Pergamon

Tetrahedron, Vol. 53, No. 30, pp. 10289-10312, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00682-0

Synthesis of Novel Cyclobutylphosphonic Acids as Inhibitors of Imidazole Glycerol Phosphate Dehydratase†

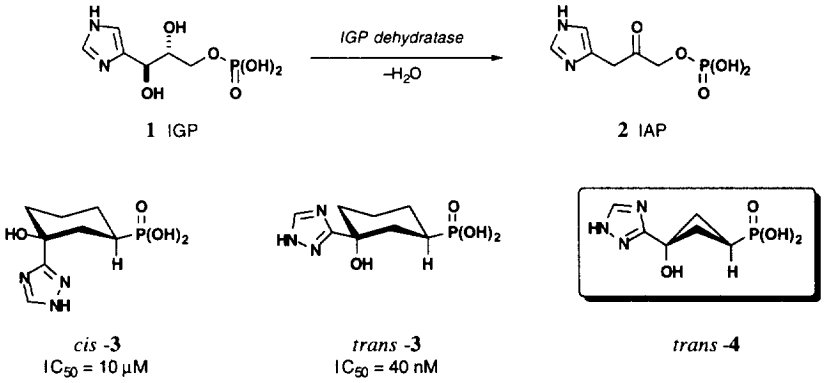
Roger D. Norcross,*,‡a Peter von Matt,‡b Hartmuth C. Kolb‡c and Daniel Bellus*,‡d

Corporate Research Units, Ciba-Geigy AG, CH-4002 Basel, Switzerland

Abstract: Diethyl 3-oxocyclobutylphosphonate (**5**) has been synthesised via a novel one-pot cyclisation reaction of the α-phenylsulphonyl-γ,δ-epoxyphosphonate **8**. Addition of 5-lithio-1-trityl-1,2,4-triazole to ketone **5** and deprotection then afforded *cis*-3-hydroxy-3-(1,2,4-triazol-3-yl)cyclobutylphosphonic acid (*cis*-**4**) which showed modest *in vitro* inhibition of the enzyme imidazole glycerol phosphate dehydratase. In an attempt to obtain the corresponding *trans* isomer (*trans*-**4**), whose inhibitory activity was anticipated to be higher, an efficient three-step synthesis was developed employing base-mediated cyclisation of the γ,δ-epoxy-γ-(1,2,4-triazol-5-yl)phosphonate **35**. Although this latter route stereoselectively afforded *cis*-**36**, an efficient epimerisation reaction could be subsequently used to obtain the desired *trans* stereochemistry. However, all attempts at deprotection of *trans*-**36** proceeded with simultaneous re-epimerisation to give the previously prepared *cis*-**4**. High level *ab initio* calculations have been used to rationalise the relative thermodynamic stability of *cis*-**4** and *trans*-**4**.

INTRODUCTION

It is a well established concept in agrochemical research that herbicidal action may be obtained by inhibition of enzymes involved in the biosyntheis of essential plant amino acids.[1] Since the relevant enzymes are lacking in mammals, this approach to herbicide design promises to be attractive from the point of view of human toxicology. Indeed, commercial herbicides have already been developed[1] which inhibit enzymes involved in the biosynthesis of aromatic amino acids[2] and branched-chain amino acids,[3] and attention is now turning to other amino acid pathways. Several recent reports and patents have documented[4–6] the promising herbicidal activity of rationally designed substrate-based inhibitors of the enzyme *imidazole glycerol phosphate dehydratase* (IGPD, EC 4.2.1.19),[7] an enzyme involved in biosynthesis of the essential plant amino acid histidine.[8] IGPD catalyses the conversion of (2*R*,3*S*)-imidazole glycerol phosphate (IGP, **1** in **Scheme 1**) to imidazole acetol phosphate (IAP, **2**).[7]



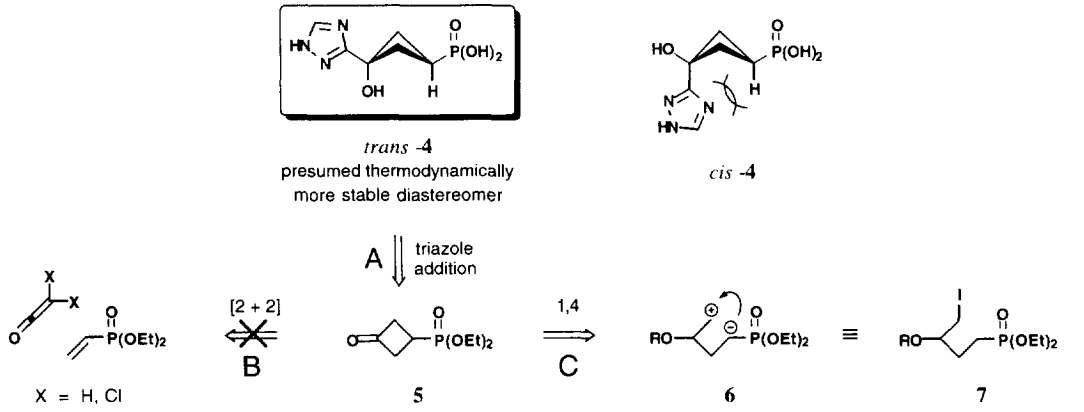
Scheme 1

The triazole phosphonate *trans*-**3** (**Scheme 1**) has recently been reported by scientists at Ciba-Geigy (Japan) as a promising lead compound showing high *in vitro* activity against wheat germ IGPD (IC_{50} = 40 nM) and slow-acting broad spectrum herbicidal activity at post-emergent application rates of 1–4 kg/ha.[4g] Key structural features of *trans*-**3** include (*i*) replacement of the imidazole of IGP by 1,2,4-triazole, (*ii*) replacement of the phosphate of IGP by phosphonate, for added hydrolytic stability,[2b,9] and (*iii*) inclusion of a cyclohexane ring to optimise inhibitory activity by restriction of conformational flexibility. Analysis of ^{1}H NMR coupling constants revealed that the cyclohexane ring of *trans*-**3** adopts a chair conformation in which the sterically demanding phosphonic acid and triazole substituents are both equatorially disposed and thus held in an extended conformation relative to each other. Note that the *cis* diastereomer, i.e. *cis*-**3**, is significantly less active.[4g]

In an attempt to improve on the inhibitory potency of *trans*-**3**, and thus achieve herbicidal activity at lower application rates, computer-aided molecular modelling (CAMM) analysis was undertaken based on correlation of the observed structure-activity relationships (SAR) of 50 already synthesised IGPD inhibitors and taking into account conformational, steric, electronic and hydrophobic parameters. The CAMM-SAR analysis predicted that the cyclobutane compound *trans*-**4** should be an extremely potent inhibitor of IGPD (predicted: IC_{50} = 1 nm, herbicidal activity = 530 g/ha).[10] *trans*-**4** is additionally attractive as a synthetic target since it possesses a plane of symmetry and is thus achiral, in contrast to *trans*-**3**.[11] This paper describes attempts to develop an efficient synthesis of *trans*-**4**, using novel methodology, and presents associated biological results.

Retrosynthetic Analysis and Synthetic Strategy

It was anticipated that the desired stereochemistry of *trans*-**4**, wherein the sterically demanding triazole and phosphonate substituents may both adopt pseudo-equatorial positions on the puckered[12] cyclobutane ring, would be thermodynamically favoured over the stereochemistry of *cis*-**4** wherein energetically unfavourable 1,3-diaxial interactions across the cyclobutane ring were expected to be more severe.[13,14] Accordingly, it was foreseen that *trans*-**4** would be selectively accessible via addition of a suitably protected 5-metallated-1,2,4-triazole nucleophile to the 3-phosphonocyclobutanone **5** (disconnection **A** in **Scheme 2**).[15] A short and practical synthesis of the key intermediate **5** was thus required.



Scheme 2

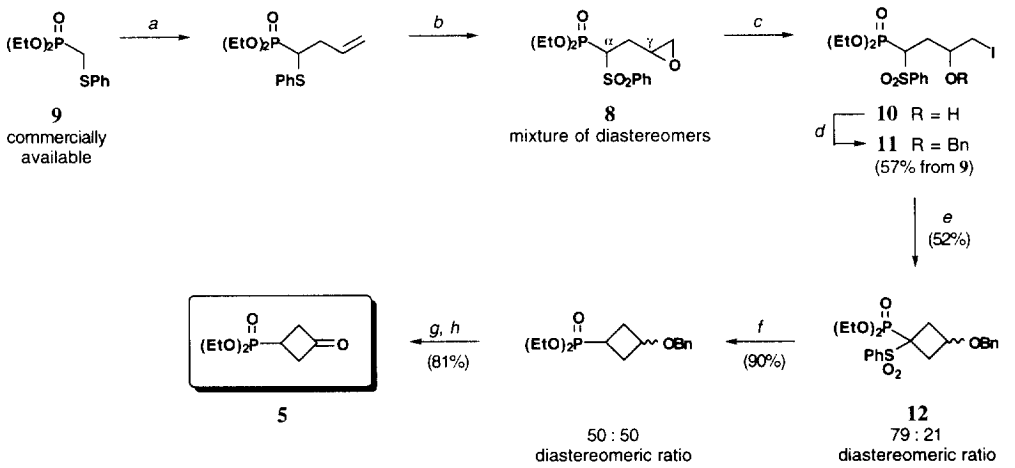
The synthesis of cyclobutanones, especially those bearing relatively few substituents, still represents a considerable challenge in organic chemistry, and to date there have been few universally applicable methods.[16] For instance, while [2 + 2] cycloaddition of olefins and ketenes is an efficient procedure for preparing cyclobutanones when using an electron-rich ketenophile,[17] this method is unsuitable when there is

an electron-withdrawing substituent on the ketenophile, as in the case of the vinylphosphonate required for **5** (disconnection **B** in **Scheme 2**). However, by exploiting the well known carbanion-stabilising ability of the phosphonate group,[18] the alternative scenario of a 1,4-cyclisation strategy employing a synthon such as **6** appeared to be an attractive option (disconnection **C**). It was thus anticipated that the desired 3-oxocyclobutylphosphonate **5** might be accessible via base-mediated cyclisation of the protected iodohydrin **7**, which serves as a suitable synthetic equivalent of synthon **6** and ought to be readily available from the corresponding γ,δ-epoxyphosphonate.[19,20] We elected to investigate this novel strategy forthwith.

RESULTS AND DISCUSSION

Strategy 1: Cyclisation Prior to Triazole Addition

Preliminary experiments revealed that an additional anion-stabilising group besides phosphonate was required for optimum cyclisation yields.[21] Accordingly, the α-phenylsulphonyl-γ,δ-epoxyphosphonate **8** was identified as a suitable iodohydrin precursor (**Scheme 3**). **8** was readily prepared by *n*-butyllithium-mediated allylation of commercially available diethyl (phenylsulphanyl)methylphosphonate (**9**)[22] followed by epoxidation and concomitant sulphide oxidation using *meta*-chloroperbenzoic acid (*m*-CPBA).[20b] **8** was obtained as a mixture of diastereomers which was not separated. Smooth conversion to the desired iodohydrin **10** was effected with complete regioselectivity (as determined by ^1H and ^{31}P NMR analysis of the crude reaction mixture) by means of tetrabutylammonium iodide and $BF_3{\cdot}OEt_2$.[23] Protection of the iodohydrin hydroxyl[24] under mildly acidic conditions[25,26] then afforded the desired cyclisation substrate **11**. Purification using flash chromatography on silica gel need only be performed at this final stage, and in this way **11** was obtained in 57% overall yield over the four steps from **9**.

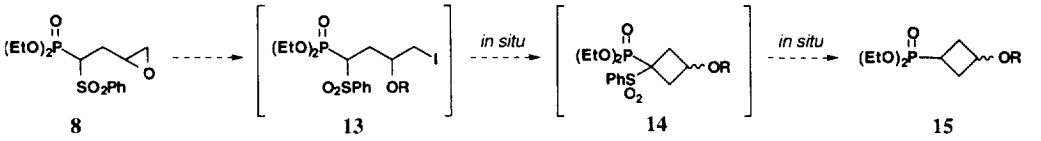


Scheme 3 (*a*) (i) ^{n}BuLi, THF, −78 °C; (ii) allyl bromide, → 0 °C; (*b*) *m*-CPBA, CH_2Cl_2, 40 °C; (*c*) $^n Bu_4NI$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C → RT; (*d*) $Cl_3CC(=NH)OBn$, cat. TfOH, Et_2O, RT; (*e*) KHMDS, THF, −78 °C → 0 °C → RT; (*f*) 2% Na(Hg), Na_2HPO_4, THF/MeOH, 0 °C; (*g*) H_2 (1 atm), 10% Pd/C, $^iPr_2O$, RT; (h) Jones oxidation, Me_2CO, 0 °C.

Gratifyingly, base-mediated 1,4-cyclisation of the protected iodohydrin **11** using potassium hexamethyldisilylazide (KHMDS) proceeded smoothly (deprotonation at −78 °C, followed by gradual warming to room temperature to effect ring-closure) to afford good yields of the cyclobutane **12**, which was obtained as a 79:21 mixture of diastereomers.[27] Reductive removal of the α-sulphonyl substituent using sodium amalgam,[28] which occurred not surprisingly with stereochemical scrambling, followed by hydrogenolysis of the benzyl ether and oxidation of the resulting alcohol, then supplied the desired

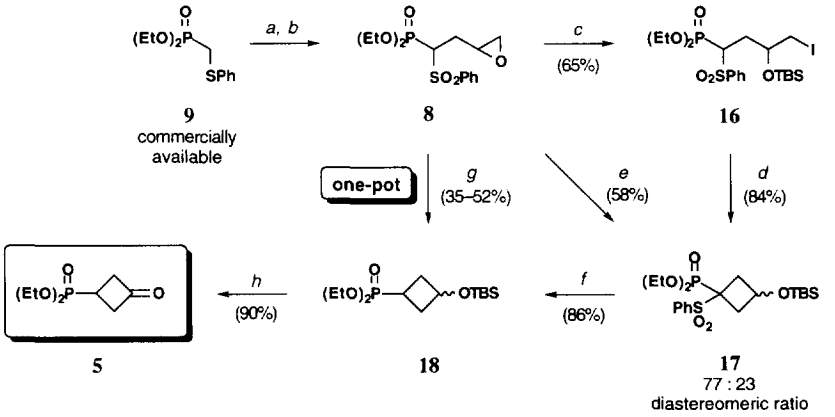
3-oxocyclobutylphosphonate **5** (characteristic[29] ν_{max} = 1 791 cm^{-1}), in an overall yield of 38% over the four steps from **11**.

It was a major aim, however, to develop a shorter synthetic route to ketone **5**. To this end, it was conceptualised that the use of an alternative choice of protecting group on the iodohydrin hydroxyl might allow direct formation of a protected iodohydrin from its epoxide precursor (i.e. **8** → **13** in **Scheme 4**), saving one synthetic step. A further goal would be to achieve *in situ* cyclisation of the protected iodohydrin (thus saving another synthetic step), and, if possible, to accomplish *in situ* desulphonation as well (i.e. **8** → **13** → **14** → **15** all in the same pot). We were delighted to discover that the selection of *tert*-butyldimethylsilyl (TBS) as hydroxyl protecting group allowed this ambitious strategy to be fully realised.



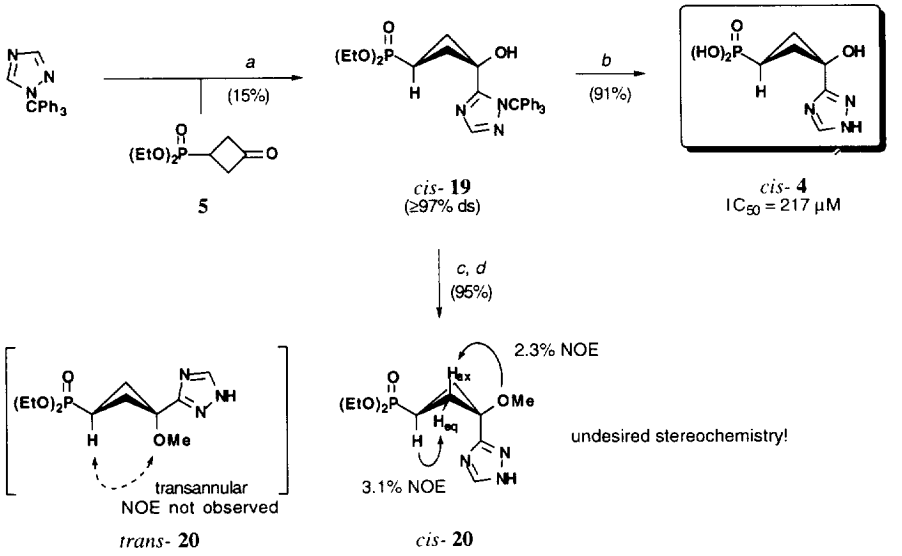
Scheme 4

Thus, by replacing the Lewis acid BF_3•OEt_2 (used in conjunction with $^nBu_4NI$ in the formation of iodohydrin **10**) with TBS triflate, and changing the reaction solvent from dichloromethane to THF, the protected iodohydrin **16** could be directly prepared from epoxide **8** (**Scheme 5**). This convenient reaction presumably proceeds via *in situ* generation of TBS iodide,[30] which in this instance does not appear to solicit the potential side reaction of phosphonate deprotection.[31] Iodohydrin **16** underwent subsequent KHMDS-mediated cyclisation to afford the cyclobutane **17** in excellent yield (84%). Moreover, by adding the base directly to the iodohydrin-forming reaction, the desired one-pot conversion of epoxide **8** to cyclobutane **17** could be accomplished in good yield. Finally, by adopting lithium naphthalenide as desulphonating agent,[32] one-pot conversion of epoxide **8** to cyclobutane **18** was possible, providing **18** in only three steps from commercial starting material (35–52% overall yield). Conversion of **18** to the desired cyclobutanone **5** was then effected by a one-pot deprotection-oxidation procedure.[33]



Scheme 5 (*a*) (i) ^{n}BuLi, THF, −78 °C; (ii) allyl bromide, → 0 °C; (*b*) *m*-CPBA, CH_2Cl_2, 40 °C; (*c*) $^nBu_4NI$, TBSOTf, THF, 0 °C; (*d*) KHMDS, THF, −78 °C → 0 °C → RT; (*e*) (i) $^nBu_4NI$, TBSOTf, THF, 0 °C; (ii) KHMDS, → RT; (*f*) 2% Na(Hg), Na_2HPO_4, THF/MeOH, 0 °C; (*g*) (i) $^nBu_4NI$, TBSOTf, THF, 0 °C; (ii) KHMDS, → RT; (iii) lithium naphthalenide, −78 °C; (*h*) (i) 1 mol% $(MeCN)_2PdCl_2$, Me_2CO, RT or 10 mol% *p*-TsOH, Me_2CO/H_2O, RT; (ii) Jones oxidation, 0 °C.

