 and 780; *m*/*z* (EI) 342.1 (M^+ − ^{t}Bu) (Found: C, 66.2; H, 7.3; N, 3.5. $C_{22}H_{29}NO_4Si$ requires C, 66.13; H, 7.32; N, 3.50%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-(2-methoxyphenyl)propyl]-4-hydroxy-1,3-oxazolan-2-one 19a

To a stirred solution of dione **18a** (3.79 g, 10.0 mmol) in methanol (100 cm^3) was added $NaBH_4$ (0.76 g, 20.0 mmol) in small portions at 0 °C. After being stirred for 30 min at the same temperature, then for a further 2 h at rt, the mixture was quenched with acetone. The solvent was evaporated off and the resulting residue was diluted with water and extracted with chloroform. The solution was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with hexane–ethyl acetate (6:1) as eluant to give *title compound* **19a** (3.12 g, 82%) as a crystalline product; mp 92–95 °C; δ_H 7.27–7.18 (m, 2H), 6.96–6.88 (m, 2H), 5.25–5.18 (m, 0.5H), 5.08–5.01 (m, 0.5H), 4.55–4.45 (m, 1H), 4.45–4.35 (m, 1H), 3.92–3.63 (m, 5H), 3.82 (s, 3H), 0.91 (m, 4.5H), 0.90 (m, 4.5H), 0.05 (s, 3H) and 0.00 (s, 3H); ν_{max}(KBr)/cm^{-1} 3311, 2929, 1747, 1475, 1107, 1008, 937 and 776; *m*/*z* (EI) 381.1 (M^+) and 324.1 (M^+ − ^{t}Bu) (Found: C, 59.7; H, 8.2; N, 3.7. $C_{19}H_{31}NO_5Si$ requires C, 59.81; H, 8.19; N, 3.67%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-(2-methoxyphenyl)propyl]-4-hydroxy-1,3-oxazolan-2-one 19b

This compound (2.75 g, 78%) was obtained from dione **18b** (3.49 g, 10.0 mmol) as a crystalline material according to the same conditions as above; mp 76–79 °C; δ_H 7.38–7.20 (m, 5H), 5.20–5.16 (m, 0.5H), 4.82–4.78 (m, 0.5H), 4.24–4.12 (m, 1H), 4.09–4.03 (m, 1H), 3.94–3.78 (m, 3H), 3.71–3.56 (m, 1H), 3.33–3.25 (m, 1H), 0.90 (s, 9H), 0.03 (s, 3H) and 0.00 (s, 3H); ν_{max}(KBr)/cm^{-1} 3319, 2932, 1719, 1475, 1251, 1109, 839, 775 and 772; *m*/*z* (EI) 352.2 (M^+ + 1) and 294.1 (M^+ − ^{t}Bu) (Found: C, 61.4; H, 8.3; N, 4.1. $C_{18}H_{29}NO_4Si$ requires C, 61.50; H, 8.32; N, 3.99%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-(1-naphthyl)propyl]-4-hydroxy-1,3-oxazolan-2-one 19c

This compound (3.14 g, 78%) was obtained from dione **18c** (3.99 g, 10.0 mmol) as a crystalline product according to the same conditions as above; mp 100–104 °C; δ_H 8.17 (d, *J* 8.4, 1H), 7.87 (d, *J* 7.7, 1H), 7.78–7.74 (m, 1H), 7.57–7.42 (m, 4H), 5.14–5.08 (m, 1H), 4.85–4.75 (m, 1H), 4.27–4.20 (m, 1H), 4.15–4.08 (m, 1H), 4.08–4.01 (m, 1H), 4.01–3.93 (m, 3H), 3.88–3.79 (m, 1H), 0.87 (s, 9H), 0.04 (s, 3H) and 0.03 (s, 3H); ν_{max}(KBr)/cm^{-1} 3348, 2958, 1742, 1475, 1241, 1115, 849 and 775; *m*/*z* (EI) 402.1 (M^+ + 1) and 344.1 (M^+ − ^{t}Bu) (Found: C, 65.8; H, 7.7; N, 3.6. $C_{22}H_{31}NO_4Si$ requires C, 65.82; H, 7.78; N, 3.49%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-(2-methoxyphenyl)propyl]-4-phenylsulfanyl-1,3-oxazolan-2-one 20a

