β-Aminophosphonic compounds derived from methyl 1-dimethoxyphosphoryl-2-succinimidocyclohex-3-ene-1-carboxylates

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Compounds **3a**,**b**, the [4 + 2] cycloadducts of trimethyl 2-phosphonoacrylate and *N*-buta-1,3-dienylsuccinimide, have been transformed into various β-aminophosphonic acid derivatives **4**–**17** by selective deprotection, epoxidation, dihydroxylation, and oxidative cleavage of the cyclohexenyl C–C double bond.

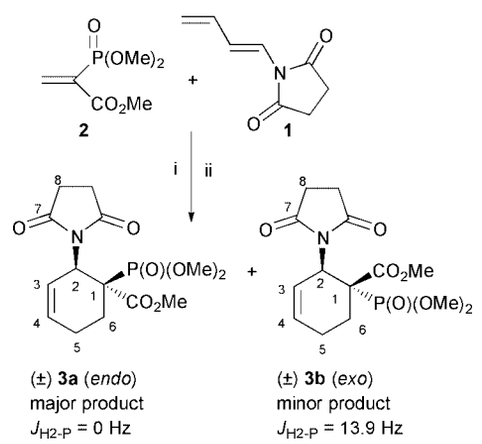
Introduction

Aminophosphonic acid derivatives with the amino substituent in other than the α-position have attracted growing interest in medicinal chemistry due to their biological properties.[1] The usual methods for the synthesis of aminophosphonic acid derivatives are the Arbuzov and Michaelis–Becker reactions,[2] the electrophilic addition on phosphonate-stabilized α-carbanions,[3] and the Michaël addition on vinyl phosphonates.[4] Some years ago, we became interested in the development of new general synthetic routes towards aromatic[5] and aliphatic[6,7] β-, γ-, and δ-aminophosphonic acid derivatives, and substituted cyclohexenes (or cyclohexa-1,4-dienes) could be the precursors of both series, either by dehydrogenation, or by oxidative ring cleavage. As the Diels–Alder reaction is a well-established regio- and stereoselective method in the construction of six-membered rings, we investigated the possibility of using aminodienes and phosphono-dienophiles as partners in [4 + 2] cycloadditions.[8] In this paper, cycloadducts **3a** and **3b** have been considered as model compounds for the investigation of various transformations leading to new β-aminophosphonic acid derivatives.

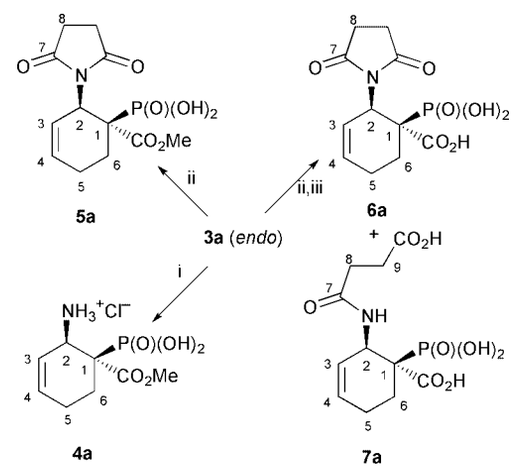
Results and discussion

N-Buta-1,3-dienylsuccinimide **1**[9] (stable under our experimental conditions), cycloadds to vinylphosphonate dienophiles, provided that they are activated by an electron-withdrawing substituent in the geminal[7] or vicinal position.[8] This is exemplified by the reaction with trimethyl 2-phosphonoacrylate **2**[10] furnishing a 65 : 35 mixture of stereoisomers **3a** and **3b** in 93% yield (Scheme 1). A pure fraction of the major isomer **3a** was isolated by crystallization from toluene; NMR data and X-ray diffraction analysis have previously established the *cis* axial/equatorial ("*endo*") orientation of the succinimido and phosphonate substituents, respectively.[6] A pure fraction of the minor isomer **3b**, and mixtures of **3a** and **3b** with different ratios, were obtained by column chromatography on silica gel; the minor isomer **3b** possesses the *trans* axial/axial ("*exo*") orientation of the succinimido and phosphonate substituents.

Hydrolysis of the succinimido group and the phosphoryl dimethyl group for compounds **3a**,**b** occurred in refluxing aqueous HCl,[11] but the methyl carboxylate group remained unchanged. The β-aminophosphonic acids **4a** (Scheme 2) and **4b** (Scheme 3) were isolated in 84% yield and characterized by NMR. The coupling constant between H(2) and phosphorus



Scheme 1 *Conditions*: i, CH_3CN, hydroquinone (0.2 equiv.), 65 °C, 48 h; ii, flash chromatography on silica gel.



Scheme 2 *Reagents and conditions*: i, 6 M HCl, reflux, 3 days; ii, $BrSiMe_3$ (excess), $CHCl_3$ or CH_3CN, 20 °C, 17 h, then H_2O; iii, 1.6 M LiOH, 100 °C, 48 h, then H^+.