With cyclobutanone **5** in hand, triazole addition could now be investigated. Following the earlier work on the cyclohexane analogue *trans* -**3**,[4g] 5-lithio-1-trityl-1,2,4-triazole,[34] prepared by treatment of 1-trityl-1,2,4-triazole with *n*-butyllithium, was added to the 3-phosphonocyclobutanone **5** (**Scheme 6**). Disappointingly, this reaction proceeded in only 15% yield (*cf.* 50% yield for addition to unsubstituted cyclobutanone,[35] 70% yield for addition to cyclohexanone,[35] and 64% yield for addition to 3-phosphonocyclohexanone[4g]).[36] Not unexpectedly, the reaction proceeded with extremely high diastereoselectivity (≥97% ds by inspection of ^{1}H and ^{31}P NMR of crude reaction mixture, *cf.* 89% ds for the cyclohexane analogue[4g]), but we were astonished to learn (*vide infra*) that in this case the reaction stereoselectively delivered the *cis* diastereomer, i.e. *cis*-**19**, in total contrast to the cyclohexane case wherein the *trans* isomer was preferentially produced.[4g] The use of a sterically less demanding protecting group on the triazole in place of trityl, such as benzyloxymethyl (BOM), changed neither the yield nor the stereochemical course of the addition reaction.



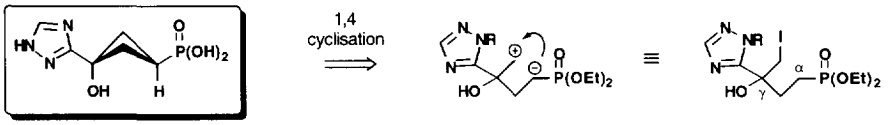
Scheme 6 (*a*) (i) 1-trityl-1,2,4-triazole, ^{n}BuLi, THF, –78 °C; (ii) **5**; (*b*) (i) TMSBr, CH_2Cl_2, RT; (ii) MeOH; (iii) propylene oxide; (*c*) (i) NaH, THF, RT; (ii) MeI; (*d*) H_2 (1 atm), 10% Pd/C, THF, RT.

The stereochemistry of *cis*-**19** was proven after methylation of the hydroxyl and subsequent hydrogenolytic removal of the trityl to obtain *cis*-**20**, which had a ^{1}H NMR spectrum in methanol sufficiently dispersed to permit NOE measurements. A transannular NOE between the methoxy and phosphonate α-proton would be indicative of *trans* relative stereochemistry. However, the observed NOE enhancements, whereby irradiation of the methoxy protons and the proton α to the phosphonate led to mutually exclusive enhancements for the axial and equatorial methylene protons, respectively, on the cyclobutane ring, were consistent with the *cis* stereochemistry shown (**Scheme 6**). This stereochemical assignment was later also confirmed by X-ray crystallographic analysis (*vide infra*).

Deprotection of *cis*-**19** was effected by treatment with TMSBr.[4g,37] The resulting phosphonic acid *cis*-**4** exhibited moderate *in vitro* inhibition of IGPD, with an IC_{50} value of 217 μM.[38] Inspection of **Scheme 1** reveals that this level of activity is comparable with the cyclohexane analogy, wherein a 1000-fold difference in potency between the *cis* and *trans* diastereomers is observed. Thus, at this juncture, although we had succeeded in developing efficient novel synthetic methodology for the preparation of the cyclobutane targets, we had been unable to obtain the desired *trans* diastereomer with its anticipated nM activity. A fundamental revision of synthetic strategy was therefore mandated.[39]

Strategy 2: Triazole Addition Prior to Cyclisation

It was decided to evaluate a revised approach whereby the order of the key C—C bond-forming reactions would be reversed, *i.e.* triazole addition would now be performed *prior to* cyclisation. In this way, it was hoped that the new cyclisation substrate (represented by synthon **21**, **Scheme 7**) might display a different sense of stereoselectivity compared to the previous route. Examination of the required iodohydrin **22** reveals that there is no longer an acidic hydrogen at the γ position, and so it appeared reasonable that selective deprotonation at the α position would no longer require additional activation of that position by means of the sulphone group.[40] In addition, since the hydroxyl is now tertiary (as opposed to secondary as in the previous cyclisation substrates **11** and **16**), it was anticipated that the corresponding alcoholate would be markedly less nucleophilic and so might not require protection in the cyclisation reaction. These two factors combined meant that the new route appeared extremely concise.



trans-**4**
presumed thermodynamically more stable diastereomer

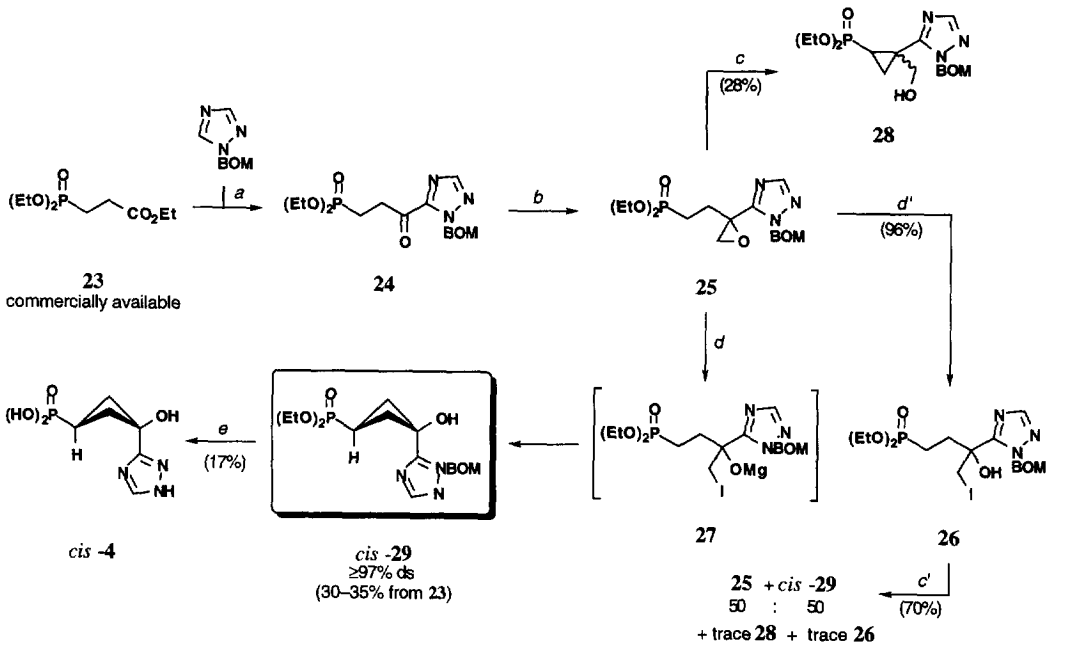
21 **22**

Scheme 7

Preparation of the new cyclisation substrate was straightforward. Thus, addition of 5-lithio-1-BOM-1,2,4-triazole to the commercially available phosphonate ester **23** occurred cleanly to afford ketone **24**, with no signs of double-addition of the triazole moiety (**Scheme 8**). Conversion of ketone **24** to its corresponding epoxide **25** was then effected most conveniently by means of sulphur ylid addition under phase-transfer conditions (50% aqueous $NaOH/CH_2Cl_2$).[41] Note that phosphonate hydrolysis was insignificant despite the high concentration of base present in the reaction medium.[42] Transformation of epoxide **25** to the iodohydrin cyclisation substrate **26** was unfortunately not possible using our previous conditions ($^nBu_4NI$, TBSOTf),[43] but was readily accomplished by treatment with MeMgI (1.3 equiv., warming only to 0 °C before work-up). We were delighted to discover that addition of excess Grignard reagent to the iodohydrin-forming reaction mixture, followed by slow warming to room temperature, effected *in situ* cyclisation to afford a single diastereomer of a cyclobutane product in good yield (30–35% over the three steps from **23**, with silica gel chromatography unnecessary until this point).[44] Use of the Grignard reagent as the base in this cyclisation reaction is critical to the course of the reaction: the *in situ* formed magnesium alkoxide **27** derived from iodohydrin **26** does not revert to epoxide **25** under the reaction conditions, and so only 1,4-cyclisation is observed. In contrast, if KHMDS (*i.e.* a base with a harder metal counter-ion) is subsequently used to cyclise iodohydrin **26**, significant re-formation of epoxide **25** and, in part, ensuing 1,3-cyclisation to afford the cyclopropane **28** is observed

We were disappointed to learn that the 1,4-cyclisation had in fact proceeded to form exclusively the unwanted *cis* diastereomer, *i.e.* *cis*-**29** as depicted in **Scheme 8**. This was proven by X-ray analysis of the crystalline product.[45,46] The unit cell was found to contain two crystallographically independent molecules **A** and **B**, each having very similar conformations (depicted in **Fig. 1**) and hydrogen bonded together through the phosphonate and hydroxyl (P=O···H–O) so as to form noncrystallographically centrosymmetric dimers (**Fig. 2**). In both **A** and **B** the cyclobutane ring is puckered slightly as expected[12] (pucker angle 28.4° for **A**, 29.1° for **B**) with the sterically demanding phosphonate group in a pseudo-equatorial orientation. Note that the triazole group is pseudo-axially disposed, however, and not pseudo-equatorial as had been anticipated originally (*vide supra*).[47]

At this juncture, an extremely efficient three-step synthesis of *cis*-**29** had been developed, but the desired *trans* diastereomer was proving extraordinarily elusive. Since the route to *cis*-**29** from **23** was so concise, however, an investigation of possible epimerisation procedures was thought justified.



Scheme 8 (*a*) (i) 1-BOM-1,2,4-triazole, ^{n}BuLi, THF, –78 °C; (ii) add to **23**; (*b*) $Me_3S^+.MeSO_4^-$, 50% aq. NaOH, CH_2Cl_2, 50 °C; (*c*) KHMDS, THF, –20 °C; (*c'*) KHMDS, THF, 0 °C; (*d*) MeMgI (4 equiv.), THF, –78 °C → RT; (*d'*) MeMgI (1.3 equiv.), THF, –78 °C → 0 °C; (*e*) (i) TMSBr, CH_2Cl_2, RT; (ii) MeOH; (iii) propylene oxide.

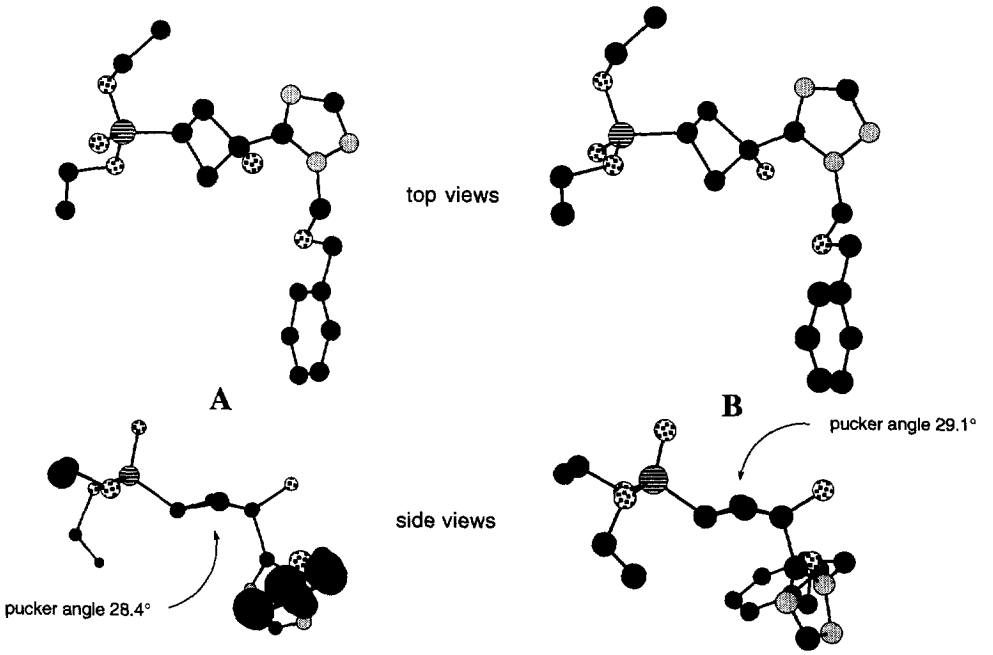


Fig. 1 X-ray crystal structure of *cis*-**29**

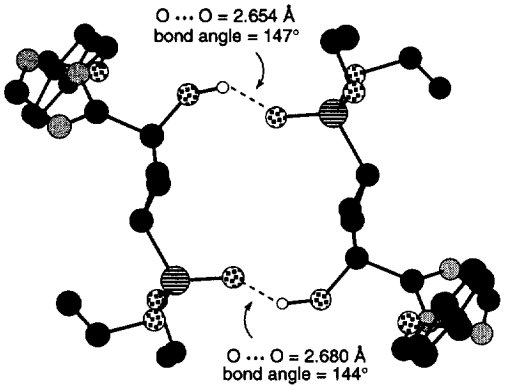
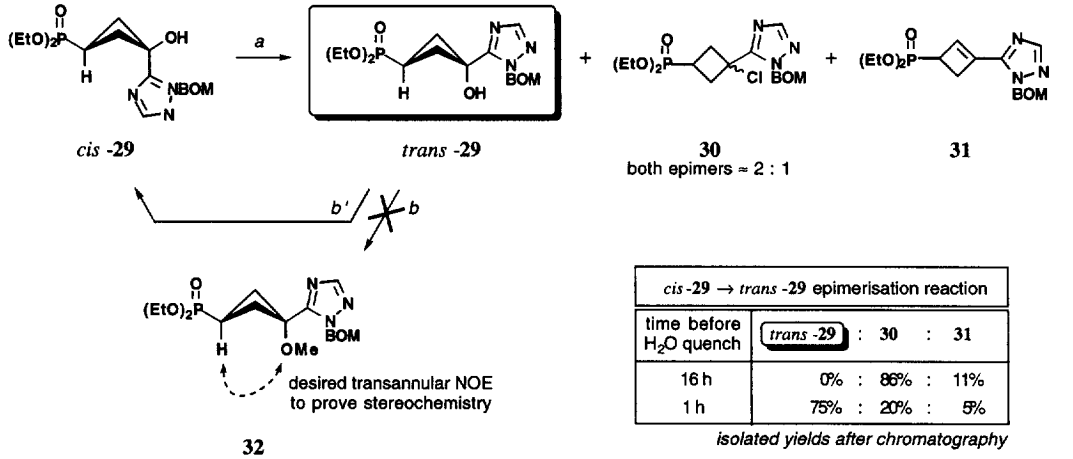


Fig. 2 H-bonded dimer in X-ray crystal structure of *cis*-**29**

In the event, epimerisation of *cis*-**29** to its *trans* isomer proved unexpectedly straightforward. Thus, treatment of *cis*-**29** with thionyl chloride in pyridine, followed by aqueous work-up after a short time (15 min – 1 hour), afforded a 75% yield of the desired *trans*-**29** (HRMS identical, ^{1}H NMR spectrum similar but not identical to starting material), together with a 20% yield of both epimers of the chlorides **30** and a small amount (5%) of the elimination product **31** (**Scheme 9**).[48] Note that leaving the reaction for a longer time (16 h) before aqueous work-up yielded predominantly the chlorination products **30**, together with olefin **31** and *none* of the alcohol epimer *trans*-**29**. Thus it would appear that an initial intermediate is formed in the reaction which is capable of breaking down with exclusive stereochemical inversion on contact with water, and which is otherwise slowly intercepted by chloride ion after prolonged reaction time.[49] In contrast, the cyclohexane analogue gives predominantly the elimination product under similar reaction conditions.[50]

Attempts to derivatise *trans*-**29** as its methyl ether **32**, with which NOE experiments might provide an unequivocal proof of stereochemistry, proved futile: *trans*-**29** re-epimerised to *cis*-**29** under all conditions tried.