To a stirred solution of compound **19a** (3.81 g, 10.0 mmol) and diphenyl disulfide (2.40 g, 11.0 mmol) in THF (40 cm^3) was added dropwise tri-*n*-butylphosphine (2.7 cm^3, 11.0 mmol) at 0 °C. After being stirred for 30 min at the same temperature and then for a further 12 h at rt, the mixture was quenched with

water and extracted with diethyl ether. The solution was dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (20:1) gave *title compound* **20a** (2.62 g, 55%) as an oil; δ_H 7.45–7.15 (m, 7H), 6.93–6.83 (m, 2H), 4.85 (dd, *J* 7.5 and 4.0, 0.5H), 4.50 (dd, *J* 8.1 and 3.4, 0.5H), 4.31–4.14 (m, 2H), 4.08–4.00 (m, 1H), 3.96–3.82 (m, 1H), 3.89–3.70 (m, 2H), 3.85 (s, 3H), 3.79–3.51 (m, 1H), 0.88 (s, 9H) and 0.02 (s, 6H); ν_{max}(neat)/cm^{-1} 2954, 1762, 1471, 1245 and 1104; *m*/*z* (EI) 474.2 ($M^+ + 1$), 416.1 ($M^+ - {}^t$Bu) and 364.2 ($M^+ -$ SPh) (Found: C, 63.5; H, 7.6; N, 3.05. $C_{25}H_{35}NO_4SSi$ requires C, 63.39; H, 7.45; N, 2.96%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-phenylpropyl]-4-phenylsulfanyl-1,3-oxazolan-2-one 20b

This compound (2.47 g, 56%) was obtained from compound **19b** (3.51 g, 10.0 mmol) as a crystalline material according to the same conditions as above; mp 63–65 °C; δ_H 7.48–7.21 (m, 10H), 4.86 (dd, *J* 7.9 and 3.4, 0.5H), 4.31–4.20 (m, 2H), 4.16 (dd, *J* 7.9 and 1.8, 0.5H), 4.08–4.00 (m, 1H), 3.95 (dd, *J* 14.0 and 6.4, 0.5H), 3.86 (d, *J* 5.9, 1H), 3.82 (t, *J* 5.1, 0.5H), 3.77–3.69 (m, 1H), 3.20–3.10 (m, 1H), 0.90 (s, 9H), 0.01 (s, 3H) and 0.00 (s, 3H); ν_{max}(KBr)/cm^{-1} 2927, 1736, 1472, 1172, 1098, 839, 752 and 697; *m*/*z* (EI) 444.1 ($M^+ + 1$) and 334.1 ($M^+ -$ SPh) (Found: C, 64.9; H, 7.3; N, 3.2. $C_{24}H_{33}NO_3SSi$ requires C, 64.97; H, 7.50; N, 3.16%).

3-[3-(*tert*-Butyldimethylsilyloxy)-2-(1-naphthyl)propyl]-4-phenylsulfanyl-1,3-oxazolan-2-one 20c

This compound (2.48 g, 50%) was obtained from compound **19c** (4.01 g, 10.0 mmol) as an oil according to the same conditions as above; δ_H 8.11 (d, *J* 8.2, 0.5H), 8.00 (d, *J* 8.2, 0.5H), 7.88–7.85 (m, 1H), 7.76 (t, *J* 8.7, 1H), 7.55–7.28 (m, 9H), 4.67 (t, *J* 5.8, 1H), 4.30–4.20 (m, 1H), 4.20–4.15 (m, 1H), 4.15–4.06 (m, 2H), 4.06–3.78 (m, 3H), 0.90 (s, 9H), 0.04 (s, 3H) and 0.03 (s, 3H); ν_{max}(neat)/cm^{-1} 3055, 1762, 1471, 1412, 1255, 1092, 838 and 779; *m*/*z* (EI) 494.1 ($M^+ + 1$) and 436.0 ($M^+ - {}^t$Bu) (HRMS, Found: M^+, 436.139. $C_{28}H_{35}NO_3SSi$ requires *M*, 436.1403).