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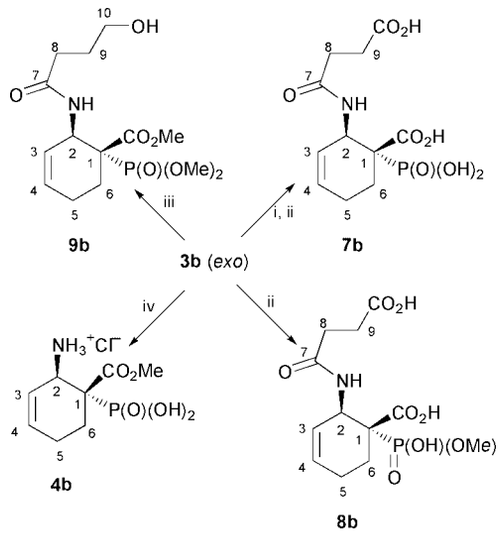


Scheme 3 *Reagents and conditions*: i, $BrSiMe_3$ (excess), CH_3CN, 20 °C, 20 h; ii, 1.6 M LiOH, 100 °C, 12 h to 48 h; iii, $NaBH_4$, *i*PrOH–H_2O 20 °C, 20 h; iv, 6 M HCl, reflux, 3 days.

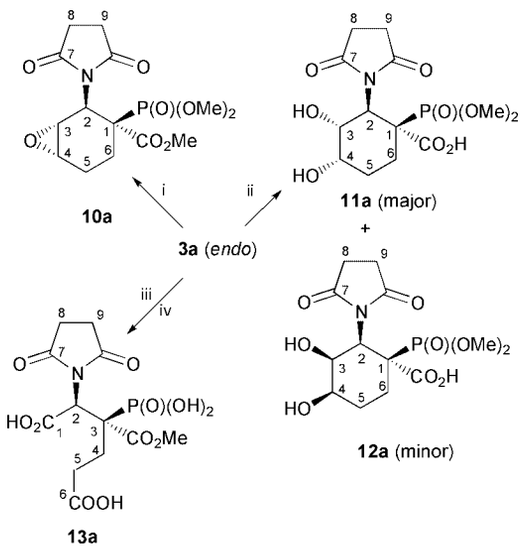
appears to be characteristic of the *endo* or *exo* configuration [12] and values of 4.9 and 8.0 Hz correspond to dihedral angles H–C–C–P of about 60° and 50°, respectively. The stability of the carboxylic ester under strongly acidic conditions is surprising,[8] and probably results from a steric protection by the geminal phosphoryl moiety.

Selective bis-demethylation of the phosphonate group was performed by treatment of **3** with a halogenotrialkylsilane.[13,14] Thus, reaction of **3a** with trimethylsilyl bromide in chloroform at room temperature furnished the phosphonic acid **5a** (Scheme 2) and the coupling constant of 2.9 Hz between H(2) and phosphorus reveals a dihedral angle H–C–C–P of about 70°.[12] When the treatment with trimethylsilyl bromide was followed by saponification (hot aqueous LiOH, 48 h), a mixture (1 : 1) of the mono-phosphoryl and dicarboxylic acids **6a** and **7a** was recovered in 82% yield after filtration on ion-exchange resin (Scheme 2). The same sequence of reactions applied to the *exo* isomer **3b** led exclusively to the phosphoryl-dicarboxylic acid **7b** (Scheme 3) and in this case the carboxylic function *cis* to the imide moiety probably catalyzes the succinimide ring opening intramolecularly. In the stereoisomer **7b**, the coupling constant between H(2) and phosphorus was 8.3 Hz.

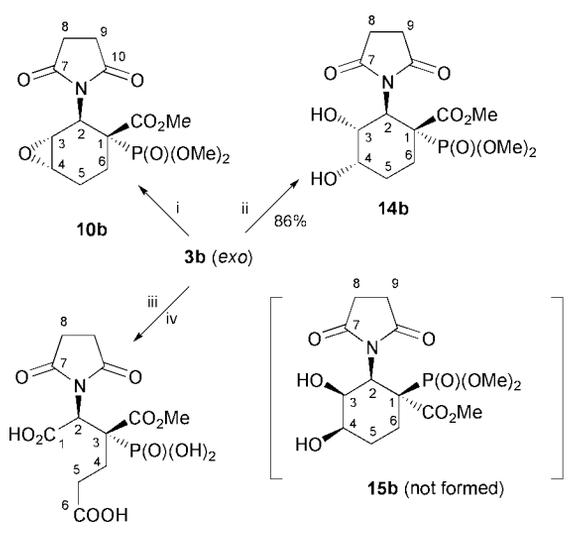
Preparation of phosphonic acid monoesters usually involves basic hydrolysis of phosphonate diesters.[15,16] Reaction of **3b** with hot aqueous LiOH gave the phosphonate monomethyl ester **8b** in which the carboxylic ester was cleaved and the imide group partially hydrolyzed due to neighbouring group participation, similarly to **7b** (Scheme 3). It should be mentioned that the carboxylate saponification is relatively facile if the phosphonate group is only partially deprotected (**8b**; short reaction time), while the conversion to di- and triacids (**6a**, **7a**, **7b**, long reaction time) is sluggish.[17] It should also be pointed out that we never observed decarboxylation of **6a**, **7a**, **7b**, and **8b**, even when the reaction was carried out in strongly acidic, or in strongly basic media, at high temperature. Also Krapcho's conditions [18] for decarboxylation of malonic esters, β-ketoesters, and α-sulfonylesters did not lead to demethoxycarbonylation of **3a**,**b**: treatment with lithium chloride and water (1 : 1) in refluxing DMSO [19] led to a slow mono-demethylation of the dimethylphosphonate group and no demethylation of the carboxylate ester, or decarboxylation occurred.