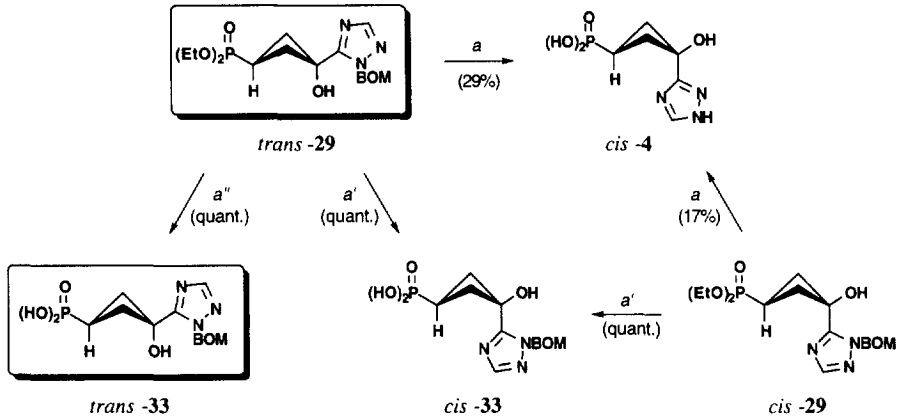


cis-29 → *trans*-29 epimerisation reaction			
time before H_2O quench	*trans*-29	: 30	: 31
16 h	0%	: 86%	: 11%
1 h	75%	: 20%	: 5%

isolated yields after chromatography

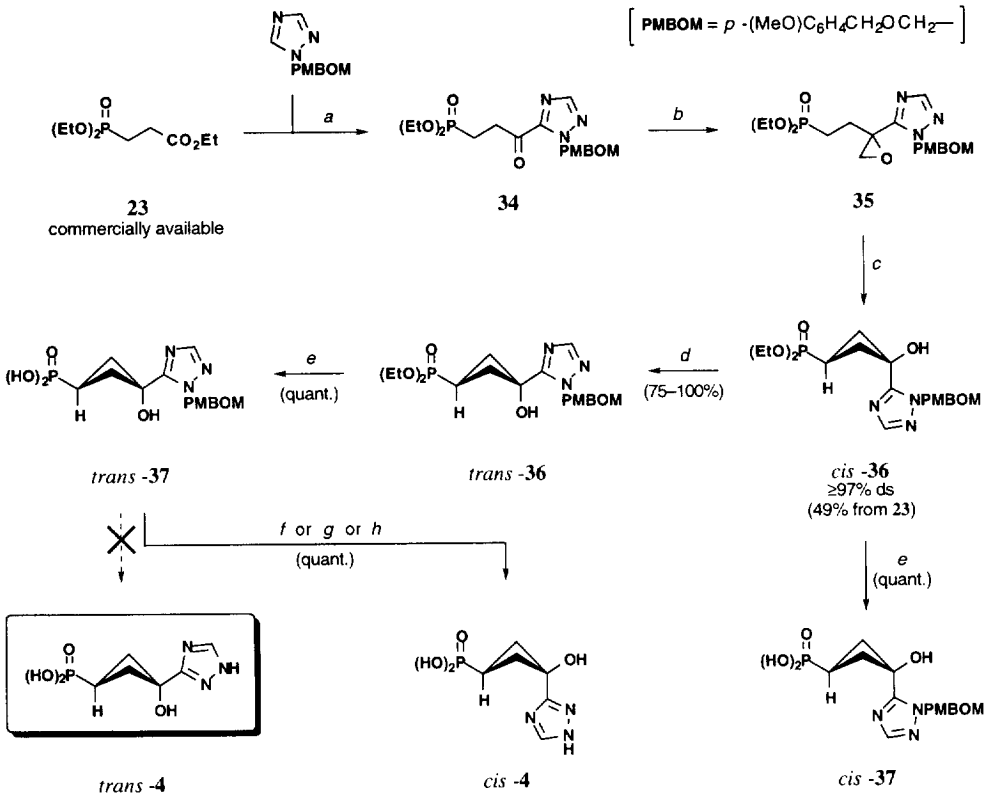
Scheme 9 (*a*) (i) $SOCl_2$, pyr, 0 °C → RT; (ii) H_2O; (*b*) (i) NaH, THF, RT; (ii) MeI *or* (i) 2,6-(^{t}Bu)$_2$py, MeOTf, CH_2Cl_2, RT; (*b'*) (i) NaH, THF, RT; *or* 2,6-(^{t}Bu)$_2$py, CH_2Cl_2, RT.

Having finally accessed *trans*-**29**, all that now remained was deprotection (**Scheme 10**). Subjection of *trans*-**29** to the standard conditions (10 equiv. TMSBr, 18 h),[4g] however, afforded only a modest yield (29%) of the fully deprotected product (due primarily to incomplete deprotection of the BOM group). Of greater concern was the discovery that the product was identical to that prepared by the first synthetic route (*cis*-**4**), *i.e.* re-epimerisation had taken place during the deprotection reaction![51] As confirmation, total deprotection of the diastereomeric *cis*-**29** afforded the same product, *cis*-**4**. By using fewer equivalents of TMSBr and much shorter reaction times, selective deprotection of the phosphonate could be accomplished in quantitative yield. However, once again, epimerisation occurred: deprotection of *trans*-**29** afforded the same product (*cis*-**33**) as that arising from deprotection of *cis*-**29**. It was reasoned that the epimerisation was being catalysed by protic acid present in the reaction medium, and that the phosphonate deprotection itself did not require such acid. Gratifyingly, use of TMSBr in the presence of the proton scavenger bis(trimethylsilyl)acetamide (BSA) effected clean phosphonate deprotection *without* epimerisation: a new product, *trans*-**33**, was obtained.[52] All that now remained to be accomplished was deprotection of the BOM group. However, hydrogenolysis over palladium on charcoal was only successful if substantial quantities of acid (conc. HCl) were added, which resulted in epimerisation again. Hence it was decided that material must be resynthesised with an alternative choice of protecting group on the triazole which could be removed under extremely mild and neutral conditions at the end of the synthesis: we elected to use the *para*-methoxybenzyloxymethyl (PMBOM) group.[53,54]



Scheme 10 (*a*) (i) TMSBr (10 equiv.), CH_2Cl_2, RT, 18 h; (ii) MeOH; (iii) propylene oxide; (*a'*) (i) TMSBr (3 equiv.), CH_2Cl_2, RT, 2.5 h; (ii) MeOH; (iii) propylene oxide; (*a''*) (i) TMSBr (3 equiv.), BSA, CH_2Cl_2, RT, 2.5 h; (ii) MeOH; (iii) propylene oxide.

Preparation of the new cyclobutane bearing the PMBOM protecting group on the triazole was straightforward, following a sequence (**23** → **34** → **35** → *cis*-**36** in **Scheme 11**, 49% yield over 3 steps) analogous to that already used to prepare the BOM derivative *cis*-**29**. Epimerisation to *trans*-**36** was again accomplished by means of $SOCl_2$, and then TMSBr-mediated selective deprotection of the phosphonate in the presence of BSA provided the phosphonic acid *trans*-**37** without concomitant re-epimerisation. This material was spectroscopically different to that produced from phosphonate deprotection of *cis*-**36**. At this stage, only the final deprotection of the protecting group on the triazole was required. The PMBOM group had been selected for its ease of removal under mild conditions, and this indeed proved to be the case: thus, DDQ oxidation,[53] photo-initiated single electron transfer reaction using naphthalene-2,6-dicarbonitrile,[55] and hydrogenolysis using carefully neutralised palladium/charcoal catalysts[56] all achieved quantitative deprotection. However, in all cases the product isolated was *cis*-**4**, rather than the desired *trans*-**4**! Under such mild and neutral reaction conditions, it appears as if the product itself is catalysing its own epimerisation to the undesired *cis* relative stereochemistry: *the desired* trans-**4** *diastereomer seems to be thermodynamically insufficiently stable to be of any use as a herbicidal agent*.[57,58]



Scheme 11 (*a*) (i) 1-PMBOM-1,2,4-triazole, ^{n}BuLi, THF, –78 °C; (ii) add to **23**; (*b*) $Me_3S^+.MeSO_4^-$, 50% aq. NaOH, CH_2Cl_2, 50 °C; (*c*) MeMgI (4 equiv.), THF, –78 °C → RT; (*d*) (i) $SOCl_2$, pyr, 0 °C → RT, 15 min; (ii) H_2O; (*e*) (i) TMSBr (3 equiv.), BSA, CH_2Cl_2, RT, 6 h; (ii) MeOH; (iii) propylene oxide; (f) H_2 (1 atm), Pd cat. MeOH/H_2O; (g) DDQ, CH_2Cl_2/H_2O, RT; (h) hv, naphthalene-1,4-dicarbonitrile, MeCN/H_2O, RT.

In order to rationalise the relative thermodynamic stabilities of *cis*-**4** and *trans*-**4**, which now appeared to be exactly opposite to that initially assumed, we turned to *ab initio* calculations.

Ab Initio Calculations

In order to accommodate correctly the specific structural complexities associated with cyclobutanes, such as ring-puckering,[12] *ab initio* calculations were performed at a high level with subsequent single-point energy determination (HF/6-311++G**//HF/6-311G**) using Gaussian 94.[59,60] Three different conformers of each diastereomer of **4** were fully optimised and the lowest energy structures are depicted in **Fig. 3**.

In the lowest energy confomer calculated for *cis*-**4** (**C** in **Fig. 3**, E_{rel} = 0.00 kJ mol^{-1}), the sterically demanding phosphonic acid moiety adopts a pseudo-equatorial orientation, whereas the sterically less-demanding triazole subsituent (sp^2 hybridised carbon attached to the cyclobutane) is pseudo-axially disposed.[61] In contrast, the lowest energy confomer of the epimer *trans*-**4** (**E** in **Fig. 3**) has both the phosphonic acid and triazole subsituents pseudo-equatorially disposed and is significantly higher in energy (E_{rel} = +3.56 kJ mol^{-1}). Thus, counter to our original expectations, it is the hydroxyl rather than the triazole subsituent which prefers to adopt a psuedo-equatorial disposition on cyclobutane **4**, and, as a consequence, *cis*-**4** is thermodynamically more stable than *trans*-**4**.

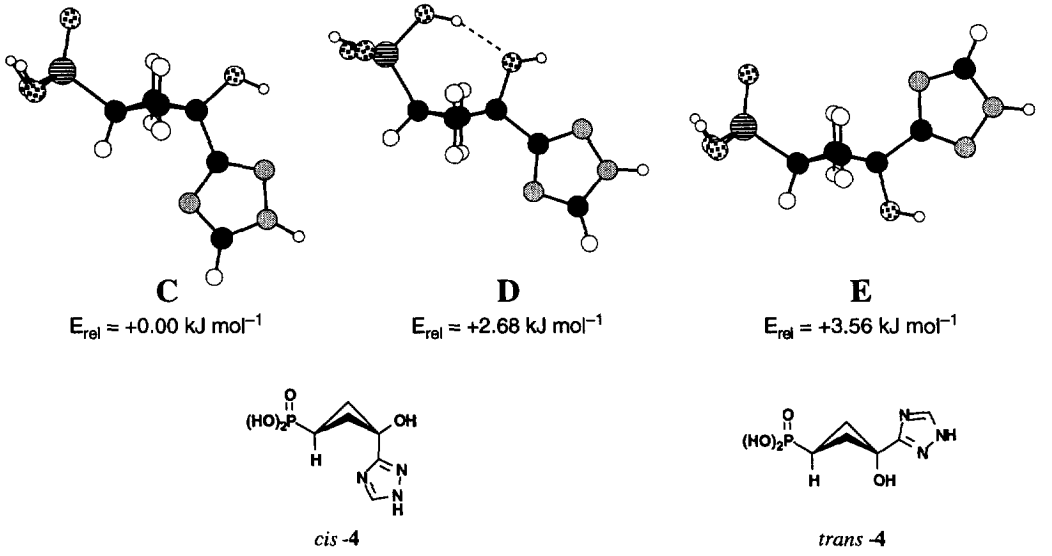


Fig. 3 *Ab initio* structures for *cis*-**4** and *trans*-**4**

Inspection of **Fig. 4** reveals a high degree of homology between the *ab initio* structure (**C**) calculated for *cis*-**4** and the observed X-ray crystal structure (**B**) of the protected analogue *cis*-**29**. Hence, we feel confident that the *ab initio* calculations have provided an accurate model of cyclobutane structure, and consider that the results are quantitatively as well as qualitatively legitimate.

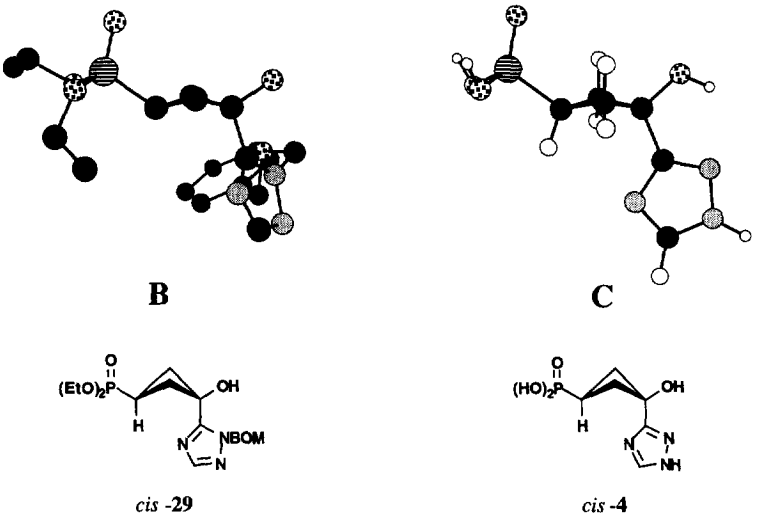


Fig. 4 Comparison of X-ray crystal structure of *cis*-**29** (conformer **B**) and *ab initio* structure of *cis*-**4** (conformer **C**)

CONCLUSIONS

Two complementary, novel and efficient synthetic routes to cyclobutanes bearing phosphonate substituents have been developed. The first, suitable for use with less-hindered substrates, involves the one-pot 1,4-cyclisation of an α-phenylsulphonyl-γ,δ-epoxyphosphonate mediated by the combined use of reagents (i) $^{n}Bu_4NI$/TBSOTf, (ii) KHMDS and (iii) lithium naphthalenide (*cf.* **8** → **18** in **Scheme 5**). The second, suitable for use with sterically more demanding substrates, involves the MeMgI-mediated 1,4-cyclisation of a γ,δ-epoxyphosphonate substrate (*cf.* **35** → *cis*-**36** in **Scheme 11**). Using such methodology, a concise synthesis of the moderately active IGPD inhibitor *cis*-**4** was achieved, but its epimer *trans*-**4** proved to be thermodynamically too labile to be synthesised. *Ab initio* calculations provided a theoretical explanation of this observed difference in thermodynamic stability between the two diastereomers.

EXPERIMENTAL

General.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX400 Fourier transform spectrometer in the indicated solvents at the following frequencies: 400 MHz (^{1}H), 101 MHz (^{13}C) and 162 MHz (^{31}P). In general, complete spectral assignments were made with the aid of COSY, DEPT and HSQC NMR experiments. ^{31}P NMR was especially valuable as an indicator of compound homogeneity. Infra-red spectra were recorded on a Perkin Elmer Paragon 1000 Fourier transform spectrometer using 5 mm sodium chloride plates. High resolution mass spectra (HRMS) were obtained by the Ciba-Geigy Central Analytical Service using fast atom bombardment (FAB) with thioglycerine matrix. Low resolution mass spectra (MS) were obtained using field desorption (FD).

Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualisation by ultraviolet light and phosphomolybdic acid solution. Flash column chromatography was performed using Merck Kieselgel 60 (230–400 mesh).

Reagents and solvents were generally of Fluka *puriss* grade, and used as received. Dichloromethane was distilled from calcium hydride and stored under a nitrogen atmosphere; tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone and stored under a nitrogen atmosphere. Anhydrous reactions were generally performed under a nitrogen atmosphere using oven-dried glassware and employing standard syringe techniques for handling air-sensitive reagents.

Diethyl 1-(phenylsulfanyl)but-3-en-1-ylphosphonate

To a cooled (–78 °C), stirred solution of diethyl (phenylsulfanyl)methylphosphonate (**9**) (50.0 g, 192 mmol) in THF (500 ml) was added dropwise *n*-butyllithium solution (132 ml, 211 mmol; 1.6 M in hexane), whereupon the reaction mixture became bright yellow. After stirring for 30 min, allyl bromide (24.4 ml, 288 mmol) was added dropwise and stirring continued for 1 h at –78 °C and then 1 h at 0 °C. The reaction mixture was quenched at 0 °C by addition of NH_4Cl solution (250 ml; sat. aqueous) and most of the THF removed *in vacuo*. After diluting the residue with ether (500 ml), the organic phase was separated and washed with brine (200 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo* to afford 65.0 g of a colourless oil (90% pure by ^{1}H NMR analysis) which was taken onto the next step without further purification. R_f (50% EtOAc in hexane) = 0.30; ^{1}H NMR ($CDCl_3$) δ 7.51 (2H, br d, J = 8 Hz), 7.32–7.20 (3H, m), 5.96 (1H, m), 5.14 (1H, d, J = 17 Hz), 5.12 (1H, d, J = 8 Hz), 4.13 (4H, m), 3.18 (1H, m), 2.77 (1H, m), 2.49 (1H, m), 1.30 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 134.8, 134.5 (d, J_{CP} = 12 Hz), 132.0, 128.9, 127.4, 117.9, 63.0 (d, J_{CP} = 7 Hz), 62.7 (d, J_{CP} = 7 Hz), 44.6 (d, J_{CP} = 148 Hz), 34.4, 16.5 (d, J_{CP} = 5 Hz); HRMS (FAB) $[M + H]^+$ found 301.1028, $C_{14}H_{22}O_3PS$ requires 301.1027.

Diethyl 3,4-epoxy-1-(phenylsulfonyl)butylphosphonate (8)

To a cooled (0 °C), stirred solution of the olefin prepared in the previous step (10.0 g aliquot of crude, theoretically 29.5 mmol) in CH_2Cl_2 (200 ml) was added portionwise *m*-CPBA (40.0 g, 55% purity, 175 mmol) and the reaction mixture allowed to warm to RT. After heating under reflux at 40 °C for 16 h, the reaction mixture was cooled to RT, diluted with CH_2Cl_2 (100 ml), and K_2SO_3 solution (sat. aqueous) added until all the remaining *m*-CPBA was consumed (reaction mixture tested negative with starch/KI indicator paper). Solid $NaHCO_3$ was added portionwise until effervescence ceased and $NaHCO_3$ solution (100 ml; sat. aqueous) then added. The organic phase was separated and washed with brine (100 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo* to afford 11.4 g of a colourless oil (diastereomeric mixture of epoxide **8**, 90% pure by ^{1}H NMR analysis) which was taken onto the next step without further purification. R_f (EtOAc) = 0.40; ^{1}H NMR ($CDCl_3$) δ 8.02–7.94 (2H, m), 7.71–7.63 (1H, m), 7.61–7.52 (2H, m), 4.16 (4H, m), 3.73 (1H, m), 3.29 (1H, br d, J = 20 Hz), 2.82 (1H, t, J = 3 Hz), 2.54 (1H, br d, J = 12 Hz), 2.46–2.17 (2 x 1H, overlapping m), 1.33–1.23 (6H, m); ^{13}C NMR ($CDCl_3$) δ 138.7 (d, J_{CP} = 31 Hz), 134.2, 129.3, 128.9, 63.7 (d, J_{CP} = 7 Hz), 63.6 (d, J_{CP} = 7 Hz), 63.4 (d, J_{CP} = 7 Hz), 63.3 (d, J_{CP} = 7 Hz), 60.8 (d, J_{CP} = 138 Hz), 60.7 (d, J_{CP} = 138 Hz), 50.2 (d, J_{CP} = 8 Hz), 49.8 (d, J_{CP} = 5 Hz), 48.5, 48.4, 29.4 (d, J_{CP} = 3 Hz), 16.2 (d, J_{CP} = 6 Hz); HRMS (FAB) $[M + H]^+$ found 349.0883, $C_{14}H_{22}O_6PS$ requires 349.0875.