3-[3-Hydroxy-2-(2-methoxyphenyl)propyl]-4-phenylsulfanyl-1,3-oxazolan-2-one 21a

A mixture of siloxane **20a** (4.73 g, 10.0 mmol), Amberlyst (1.00 g) and methanol (75 cm^3) was heated under reflux for 15 h. After removal of Amberlyst by filtration, the solvent was evaporated off *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (2:1) gave *title compound* **21a** (3.13 g, 87%) as an oily diastereomeric mixture δ_H 7.38–7.32 (m, 5H), 7.32–7.19 (m, 1H), 7.13–7.10 (m, 1H), 6.96–6.86 (m, 2H), 4.74–4.68 (m, 0.5H), 4.48–4.39 (m, 1H), 4.36–4.29 (m, 0.5H), 4.29–4.20 (m, 1H), 4.03–3.96 (m, 1H), 3.90–3.86 (m, 2H), 3.83 (s, 3H), 3.80–3.74 (m, 1H), 3.65–3.55 (m, 0.5H) and 3.51–3.41 (m, 0.5H); δ_C 157.3 (0.5 carbon), 157.2 (0.5 carbon), 135.3 (0.5 carbon), 135.0 (0.5 carbon), 129.6 (0.5 carbon), 129.4 (0.5 carbon), 128.9 (0.5 carbon), 128.8 (0.5 carbon), 128.3, 127.6, 127.3, 120.9, 110.7, 68.2 (0.5 carbon), 68.0 (0.5 carbon), 65.4 (0.5 carbon), 64.4 (0.5 carbon), 63.3 (0.5 carbon), 62.6 (0.5 carbon), 55.4 (0.5 carbon), 55.3 (0.5 carbon), 42.1 (0.5 carbon), 41.4 (0.5 carbon), 39.9 (0.5 carbon) and 39.2 (0.5 carbon); ν_{max}(KBr)/cm^{-1} 3447, 2360, 1747, 1244 and 1027; *m*/*z* (EI) 360.1 ($M^+ + 1$) and 250.0 ($M^+ -$ SPh) (HRMS, Found: $M^+ -$ SPh, 250.1050. $C_{13}H_{16}NO_4$ requires *m*/*z* 250.1079).

3-(3-Hydroxy-2-phenylpropyl)-4-phenylsulfanyl-1,3-oxazolan-2-one 21b

This compound (2.29 g, 72%) was obtained from compound **20b** (4.43 g, 10.0 mmol) as an oil according to the same conditions as above; δ_H 7.34–7.04 (m, 10H), 4.43–4.39 (m, 1H), 4.34–4.26 (m, 1H), 4.17–4.11 (m, 1H), 4.10–4.00 (m, 0.5H), 3.97–3.86 (m, 1H), 3.81–3.60 (m, 3H) and 3.59–3.51 (m, 0.5H); δ_C 157.7 (0.5 carbon), 157.1 (0.5 carbon), 140.0 (0.5 carbon), 139.2 (0.5 carbon), 135.2 (0.5 carbon), 135.0 (0.5 carbon), 129.5 (2 carbon), 128.8 (2 carbon), 128.6, 128.5, 128.0, 127.8, 127.6 (0.5 carbon), 127.4 (0.5 carbon), 127.3, 68.2 (0.5 carbon), 67.9 (0.5 carbon), 65.4 (0.5 carbon), 64.7 (0.5 carbon), 64.3 (0.5 carbon), 63.3 (0.5 carbon), 46.0 (0.5 carbon), 45.9 (0.5 carbon), 43.5 (0.5 carbon) and 43.0 (0.5 carbon); ν_{max}(neat)/cm^{-1} 3451, 3060, 1752, 1418, 1217, 1070, 1039, 752 and 702; *m*/*z* (EI) 330.1 ($M^+ + 1$) and 220.1 ($M^+ -$ SPh) (HRMS, Found: $M^+ -$ SPh, 220.0973. $C_{12}H_{14}NO_3$ *m*/*z*, requires 220.0974).

3-[3-Hydroxy-2-(1-naphthyl)propyl]-4-phenylsulfanyl-1,3-oxazolan-2-one 21c

This compound (2.80 g, 74%) was obtained from compound **20c** (4.93 g, 10.0 mmol) as an oil according to the same conditions as above; δ_H 8.09–8.00 (m, 1H), 7.85–7.80 (m, 1H), 7.80–7.65 (m, 1H), 7.54–7.10 (m, 9H), 4.41–4.32 (m, 1H), 4.32–4.21 (m, 1H), 4.21–4.07 (m, 3H) and 4.07–3.80 (m, 3H); δ_C 157.9 (0.5 carbon), 157.3 (0.5 carbon), 136.1, 135.2, 134.8, 134.7, 134.0, 129.6, 129.5, 129.4, 129.2 (0.5 carbon), 129.1 (0.5 carbon), 127.9, 127.8 (0.5 carbon), 126.7 (0.5 carbon), 126.5, 125.8, 125.5 (0.5 carbon), 125.3 (0.5 carbon), 123.8, 122.5, 68.6, 68.0 (0.5 carbon), 67.9 (0.5 carbon), 64.7 (0.5 carbon), 64.4 (0.5 carbon), 46.1 and 40.0; ν_{max}(neat)/cm^{-1} 2360, 1747, 1472, 1418, 1217, 1039 and 780; *m*/*z* (EI) 380.10 ($M^+ + 1$) and 270.0 ($M^+ -$ SPh) (HRMS, Found: $M^+ -$ SPh, 270.1137. $C_{16}H_{16}NO_3$ requires *m*/*z*, 270.1130).