All attempts to selectively deprotect the succinimide moiety using the methods classically recommended for the cleavage of a phthalimide group [20–22] failed. Reaction of **3a**,**b** with hydrazine hydrate or methyl hydrazine in refluxing methanol led to monodealkylation of the phosphonate ester and to succinimide opening without liberation of the amine function (see **7b** or **8b**). In addition, reduction of **3b** with sodium borohydride in aqueous propan-2-ol followed by acidification furnished **9b** (Scheme 3), that is, the intramolecular nucleophilic attack of the hydroxy group onto the amide function to induce C(7)–N bond cleavage did not occur. The coupling constant of 8.9 Hz between H(2) and phosphorus corresponds to a dihedral angle H–C–C–P of 45°.[12] The isomer **3a** gave the analogous reduction product.

We also examined the oxidation of the C–C double bond of the cyclohexene substrate **3**. The epoxides **10a** (Scheme 4) and



Scheme 4 *Reagents and conditions*: i, MCPBA, CH_2Cl_2, 20 °C, 17 h; ii, NMO, OsO_4 (catal.), CH_2Cl_2, 20 °C, 3 days and acidic work-up; iii, O_3, MeOH, −78 °C to 20 °C; iv, H_2O_2, HCO_2H, −78 °C to 100 °C.



Scheme 5 *Reagents and conditions*: i, MCPBA, CH_2Cl_2, 20 °C, 17 h; ii, NMO, OsO_4 (catal.), CH_2Cl_2, 20 °C, 2 days; iii, O_3, MeOH, −78 °C to 20 °C; iv, H_2O_2, HCO_2H, −78 °C to 100 °C.

10b (Scheme 5) were obtained, respectively, by treatment of **3a** and **3b** with *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature. As expected, oxidation took place exclusively from the less hindered face. The *trans* orientation of the oxirane moiety and the succinimido substituent is evidenced in the ^1H NMR spectra by the absence of a coupling between H(2) and H(3). The *exo* isomer **10b** showed a coupling constant of 14.9 Hz between H(2) and phosphorus typical of a dihedral angle of 30°, while the corresponding constant was zero in the *endo* isomer **10a** (H(2)–C–C–P dihedral angle of 90°).[12] The structure of **10b** was unambiguously confirmed by X-ray diffraction

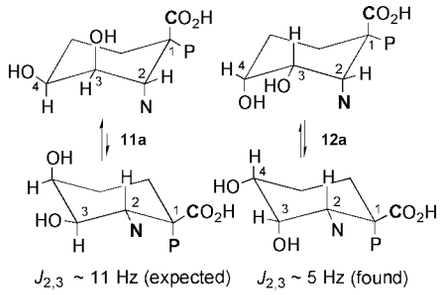


Fig. 1 Preferred conformers of **11a** and **12a**.

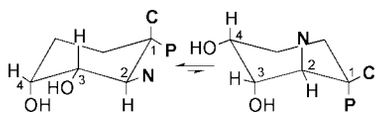
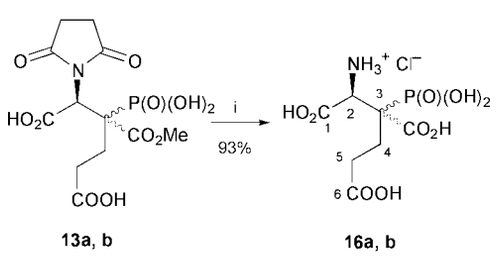


Fig. 2 Preferred conformer of **14b**.

analysis; the epoxide, succinimide and phosphonate groups are *trans* with respect to each other.

cis-Diols **11a** and **12a** (Scheme 4) were obtained by treatment of **3a** with osmium tetraoxide and *N*-methylmorpholine oxide[23] in 2-methylpropan-2-ol: the two isomers were formed in a 70 : 30 ratio and under our experimental conditions (acidic work-up), the carboxylate function was hydrolyzed. Both stereoisomers exhibited a coupling constant of 5 Hz between H(2) and H(3); the major isomer **11a** should correspond to the *cis*-hydroxylation occurring from the less hindered face. In this case, assuming chair conformations, the preferred conformer could be stabilized by hydrogen-bonding interactions between the carboxy group and OH(3) (Fig. 1). A similar oxidation of **3b** led to the formation of a single stereoisomer **14b** (Scheme 5) in which the carboxylate is not hydrolyzed (weakly acidic work-up). The coupling constant of 11.3 Hz between H(2) and H(3) is typical of the *trans*-diaxial configuration corresponding to a preferred chair conformer with the bulky substituents in equatorial positions (Fig. 2).