Diethyl 3-hydroxy-4-iodo-1-(phenylsulfonyl)butylphosphonate (10)

To a cooled (0 °C), stirred solution of epoxide **8** (1.13 g aliquot of crude, theoretically 2.92 mmol) in CH_2Cl_2 (10 ml) in a foil-wrapped flask was added tetra-*n*-butylammonium iodide (1.40 g, 3.79 mmol). BF_3•OEt_2 (0.48 ml, 3.82 mmol) was then added dropwise and the reaction mixture warmed to RT. After 5 min the homogeneous mixture was partitioned between pH 7 buffer solution (25 ml) and ether (3 x 25 ml). The combined organic extracts were washed with K_2SO_3 solution (25 ml; sat. aqueous) and then triturated with ether to precipitate tetra-*n*-butylammonium salts. After filtration through celite (washing the filter pad with more ether), concentration of the filtrate *in vacuo* afforded 1.54 g of a colourless oil (diastereomeric mixture of iodohydrin **10**, 90% pure by ^1H NMR analysis) which was taken onto the next step without further purification. R_f (EtOAc) = 0.45; ^1H NMR ($CDCl_3$) δ 8.03–7.94 (2H, m), 7.71–7.63 (1H, m), 7.62–7.54 (2H, m), 4.17 (4H, m), 3.90 (1H, m), 3.78 (1H, m), 3.26 (2H, m), 2.50 (1H, m), 2.34–2.12 (2 x 1H, overlapping m), 1.33–1.24 (6H, m); ^{13}C NMR ($CDCl_3$) δ 138.6 (d, J_{CP} = 16 Hz), 134.2, 129.3, 129.1, 68.9, 67.7, 63.9 (d, J_{CP} = 6 Hz), 63.7 (d, J_{CP} = 7 Hz), 60.0 (d, J_{CP} = 137 Hz), 59.6 (d, J_{CP} = 137 Hz), 32.8 (d, J_{CP} = 16 Hz), 16.2 (d, J_{CP} = 6 Hz), 15.3; HRMS (FAB) $[M + H]^+$ found 477.0007, $C_{14}H_{23}O_6IPS$ requires 476.9997.

Diethyl 3-(benzyloxy)-4-iodo-1-(phenylsulfonyl)butylphosphonate (11)

To a cooled (0 °C), stirred solution of iodohydrin **10** (556 mg aliquot of crude, theoretically 1.05 mmol) in ether (10 ml) in a foil-wrapped flask were added dropwise benzyl-2,2,2-trichloroacetimidate (0.30 ml, 1.61 mmol) and triflic acid solution (1 ml aliquot of a solution containing 100 µl triflic acid in 10 ml ether). After stirring for 16 h at RT, the reaction mixture was diluted with ether (50 ml) and washed with $NaHCO_3$ solution (25 ml; sat. aqueous) and then brine (25 ml; sat.) The organic phase was then dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (60% EtOAc in hexane) afforded the desired benzyl ether **11** as a colourless oil (340 mg, 57% over 4 steps from **9**, approx. 1:1 diastereomeric mixture). R_f (60% EtOAc in hexane) = 0.44; ^1H NMR ($CDCl_3$) δ 7.98–7.86 (2H, m), 7.68–7.47 (3H, m), 7.38–7.28 (5H, m), 4.70 (1/2 x 1H, d, *J* = 12 Hz), 4.60 (1/2 x 1H, d, *J* = 12 Hz), 4.43 (1/2 x 1H, d, *J* = 12 Hz), 4.36 (1/2 x 1H, d, *J* = 12 Hz), 4.12 (4H, m), 3.92–3.65 (2 x 1H, overlapping m), 3.36–3.19 (2 x 1H, overlapping m), 2.45–2.20 (2 x 1H, overlapping m), 1.34–1.20 (6H, m); HRMS (FAB) $[M + H]^+$ found 567.0466, $C_{21}H_{29}O_6IPS$ requires 567.0466.

Diethyl 3-(benzyloxy)-1-(phenylsulfonyl)cyclobutylphosphonate (12)

To a cooled (–78 °C), stirred solution of protected iodohydrin **11** (300 mg, 0.53 mmol) in THF (15 ml) in a foil-wrapped flask was added dropwise KHMDS solution (1.00 ml, 0.50 mmol; 0.5 M in toluene). Stirring was continued for 30 min at –78 °C, 1 h at 0 °C and 3 h at RT. The reaction mixture was then quenched by addition of NH_4Cl solution (25 ml; sat. aqueous) and extracted with ether (3 x 25 ml). The combined organic extracts were washed with brine (25 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (50% EtOAc in hexane) afforded the desired cyclobutane **12** as a colourless oil (120 mg, 52%) which ^1H NMR indicated was a 79:21 mixture of diastereomers. Further chromatography of an aliquot afforded pure samples of each diastereomer for characterisation. Major (Less Polar) Isomer: R_f (50% EtOAc in hexane) = 0.32; ^1H NMR ($CDCl_3$) δ 8.01 (2H, d, *J* = 8 Hz), 7.65 (1H, t, *J* = 8 Hz), 7.54 (2H, t, *J* = 8 Hz), 7.38–7.26 (5H, m), 4.51 (1H, qn, *J* = 8 Hz), 4.44 (2H, s), 4.07 (4H, m), 3.04 (2H, m), 2.81 (2H, m), 1.21 (6H, t, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 137.7, 137.2, 134.1, 130.5, 128.8, 128.5, 128.4, 127.8, 70.5, 69.2 (d, J_{CP} = 17 Hz), 63.4 (d, J_{CP} = 7 Hz), 59.3 (d, J_{CP} = 146 Hz), 35.7 (d, J_{CP} = 4 Hz), 16.2 (d, J_{CP} = 6 Hz); HRMS (FAB) $[M + H]^+$ found 439.1347, $C_{21}H_{28}O_6PS$ requires 439.1344. Minor (More Polar) Isomer: R_f (50% EtOAc in hexane) = 0.30; ^1H NMR ($CDCl_3$) δ 7.94 (2H, d, *J* = 8 Hz), 7.63 (1H, t, *J* = 8 Hz), 7.52 (2H, t, *J* = 8 Hz), 7.38–7.26 (5H, m), 4.45 (2H, s), 4.29 (1H, qn, *J* = 8 Hz), 4.07 (4H, m), 3.04 (2H, m), 2.81 (2H, m), 1.21 (6H, t, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 137.7, 137.6, 133.8, 130.2, 128.5, 128.4, 127.9, 127.8, 70.4, 69.2 (d, J_{CP} = 17 Hz), 63.4 (d, J_{CP} = 7 Hz), 56.8 (d, J_{CP} = 148 Hz), 35.7 (d, J_{CP} = 4 Hz), 16.2 (d, J_{CP} = 6 Hz); HRMS (FAB) $[M + H]^+$ found 439.1346, $C_{21}H_{28}O_6PS$ requires 439.1344.

Diethyl 3-(benzyloxy)cyclobutylphosphonate

To a cooled (0 °C), stirred solution of cyclobutane **12** (40 mg, 0.09 mmol) in THF (3 ml) and methanol (3 ml) were added Na_2HPO_4 (52 mg, 0.37 mmol) and sodium amalgam (410 mg; 2%). After stirring for 1 h, a further aliquot of sodium amalgam (200 mg; 2%) was added and stirring continued for a further 1 h. The reaction mixture was then filtered through celite, washing the filter pad with methanol (5 ml), and partitioned between NH_4Cl solution (25 ml; sat. aqueous) and EtOAc (3 x 25 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired cyclobutane as a colourless oil (25 mg, 90%) which ^1H NMR indicated was a 1:1 mixture of diastereomers. R_f (70% EtOAc in hexane) = 0.25; ^1H NMR ($CDCl_3$) δ 7.37–7.27 (5H, m), 4.43 (1/2 x 2H, s), 4.41 (1/2 x 2H, s), 4.31 (1/2 x 1H, qn, *J* = 8 Hz), 4.10 (4H, m), 4.04 (1/2 x 1H, qn, *J* = 8 Hz), 2.60–2.07 (5H, overlapping m), 1.31 (6H, m); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.4, 127.9, 127.7, 71.5, 70.2, 70.0, 61.8 (d, J_{CP} = 7 Hz), 31.8 (d, J_{CP} = 6 Hz), 30.8 (d, J_{CP} = 6 Hz), 22.7 (d, J_{CP} = 151 Hz), 21.1 (d, J_{CP} = 156 Hz), 16.5 (d, J_{CP} = 6 Hz); HRMS (FAB) $[M + H]^+$ found 299.1412, $C_{15}H_{24}O_4P$ requires 299.1412.

Diethyl 3-hydroxycyclobutylphosphonate

To a solution of the cyclobutane prepared in the previous step (22 mg, 0.07 mmol) in diisopropyl ether (5 ml) was added palladium on activated charcoal (20 mg; 10% Pd content), and the reaction mixture was then stirred under 1 atm of hydrogen (balloon). After 3 h, the catalyst was removed by filtration through celite, washing the filter pad with ether. Concentration *in vacuo* then afforded the desired cyclobutanol as a colourless oil (15 mg, quant.) which ^1H NMR indicated was a 1:1 mixture of diastereomers. R_f (EtOAc) = 0.08; ^1H NMR ($CDCl_3$) δ 4.57 (1/2 x 1H, qn, *J* = 8 Hz), 4.26 (1/2 x 1H, qn, *J* = 8 Hz), 4.10 (4H, m), 2.66–2.45 (2H, overlapping m), 2.36–2.08 (3H, overlapping m), 1.32 (6H, t, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 65.4, 64.9, 62.0 (d, J_{CP} = 7 Hz), 61.8 (d, J_{CP} = 7 Hz), 34.4 (d, J_{CP} = 5 Hz), 33.5 (d, J_{CP} = 6 Hz), 22.0 (d, J_{CP} = 151 Hz), 20.9 (d, J_{CP} = 151 Hz), 16.5 (d, J_{CP} = 6 Hz); MS (FD) found 209 ($[M + H]^+$), 208 (M^+).

Diethyl 3-oxocyclobutylphosphonate (5)

To a cooled (0 °C), stirred solution of the cyclobutanol prepared in the previous step (15 mg, 0.07 mmol) in acetone (5 ml) was added dropwise Jones reagent[62] until a red colour persisted in the reaction mixture. Excess Jones reagent was then destroyed by dropwise addition of isopropanol, until the reaction mixture was pale green. After decanting from the precipitated chromium salts, the reaction mixture was partitioned between $NaHCO_3$ solution (5 ml; sat, aqueous) and CH_2Cl_2 (3 x 5 ml). The combined organic extracts were washed with brine (10 ml; sat.) and then dried ($MgSO_4$). Concentration *in vacuo* afforded the desired cyclobutanone **5** as a colourless oil (12 mg, 81%). R_f (6% isopropanol in CH_2Cl_2) = 0.35; ν_{max} (film) = 1 791 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.17 (4H, m), 3.45–3.24 (2 x 2H, overlapping m), 2.67 (1H, br sextet, J = 9 Hz), 1.35 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 203.6 (d, J_{CP} = 23 Hz), 62.7 (d, J_{CP} = 7 Hz), 49.8 (d, J_{CP} = 4 Hz), 19.4 (d, J_{CP} = 151 Hz), 16.9 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 31.3; HRMS (FAB) $[M + H]^+$ found 207.0790, $C_8H_{16}O_4P$ requires 207.0786.

Diethyl 3-[(tert-butyldimethylsilyl)oxy]-4-iodo-1-(phenylsulfonyl)butylphosphonate (16) — 'One-pot' Protected Iodohydrin Formation

To a stirred solution of epoxide **8** (330 mg aliquot of crude, theoretically 0.85 mmol) in THF (15 ml) in a foil-wrapped flask was added tetra-*n*-butylammonium iodide (350 mg, 0.95 mmol). The reaction mixture was cooled to –78 °C and TBSOTf (0.22 ml, 0.96 mmol) added dropwise. After stirring for 15 min at –78 °C and then 10 min at 0 °C, the reaction mixture was partitioned between NH_4Cl solution (25 ml) and ether (3 x 25 ml). The combined organic extracts were washed with K_2SO_3 solution (25 ml; sat. aqueous) and then concentrated *in vacuo*. Flash chromatography (60% EtOAc in hexane) afforded the silyl ether **16** as a colourless oil (330 mg, 65% over 3 steps from **9**, approx. 1:1 diastereomeric mixture). R_f (60% EtOAc in hexane) = 0.47; ^1H NMR ($CDCl_3$) δ 7.99–7.84 (2H, m), 7.63–7.44 (3H, m), 4.14 (4H, m), 3.95–3.73 (1H, m), 3.73–3.52 (1H, m), 3.24–3.01 (2 x 1H, overlapping m), 2.49–2.00 (2 x 1H, overlapping m), 1.32–1.17 (6H, m); 0.84 (1/2 x 9H, s), 0.76 (1/2 x 9H, s), 0.10 (1/2 x 3H, s), 0.08 (1/2 x 3H, s), 0.00 (1/2 x 3H, s), –0.01 (1/2 x 3H, s); HRMS (FAB) $[M + H]^+$ found 591.0867. $C_{20}H_{37}O_6IPSSi$ requires 591.08616.

Diethyl 3-[(tert-butyldimethylsilyl)oxy]-1-(phenylsulfonyl)cyclobutylphosphonate (17) — Standard Procedure for 1,4-Cyclisation

To a cooled (–78 °C), stirred solution of protected iodohydrin **16** (290 mg, 0.49 mmol) in THF (15 ml) in a foil-wrapped flask was added dropwise KHMDS solution (0.93 ml, 0.47 mmol; 0.5 M in toluene). Stirring was continued for 5 min at –78 °C, 30 min at 0 °C and 90 min at RT. The reaction mixture was then quenched by addition of NH_4Cl solution (25 ml; sat. aqueous) and extracted with ether (3 x 25 ml). The combined organic extracts were washed with brine (25 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (70% EtOAc in hexane) afforded the desired cyclobutane **17** as a colourless oil (190 mg, 84%) which ^1H NMR indicated was a 77:23 mixture of diastereomers. R_f (70% EtOAc in hexane) = 0.60 (Major Diastereomer) & 0.55 (Minor Diastereomer); ^1H NMR ($CDCl_3$) δ 8.00 (0.77 x 2H, d, J = 8 Hz), 7.91 (0.23 x 2H, d, J = 8 Hz), 7.68–7.57 (1H, m), 7.57–7.45 (2H, m), 4.65 (0.77 x 1H, qn, J = 8 Hz), 4.46 (0.23 x 1H, qn, J = 8 Hz), 4.04 (4H, m), 3.12–2.88 (2H, m), 2.88–2.62 (2H, m), 1.20 (6H, t, J = 7 Hz), 0.85 (9H, s), 0.00 (6H, s); ^{13}C NMR ($CDCl_3$) δ 137.5, 134.0, 130.5, 128.5, 63.5, 63.3 (d, J_{CP} = 7 Hz), 61.6 (d, J_{CP} = 149 Hz), 59.3 (d, J_{CP} = 149 Hz), 38.7 (d, J_{CP} = 4 Hz), 25.7, 17.8, 16.2 (d, J_{CP} = 6 Hz), –4.8; ^{31}P NMR ($CDCl_3$) δ 21.1 (Major Diastereomer), 17.9 (Minor Diastereomer); HRMS (FAB) $[M + H]^+$ found 463.1739. $C_{20}H_{36}O_6PSSi$ requires 463.1739.

Diethyl 3-[(tert-butyldimethylsilyl)oxy]-1-(phenylsulfonyl)cyclobutylphosphonate (17) — 'One-pot' Iodohydrin Formation and 1,4-Cyclisation

To a stirred solution of epoxide **8** (735 mg aliquot of crude, theoretically 1.90 mmol) in THF (25 ml) in a foil-wrapped flask was added tetra-*n*-butylammonium iodide (770 mg, 2.08 mmol). The reaction mixture was cooled to 0 °C and TBSOTf (0.48 ml, 2.09 mmol) added dropwise. After stirring for 15 min at 0 °C, KHMDS solution (3.79 ml, 1.90 mmol; 0.5 M in toluene) was added dropwise and stirring continued for 2 h at RT. The reaction mixture was then quenched by addition of NH_4Cl solution (25 ml; sat. aqueous) and extracted with ether (3 x 25 ml). The combined organic extracts were washed with brine (25 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (70% EtOAc in hexane) afforded the desired cyclobutane **17** as a colourless oil (510 mg, 58% over 3 steps from **9**) which ^1H NMR indicated was a 77:23 mixture of diastereomers. Spectroscopic properties were identical to those of material prepared previously (*vide supra*).