3-[2-Formyl-2-(2-methoxyphenyl)propyl]-4-phenylsulfanyl-1,3-oxazolan-2-one 22a

DMSO (1.88 cm^3, 24 mmol) was added to a stirred solution of oxalyl dichloride (1.46 cm^3, 11.5 mmol) in methylene dichloride (10 cm^3) at −78 °C. After 15 min, a solution of the alcohol **21a** (3.59 g, 10.0 mmol) in methylene dichloride (5 cm^3) was slowly added to the mixture at −78 °C. After the mixture had been stirred for 1 h at the same temperature, triethylamine (4.05 cm^3, 40 mmol) was added. The mixture was warmed to rt and kept for 2 h, and then was diluted with water (10 cm^3). The mixture was extracted with chloroform. The extract was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (4:1) gave *title compound* **22a** (3.40 g, 95%) as an oil; δ_H 9.58 (s, 0.5H), 9.54 (s, 0.5H), 7.50–6.80 (m, 9H), 5.23–5.18 (m, 1H), 4.52–3.98 (m, 3H), 3.89–3.68 (m, 1H), 3.76 (s, 3H) and 3.52–3.30 (m, 1H); ν_{max}(neat)/cm^{-1} 2360, 1757, 1494 and 1250; *m*/*z* (EI) 358.0 ($M^+ + 1$) and 248.1 ($M^+ -$ SPh) (HRMS, Found: $M^+ -$ SPh, 248.0929. $C_{13}H_{14}NO_4$ requires *m*/*z*, 248.0923).

3-(2-Formyl-2-phenylpropyl)-4-phenylsulfanyl-1,3-oxazolan-2-one 22b

This compound (3.01 g, 92%) was obtained from compound **21b** (3.29 g, 10.0 mmol) as an oil according to the same conditions as above; δ_H 9.64 (s, 0.5H), 9.63 (s, 0.5H), 7.42–7.01 (m, 10H), 5.15–5.05 (m, 0.5H), 4.42–4.33 (m, 0.5H), 4.24–4.16 (m, 1H), 4.16–4.01 (m, 2H), 3.96–3.89 (m, 1H), and 3.81–3.62 (m, 1H); ν_{max}(neat)/cm^{-1} 1757, 1413, 1216, 1170, 1038, 752, 701; *m*/*z* (EI) 328.1 ($M^+ + 1$) and 218.1 ($M^+ -$ SPh) (HRMS, Found: $M^+ -$ SPh, 218.0826. $C_{12}H_{12}NO_3$ requires *m*/*z*, 218.0817).

3-[2-Formyl-2-(1-naphthyl)propyl]-4-phenylsulfanyl-1,3-oxazolan-2-one 22c

This compound (3.28 g, 87%) was obtained from compound **21c** (3.79 g, 10.0 mmol) as an oil according to the same conditions as above; δ_H 9.71 (s, 0.5H), 9.70 (s, 0.5H), 8.31 (s, 0.5H), 8.30 (s, 0.5H), 7.85–7.75 (m, 2H), 7.61–7.53 (m, 1H), 7.51–7.45 (m, 2H), 7.40–7.37 (m, 1H), 7.37–7.11 (m, 5H), 5.30 (dd, *J* 8.2

and 3.2, 0.5H), 4.98 (dd, *J* 10.2 and 3.9, 0.5H), 4.44 (dd, *J* 9.8 and 8.2, 0.5H), 4.25 (dd, *J* 12.8 and 3.2, 0.5H), 4.06–3.95 (m, 2H), 3.92–3.82 (m, 1H), 3.72–3.67 (m, 1H); ν_{max}(neat)/cm^{-1} 2362, 1752, 1412, 1212, 1070 and 782 cm^{-1}, *m*/*z* (EI) 377.0 (M^+) and 268.1 ($M^+ - SPh$) (HRMS, Found: M^+, 377.1098. $C_{22}H_{19}NO_3S$ requires *M*, 377.1086).

Diethyl [(*E*)-3-(2-methoxyphenyl)-4-(2-oxo-4-phenylsulfanyl-1,3-oxazolan-3-yl)but-1-enyl]phosphonate 23a