Ozonolysis of **3a**,**b** followed by treatment with hydrogen peroxide in formic acid[24] gave the dicarboxylic acids **13a**,**b** (Schemes 4 and 5) in which the phosphonate diester has been hydrolyzed. The *endo* and *exo* isomers are characterized by their H(2)–P coupling constants of 9.1 and 7.0 Hz, respectively. Further treatment in refluxing 6 M HCl led to complete deprotection, furnishing **16a**,**b** (Scheme 6). Here again, a significant



Scheme 6 *Reagents and conditions*: i, 6 M HCl, 100 °C, 17 h.

difference between the H(2)–P coupling constant values of the *endo* (**16a**, $J_{2\text{–}P}$ = 8.5 Hz) and *exo* (**16b**, $J_{2\text{–}P}$ = 3.1 Hz) isomers was observed.

Finally, we transformed the epoxide **10b** into the *trans*-dihydroxycyclohexane derivative **17b** (Scheme 7) in two steps, *i.e.* nucleophilic opening of the oxirane with lithium hydroxide followed by acidic hydrolysis of the protected functions in 6 M HCl. Owing to the steric and electronic factors governing the S_N2 substitution of the epoxide,[25] the final product **17b** exhibits a *trans* orientation between H(2) and H(3). From the coupling constant values of 2.2 Hz for $J_{2\text{–}3}$, and 9.1 Hz for $J_{2\text{–}P}$, assuming chair conformations, we speculate that the conformer with the hydroxy functions in the di-axial positions should be preferred

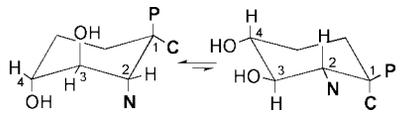
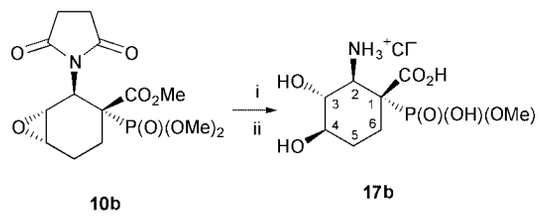


Fig. 3 Postulated conformers of **17b**.



Scheme 7 *Reagents and conditions*: i, LiOH, CH_3CH–H_2O, 100 °C, 17 h; ii, 6 M HCl, 20 °C.

due to favourable hydrogen bonding interactions between OH(4) and NH_3^+(2), and OH(3) and P=O(1) (Fig. 3). However, a twist-boat conformer (di-equatorial hydroxy groups) which minimises interaction of the polar groups could also account for the NMR data.

Throughout this study, the relative ease of hydrolysis of the geminal carboxylate and phosphonate groups appeared quite different, and not easily predictable, in the cyclohexene (**4**, **6**, **7**, **8**) and cyclohexane derivatives (**11**, **12**, **17**). Under acidic conditions, the methoxycarbonyl group was not cleaved in the cyclohexene series (**4a**,**b**), but it was hydrolyzed in the more flexible cyclohexane series (**11a**, **12a**); in this case, hydroxy neighbouring group participation should help. Under basic conditions, saponification of the ester group occurred in the cyclohexene (**6a**, **7a**,**b**, **8b**) and cyclohexane series (**17b**). Under the same conditions, mono-demethylation of the phosphonate group was observed in both series (**8b**, **11a**, **12a**, **17b**), while bis-demethylation required either acidic treatment (**4a**,**b**), or reaction with trimethylsilyl bromide (**5a**). All deprotections were more easily performed on the non-constrained aliphatic derivatives (**13a**,**b**, **16a**,**b**).

Generally, the products from the chemical transformations of **3a**,**b** are highly polar, hygroscopic, and not easily purifiable. They were isolated by extraction and chromatography on ion-exchange resins.[26–28] The free phosphonic acid derivatives often associate as dimers, and this was visible in both IR and mass spectrometry using the APCI (atmospheric pressure chemical ionisation) mode. The structural assignments and relative configurations were made by NMR spectroscopy.[12] For the cyclohexene/cyclohexane derivatives, the most typical feature was the ^{1}H NMR coupling constant between H(2) and phosphorus; the experimental values are within 0–5 Hz in the *endo* series and 8–14 Hz in the *exo* series (Table 1). The ^{13}C NMR coupling constants between carbon atoms and phosphorus were less characteristic of each series: the ^1J, ^2J, and ^3J values ranged from 118 to 147 Hz, 0 to 5 Hz and 7 to 13 Hz, respectively.

Compounds **4** to **17** have been evaluated as potential inhibitors of Protein Tyrosine Phosphatase 1B,[29–31] an enzyme involved in the regulation of insulin action;[32] no significant activities were found.