Diethyl 3-[(tert-butyldimethylsilyl)oxy]cyclobutylphosphonate (18)

To a cooled (0 °C), stirred solution of cyclobutane **17** (100 mg, 0.22 mmol) in THF (7 ml) and methanol (7 ml) were added Na_2HPO_4 (123 mg, 0.87 mmol) and sodium amalgam (972 mg; 2%). After stirring for 1 h, a further aliquot of sodium amalgam (400 mg; 2%) was added and stirring continued for a further 1 h. The reaction mixture was then filtered through celite, washing the filter pad with methanol (10 ml), and partitioned between NH_4Cl solution (50 ml; sat. aqueous) and EtOAc (3 x 25 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford the desired cyclobutane **18** as a colourless oil (60 mg, 86%) which ^1H NMR indicated was a 1:1 mixture of diastereomers. R_f (80% EtOAc in hexane) = 0.47; ^1H NMR ($CDCl_3$) δ 4.49 (1/2 x 1H, qn, J = 8 Hz), 4.19 (1/2 x 1H, qn, J = 8 Hz), 4.07 (4H, m), 2.57–2.44 (1H, m), 2.44–2.32 (1H, m), 2.31–2.09 (2 x 1H, overlapping m), 2.09–1.96 (1H, m), 1.30 (6H, t, J = 7 Hz), 0.83 (9H, s), 0.00 (6H, s); ^{13}C NMR ($CDCl_3$) δ 65.5, 64.7 (d, J_{CP} = 38 Hz), 61.7 (d, J_{CP} = 6 Hz), 35.0 (d, J_{CP} = 5 Hz), 34.1 (d, J_{CP} = 6 Hz), 25.8, 22.0 (d, J_{CP} = 151 Hz), 20.8 (d, J_{CP} = 156 Hz), 18.0, 16.5 (d, J_{CP} = 6 Hz), –4.8, –4.9; HRMS (FAB) $[M + H]^+$ found 323.1814, $C_{14}H_{32}O_4PSi$ requires 323.1808.

Diethyl 3-[(tert-butyldimethylsilyl)oxy]cyclobutylphosphonate (18) — 'One-pot' Iodohydrin Formation, 1,4-Cyclisation and Desulphonation

To lithium dispersion (1.90 g; 30% in oil) *under an argon atmosphere* at RT was added via cannula, with stirring, a solution of naphthalene (5.25 g, 41.0 mmol) in THF (180 ml). Stirring was continued for 2 h, and the resulting dark green solution of lithium naphthalenide (approx. 0.23 M) was then cooled to –78 °C prior to use in the desulphonation reaction (*vide infra*).

Meanwhile, to a stirred solution of epoxide **8** (3.29 g aliquot of crude, theoretically 8.52 mmol) in THF (125 ml) *under an argon atmosphere* in a foil-wrapped flask was added tetra-*n*-butylammonium iodide (4.16 g, 11.3 mmol). The reaction mixture was cooled to 0 °C and TBSOTf (2.59 ml, 11.3 mmol) added dropwise. After stirring for 30 min at 0 °C, KHMDS solution (20.5 ml, 10.3 mmol; 0.5 M in toluene) was added dropwise and stirring continued for 2.5 h at RT. The reaction mixture was then cooled to –78 °C and lithium naphthalenide solution (80 ml, approx. 18 mmol) added dropwise. After stirring for 45 min at –78 °C, the reaction mixture was quenched at the same temperature by addition of NH_4Cl solution (100 ml; sat. aqueous) and then warmed to room temperature. After extraction with EtOAc (3 x 100 ml), the combined organic extracts were washed with brine (100 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (80% EtOAc in hexane) afforded the desired cyclobutane **17** as a colourless oil (1.44 g, 52% over 3 steps from **9**) which ^1H NMR indicated was a 1:1 mixture of diastereomers. Spectroscopic properties were identical to those of material prepared previously (*vide supra*).

Diethyl 3-oxocyclobutylphosphonate (5)

To a stirred solution of cyclobutane **18** (700 mg, 2.17 mmol) in acetone (25 ml) at RT was added $(MeCN)_2PdCl_2$ (6 mg, 0.02 mmol) and stirring continued for 24 h.[63,64] The reaction mixture was then cooled to 0 °C and Jones reagent[62] added dropwise until a red colour persisted in the reaction mixture (approx. 1 ml reagent required). Excess Jones reagent was then destroyed by dropwise addition of isopropanol, until the reaction mixture was pale green. After decanting from the precipitated chromium salts, the reaction mixture was partitioned between $NaHCO_3$ solution (50 ml; sat. aqueous) and CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with brine (50 ml; sat.) and then dried ($MgSO_4$). Concentration *in vacuo* afforded the desired cyclobutanone **5** as a colourless oil (405 mg, 90%) having identical spectroscopic properties to material prepared previously (*vide supra*).

1-Trityl-1,2,4-triazole

To a cooled (0 °C), stirred solution of 1,2,4-triazole (24.8 g, 359 mmol) and chlorotriphenylmethane (100 g, 359 mmol) in DMF (400 ml) was added triethylamine (59.5 ml, 429 mmol) and stirring continued for 16 h at RT. Water (500 ml) was then added slowly (exotherm) and the resulting precipitate collected on a glass sintered filter. The crystals were washed with water (5 x 100 ml) followed by ether (5 x 100 ml) and then dried *in vacuo* to afford the desired product as a white crystalline solid (97.1 g, 87%). R_f (EtOAc) = 0.85; ^1H NMR ($CDCl_3$) δ 8.08 (1H, s), 8.03 (1H, s), 7.39–7.29 (9H, m), 7.18–7.09 (6H, m); ^{13}C NMR ($CDCl_3$) δ 151.8, 145.7, 141.8, 129.9, 128.3, 128.0, 78.0, ; HRMS (FAB) $[M + H]^+$ found 312.1495, $C_{21}H_{18}N_3$ requires 312.1501.

***Diethyl* cis-*3-hydroxy-3-(1-trityl-1,2,4-triazol-5-yl)cyclobutylphosphonate* (cis-*19*)**

A stirred solution of 1-trityl-1,2,4-triazole (700 mg, 2.25 mmol) in hot THF (40 ml) was cooled to –78 °C and *n*-butyllithium solution (1.40 ml, 2.24 mmol; 1.6 M in hexane) added dropwise. Stirring was continued for 45 min at –78 °C, and then to the resulting bright red solution was added dropwise via cannula a solution of cyclobutanone **5** (405 mg, 1.96 mmol) in THF (3 ml + 1 ml washings). After stirring the reaction mixture for 1 h at –78 °C and then 1 h at 0 °C, the reaction was quenched by addition of NH_4Cl solution (25 ml; sat. aqueous) and most of the THF removed *in vacuo*. The residue was extracted with CH_2Cl_2 (3 x 50 ml) and the organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. ^1H and ^{31}P NMR analysis of the crude reaction product indicated formation of a single adduct diastereomer. Flash chromatography (4% isopropanol in CH_2Cl_2) afforded the product *cis*-**19** as a white amorphous solid (150 mg, 15%). R_f (EtOAc) = 0.35; R_f (4% isopropanol in CH_2Cl_2) = 0.37; ^1H NMR ($CDCl_3$) δ 7.85 (1H, s), 7.30–7.21 (9H, m), 7.12–7.06 (6H, m), 3.99 (4H, qn, J = 7 Hz), 3.79 (1H, s), 2.80 (2H, m), 2.36 (1H, m), 1.60 (2H, m), 1.24 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 159.5, 148.2, 143.7, 131.4, 128.0, 127.8, 80.7, 72.7 (d, J_{CP} = 11 Hz), 62.9 (d, J_{CP} = 7 Hz), 38.7 (d, J_{CP} = 6 Hz), 22.7 (d, J_{CP} = 148 Hz), 17.2 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 36.5; HRMS (FAB) $[M + H]^+$ found 518.2207, $C_{29}H_{33}N_3O_4P$ requires 518.2209.

Cis-*3-hydroxy-3-(1,2,4-triazol-3-yl)cyclobutylphosphonic acid* (cis-*4*)

To a stirred solution of cyclobutane *cis*-**19** (130 mg, 0.25 mmol) in CH_2Cl_2 (3.5 ml) at RT was added TMSBr (0.17 ml, 1.31 mmol) and the reaction mixture stirred for 18 h. Methanol (1.7 ml) was added and stirring continued for a further 1 h, then propylene oxide (0.34 ml) was added and stirring continued for another 1 h. Ether (13.7 ml) was then added slowly to the reaction mixture whereupon precipitation of the product occurred. The hygroscopic crystals were collected on a sintered glass filter under a stream of nitrogen and washed with ether (5 x 1 ml). After drying *in vacuo*, the product *cis*-**4** was obtained as a white microcrystalline solid (50.2 mg, 91%). ^1H NMR ($CDCl_3$) δ 8.75 (1H, s), 2.71 (2H, m), 2.49 (2H, m), 2.32 (1H, br sextet, J = 10 Hz); ^{13}C NMR ($CDCl_3$) δ 155.0, 144.7, 68.7 (d, J_{CP} = 11 Hz), 37.3 (d, J_{CP} = 5 Hz), 22.1 (d, J_{CP} = 147 Hz); ^{31}P NMR ($CDCl_3$) δ 26.2; HRMS (FAB) $[M + H]^+$ found 220.0485, $C_6H_{11}N_3O_4P$ requires 220.0487.

Diethyl* cis-*3-methoxy-3-(1-trityl-1,2,4-triazol-5-yl)cyclobutylphosphonate

To NaH (9 mg, 0.23 mmol; 60% dispersion in oil) at RT was added dropwise via cannula a solution of cyclobutane *cis*-**19** (30 mg, 0.06 mmol) in THF (5 ml). The reaction mixture was stirred for 30 min and then iodomethane (0.1 ml, 1.6 mmol) was

added. Stirring was continued for 30 min and then the reaction mixture was quenched by addition of NH_4Cl solution (10 ml; sat. aqueous) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (EtOAc) afforded the product methyl ether as a colourless viscous oil (30 mg, 97%). R_f (EtOAc) = 0..25; ^1H NMR ($CDCl_3$) δ 7.91 (1H, s), 7.29–7.21 (9H, m), 7.11–7.05 (6H, m), 4.00 (4H, br qn, J = 7 Hz), 2.60 (3H, s), 2.43 (1H, sextet, J = 10 Hz), 2.38–2.18 (2 x 2H, overlapping m), 1.25 (6H, t, J = 7 Hz); ^1H NMR (C_6D_6) δ 8.01 (1H, s), 7.30–7.23 (9H, m), 7.10–7.01 (6H, m), 3.92 (4H, m), 2.90 (1H, sextet, J = 10 Hz), 2.69 (2H, m), 2.63 (3H, s), 2.57 (2H, m), 1.05 (6H, t, J = 7 Hz); ^1H NMR (MeOD) δ 7.80 (1H, s), 7.18–7.10 (9H, m), 6.98–6.91 (6H, m), 3.98 (4H, br qn, J = 7 Hz), 2.47 (3H, s), 2.31 (1H, sextet, J = 10 Hz), 2.18–2.07 (2 x 2H, overlapping m), 1.25 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 158.6, 147.6, 143.1, 130.8, 127.7, 127.4, 80.8, 71.4 (d, J_{CP} = 11 Hz), 62.0 (d, J_{CP} = 6 Hz), 49.6, 32.4 (d, J_{CP} = 5 Hz), 20.6 (d, J_{CP} = 153 Hz), 16.9 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 32.3; ^{31}P NMR (MeOD) δ 32.1; HRMS (FAB) $[M + H]^+$ found 532.2367, $C_{30}H_{35}N_3O_4P$ requires 532.2365.

***Diethyl* cis-*3-methoxy-3-(1,2,4-triazol-3-yl)cyclobutylphosphonate* (cis-*20*)**

To a solution of the methyl ether prepared in the previous step (30 mg, 0.06 mmol) in THF (5 ml) was added palladium on activated charcoal (10 mg; 10% Pd content), and the reaction mixture was then stirred under 1 atm of hydrogen (balloon). After 16 h, the catalyst was removed by filtration through celite, washing the filter pad with CH_2Cl_2. Concentration *in vacuo* then afforded the desired product *cis*-**20** (contaminated by triphenylmethane, but this was of no concern for the subsequent NOE experiment). ^1H NMR (MeOD) δ 8.24 (1H, s), 4.01 (4H, m), 2.95 (3H, s), 2.68 (2H, m), 2.51 (2H, m), 2.34 (1H, sextet, J = 10 Hz), 1.21 (6H, t, J = 7 Hz); ^{31}P NMR (MeOD) δ 32.2.

1-[(Benzyloxy)methyl]-1,2,4-triazole

To a stirred suspension of 1,2,4-triazole (20.0 g, 290 mmol) in MeCN (500 ml) at RT was added dropwise DBU (60.4 ml, 405 mmol). Benzyl chloromethyl ether[65] (56.2 ml, 406 mmol) was then added dropwise while the reaction mixture was cooled in a water bath. Stirring was continued for 16 h and then most of the MeCN was removed *in vacuo*. The residue was resuspended in EtOAc (200 ml) and washed with NH_4Cl solution (100 ml; sat. aqueous) followed by brine (100 ml; sat.), The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired product as a colourless oil (49.5 g, 90%). R_f (EtOAc) = 0.45; ^1H NMR ($CDCl_3$) δ 8.27 (1H, s), 8.01 (1H, s), 7.40–7.29 (5H, m), 5.56 (2H, s), 4.60 (2H, s); ^{13}C NMR ($CDCl_3$) δ 152.3, 143.9, 136.0, 128.7, 128.3, 128.1, 76.9, 71.3; HRMS (FAB) $[M + H]^+$ found 190.0994, $C_{10}H_{12}N_3O$ requires 190.0980.

Diethyl 3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3-oxopropylphosphonate (24)

To a cooled (–78 °C), stirred solution of 1-[(benzyloxy)methyl]-1,2,4-triazole (30.0 g, 159 mmol) in THF (500 ml) was added dropwise *n*-butyllithium solution (100 ml, 160 mmol; 1.6 M in hexane). After stirring for 1 h at –78 °C, the red solution was added dropwise via cannula to a cooled (–78 °C), stirred solution of triethyl 3-phosphonopropionate (**23**) (34.5 ml, 158 mmol) in THF (100 ml). The reaction mixture was stirred for 1 h before being quenched at –78 °C by addition of NH_4Cl solution (150 ml; sat. aqueous) followed by water (150 ml). Most of the THF was removed *in vacuo* and the residue extracted with EtOAc (3 x 200 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford 64.9 g of a colourless oil (85% conversion to ketone **24**, according to ^1H NMR analysis, with 15% of each starting material remaining) which was taken onto the next step without further purification. R_f (EtOAc) = 0.27; ^1H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.35–7.26 (5H, m), 5.93 (2H, s), 4.65 (2H, s), 4.11 (4H, m), 3.45 (2H, dt, J = 11 & 8 Hz), 2.15 (2H, dt, J = 18 & 8 Hz), 1.33 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 190.0 (d, J_{CP} = 16 Hz), 151.0, 149.2, 136.9, 128.8, 128.5, 128.3, 78.6, 72.1, 62.2 (d, J_{CP} = 7 Hz), 34.1 (d, J_{CP} = 3 Hz), 19.7 (d, J_{CP} = 146 Hz), 16.8 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 31.5; HRMS (FAB) $[M + H]^+$ found 382.1532, $C_{17}H_{25}N_3O_5P$ requires 382.1532.

Diethyl 3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3,4-epoxybutylphosphonate (25)

To a vigorously stirred solution of ketone **24** (20.2 g aliquot of crude, theoretically 49.2 mmol) in CH_2Cl_2 (700 ml) was added trimethylsulphonium methylsulphate (15.0 g, 79.7 mmol). Sodium hydroxide solution (320 ml; 50% aqueous) was then added and the mixture heated at 50 °C for 4.5 h. After cooling to RT, the mixture was added to water (2.67 l) while cooling the flask in an ice-bath. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 250 ml). The combined organic extracts were washed with water (2 x 250 ml) followed by brine (250 ml; sat.), and then dried ($MgSO_4$). Concentration *in vacuo* afforded 15.2 g of a colourless oil (comprising 72% epoxide **25** and 28% 1-BOM-1,2,4-triazole remaining from first step, according to ^1H NMR analysis) which was taken onto the next step without further purification. R_f (EtOAc) = 0.28; R_f (5% MeOH in CH_2Cl_2) = 0.35; ^1H NMR ($CDCl_3$) δ 7.88 (1H, s), 7.40–7.26 (5H, m), 5.69 (1H, d, J = 11 Hz), 5.60 (1H, d, J = 11 Hz), 4.63 (2H, s), 4.06 (4H, m), 3.20 (1H, d, J = 6 Hz), 3.06 (1H, d, J = 6 Hz), 2.56 (1H, m), 2.19 (1H, m), 1.90 (2H, m), 1.28 (6H, td, J = 7 & 2 Hz); ^{13}C NMR ($CDCl_3$) δ 153.2, 150.5, 136.5, 128.5, 128.1, 128.0, 77.2, 71.4, 61.7 (d, J_{CP} = 6 Hz), 60.4, 53.6, 28.3 (d, J_{CP} = 3 Hz), 21.1 (d, J_{CP} = 143 Hz), 16.4 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 31.5; HRMS (FAB) $[M + H]^+$ found 396.1693, $C_{18}H_{27}N_3O_5P$ requires 396.1688.

Diethyl* cis-*3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3-hydroxycyclobutylphosphonate* (cis-*29*) — *'One-pot' Iodohydrin Formation and 1,4-Cyclisation

To a cooled (–78 °C), stirred solution of epoxide **25** (15.2 g of crude, theoretically 49.2 mmol) in THF (600 ml) in a foil-wrapped flask was added dropwise MeMgI solution (65.8 ml, 197 mmol; 3 M in ether). Stirring was continued for 20 h while the reaction mixture was allowed to warm to RT. The reaction was then quenched by dropwise addition of NH_4Cl solution (500 ml;

sat. aqueous) and most of the THF removed *in vacuo*. The residue was extracted with EtOAc (3 x 250 ml) and the combined organic extracts were washed with brine (250 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo*. ^1H and ^{31}P NMR analysis of the crude reaction product indicated formation of a single cyclobutane diastereomer. Flash chromatography (gradient elution: 0% → 5% → 10% EtOH in EtOAc) afforded the product cyclobutane *cis*-**29** as a viscous colourless oil (6.20 g, 32% over 3 steps from **23**) which solidified on standing in the refrigerator. Slow recrystallisation from EtOAc at 0 °C (several days standing in refrigerator) afforded crystals of a quality suitable for X-ray diffraction analaysis. R_f (EtOAc) = 0.41; ^1H NMR ($CDCl_3$) δ 7.85 (1H, s), 7.35–7.26 (5H, m), 6.30 (1H, s), 5.79 (2H, s), 4.65 (2H, s), 4.10 (4H, m), 3.10 (2H, m), 2.75 (2H, m), 2.51 (1H, br sextet, J = 10 Hz), 1.30 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 158.8, 150.3, 137.7, 129.2, 128.8, 128.7, 78.0, 71.9, 71.6 (d, J_{CP} = 21 Hz), 63.1 (d, J_{CP} = 7 Hz), 38.4 (d, J_{CP} = 5 Hz), 22.0 (d, J_{CP} = 152 Hz), 17.2 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 36.2; HRMS (FAB) $[M + H]^+$ found 396.1691, $C_{18}H_{27}N_3O_5P$ requires 396.1688.