To a solution of tetraethyl methylenebisphosphonate in THF (35 cm^3) was added a solution of 1.6 M ^{n}BuLi in hexane (12.0 mmol) at −30 °C in small portions. The mixture was stirred for 0.5 h and to this solution was added a solution of aldehyde **22a** (3.57 g, 10.0 mmol) in THF (7 cm^3) at −78 °C. After being stirred at 10 °C for 5 h, the mixture was quenched with aq. ammonium chloride (15 cm^3) and extracted with ethyl acetate. The extract was dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on silica gel [hexane–ethyl acetate (50 : 1)] to give title phosphonate **23a** (3.47 g, 71%) as an oil; δ_H 7.44–7.33 (m, 7H), 7.27–7.24 (m, 1H), 7.16–7.13 (m, 1H), 6.97–6.87 (m, 1H), 5.85–5.63 (m, 1H), 4.90 (dd, *J* 8.1 and 3.2, 0.5H), 4.36–4.30 (m, 0.5H), 4.28–3.98 (m, 9H), 3.82 (s, 1.5H), 3.81 (s, 1.5H) and 1.49–1.36 (m, 6H); δ_C 156.7 (0.5 carbon), 156.2 (0.5 carbon), 151.2 (0.5 carbon), 150.8 (0.5 carbon), 134.9 (0.5 carbon), 134.7 (0.5 carbon), 129.2 (2 carbons), 129.1, 129.0, 128.8, 128.6, 128.4, 128.2, 128.1, 119.8 (0.5 carbon), 119.4 (0.5 carbon), 117.7 (0.5 carbon), 117.3 (0.5 carbon), 67.6 (0.5 carbon), 67.4 (0.5 carbon), 64.2 (0.5 carbon), 64.1 (0.5 carbon), 61.7, 61.4 (2 carbons), 55.0, 43.4 (0.5 carbon), 43.3 (0.5 carbon) and 16.0 (2 carbons); δ_P 19.02; ν_{max}(neat)/cm^{-1} 2982, 1757, 1494, 1246, 1026, 964 and 754; *m*/*z* (EI) 492.1 ($M^+ + 1$) and 382.1 ($M^+ - SPh$) (Found: $M^+ - SPh$, 382.1410. $C_{18}H_{25}NO_6P$ requires *m*/*z*, 382.1420).

Diethyl [(*E*)-4-(2-oxo-4-phenylsulfanyl-1,3-oxazolan-3-yl)-3-phenylbut-1-enyl]phosphonate 23b

This compound (3.31 g, 72%) was obtained from aldehyde **22b** (3.57 g, 10.0 mmol) as an oil according to the same conditions as above; δ_H 7.26–6.87 (m, 10H), 6.78–6.61 (m, 1H), 5.62–5.45 (m, 1H), 4.11–4.06 (m, 1H), 3.99–3.92 (m, 1H), 3.92–3.72 (m, 6H), 3.67–3.55 (m, 1H), 3.53–3.44 (m, 1H) and 1.18–1.01 (m, 6H); δ_C 156.4 (0.5 carbon), 156.3 (0.5 carbon), 151.4 (0.5 carbon), 150.8 (0.5 carbon), 135.1, 129.5, 129.4, 129.0, 128.6, 128.4, 128.2, 127.9, 127.7, 127.6, 127.5, 120.5 (0.5 carbon), 120.1 (0.5 carbon), 118.7 (0.5 carbon), 118.3 (0.5 carbon), 67.8 (0.5 carbon), 67.6 0.5 carbon), 64.7, 61.8, 61.7, 48.3 (0.5 carbon), 48.0 (0.5 carbon), 45.2 (0.5 carbon), 45.0 (0.5 carbon), 16.3 and 16.2; δ_P 18.51; ν_{max}(neat)/cm^{-1} 1757, 1416, 1242, 1052, 1025, 965, 751 and 702; *m*/*z* (EI) 462.1 ($M^+ + 1$) and 352.1 ($M^+ - SPh$) (HRMS, Found: $M^+ - SPh$, 352.1314. $C_{17}H_{23}NO_5P$ requires *m*/*z*, 352.1314).

Diethyl [(*E*)-3-(1-naphthyl)-4-(2-oxo-4-phenylsulfanyl-1,3-oxazolan-3-yl)but-1-enyl]phosphonate 23c

This compound (3.68 g, 72%) was obtained from aldehyde **22c** (3.77 g, 10.0 mmol) as an oil according to the same conditions as above; δ_H 8.03–7.93 (m, 1H), 7.86–7.70 (m, 2H), 7.52–7.14 (m, 9H), 7.15–6.94 (m, 1H), 5.91–5.61 (m, 1H), 4.89–4.50 (m, 2H), 4.33–3.73 (m, 8H) and 1.38–1.12 (m, 6H); δ_C 156.3 (0.5 carbon), 156.0 (0.5 carbon), 151.1 (0.5 carbon), 150.9 (0.5 carbon), 135.0, 129.4, 129.3, 129.2, 128.9, 128.8, 128.7, 128.2, 128.1, 128.0, 126.4, 125.8, 125.6, 125.3, 125.2, 124.3, 120.5 (0.5 carbon), 120.1 (0.5 carbon), 118.6 (0.5 carbon), 118.2 (0.5 carbon), 67.7 (0.5 carbon), 67.6 (0.5 carbon), 65.0 (0.5 carbon), 64.4 (0.5 carbon), 61.6, 61.5, 45.4, 44.6 and 16.0 (2 carbons); δ_P 18.58; ν_{max}(neat)/cm^{-1} 1756, 1473, 1416, 1244, 1162 and 963; *m*/*z* (EI) 511.1 (M^+) and 402.1 ($M^+ - SPh$) (HRMS, Found: $M^+ - SPh$, 402.1470. $C_{21}H_{25}NO_5P$ *m*/*z*, requires 402.1470).