Experimental

General

Solvents were purified by conventional methods prior to use. Reagents were purchased from common commercial suppliers. Column chromatography was performed over silica gel Merck 60 (230–400 mesh), and over ion exchange resin Dowex 50 WX4–400. Mps were taken on an Electrothermal apparatus and are uncorrected. Elemental microanalyses were performed at Imperial College London. HRMS measurements were

Table 1 Coupling constants between H(2) and phosphorus

Cpd	$^3J_{H(2)-P}$/Hz	
	endo (**a**)	*exo* (**b**)
3	0	13.9
4	4.9	8.0
5	2.9	—
6	5.0	—
7	5.0	8.3
8	—	8.3
9	—	8.9
10	0	14.4
11	0	—
12	0	—
14	—	10.1
17	—	9.1

obtained at the University of Liège (Belgium). MS were recorded on a Finnigan MAT TSQ-70 apparatus (in positive or negative mode), in APCI mode (100 eV), or FAB mode (Xenon Ion Tech 8 KeV, matrix: glycerol or *m*-nitrobenzyl alcohol). NMR spectra were recorded on a Bruker 500 spectrometer operating at 500 MHz for proton and 125 MHz for carbon; chemical shifts (δ) are expressed in ppm relative to TMS or DSS (sodium 3-trimethylsilylpropane-1-sulfonate); coupling constants (J) are given in Hz (they were determined by selective decoupling experiments); coupling multiplicities are reported using conventional abbreviations. IR spectra were obtained with a Bio-Rad FTS-135 apparatus.

Methyl 1-dimethoxyphosphoryl-2-succinimidocyclohex-3-ene-1-carboxylates 3a (*endo*) and 3b (*exo*)

A mixture of *N*-buta-1,3-dienylsuccinimide **2** (300 mg, 1.98 mmol), trimethyl 2-phosphonoacrylate **1** (308 mg, 1.58 mmol), and hydroquinone (60 mg, 0.54 mmol) in acetonitrile (2 cm^3) was heated at 65 °C for 48 h, under an argon atmosphere. Column chromatography on silica gel (CH_2Cl_2–iPrOH, 50 : 50) gave a 65 : 35 mixture of **3a** and **3b** (638 mg, 93%); the major isomer crystallized from toluene (Found: C, 48.66; H, 5.80; N, 3.59. $C_{14}H_{20}NO_7P$ requires C, 48.69; H, 5.83; N, 4.05%); mp 99–101 °C; FAB-MS *m*/*z* 346 ([M]$^+$) (30%); ν_{max}/cm^{-1}/(film) 3458, 2959, 1709, 1600, 1434, 1389, 1358, 1250, 1177, 1030; δ_H ($CDCl_3$) **3a** 2.20 (1H, m, *J* 18.7, 10.6, 5.5, 2.2, 2.2, and 2.2, H-5), 2.30 (1H, m, *J* 18.7, 6.6, 4.9, 2.2 and 2, H-5′), 2.40 (1H, ddd, *J* 13.4, 5.5 and 5.5, H-6), 2.68 (4H, br s, H-8), 2.75 (1H, m, *J* 13.4, 10.6, 6.6 and 6.6, H-6′), 3.71 (3H, d, *J* 11, C*H*$_3$OP), 3.79 (3H, d, *J* 11, C*H*$_3$OP), 3.80 (3H, s, C*H*$_3$O), 5.44 (1H, m, *J* 10.3, 4.9, 5.1, 2.2 and 2.2, H-3), 5.65 (1H, m, *J* 4.9, 2.2 and 2, H-2), 6.00 (1H, m, *J* 10.3, 4.9, 2.2 and 2.2, H-4); δ_H ($CDCl_3$) **3b** 2.25 (2H, m, H-5 + H-6), 2.55 (2H, m, H-5′ + H-6′), 2.65 (4H, s, H-8), 3.65 (3H, s, C*H*$_3$O), 3.76 (3H, d, *J* 11, C*H*$_3$OP), 3.80 (3H, d, *J* 11, C*H*$_3$OP), 5.32 (1H, m, *J* 13.9, 5.1, 2.6 and 2.6, H-2), 5.35 (1H, m, H-3), 5.98 (1H, m, H-4); δ_C ($CDCl_3$) **3a** 21.2 (d, *J* 12.5, C-5), 21.6 (d, *J* 2.7, C-6), 27.5 (C-8), 45.4 (d, *J* 5.5, C-2), 52.2 (d, *J* 133.2, C-1), 52.4 (O*C*H$_3$), 52.8 (d, *J* 8.3, P-O*C*H$_3$), 53.7 (d, *J* 6.9, P-O*C*H$_3$), 120.3 (d, *J* 8.3, C-3), 131.0 (C-4), 168.8 (d, *J* 5.5, *C*O$_2$Me), 176.5 (C-7); δ_C ($CDCl_3$) **3b** 21.6 (d, *J* 6.9, C-5), 24.1 (d, *J* 5.5, C-6), 27.5 (C-8), 46.2 (s, *J* ~ 0, C-2), 49.7 (d, *J* 134.5, C-1), 51.9 (O*C*H$_3$), 52.9 (d, *J* 6.9, P–O*C*H$_3$), 53.7 (d, *J* 6.9, P–O*C*H$_3$), 121.5 (d, *J* 6.9, C-3), 129.8 (C-4), 168.6 (d, *J* 2.8, *C*O$_2$Me), 175.8 (C-7).