Diethyl 3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3-hydroxy-4-iodobutylphosphonate (26) — Iodohydrin Formation

To a cooled (–78 °C), stirred solution of epoxide **25** (630 mg, 1.59 mmol, purified by flash chromatography using 5% MeOH in CH_2Cl_2) in THF (20 ml) in a foil-wrapped flask was added dropwise MeMgI solution (0.69 ml, 2.07 mmol; 3 M in ether). Stirring was continued for 5 min at –78 °C and then 5 min at 0 °C. The reaction was then quenched at 0 °C by dropwise addition of NH_4Cl solution (25 ml; sat. aqueous) and extracted with EtOAc (3 x 25 ml). The combined organic extracts were washed with brine (25 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo* to afford the desired iodohydrin **26** as a colourless oil (800 mg, 96%) which was taken onto the next step without further purification. R_f (EtOAc) = 0.54; ^1H NMR ($CDCl_3$) δ 7.87 (1H, s), 7.40–7.29 (5H, m), 5.91 (1H, d, J = 11 Hz), 5.74 (1H, d, J = 11 Hz), 5.06 (1H, s), 4.66 & 4.60 (2H, ABq, J = 12 Hz), 4.12 (2H, qn, J = 7 Hz), 4.01 (2H, qn, J = 7 Hz), 3.85 (1H, d, J = 12 Hz), 3.63 (1H, d, J = 12 Hz), 2.55 (1H, m), 2.34 (1H, m), 1.97 (1H, m), 1.63 (1H, m), 1.33 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 157.4, 150.6, 137.1, 129.3, 129.0, 128.8, 79.1, 72.1, 62.8 (d, J_{CP} = 6 Hz), 61.1, 33.8 (d, J_{CP} = 4 Hz), 21.5 (d, J_{CP} = 142 Hz), 19.3, 17.1 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 33.4; HRMS (FAB) $[M + H]^+$ found 524.0822, $C_{18}H_{28}N_3O_5IP$ requires 524.0810.

KHMDS-Mediated Cyclisation of Isolated Iodohydrin

To a cooled (0 °C), stirred solution of iodohydrin **26** (800 mg of crude, theoretically 1.53 mmol if pure) in THF (20 ml) in a foil-wrapped flask was added dropwise KHMDS solution (7.65 ml, 3.83 mmol; 0.5 M in toluene). Stirring was continued for 2 h while the reaction mixture was allowed to warm to RT. The reaction was then quenched by dropwise addition of NH_4Cl solution (25 ml; sat. aqueous) and extracted with EtOAc (3 x 25 ml). The combined organic extracts were washed with brine (25 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo* to afford 440 mg (70% mass recovery over 2 steps from **25**) of a colourless oil comprising approx. 50% epoxide **25**, approx. 50% cyclobutane *cis*-**29**, and trace amounts of iodohydrin **26** and cyclopropane **28**, according to ^1H and ^{31}P NMR analysis.

Diethyl 2-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-2-(hydroxymethyl)cyclopropylphosphonate (28) — KHMDS-Mediated Cyclisation of Epoxide

To a cooled (–20 °C), stirred solution of epoxide **25** (1.00 g, 2.53 mmol, purified by flash chromatography using 5% MeOH in CH_2Cl_2) in THF (40 ml) was added dropwise KHMDS solution (5.60 ml, 2.80 mmol; 0.5 M in toluene). After stirring for 30 min, the reaction mixture was then quenched at –20 °C by dropwise addition of NH_4Cl solution (25 ml; sat. aqueous) and extracted with EtOAc (3 x 25 ml). The combined organic extracts were washed with brine (25 ml; sat.), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (10% MeOH in CH_2Cl_2) afforded the cyclopropane **28** as a colourless oil (280 mg, 28%). R_f (5% MeOH in CH_2Cl_2) = 0.25; ^1H NMR ($CDCl_3$) δ 7.86 (1H, s), 7.36–7.25 (5H, m), 6.01 (1H, d, J = 12 Hz), 5.47 (1H, d, J = 12 Hz), 4.74 (1H, d, J = 12 Hz), 4.66 (1H, d, J = 12 Hz), 4.00 (2H, qn, J = 7 Hz), 3.88–3.67 (2 x 2H, overlapping m), 2.39 (1H, br s), 1.93 (1H, m), 1.58–1.48 (2 x 1H, overlapping m), 1.22 (3H, t, J = 7 Hz), 1.11 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 155.4, 150.9, 137.2, 129.3, 129.0, 128.9, 78.1, 72.2, 67.7 (d, J_{CP} = 3 Hz), 63.1 (d, J_{CP} = 7 Hz), 62.6 (d, J_{CP} = 6 Hz), 26.7 (d, J_{CP} = 6 Hz), 16.5 (d, J_{CP} = 195 Hz), 17.0 (d, J_{CP} = 6 Hz), 15.3 (d, J_{CP} = 5 Hz); ^{31}P NMR ($CDCl_3$) δ 25.7; HRMS (FAB) $[M + H]^+$ found 396.1695, $C_{18}H_{27}N_3O_5P$ requires 396.1688.

Diethyl* trans*-3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3-hydroxycyclobutylphosphonate (*trans*-29) — Epimerisation Reaction

To a cooled (0 °C), stirred solution of cyclobutane *cis*-**29** (1.61 g, 4.07 mmol) in pyridine (17 ml) was added dropwise $SOCl_2$ (0.59 ml, 8.11 mmol). After stirring for 15 min at RT, the reaction mixture was poured into water (50 ml) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with water (2 x 50 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was azeotroped with $CHCl_3$ (3 x 10 ml) on a rotary evaporator to remove remaining traces of pyridine. Flash chromatography (10% EtOH in EtOAc) afforded the desired *trans*-**29** as a colourless oil (1.37 g, 85%). R_f (10% EtOH in EtOAc) = 0.43; ^1H NMR ($CDCl_3$) δ 7.86 (1H, s), 7.37–7.27 (5H, m), 5.52 & 5.47 (2H, ABq, J = 12 Hz), 4.63 (2H, s), 4.09 (4H, m), 3.14 (2H, m), 2.94 (2H, m), 2.37 (1H, br sextet, J = 10 Hz), 1.31 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 154.5, 149.8, 136.3, 128.6, 128.2, 128.1, 77.4, 74.3 (d, J_{CP} = 36 Hz), 71.5, 62.1 (d, J_{CP} = 7 Hz), 36.3 (d, J_{CP} = 5 Hz), 36.1 (d, J_{CP} = 5 Hz), 22.5 (d, J_{CP} = 158 Hz), 16.5 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 28.9; HRMS (FAB) $[M + H]^+$ found 396.1694, $C_{18}H_{27}N_3O_5P$ requires 396.1688.

***Diethyl 3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3-chlorocyclobutylphosphonate* (30) & *Diethyl 3-{1-[(Benzyloxy)methyl]-1,2,4-triazol-5-yl}cyclobut-2-en-1-ylphosphonate* (31)**

In a variation of the procedure described above: to a cooled (0 °C), stirred solution of cyclobutane *cis*-**29** (110 mg, 0.28 mmol) in pyridine (3 ml) was added dropwise $SOCl_2$ (0.10 ml, 1.37 mmol). After stirring for 1 h at RT, the reaction mixture was poured into water (20 ml) and worked up as above. Flash chromatography (10% EtOH in EtOAc) afforded the chlorides **30** (23 mg, 20%, 2:1 ratio of epimers according to ^{1}H NMR), the desired *trans*-**29** (50 mg, 45%), and a mixture of *trans*-**29** and the alkene **31** (40 mg, 35%, 6:1 ratio of *trans*-**29**:**31** according to ^{1}H NMR), all as colourless oils. Further chromatography of an aliquot of the chlorides **30** afforded pure samples of each diastereomer for characterisation.

In a further variation of the procedure described above: to a cooled (0 °C), stirred solution of cyclobutane *cis*-**29** (100 mg, 0.25 mmol) in pyridine (5 ml) was added dropwise $SOCl_2$ (0.11 ml, 1.51 mmol). After stirring for 16 h at RT, the reaction mixture was poured into water (20 ml) and worked up as above. Flash chromatography (gradient elution: 5% → 10% EtOH in EtOAc) afforded the chlorides **30** (90 mg, 86%, 2:1 ratio of epimers according to ^{1}H NMR) and the alkene **31** (10 mg, 11%) as colourless oils. **30** (Less Polar Isomer): R_f (5% EtOH in EtOAc) = 0.57; R_f (10% EtOH in EtOAc) = 0.69; ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, s), 7.39–7.29 (5H, m), 5.68 (2H, s), 4.72 (2H, s), 4.10 (4H, m), 3.48 (2H, m), 3.12 (2H, m), 2.49 (1H, br sextet, J = 10 Hz), 1.32 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 156.4, 149.5, 136.3, 128.7, 128.3, 128.1, 76.8, 71.6, 62.1 (d, J_{CP} = 6 Hz), 56.1 (d, J_{CP} = 36 Hz), 39.7 (d, J_{CP} = 5 Hz), 24.3 (d, J_{CP} = 156 Hz), 16.5 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 28.6; HRMS (FAB) $[M + H]^+$ found 414.1348, $C_{18}H_{26}N_3O_4{}^{35}ClP$ requires 414.1349. **30** (More Polar Isomer): R_f (5% EtOH in EtOAc) = 0.50; R_f (10% EtOH in EtOAc) = 0.62; ^{1}H NMR ($CDCl_3$) δ 7.86 (1H, s), 7.39–7.29 (5H, m), 5.60 (2H, s), 4.63 (2H, s), 4.05 (4H, qn, J =7 Hz), 3.41 (2H, m), 3.22 (1H, br sextet, J = 10 Hz), 2.93 (2H, m), 1.26 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 156.8, 149.9, 136.2, 128.6, 128.2, 128.2, 77.3, 71.3, 62.0 (d, J_{CP} = 7 Hz), 58.4 (d, J_{CP} = 36 Hz), 38.5 (d, J_{CP} = 5 Hz), 25.0 (d, J_{CP} = 157 Hz), 16.5 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 29.7; HRMS (FAB) $[M + H]^+$ found 414.1349, $C_{18}H_{26}N_3O_4{}^{35}ClP$ requires 414.1349. **31**: R_f (10% EtOH in EtOAc) = 0.39; ^{1}H NMR ($CDCl_3$) δ 7.88 (1H, s), 7.38–7.27 (5H, m), 6.59 (1H, s), 5.61 & 5.56 (2H, ABq, J = 12 Hz), 4.56 (2H, s), 4.13 (4H, m), 3.39 (1H, br d, J = 13 Hz), 3.29–3.15 (2 x 1H, overlapping m), 1.32 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 150.8, 149.1, 148.2, 136.2, 133.6 (d, J_{CP} = 11 Hz), 128.5, 128.2, 128.1, 76.9, 70.9, 62.1 (d, J_{CP} = 7 Hz), 37.7 (d, J_{CP} = 152 Hz), 36.1 (d, J_{CP} = 5 Hz), 31.6 (d, J_{CP} = 7 Hz), 16.5 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 27.4; HRMS (FAB) $[M + H]^+$ found 378.1583, $C_{18}H_{25}N_3O_4P$ requires 378.1583.

Cis-*3-hydroxy-3-(1,2,4-triazol-3-yl)cyclobutylphosphonic acid* (cis-*4*)

To a stirred solution of cyclobutane *cis*-**29** (130 mg, 0.33 mmol) in CH_2Cl_2 (4.5 ml) at RT was added TMSBr (0.42 ml, 3.25 mmol) and the reaction mixture stirred for 18 h. Methanol (4.4 ml) was added and stirring continued for a further 1 h, then propylene oxide (0.88 ml) was added and stirring continued for another 1 h. Ether (35 ml) was then added slowly to the reaction mixture whereupon precipitation of the product occurred. The hygroscopic crystals were collected on a sintered glass filter under a stream of nitrogen and washed with ether (5 x 2 ml). After drying *in vacuo*, the product *cis*-**4** was obtained as a white microcrystalline solid (12 mg, 17%) having identical spectroscopic properties to material prepared previously (*vide supra*).

Subjection of cyclobutane *trans*-**29** (30 mg, 0.08 mmol) to identical deprotection conditions using TMSBr (0.10 ml, 0.77 mmol), methanol (1.0 ml) and propylene oxide (0.20 ml) also afforded the product *cis*-**4** as a white microcrystalline solid (5 mg, 29%).

Cis-*3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3-hydroxycyclobutylphosphonic acid* (cis-*33*)

To a stirred solution of cyclobutane *cis*-**29** (300 mg, 0.76 mmol) in CH_2Cl_2 (3 ml) at RT was added TMSBr (0.29 ml, 2.24 mmol) and the reaction mixture stirred for 2.5 h. Methanol (3.0 ml) was added and stirring continued for a further 1 h, then propylene oxide (1.0 ml) was added and stirring continued for another 1 h. After concentration *in vacuo*, the residue was resuspended in water (3 ml) and filtered through a sintered glass frit. Freeze-drying of the filtrate *in vacuo* afforded the product *cis*-**33** as a white amorphous solid (255 mg, quant.).

Subjection of cyclobutane *trans*-**29** (90 mg, 0.23 mmol) to identical deprotection conditions using TMSBr (0.09 ml, 0.70 mmol), methanol (1.0 ml) and propylene oxide (0.33 ml) also afforded the product *cis*-**33** as a white amorphous solid (75 mg, quant.). ^{1}H NMR (D_2O) δ 7.93 (1H, s), 7.31–7.20 (5H, m), 5.64 (2H, s), 4.57 (2H, s), 2.78 (2H, m), 2.46 (2H, m), 2.19 (1H, br sextet, J = 10 Hz); ^{31}P NMR (D_2O) δ 27.7; HRMS (FAB) $[M + H]^+$ found 340.1061, $C_{14}H_{19}N_3O_5P$ requires 340.1062.

Trans-*3-{1-[(benzyloxy)methyl]-1,2,4-triazol-5-yl}-3-hydroxycyclobutylphosphonic acid* (trans-*33*)

To a stirred solution of cyclobutane *trans*-**29** (30 mg, 0.08 mmol) in CH_2Cl_2 (0.5 ml) at RT were added sequentially BSA (0.09 ml, 0.37 mmol) and TMSBr (0.03 ml, 0.23 mmol) and the reaction mixture stirred for 2.5 h. Propylene oxide (0.15 ml) and methanol (0.3 ml) were added sequentially and stirring continued for a further 1 h. After concentration *in vacuo*, the residue was resuspended in water (3 ml) and filtered through a sintered glass frit. Freeze-drying of the filtrate *in vacuo* afforded the product *trans*-**33** as a white amorphous solid (25 mg, quant.). ^{1}H NMR (D_2O) δ 7.90 (1H, s), 7.19–7.01 (5H, m), 5.32 & 5.27 (2H, ABq, J = 12 Hz), 4.33 (2H, s), 2.91–2.80 (2 x 2H, overlapping m), 2.25 (1H, br sextet, J = 10 Hz); ^{31}P NMR (D_2O) δ 25.3; HRMS (FAB) $[M + H]^+$ found 340.1061, $C_{14}H_{19}N_3O_5P$ requires 340.1062.

1-{[(para-methoxybenzyl)oxy]methyl}-1,2,4-triazole

To a stirred suspension of 1,2,4-triazole (2.47 g, 35.8 mmol) in MeCN (60 ml) at RT was added dropwise DBU (7.45 ml, 405 mmol). A solution of chloromethyl *para*-methoxybenzyl ether[64] (crude, theoretically 50.4 mmol) in MeCN (10 ml) was then

added dropwise via cannula while the reaction mixture was cooled in a water bath. Stirring was continued for 16 h and then most of the MeCN was removed *in vacu.o*. The residue was resuspended in EtOAc (75 ml) and washed with NH_4Cl solution (50 ml; sat. aqueous) followed by brine (3 x 50 ml; sat.), The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (EtOAc) afforded the desired product as a colourless oil (4.34 g, 55%). R_f (EtOAc) = 0.39; ^1H NMR ($CDCl_3$) δ 8.25 (1H, s), 8.01 (1H, s), 7.24 (2H, br d, J = 9 Hz), 6.89 (2H, br d, J = 9 Hz), 5.52 (2H, s), 4.52 (2H, s), 3.80 (3H, s); ^{13}C NMR ($CDCl_3$) δ 159.7, 152.2, 143.9, 129.9, 128.0, 114.0, 76.6, 71.0, 55.3; HRMS (FAB) $[M + H]^+$ found 220.1078, $C_{11}H_{14}N_3O_2$ requires 220.1086.