Diethyl [{(6*S,7*R**,7a*S**)-6-(2-methoxyphenyl)-3-oxoperhydropyrrolo[1,2-*c*][1,3]oxazol-7-yl}methyl]phosphonate 29a**

A solution of tributyltin hydride (0.44 g, 1.50 mmol) in benzene (100 cm^3) and AIBN (16.4 mg, 0.1 mmol) was slowly added to a solution of compound **23a** (0.49 g, 1.0 mmol) in boiling benzene (100 cm^3). After the addition, the mixture was further refluxed for 5 h and was then evaporated. The resulting residue was chromatographed on silica gel. After removal of non-polar material by elution with hexane, elution with ethyl acetate–methanol (50 : 1) gave *title bicycle* **29a** (0.33 g, 86%) as a crystalline product; mp 73–76 °C; δ_H 7.29–7.22 (m, 1H), 7.17–7.11 (m, 1H), 6.98–6.85 (m, 2H), 4.56 (dd, *J* 8.3 and 9.3, 1H), 4.49–4.41 (m, 1H), 4.31 (dd, *J* 6.6 and 9.3, 1H), 4.09–3.93 (m, 5H), 3.81 (s 3H), 3.28–3.14 (m, 2H), 2.91–2.80 (m, 1H), 1.80–1.72 (m, 2H), 1.28 (t, *J* 7.1, 3H) and 1.25 (t, *J* 7.1, 3H); δ_C 160.3, 155.2, 128.6, 127.7, 125.2, 120.8, 110.8, 65.9, 61.8 (2 carbons), 59.3, 55.2, 51.6, 46.6, 41.2, 24.1 (d, J_{CP} 141.6 and 16.3 (2 carbons); δ_P 30.18; ν_{max}(KBr)/cm^{-1} 2998, 1757, 1494, 1392, 1239, 1061, 1024, 964, 761; *m*/*z* (EI) 383.1 (M^+) (Found: C, 56.2; H, 6.8; N, 3.75. $C_{18}H_{26}NO_6P$ requires C, 56.40; H, 6.83; N, 3.65%).

Diethyl{(6*S,7*R**,7a*S**)-(3-oxo-6-phenylperhydropyrrolo[1,2-*c*]-[1,3]oxazol-7-yl)methyl}phosphonate 29b**

The mixture of compound **23b** (0.46 g, 1.0 mmol) was treated with tributyltin hydride (0.44 g, 1.50 mmol) in toluene in the presence of AIBN (16 mg, 0.1 mmol) according to the same method as above. After the addition, the mixture was further refluxed for 5 h and was then evaporated. The resulting residue was chromatographed on silica gel. Non-polar material was removed by elution with hexane, and successive elution with ethyl acetate–methanol (50 : 1) gave *title compound* **29b** (0.30 g, 85%) as a solid; mp 37–39 °C; δ_H 7.32–7.13 (m, 5H), 4.50 (dd, *J* 8.5 and 9.6, 1H), 4.43–4.36 (m, 1H), 4.21 (dd, *J* 6.3 and 9.6, 1H), 4.02–3.89 (m, 5H), 3.14 (dd, *J* 9.4 and 11.9, 1H), 2.87–2.82 (m, 1H), 2.67–2.56 (m, 1H), 1.73–1.66 (m, 2H) and 1.28–1.19 (m, 6H); δ_C 161.0, 138.0, 129.9 (2 carbons), 128.8, 127.5, 127.4, 65.6, 61.8 (2 carbons), 59.2, 52.9, 52.0, 51.9, 43.5, 23.6 (d, J_{CP} 141.8), 16.2 and 16.1; δ_P 29.74; ν_{max}(KBr)/cm^{-1} 2361, 1751, 1397, 1220, 1054, 1024 and 773; *m*/*z* (EI) 353.1 (M^+) and 309.1 ($M^+ - OEt$) (Found: C, 57.5; H, 6.9; N, 4.0. $C_{17}H_{24}NO_5P$ requires C, 57.58; H, 6.85; N, 3.96%).

Radical cyclisation of compound 23c; Synthesis of diethyl [{(6*S,7*R**,7a*S**)-6-(1-naphthyl)-3-oxoperhydropyrrolo[1,2-*c*][1,3]-oxazol-7-yl}methyl]phosphonate 29c and (6*S**,7*R**,7a*R**)-isomer 30c**

A mixture of compound **23c** (0.51 g, 10.0 mmol) and tributyltin hydride (0.44 g, 1.50 mmol) in benzene was heated in the presence of AIBN (16 mg, 0.1 mmol) for 3 h, the solvent was removed, and the resulting residue was chromatographed on silica gel. Elution with ethyl acetate–methanol (50 : 1) afforded a mixture of diastereomers **29c** and **30c**; these were separated on a preparative packed column (Inertsil PREP-SIL, GL science) by elution with hexane–ethyl acetate (11 : 89) at a flow rate of 1.5 cm^3 min^{-1}.