Methyl 1-phosphoryl-2-aminocyclohex-3-ene-1-carboxylates 4a (*endo*) and 4b (*exo*)

A 85 : 15 mixture of **3b** and **3a** (0.5 g, 1.45 mmol) was refluxed during 3 days in 6 M aqueous HCl (5 cm^3). After concentration *in vacuo*, water (2 cm^3) and diethyl ether (100 cm^3) were added. The solution was stored for 20 h at 0 °C; **4b** precipitated and **4a** remained in solution. After filtration of **4b**, the aqueous phase was extracted several times with diethyl ether to remove succinimide, then concentrated to afford **4a**. Compounds **4a** and **4b** were isolated as hygroscopic hydrochlorides (0.328 g, 84%); FAB-MS *m*/*z* 235.9 ([M(NH$_3$)]$^+$) (30%) and APCI *m*/*z* 236 ([M(NH$_3$)]$^+$) (28%); ν_{max}/cm^{-1} (film) 3500–3000, 1704, 1651, 1457, 1437, 1295, 1248, 1045; δ_H (D_2O) **4a** 1.98–2.46 (4H, m, H-5 + H-6), 3.76 (3H, s, O*CH*$_3$), 4.38 (1H, m, H-2, $^3J_{2-P}$ 4.9), 5.64 (1H, dd, *J* 10.1 and 4.9, H-3), 6.12 (1H, m, H-4); δ_H (D_2O) **4b** 1.98 (1H, m, H-6), 2.25 (2H, m, H-5), 2.46 (1H, m, H-6′), 3.79 (3H, s, O*CH*$_3$), 4.29 (1H, m, H-2, $^3J_{2-P}$ 8.0), 5.64 (1H, dd, *J* 10.1 and 2.0, H-3), 5.98 (1H, m, H-4); δ_C (D_2O) **4a** 23.4 (C-6), 25.0 (d, *J* 10.8, C-5), 49.5 (C-2), 52.8 (d, *J* 118.0, C-1), 55.8 (O*C*H$_3$), 124.4 (C-3), 137.7 (C-4), 175.8 (*C*O$_2$Me); δ_C (D_2O) **4b** 24.8 (d, *J* 10.8, C-5), 29.1 (C-6), 52.6 (d, *J* 118.0, C-1), 53.2 (C-2), 55.8 (O*C*H$_3$), 124.5 (d, *J* 9, C-3), 135.2 (C-4), 175.8 (*C*O$_2$Me).

Methyl 1-phosphoryl-2-succinimidocyclohex-3-ene-1-carboxylate 5a (*endo*)

A mixture of **3a** (0.21 g, 0.61 mmol) and bromotrimethylsilane (0.32 cm^3, 2.44 mmol) in $CHCl_3$ (5 cm^3) was stirred at 20 °C for 17 h, under an argon atmosphere. After addition of water (0.3 cm^3), the mixture was concentrated *in vacuo*. The residue was passed through a Dowex resin with water as the eluent. Concentration gave **5a** as a colourless oil (0.174 g, 90%) (HRMS-EI required for $C_{12}H_{16}NO_7P$ (*M*): 317.0664. Found: *M* = 317.0661); ν_{max}/cm^{-1} (film) 3400, 1781, 1457, 1439, 1323, 1295, 1200, 1091, 1053; δ_H (D_2O, 57 °C) 2.17 (1H, m, *J* 18.7, 11.0, 5.9, 2.2, 2.2 and 2.2, H-5), 2.26 (1H, m, *J* 18.7, 6.6, 0.1, 4.4, 2.2 and 2.0, H-5′), 2.35 (1H, m, *J* 13.4, 5.9, 5.9 and 0.1, H-6), 2.48 (1H, m, *J* 13.4, 11.0, 6.6 and 6.6, H-6′), 2.72 (4H, s, H-8), 3.79 (3H, s, O*CH*$_3$), 5.47 (1H, m, *J* 10.3, 4.9, 4.0, 2.2 and 2.2, H-3), 5.55 (1H, m, *J* 4.9, 2.9, 2.2, 2.2 and 2.0, H-2), 6.07 (1H, m, *J* 10.3, 4.4, 2.2 and 2.2, H-4); δ_C ($CDCl_3$, 57 °C) 24.4 (d, *J* 12.7, C-5), 25.3 (d, *J*, 2.0, C-6), 30.9 (C-8), 49.5 (d, *J* 5.5, C-2), 55.5 (d, *J* 129.0, C-1), 56.5 (O*C*H$_3$), 123.4 (d, *J* 8.1, C-3), 135.3 (C-4), 175.1 (d, *J* 5.5, *C*O$_2$Me), 184.1 (C-7); APCI-MS *m*/*z* 634.9 ([2M + 1]$^+$) (35%), 318.2 ([M + 1]$^+$) (100%).