Diethyl 3-(1-{[(para-methoxybenzyl)oxy]methyl}-1,2,4-triazol-5-yl)-3-oxopropylphosphonate (34)

Following the procedure for preparation of ketone **24** (*vide supra*), this time using 1-*para*-methoxybenzyloxymethyl-1,2,4-triazole (5.77 g, 26.3 mmol) and triethyl 3-phosphonopropionate (**23**) (5.73 ml, 26.3 mmol), afforded 11.6 g of a colourless oil (85% conversion to ketone **34**, according to ^1H NMR analysis, with 15% of each starting material remaining) which was taken onto the next step without further purification. R_f (EtOAc) = 0.25; ^1H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.23 (2H, br d, J = 9 Hz), 6.86 (2H, br d, J = 9 Hz), 5.89 (2H, s), 4.56 (2H, s), 4.11 (4H, m), 3.80 (3H, s), 3.46 (2H, dt, J = 11 & 8 Hz), 2.17 (2H, dt, J = 21 & 8 Hz), 1.33 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 189.6 (d, J_{CP} = 16 Hz), 159.6, 150.6, 148.8 (d, J_{CP} = 1 Hz), 129.7, 128.5, 113.9, 77.8, 71.3, 61.8 (d, J_{CP} = 7 Hz), 55.3, 33.8 (d, J_{CP} = 3 Hz), 19.3 (d, J_{CP} = 146 Hz), 16.4; ^{31}P NMR ($CDCl_3$) δ 31.6; HRMS (FAB) $[M + H]^+$ found 412.1633, $C_{18}H_{27}N_3O_6P$ requires 412.1637.

Diethyl 3,4-epoxy-3-(1-{[(para-methoxybenzyl)oxy]methyl}-1,2,4-triazol-5-yl)butylphosphonate (35)

Following the procedure for preparation of epoxide **25** (*vide supra*), this time using ketone **34** (11.6 g of crude, theoretically 26.3 mmol) and trimethylsulphonium methylsulphate (7.97 g, 42.3 mmol) and a reaction time of 2.5 h, afforded 10.8 g of a colourless oil (comprising 76% epoxide **35** and 24% 1-PMBOM-1,2,4-triazole remaining from first step, according to ^1H NMR analysis) which was taken onto the next step without further purification. R_f (10% EtOH in EtOAc) = 0.41; ^1H NMR ($CDCl_3$) δ 7.86 (1H, s), 7.24 (2H, br d, J = 9 Hz), 6.86 (2H, br d, J = 9 Hz), 5.65 (1H, d, J = 11 Hz), 5.55 (1H, d, J = 11 Hz), 4.52 (2H, s), 4.07 (4H, m), 3.79 (3H, s), 3.19 (1H, d, J = 6 Hz), 3.05 (1H, d, J = 6 Hz), 2.53 (1H, m), 2.18 (1H, m), 1.89 (2H, m), 1.29 (6H, td, J = 7 & 2 Hz); ^{13}C NMR ($CDCl_3$) δ 159.6, 153.1, 150.4, 129.8, 128.5, 113.9, 76.8, 71.0, 61.7 (d, J_{CP} = 6 Hz), 55.8, 55.3, 53.6, 28.3 (d, J_{CP} = 3 Hz), 21.1 (d, J_{CP} = 143 Hz), 16.4 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 31.5; HRMS (FAB) $[M + Na]^+$ found 448.1616., $C_{19}H_{28}N_3O_6NaP$ requires 448.1613.

Diethyl* cis-*3-hydroxy-3-(1-{[(para-methoxybenzyl)oxy]methyl}-1,2,4-triazol-5-yl)cyclobutylphosphonate* (cis-*36*) — *'One-pot' Iodohydrin Formation and 1,4-Cyclisation

Following the procedure for preparation of cyclobutane *cis*-**29** (*vide supra*), this time using epoxide **35** (10.8 g of crude, theoretically 26.3 mmol) and MeMgI solution (35.1 ml, 105 mmol), afforded 9.48 g of a colourless oil. ^1H and ^{31}P NMR analysis of the crude reaction product indicated formation of a single cyclobutane diastereomer. Flash chromatography (gradient elution: 0% → 5% → 10% EtOAc in hexane) afforded recovered 1-PMBOM-1,2,4-triazole (1.14 g) and the product cyclobutane *cis*-**36** (5.45 g, 49% over 3 steps from **23**, 61% based on recovered 1-PMBOM-1,2,4-triazole), both as colourless oils. *cis*-**36**: R_f (5% EtOH in EtOAc) = 0.43; ^1H NMR ($CDCl_3$) δ 7.84 (1H, s), 7.25 (2H, br d, J = 9 Hz), 6.85 (2H, br d, J = 9 Hz), 6.15 (1H, s), 5.75 (2H, s), 4.55 (2H, s), 4.11 (4H, m), 3.80 (3H, s), 3.13 (2H, m), 2.72 (2H, m), 2.51 (1H, br sextet, J = 10 Hz), 1.32 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 159.5, 158.0, 149.6, 129.8, 128.9, 113.9, 77.1, 71.1 (d, J_{CP} = 19 Hz), 70.8, 62.3 (d, J_{CP} = 7 Hz), 55.3, 37.5 (d, J_{CP} = 5 Hz), 21.7 (d, J_{CP} = 151 Hz), 16.5 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 35.0; HRMS (FAB) $[M + H]^+$ found 426.1803, $C_{19}H_{29}N_3O_6P$ requires 426.1794.

Diethyl* trans-*3-hydroxy-3-(1-{[(para-methoxybenzyl)oxy]methyl}-1,2,4-triazol-5-yl)cyclobutylphosphonate* (trans-*36*) — *Epimerisation Reaction

Following the procedure for epimerisation of cyclobutane *cis*-**29** (*vide supra*), this time using cyclobutane *cis*-**36** (1.55 g, 3.64 mmol) and $SOCl_2$ (0.59 ml, 8.11 mmol) and a reaction time of 15 min, afforded, after flash chromatography (gradient elution: 10% → 15% EtOH in EtOAc), the desired *trans*-**36** as a colourless oil (1.55 g, quant.). R_f (10% EtOH in EtOAc) = 0.27; ^1H NMR ($CDCl_3$) δ 7.88 (1H, s), 7.25 (2H, br d, J = 9 Hz), 6.87 (2H, br d, J = 9 Hz), 5.50 & 5.45 (2H, ABq, J = 12 Hz), 4.58 (2H, s), 4.11 (4H, m), 3.81 (3H, s), 3.14 (2H, m), 2.95 (2H, m), 2.38 (1H, m), 1.32 (6H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 159.6, 154.4, 149.8, 129.9, 128.3, 113.9, 76.5, 74.3 (d, J_{CP} = 36 Hz), 71.1, 62.1 (d, J_{CP} = 7 Hz), 55.3, 36.3 (d, J_{CP} = 5 Hz), 36.1 (d, J_{CP} = 5 Hz), 22.6 (d, J_{CP} = 158 Hz), 16.5 (d, J_{CP} = 6 Hz); ^{31}P NMR ($CDCl_3$) δ 28.9; HRMS (FAB) $[M + H]^+$ found 426.1807, $C_{19}H_{29}N_3O_6P$ requires 426.1794.

Cis-*3-hydroxy-3-(1-{[(para-methoxybenzyl)oxy]methyl}-1,2,4-triazol-5-yl)cyclobutylphosphonic acid* (cis-*37*)

Following the procedure for preparation of phosphonic acid *trans*-**33** (*vide supra*), this time using cyclobutane *cis*-**36** (170 mg, 0.40 mmol), BSA (0.49 ml, 2.00 mmol), TMSBr (0.16 ml, 1.24 mmol) and a reaction time of 6 h, followed by propylene oxide (0.4 ml) and methanol (0.8 ml), afforded the product *cis*-**37** as a white amorphous solid (146 mg, quant.). ^1H NMR (D_2O) δ 7.92 (1H, s), 7.17 (2H, br d, J = 9 Hz), 6.85 (2H, br d, J = 9 Hz), 5.60 (2H, s), 4.48 (2H, s), 3.79 (3H, s), 2.76 (2H, m), 2.45 (2H, m), 2.17 (1H, br sextet, J = 10 Hz); ^1H NMR (MeOD) δ 7.81 (1H, s), 7.14 (2H, br d, J = 9 Hz), 6.77 (2H, br d, J = 9 Hz), 5.62 (2H, s), 4.46 (2H, s), 3.67 (3H, s), 2.85 (2H, m), 2.50 (2H, m), 2.19 (1H, br sextet, J = 10 Hz); ^{31}P NMR (D_2O) δ 27.6; ^{31}P NMR (MeOD) δ 28.7.

Trans-*3-hydroxy-3-(1-{[(para-methoxybenzyl)oxy]methyl}-1,2,4-triazol-5-yl)cyclobutylphosphonic acid* (trans-*37*)

Following the procedure for preparation of phosphonic acid *trans*-**33** (*vide supra*), this time using cyclobutane *trans*-**36** (1.55 g, 3.64 mmol), BSA (4.45 ml, 18.2 mmol), TMSBr (1.41 ml, 10.9 mmol) and a reaction time of 6 h, followed by propylene oxide (3.7 ml) and methanol (7.4 ml), afforded the product *trans*-**37** as a white amorphous solid (1.34 g, quant.). ^{1}H NMR (D_2O) δ 7.90 (1H, s), 6.95 (2H, br d, J = 9 Hz), 6.64 (2H, br d, J = 9 Hz), 5.54 & 5.25 (2H, ABq, J = 12 Hz), 4.21 (2H, s), 3.54 (3H, s), 3.00–2.82 (2 x 2H, overlapping m), 2.28 (1H, br sextet, J = 10 Hz); ^{1}H NMR (MeOD) δ 7.84 (1H, s), 7.08 (2H, br d, J = 9 Hz), 6.74 (2H, br d, J = 9 Hz), 5.41 & 5.34 (2H, ABq, J = 12 Hz), 4.39 (2H, s), 3.66 (3H, s), 3.00 (4H, m), 2.24 (1H, br sextet, J = 10 Hz); ^{31}P NMR (D_2O) δ 25.6; ^{31}P NMR (MeOD) δ 26.0.

Cis-*3-hydroxy-3-(1,2,4-triazol-3-yl)cyclobutylphosphonic acid* (cis-*4*)

To a stirred solution of phosphonic acid *trans*-**37** (434 mg, 1.18 mmol) in CH_2Cl_2 (15 ml) at RT were added water (1 ml) and DDQ (1. 33 g, 5.86 mmol). After stirring for 18 h, water (20 ml) and CH_2Cl_2 (10 ml) were added. The mixture was filtered through a plug of glass wool, and the layers separated. Freeze-drying of the aqueous layer *in vacuo* afforded the product *cis* **4** as a white solid (255 mg, quant.) having identical spectroscopic properties to material prepared previously (*vide supra*).

Alternatively: A stirred solution of phosphonic acid *trans*-**37** (278 mg, 0.75 mmol) and naphthalene-1,4-dicarbonitrile[66] (134 mg, 0.75 mmol) in MeCN (120 ml) and water (30 ml) was irradiated using a 145W medium pressure mercury lamp immersed in a water-jacket-cooled Pyrex reaction vessel. After 14.5 h of irradiation, the reaction mixture was concentrated *in vacuo*. The residue was resuspended in water and centrifuged at 5000 rpm. The supernatant was then freeze-dried *in vacuo* to afford the product *cis* **4** as a white solid (162 mg, quant.) having identical spectroscopic properties to material prepared previously (*vide supra*).

ACKNOWLEDGEMENT

We thank Dr Anthony O'Sullivan (Ciba-Geigy, Basel) and Dr Ichiro Mori (International Research Laboratories, Ciba-Geigy, Japan) for helpful discussions; also Grety Rihs for X-ray crystallographic analysis, Dr Josef Schneider for NOE measurements, and Dr Hans-Peter Kriemler and Roland Dahinden for high resolution mass spectroscopy (all Ciba-Geigy, Basel).

REFERENCES AND NOTES

† 'Synthesis and Reactivity of Compounds with Cyclobutane Ring(s): Part 20.' For Part 19, see: Alder, A.; Belluš, D. *J. Am. Chem. Soc.* **1983**, *105*, 6712.

‡ Present addresses of the authors: (a) F. Hoffmann–La Roche Ltd, Pharmaceuticals Division, CH-4070 Basel, Switzerland. (b) Novartis Pharmaceuticals Inc., East Hanover, NJ 07936, USA. (c) Novartis Pharma AG, CH-4002 Basel, Switzerland. (d) University of Fribourg, Institute of Organic Chemistry, CH-1700 Fribourg, Switzerland.

1. (a) Kishore, G. M.; Shah, D. M. *Ann. Rev. Biochem.* **1988**, *57*, 627. (b) Ray, T. B. In *Target Sites of Herbicide Action;* Böger, P.; Sandmann, G., Eds.; CRC Press Inc.: Boca Raton, Florida, **1989**, p 105. (c) *Physiology of Herbicide Action* Devine, M. D.; Duke, S. O.; Fedke, C., Eds.; PTR Prentice Hall: Englewood Cliffs, New Jersey, **1993**, p 251. (d) Moreland, D. E. *Z. Naturforsch. C* **1993**, *48*, 121.

2. For more recent studies, see: (a) Bartlett, P. A.; Nakagawa, Y.; Johnson, C. R.; Reich, S. H.; Luis, A. *J. Org. Chem.* **1988**, *53*, 3195. (b) Myrvold, S.; Reimer, L. M.; Pompliano, D. L.; Frost, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1861. (c) Bender, S. L.; Widlanski, T.; Knowles, J. R. *Biochemistry* **1989**, *28*, 7560. (d) Widlanski, T.; Bender, S. L.; Knowles, J. R. *Biochemistry* **1989**, *28*, 7572. (e) Montchamp, J.-L.; Piehler, L. T.; Frost, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 4453. (f) Marzabadi, M. R.; Font, J. L.; Gruys, K. J.; Pansegrau, P. D.; Sikorski, J. A. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1435. (g) Peterson, M. L.; Corey, S. D.; Font, J. L.; Walker, M. C.; Sikorski, J. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2853. (h) Forlani, G.; Lejczak, B.; Kafarski, P. *Pesticide Biochem. Physiol.* **1996**, *55*, 180.

3. For more recent studies, see: (a) Pirrung, M. C.; Holmes, C. P.; Horowitz, D. M.; Nunn, D. S. *J. Am. Chem. Soc.* **1991**, *113*, 1020 and references cited therein. (b) Hawkes, T. R.; Cox, J. M.; Fraser, T. E. M.; Lewis, T. *Z. Naturforsch. C* **1993**, *48*, 364.

4. Work reported by Ciba-Geigy: (a) Mori, I.; Iwasaki, G.; Scheidegger, A.; Koizumi, S.; Hayakawa, K.; Mano, J. WO 92/19629, **1992**. (b) Hayakawa, K.; Mori, I.; Iwasaki, G.; Matsunaga, S. EP 0528760, **1993**. (c) Mori, I.; Matsunaga, S.; Kimura, Y. GB 2271113, **1994**. (d) Ward, E. R.; Volrath, S.; Koizumi, S.; Tada, S.; Mori, I.; Iwasaki, G. WO 94/26909, **1994**. (e) Mori, I.; Kimura, Y.; Matsunaga, S.; Nakano, T.; O'Sullivan, A. C. WO 95/18811, **1995**. (f) Mori, I.; Fonné-Pfister, R.; Matsunaga, S.; Tada, S.; Kimura, Y.; Iwasaki, G.; Mano, J.; Hatano, M.; Nakano, T.; Koizumi, S.; Scheidegger, A.; Hayakawa, K.; Ohta, D. *Plant Physiol.* **1995**, *107*, 719. (g) Mori, I.; Iwasaki, G.; Kimura, Y.; Matsunaga, S.; Ogawa, A.; Nakano, T.; Buser, H.-P.; Hatano, M.; Tada, S.; Hayakawa, K. *J. Am. Chem. Soc.* **1995**, *117*, 4411. (h) Mori, I.; Iwasaki, G.; Hayakawa, K. *Yuki Gosei Kagaku Kyokaishi* **1996**, *54*, 514.

5. Work reported by ICI/Zeneca: (a) Cox, J. M. EP 0078613, **1983**. (b) Hawkes, T. R.; Cox, J. M.; Barnes, N. J.; Beautement, K.; Edwards, L. S.; Kipps, M. R.; Langford, M. P.; Lewis, T.; Ridley, S. M.; Thomas, P. G. *Proceedings of British Crop Protection Conference (Weeds)*; **1993**, 739. (c) Cox, J. M.; Bellini, P.; Barrett, R.; Ellis, R. M.; Hawkes, T. R. WO 93/15610, **1993**. (d) Barnes, N. J.; Cox, J. M.; Hawkes, T. R.; Knee, A. G. GB 2280676, **1995**.

6. Work reported by AgrEvo: (a) Pillmoor, J. B.; Lindell, S. D.; Briggs, G. G.; Wright, K. In *Eighth International Congress of Pesticide Chemistry: Options 2000*; Ragsdale, N. N.; Kearney, P. C.; Plimmer, J. R., Eds.; ACS Symposium Series, American Chemical Society, Washington, D.C., **1995**, p 292. (b) Wright, B. J.; Lindell, S. D.; Foster, S. G.; Milling, R. J. WO 95/14385, **1995**. (c) Lindell, S. D.; Earnshaw, C. G.; Wright, B. J.; Carver, D. S.; O'Mahoney, M. J.; Saville-Jones, E. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 547.

7. Biochemistry and mechanism of imidazole glycerol phosphate dehydratase: (a) Ames, B. N.; Mitchell, H. K. *J. Biol. Chem.* **1955**, *212*, 687. (b) Ames, B. N. *J. Biol. Chem.* **1957**, *228*, 131. (c) Mano, J.; Hatano, M.; Koizumi, S.; Tada, S.; Hashimoto, M.; Scheidegger, A. *Plant Physiol.* **1993**, *103*, 733. (d) Saika, H.; Früh, T.; Iwasaki, G.; Koizumi, S.; Mori, I.; Hayakawa, K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2129. (e) Moore, J. A.; Parker, A. R.; Davisson, V. J.; Schwab, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 3338. (f) Parker, A. R.; Moore, J. A.; Schwab, J. M.; Davisson, V. J. *J. Am. Chem. Soc.* **1995**, 117, 10605.

8. Histidine biosynthesis: (a) Martin, R. G.; Berbereich, M. A.; Ames, B. N.; Davis, W. W.; Goldberger, R. F.; Yourno, J. D. In *Methods in Enzymology*; Tabor, H.; Tabor, C. W., Eds.; Academic Press: New York, **1971**; Vol. 17B, pp 3–44. (b) Miflin, B. J. In *The Biochemistry of Plants*; Miflin, B. J., Ed.; Academic Press: New York, **1980**; Vol. 5, pp 533–539.