Diethyl [{(6*S,7*R**,7a*S**)-6-(1-naphthyl)-3-oxoperhydropyrrolo-[1,2-*c*][1,3]oxazol-7-yl}methyl]phosphonate 29c**

Retention time t_R 41.28 min; δ_H 8.18 (d, *J* 8.4, 1H), 7.86 (d, *J* 8.0, 1H), 7.78 (d, *J* 8.0, 1H), 7.57–7.39 (m, 4H), 4.58 (dd, *J* 8.6 and 9.4, 1H), 4.53–4.43 (m, 1H), 4.39 (dd, *J* 5.6 and 9.6, 1H), 4.17 (dd, *J* 11.9 and 6.8, 1H), 4.14–4.00 (m, 4H), 3.95 (dd, *J* 14.6 and 7.3, 1H), 3.31 (dd, *J* 11.9 and 7.6, 1H), 2.96–2.86 (m, 1H), 1.91–1.74 (m, 2H), 1.28 (t, *J* 7.1, 3H) and 1.26 (t, *J* 7.1, 3H); δ_C 161.9, 134.4, 133.9, 132.1, 128.9, 128.0, 126.5, 125.9, 125.2, 122.9 (2 carbons), 65.3, 61.9 (2 carbons), 59.7, 52.5, 46.9, 41.6, 24.0 (d, J_{CP} 143.1), 16.3 and 16.2; δ_P 29.88; ν_{max}(neat)/cm^{-1} 2930, 2342, 1752, 1394, 1243, 1025 and 779; *m*/*z* (EI) 403.1 (M^+)

(HRMS, Found: M^+, 403.1547. $C_{21}H_{26}NO_5P$ requires *M*, 403.1549).

Diethyl [{(6*S,7*R**,7a*R**)-6-(1-naphthyl)-3-oxoperhydropyrrolo-[1,2-*c*][1,3]oxazol-7-yl}methyl]phosphonate 30c**

Retention time t_R 51.59 min; mp 117–120 °C; δ_H 8.10 (d, *J* 8.5, 1H), 7.88 (d, *J* 8.5, 1H), 7.78 (d, *J* 8.1, 1H), 7.59–7.33 (m, 4H), 4.57 (dd, *J* 8.8 and 9.3, 1H), 4.37 (dd, *J* 6.3 and 9.3, 1H), 4.27–4.22 (m, 1H), 4.21–4.10 (m, 4H), 4.03–3.95 (m, 1H), 3.64–3.54 (m, 1H), 2.96 (dd, *J* 11.6 and 13.2, 1H), 2.49–2.40 (m, 1H), 2.25–2.04 (m, 2H) and 1.35 (t, *J* 7.1, 6H); δ_C 156.7, 136.7, 134.0, 131.2, 129.1, 127.9, 126.7, 125.9, 125.3, 122.7, 122.5, 67.5, 62.5, 62.3, 54.2, 47.1, 39.7 (d, J_{CP} 141.8), 36.5, 31.2 (d, J_{CP} 141.8), 16.6 and 16.5; δ_P 27.22; ν_{max}(neat)/cm^{-1} 2927, 1758, 1426, 1242, 1051, 965 and 781; *m*/*z* (EI) 403.1 (M^+) (HRMS, Found: M^+, 403.1550. $C_{21}H_{26}NO_5P$ requires $C_{21}H_{26}NO_5P$, *M*, 403.1549).

X-Ray crystallographic analysis on compound 29a

X-ray crystal data of compound **29a** were collected by Mac-Science MXC 18 diffractometers. The structure was solved by direct methods using SIR 92 (Giacovazzo, 1994)[15] and refined with a full matrix least-squares method.