1-Phosphoryl-2-succinimidocyclohex-3-ene-1-carboxylic acid 6a (*endo*)

A mixture of **3a** (0.18 g, 0.54 mmol) and bromotrimethylsilane (2.4 cm^3, 18.2 mmol) in CH_3CN (14 cm^3) was stirred at 20 °C for 20 h, under an argon atmosphere. After concentration *in vacuo*, the crude **5a** residue was treated with a saturated aqueous LiOH solution (5 cm^3) at 100 °C for 48 h. The solution was passed through a Dowex resin to furnish a 1 : 1 mixture of **6a** and **7a** as a colourless oil (0.134 g, 82%); δ_H (D_2O, 57 °C) **6a** 2.04 (1H, m, H-6), 2.19 (1H, m, H-5), 2.29 (1H, m, H-5′), 2.43 (1H, m, H-6), 2.67 (4H, s, H-8), 5.11 (1H, m, H-2), 5.72 (1H, m, *J* 5.0, 3.2, 2.4 and 2.4, H-3), 5.91 (1H, m, H-4); δ_C (D_2O, 57 °C) **6a** 23.5 (C-6), 24.3 (d, *J* 10.8, C-5), 31.4 (C-8), 48.3 (C-2), 52.6 (d, *J* 115.0, C-1), 127.2 (d, *J* 9.0, C-3), 133.2 (C-4), 176.0 (d, *J* 3.5 *C*O$_2$H), 179.2 (C-7); δ_H (D_2O, 57 °C) **7a** 2.04 (1H, m, H-6), 2.29 (2H, m, H-5), 2.32 (1H, m, H-6′), 2.57 (2H, t, H-6), 2.67 (2H, t, H-9), 4.40 (1H, m, H-2), 5.87 (1H, m, *J* 10.3, 5.0, 3.2, 2.4 and 2.4, H-3), 6.12 (1H, m, *J* 10.3, 4.4 and 2.4, H-4); δ_C (D_2O, 57 °C) **7a** 23.7 (C-6), 24.8 (d, *J* 10.8, C-5), 31.9 (C-8), 33.3 (C-9), 49.6 (C-2), 54.1 (d, *J* 126.0, C-1), 124.2 (d, *J* 9.0, C-3), 137.5 (C-4), 176.3 (d, *J* 3.5, CO$_2$H), 176.7 (C-7), 179.3 (*C*O$_2$H).

1-Phosphoryl-2-(3-carboxy-1-oxopropyl)aminocyclohex-3-ene-1-carboxylic acid 7b (*exo*)

3b (0.2 g, 0.58 mmol; containing 15% of **3a**) was treated as above to furnish **7b** as a yellow oil (0.134 g, 75%); APCI-MS *m*/*z* 643 ([2M + 1]$^+$) (13%), 322 ([M + 1]$^+$) (100%), 304 ([M + 1 − H$_2$O]$^+$) (35%); δ_H (D_2O, 50 °C) 2.05 (1H, m, *J* 13.6, 9.3, 6.8 and 6.8, H-6), 2.19 (2H, m, H-5), 2.47 (1H, m, *J* 13.6, 10.7, 5.6

and 2.9, H-6′), 2.60 (2H, t, H-8), 2.67 (2H, t, H-9), 5.01 (1H, m, *J* 8.3, 2.6, 2.4, 2.4 and 2.4, H-2), 5.47 (1H, m, *J* 10.3, 3.6, 2.4, 2.4 and 2.4, H-3), 5.82 (1H, m, *J* 10.3, 2.6, 2.6 and 2.6, H-4); δ_C (D_2O, 50 °C) 24.4 (d, *J* 10.8, C-5), 29.4 (d, *J* 2.7, C-6), 31.9 (C-8), 33.2 (C-9), 50.7 (C-2), 53.8 (d, *J* 127.0, C-1), 129.8 (d, *J* 8.9, C-3), 131.3 (C-4), 176.5 (d, *J* 2.0, *C*O_2H), 176.6 (C-7), 179.4 (*C*O_2H).

1-Methoxyphosphoryl-2-(3-carboxy-1-oxopropyl)aminocyclohex-3-ene-1-carboxylic acid 8b (*exo*)

A solution of **3b** (0.138 g, 0.4 mmol, containing 15% of **3a**) in CH_3CN (2 cm^3) was treated with saturated aqueous LiOH (3 cm^3) at 100 °C for 12 h. After concentration and purification on Dowex resin, **8b** was obtained as a yellow oil (0.12 g, 96%) (HRMS-EI required for $C_{12}H_{16}NO_7P$ (*M*): 317.0664. Found: *M* = 317.0682); ν_{max}/cm^{-1} (film) 3500–2500, 1712, 1695, 1647, 1534, 1518, 1473, 1288, 1241, 1196, 1038; δ_H (D_2O, 57 °C) 2.05 (1H, m, *J* 13.6, 9.3, 6.8 and 6.8, H-6), 2.17 (2H, m, H-5), 2.46 (1H, m, *J* 13.6, 10.7, 5.6 and 2.9, H-6′), 2.60 (2H, t, H-8), 2.67 (2H, t, H-9), 3.69 (3H, d, *J* 11.0, P-OCH_3), 4.98 (1H, m, *J* 8.3, 2.6, 2.6, 2.6 and 2.4, H-2), 5.45 (1H, m, *J* 10.3, 3.6, 2.4, 2.4 and 2.4, H-3), 5.80 (1H, m, *J* 10.3, 2.6, 2.6 and 2.6, H-4); δ_C (D_2O, 57 °C) 24.8 (d, *J* 10.8, C-5), 29.9 (C-6), 32.3 (C-8), 33.7 (C-9), 51.2 (C-2), 54.3 (d, *J* 129.0, C-1), 56.0 (d, *J* 6.9, P-O*C*H_3), 130.6 (d, *J* 9.0, C-3), 131.6 (C-4), 176.6 (d, *J* 2.0, *C*O_2H), 176.8 (C-7), 179.5 (CO_2H); APCI-MS *m*/*z* 670.9 $([2M])^+$ (66%), 336 $([M + 1]^+)$ (100%), 318, 292 (35%).