9. (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349. (b) Blackburn, G. M. *Chem. Ind. (London)* **1981**, *7*, 134.

10. We thank Dr Keigo Gohda (International Research Laboratories, Ciba-Geigy, Japan) for the CAMM analysis.

11. Note that the individual enantiomers of *trans*-**3**, which were separated by chiral HPLC, show significantly different inhibition levels: IC_{50} = 18 nM for (+)-*trans*-**3** *cf.* IC_{50} = 1800 nM for (−)-*trans* **3**. See ref. 4g.

12. For reviews of puckering in cyclobutanes, see: (a) Cotton, F. A.; Frenz, B. A. *Tetrahedron* **1974**, *30*, 1587. (b) Legon, A. C. *Chem. Rev.* **1980**, *80*, 231. (c) Crabb, T. A.; Patel, A. V. In *Second Supplements to the Second Edition of Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, **1992**, Vol. IIA and IIB (Partial), pp 8–13.

13. *Cf. Cis*-1,3-disubstituted cyclobutanes, in which both substituents may adopt pseudo-equatorial positions on the ring, are known to be energetically preferred over their 1,3-*trans* isomers. See: (a) Allinger, N. L.; Tushaus, L. A. *J. Org. Chem.* **1965**, *30*, 1945. (b) Wiberg, K. B.; Lampman, G. M. *J. Am. Chem. Soc.* **1966**, *88*, 4429. (c) Jonvik, T.; Griesbaum, K. *J. Mol. Struct.* **1988**, *172*, 203.

14. For reviews concerning the stereochemistry of four-membered rings, see: (a) Moriarty, R. M. *Top. Stereochem.* **1974**, *8*, 271. (b) ref. 12c.

15. A similar strategy had already been successfully employed in the synthesis of the cyclohexyl analogue *trans*-**3**, which was prepared via triazole addition to 3-phosphonocyclohexanone. See ref. 4g.

16. For a review, see: Belluš, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797 and references cited therein.

17. For examples, see *inter alia*: (a) Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 130. (b) Belluš, D.; Fischer, H.-P.; Greuter, H.; Martin, P. *Helv. Chim. Acta* **1978**, *61*, 1784. (c) Belluš, D. *J. Am. Chem. Soc.* **1978**, *100*, 8026. (d) Belluš, D. *J. Org. Chem.* **1979**, *44*, 1208. (e) Brady, W. T.; Lloyd, R. M. *J. Org. Chem.* **1979**, *44*, 2560. (f) Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525. For reviews, see: (g) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. (h) Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159. (i) Tidwell, T. T. *Ketenes*; John Wiley: New York, **1995**, pp 459–536.

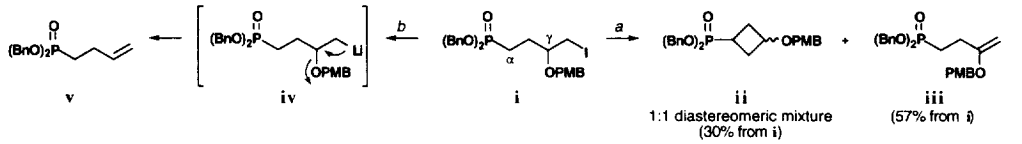
18. For reviews on the synthetic applications of phosphonate-stabilized carbanions, see: (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87. (b) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

19. Base-mediated cyclisation of the γ,δ-epoxyphosphonate itself appears to be unsuitable in this instance, since it might be expected to proceed in 1,3 fashion to afford the corresponding cyclopropane rather than the cyclobutane, according to precedent from similar cyclisation reactions employing γ,δ-epoxynitriles (ref. 19a) and γ,δ-epoxysulphones (ref 19b): where substrates have a choice between 1,3 and 1,4-cyclisation, the former is almost always exclusively observed. See: (a) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. (b) Gaoni, Y. *Tetrahedron Lett.* **1976**, 503.

20. *Cf.* 1,4-cyclisation of iodohydrins obtained from γ,δ-epoxynitriles and γ,δ-epoxysulphones has already been reported: (a) Corbel, B.; Durst, T. *J. Org. Chem.* **1976**, *41*, 3648. (b) Corbel, B.; Decesare, J. M.; Durst, T. *Can. J. Chem.* **1978**, *56*, 505. (c) Decesare, J. M.; Corbel, B.; Durst, T.; Blount, J. F. *Can. J. Chem.* **1981**, *59*, 1415. However, we are not aware of any precedent for the cyclisation of iodohydrins obtained from γ,δ-epoxyphosphonates.

21. Substrates lacking a sulphone group in the α position were originally prepared (**i**, **Scheme i**). In this case, KHMDS-mediated cyclisation proceeded in lower yield (30% yield of **ii** from **i**), the major side reaction being competing deprotonation at the γ position with concomitant elimination of iodide to produce the enol ether **iii**. Introduction of a sulphone group at the

α position successfully enhanced the acidity of the α position relative to γ, so eradicating the side reaction. Note that use of ^{n}BuLi as base was completely unsuccessful: metal-halogen exchange occurred in preference to deprotonation, and the resulting alkyllithium **iv** then underwent facile elimination to afford alkene **v** as the only product.



v **iv** **i** **ii** 1:1 diastereomeric mixture (30% from **i**) **iii** (57% from **i**)

Scheme i (*a*) KHMDS, THF, –78 °C → RT; (*b*) ^{n}BuLi, THF, –78 °C → RT.

22. *Cf.* (a) Blumenkopf, T. A. *Synth. Commun.* **1986**, *16*, 139. (b) Motoyoshiya, J.; Hongo, Y.; Tanaka, H.; Hayasahi, S. *Synth. Commun.* **1991**, *21*, 997.

23. Mandal, A. K.; Soni, N. R.; Ratnam, K. R. *Synthesis* **1985**, 274.

24. The iodohydrin hydroxyl must be protected, otherwise the epoxide **8** may re-form during base-mediated cyclisation. The presence of any epoxide in the cyclisation reaction mixture could lead to significant amounts of 1,3-cyclisation occurring (*cf.* footnote 19).

25. Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

26. Under basic conditions, significant re-formation of epoxide **8** could occur instead of the desired hydroxyl protection.

27. The formation of diastereomers is inconsequential, since this centre is later oxidised to the ketone.

28. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

29. Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*; Fourth Edition; McGraw-Hill: Maidenhead, England, **1987**, p 48.

30. TBS iodide has already been used in epoxide-opening reactions to form silylated iodohydrins, but a more demanding experimental procedure was required involving the initial preparation of (phenylselanyl)-*tert*-butyldimethylsilane. See: (a) Detty, M. R. *J. Org. Chem.* **1980**, *45*, 924. (b) Detty, M. R.; Seidler, M. D. *J. Org. Chem.* **1981**, *46*, 1283. (c) Detty, M. R.; Seidler, M. D. *Tetrahedron Lett.* **1982**, *23*, 2543. For the use of TMS iodide, see: (d) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1980**, *21*, 2329. (e) Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 1429.

31. TMS bromide is already known as a phosphonate deprotecting reagent (see ref. 37). TBS iodide is presumably insufficiently reactive to cleave the diethyl phosphonate **8**, but note that the more reactive dibenzyl phosphonates may not be used under these reaction conditions, since in this case we observed phosphonate cleavage in place of epoxide-opening.

32. (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064. (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713.

33. For another example of a one-pot silyl ether deprotection-oxidation procedure which was published during the course of this work, see: Wilson, N. S.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2918.

34. Anderson, D. K.; Sikorski, J. A.; Reitz, D. B.; Pilla, L. T. *J. Heterocyclic Chem.* **1986**, *23*, 1257.

35. Norcross, R. D.; Belluš, D. unpublished results.

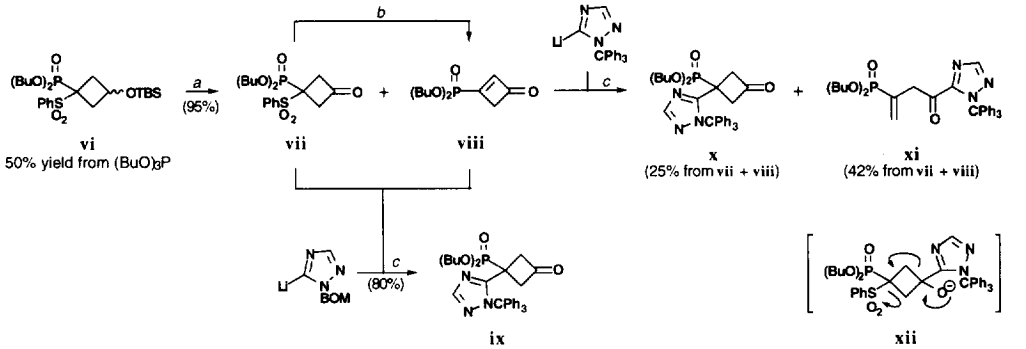
36. We postulate that the low conversion may be due to the lithiated triazole preferentially functioning as a base rather than as a nucleophile, and deprotonating **5** α to the phosphonate (or α to the ketone). This may also have a bearing on the diastereoselectivity of the reaction (*vide infra*).

37. (a) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, 155. (b) McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, 739.

38. We thank Dr Ichiro Mori (International Research Laboratory, Ciba-Geigy, Japan) for supplying the IGPD assay results. For details of the assay protocol, see footnote 12 in ref. 4g.

39. In a further attempt to access the desired *trans* diastereomer using the existing route, triazole addition *prior to* desulphonation was examined. Thus deprotection and oxidation of cyclobutane **vi** (prepared in the same way as **17** used previously, but now employing a dibutyl phosphonate to reduce the volatility of later intermediates) afforded the ketone **vii** (**Scheme ii**). Chromatographic purification of ketone **vii** on silica gel led to varying amounts of elimination to afford a mixture of ketone **vii** and enone **viii**. If required, complete conversion to the enone could be achieved by stirring the mixture over basic alumina (see: Vidal, J.; Huet, F. *Tetrahedron Lett.* **1986**, *27*, 3733), but in general the subsequent addition reactions were performed with mixtures of **vii** and **viii**. It was envisaged that triazole addition to the disubstituted ketone **vii** might give rise to a mixture of diastereomers, so providing at least some of the desired *trans* adduct. Alternatively, regioselective addition of

triazole to the carbonyl group of enone **viii**, followed by hydrogenation of the olefin using heterogeneous catalysis, might conceivably also provide the desired *trans* diastereomer of the adduct. In the event, the outcome of the addition reactions was critically dependent on the choice of protecting group used on the triazole. Thus, use of 5-lithio-1-(BOM)-1,2,4-triazole afforded only the undesired adduct **ix** in high yield (implying complete *in situ* elimination to the enone **viii**, followed by exclusively undesired conjugate addition to the enone). In contrast, use of 5-lithio-1-trityl-1,2,4-triazole gave a mixture of products: one (**x**) arising from conjugate addition to the enone, the other (**xi**) arising from addition to the ketone followed by Grob-style fragmentation of the resulting adduct **xii**. Thus in neither case were the reaction products of any use for the task in hand. Note, however, that the yields for these latter addition reactions were generally much higher than the yields for addition to ketone **5**, suggesting that the presence of an acidic proton α to the phosphonate in ketone **5** is detrimental in addition reactions with lithiated triazoles.



Scheme ii (*a*) (i) 10 mol% *p*-TsOH, Me_2CO/H_2O, RT; (ii) Jones oxidation, RT; (b) basic Al_2O_3, CH_2Cl_2, RT; (c) THF, –78 °C.

40. *cf.* Footnote 21.

41. Mosset, P.; Grée, R. *Synth. Commun.* **1985**, *15*, 749. See also: Kutsuma, T.; Nagayama, I.; Okazaki, T.; Sakamoto, T.; Akaboshi, S. *Heterocycles* **1977**, *8*, 397.

42. This fortuitous result is presumably due to the non-polar nature of the BOM protecting group on the triazole, which reduces the propensity of the substrate to partition into the basic aqueous phase. Use of the trityl protecting group is similarly successful, but when more polar triazole protecting groups such as *N,N*-dimethylsulfonamide are used, complete phosphonate hydrolysis is observed.

43. We postulate that in this instance the epoxide is now sterically more encumbered than in the previous substrate **8**, thus TBS iodide-mediated phosphonate cleavage now occurs in preference to epoxide opening. See also footnote 31.

44. Similar conditions were introduced by Durst and co-workers to obtain cyclobutane formation from γ,δ-epoxysulphones (see ref. 20). Note that these cyclisation conditions were unsuccessful when using epoxide **8**, in which case problems arose due to the nucleophilicity of the ensuing unprotected secondary alcoholate.

45. X-ray crystallographic data, including a table of refined atomic coordinates, have been deposited by the Editor with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44-1223-336033 or e-mail: teched@chemcrys.cam.ac.uk).

46. Confirmation of stereochemistry, prior to obtaining the X-ray crystal structure of *cis*-**29**, was provided by using 5-lithio-1-trityl-1,2,4-triazole in place of 5-lithio-1-BOM-1,2,4-triazole in the latest route: the cyclobutane product was spectroscopically identical (^1H, ^{13}C, ^{31}P NMR) to material prepared by the original route whose stereochemistry had been determined by NOE experiments (*cis*-**19**). Also, total deprotection of the latest material, *cis*-**29**, under standard conditions (excess TMSBr, 18 h) afforded material which was spectroscopically identical (^1H, ^{13}C, ^{31}P NMR) to material prepared in the original route (*cis*-**4**).

47. For another example of X-ray crystal structures of 1,1,3-trisubstituted cyclobutanes, see: Allan, R. D.; Hanrahan, J. R.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Mitrovic, A. D. *J. Med. Chem.* **1990**, *33*, 2905.

48. By using only a stoichiometric equivalent of $SOCl_2$, the yield of *trans*-**29** could be improved to 85%.

49. We initially suspected the intermediacy of a long-lived carbocation, but this does not appear to be the case: quenching the reaction with methanol does not lead to production of the corresponding methyl ether **32**, nor does quenching the reaction with triethylsilane afford any of the corresponding deoxy product.

50. O'Sullivan, A. C.; Cederbaum, F. (Ciba-Geigy, Basel), unpublished results. Note that elimination would be expected to be far less likely in the case of the cyclobutane due to the increased ring-strain.

51. Note that the cyclohexane analogue is configurationally stable under the same reaction conditions; the stereochemical lability of *trans*-**4** appears to be a unique, and unanticipated, consequence of the cyclobutane ring.

52. On treatment of a D_2O solution of *trans*-**33** with aliquots of formic acid, slow epimerisation to *cis*-**33** was observed. The epimerisation could be monitored by ^1H and ^{31}P NMR.

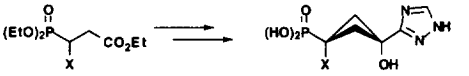
53. The PMBOM group was originally introduced for the protection of alcohols. See: Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125.

54. The use of the trityl protecting group was not possible, since this group was found not to survive the $SOCl_2$-mediated epimerisation reaction.

55. Pandey, G.; Krishna, A. *Synth. Commun.* **1988**, *18*, 2309.

56. We thank Bernhard Walliser of the Hydrogenation Laboratory of Ciba-Geigy (Basel) for performing several hydrogenolysis reactions using a variety of specially purified catalysts.

57. We postulate that the extremely facile epimerisation of *trans*-**4** occurs via deprotonation α to the phosphonate group, although it is presently unclear why this proton should be so much more acidic than in the corresponding cyclohexane analogue *trans*-**3**. If this is the case, then simply blocking this site with a small non-removable substituent, such as methyl (**xii**) or fluorine (**xiii**) — both of which should be synthetically accessible via the existing route — may allow the preparation of a configurationally stable herbicide candidate.



X = Me, F

trans-**xii** X = Me
trans-**xiii** X = F

58. For a recent example of a chiral phosphonate which proved susceptible to ready epimerisation, see: Lawrence, R. M.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V. H.; Magnin, D. R.; Sulsky, R. B.; DiMarco, J. D.; Gougoutas, J. Z.; Beyer, B. D.; Taylor, S. C.; Lan, S.-J.; Ciosek, C. P., Jr.; Harrity, T. W.; Jolibois, K. G.; Kunselmann, L. K.; Slusarchyk, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 11688.

59. Gaussian 94, Revision D3: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian Inc., Pittsburgh PA, **1995**.

60. Using test calculations to try and reproduce the established structure of cyclobutanone (see: footnote 7 in ref. 16), accurate ring puckering was only obtained using levels as high as HF/6-311G**; lower levels of calculation (HF/6-31G** and below) generated flat cyclobutane rings as the lowest energy conformers.

61. Note that a higher energy 'ring-flipped' conformer was found for *cis*-**4** (**D** in **Fig. 3**, E_{rel} = +2.68 kJ mol^{-1}), in which there is an intramolecular hydrogen bond between the phosphonic acid and hydroxyl groups. This conformer was found to be energetically much more significant at lower levels of calculation (at HF/6-311G** level, **C** had E_{rel} = +0.87 kJ mol^{-1} *cf* **D** had E_{rel} = +0.00 kJ mol^{-1}), and thus appears to be an artefact of the method of calculation used: the calculations were performed in the gas phase and at lower levels of calculation, i.e. when diffuse orbitals were not used, the energetic contribution from internal hydrogen bonds may be over-emphasised.

62. Jones reagent was prepared by dropwise addition of H_2SO_4 (17.4 ml; 98%) to a cooled (0 °C), stirred solution of CrO_3 (20.6 g) in water (60 ml).

63. Pd(II)-mediated cleavage of TBS ethers: Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

64. Alternatively, to a solution of cyclobutane **18** in acetone/water (20:1) was added *para*-toluenesulphonic acid (10 mol%) and stirring continued for 24 h.

65. Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.

66. Heiss, L.; Paulus, E. F.; Rehling, H. *Liebigs Ann. Chem.* **1980**, 1583.

(*Received in Germany* 30 *April* 1997; *accepted* 4 *June* 1997)