Crystal data of compound 29a. $C_{18}H_{26}O_6P$, $M_r = 383.00$, orthorhombic, space group *Pca* 21, $a = 16.132(7)$, $b = 14.507(7)$, $c = 8.162(6)$, $V = 1910(2)$ Å^3, $T = 298$ K, $Z = 4$, $D_x = 1.331$ Mg cm^{-3}, (Cu-Kα) = 1.54178 Å, $\mu = 15.554$ mm^{-1}, $R = 0.065$ over 1833 independent reflections.‡

***tert*-Butyl (2*S**,3*R**,4*S**)-3-{[ethoxy(methoxy)phosphoryl]-methyl}-2-hydroxymethyl-4-(2-methoxyphenyl)tetrahydro-pyrrole-1-carboxylate 32**

A mixture of bicycle **29a** (0.38 g, 1.0 mmol) and 10% aq. sodium hydroxide (0.5 cm^3) in 1,4-dioxane (8 cm^3) was heated under reflux for 17 h. After the mixture had warmed to 0 °C in an ice-bath, a solution of di-*tert*-butyl dicarbonate (0.52 g, 2.4 mmol) in 1,4-dioxane (8 cm^3) was slowly added to the reaction mixture and stirring was maintained for 2 h. The mixture was then quenched with water and extracted with ethyl acetate. The extract was acidified carefully with 5% hydrochloric acid (0.5 cm^3) and then further extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$), and evaporated *in vacuo*. To a solution of the residue, without purification, in methanol was slowly added a solution of diazomethane in diethyl ether at 0 °C, until the yellow colour persisted. After 20 min, the solvent was evaporated off *in vacuo*, and the residue was chromatographed on silica gel. Elution with chloroform–methanol (20 : 1) gave *title alcohol* **32** (0.209 g, 47%) as an oil; δ_H 7.21–7.03 (m, 2H), 6.87–6.80 (m, 2H), 4.12–4.03 (m, 1H), 3.80 (s, 3H), 3.74–3.71 (m, 1H), 3.71–3.67 (m, 2H), 3.67–3.64 (m, 1H), 3.62 (s, 3H), 3.58–3.23 (m, 2H), 3.03–2.87 (br s, 1H), 2.84 (d, *J* 15.6, 1H), 2.76 (d, *J* 15.6, 1H), 2.01–1.70 (m, 2H), 1.48–1.33 (m, 9H) and 1.28–1.10 (m, 3H); δ_C 170.1, 157.8, 128.5, 128.4, 125.3, 120.8, 110.8, 80.2, 66.5, 66.0, 60.3, 55.4, 54.6, 53.5, 53.1, 43.4, 43.0, 28.3 (3 carbons) and 16.2; δ_P 29.25; ν_{max}(neat)/cm^{-1} 2955, 2342, 1693, 1397, 1247, 1170 and 1028; *m*/*z* (EI) 444.1 ($M^+ + 1$) and 340.9 ($M^+ - Bu^t - CH_2OH - CH_3$) [HRMS, Found: ($M^+ - Bu - CH_2OH - CH_3$), 340.0960. $C_{15}H_{19}NO_6P$ requires *m*/*z*, 340.0950].

1-*tert*-Butyl 2-methyl (2*S,3*R**,4*S**)-3-{[ethoxy(methoxy)-phosphoryl]methyl}-4-(2-methoxyphenyl)tetrahydropyrrole-1,2-dicarboxylate 33**

To a solution of the alcohol **32** (44.30 mg, 0.11 mmol) in a mixture of acetonitrile (1 cm^3), carbon tetrachloride (1 cm^3) and water (1.5 cm^3) was added sodium metaperiodate (93.77 mg, 0.41 mmol). Ruthenium trichloride hydrate (1.0 mg, 0.005 mmol) was added to this biphasic mixture, which was stirred vigorously for 3.5 h at rt and then extracted with chloroform. The extract was dried (Na_2SO_4) and the solvent was evaporated off *in vacuo*. To a solution of the residue (without purification) was added a solution of diazomethane in diethyl ether at 0 °C. After 20 min the solvent was evaporated off *in vacuo*, and the remaining oil was chromatographed on silica gel. Elution with chloroform–methanol (10 : 1) gave *title ester* **33** (19.78 mg, 42%) as an oil; δ_H 7.28–7.06 (m, 2H), 6.97–6.82 (m, 2H), 4.24–4.01 (m, 1H), 4.01–3.58 (m, 13H), 3.51 (d, *J* 11.0, 1H), 3.46 (d, *J* 11.0, 1H), 2.93–2.04 (m, 2H), 1.56–1.37 (m, 9H) and 1.37–1.13 (m, 3H); δ_C 172.7, 158.2, 128.5, 128.4, 125.6, 120.7, 110.7, 80.5, 66.4, 62.1, 61.6, 55.2 (3 carbons), 52.2, 51.9, 51.1, 48.3, 28.3, 28.1, 27.9 and 16.3; δ_P 30.92; ν_{max}(neat)/cm^{-1} 2360, 1698, 1398, 1249, 1028 and 773; *m*/*z* (EI) 471.1 (M^+) and 415.0 ($M^+ - {}^t$Bu) (HRMS, Found: $M^+ - {}^t$Bu, 415.1387. $C_{18}H_{25}NO_8P$ requires *m*/*z*, 415.1396).

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‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/255.