Methyl 1-dimethoxyphosphoryl-2-(4′-hydroxybutyryl)aminocyclohex-3-ene-1-carboxylate 9b (*exo*)

A solution of **3b** (0.306 g, 0.86 mmol, containing 15% of **3a**) in *i*PrOH (8 cm^3) and water (1.3 cm^3) was treated with $NaBH_4$ (0.085 g, 2.15 mmol) and stirred at 20 °C for 20 h. After filtration on Dowex resin and concentration *in vacuo*, **9b** was recovered as a colourless oil (0.243 g, 81%) (HRMS-CI requires for $C_{14}H_{27}NO_7P$ (*MH*) 350.1392. Found: *MH* = 350.1381); ν_{max}/cm^{-1} 3418, 2960, 1727, 1645, 1516, 1453, 1242, 1182, 1036; δ_H (D_2O, 37 °C) 1.82 (2H, m, *J* 7.0 and 7.0, H-9), 2.07 (1H, m, H-5), 2.12 (1H, m, H-6), 2.23 (1H, m, H-5′), 2.35 (2H, t, *J* 7.0, H-8), 2.47 (1H, m, H-6′), 3.60 (2H, t, *J* 7.0, H-10), 3.80 (3H, d, *J* 11.0, P-OCH_3), 3.82 (3H, d, *J* 11.0, P-OCH_3), 3.82 (3H, s, OCH_3), 5.08 (1H, m, *J* 8.9, H-2), 5.47 (1H, m, H-3), 5.82 (1H, m, H-4); δ_C (D_2O, 37 °C) 24.3 (d, *J* 10.8, C-5), 28.9 (d, *J* 5.4, C-6), 30.4 (C-9), 35.2 (C-8), 49.9 (d, *J* 3.6, C-2), 54.4 (d, *J* 137.0, C-1), 56.1 (O*C*H_3), 57.2 (d, *J* 7.2, P–O*C*H_3), 57.3 (d, *J* 7.2, P–O*C*H_3), 63.5 (C-10), 129.2 (d, *J* 9.0, C-3), 131.6 (C-4), 173.9 (*C*O_2Me), 177.9 (C-7); APCI-MS *m*/*z* 350.1 $([M + 1]^+)$ (64%).

Methyl 1-dimethoxyphosphoryl-2-succinimido-3,4-*trans*-epoxycyclohexane-1-carboxylate 10a (*endo*) and 10b (*exo*)

A mixture of **3a** (*endo*) (0.2 g, 0.58 mmol) and *m*-chloroperbenzoic acid (0.713 g, 2.9 mmol) in CH_2Cl_2 (10 cm^3) was stirred at 20 °C for 20 h. After washing with 10% aq. sodium sulfite (10 cm^3) and 10% aq. $NaHCO_3$ (10 cm^3), the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica gel (CH_2Cl_2–*i*PrOH, 95 : 5; R_f = 0.34) gave **10a** as colourless crystals (0.157 g, 75%); mp 152–153 °C (Found: C, 47.16; H, 5.86; N, 3.38. $C_{14}H_{20}NO_8P$ requires C, 46.54; H, 5.57; N, 3.87%); FAB-MS *m*/*z* 362 $([M + 1]^+)$ (25%); ν_{max}/cm^{-1} 3472, 2957, 1734, 1708, 1435, 1390, 1249, 1185, 1092, 1056; δ_H ($CDCl_3$, 25 °C, 200 MHz) 2.07–2.32 (3H, m, H-6 + H-6′ + H-5), 2.64 (1H, m, H-5′), 2.75 (4H, br s, H-8 + H-9), 3.07 (1H, dd, *J* 4.0 and 3.0, H-3), 3.30 (1H, m, H-4), 3.68 (3H, s, OCH_3), 3.72 (3H, d, *J* 10.0, P–OCH_3), 3.76 (3H, d, *J* 10.0, P–OCH_3), 5.69 (m, 1H, H-2); δ_C ($CDCl_3$, 25 °C, 50 MHz) 18.5 (d, *J* 12.4, C-5), 18.8 (C-6), 27.9 (C-8 + C-9), 49.5 (d, *J* 132.6, C-1), 46.4 (d, *J* 4.8, C-2), 52.1 (d, *J* 9.9, C-3), 52.6 (C-4), 53.2 (d, *J* 7.3, P–O*C*H_3), 54.4 (d, *J* 7.0, P–O*C*H_3), 167.9 (d, *J* 7.2, *C*O_2Me), 177.2 (C-7). **10b** was similarly prepared from **3b** (*exo*) treated with MCPBA (HRMS-FAB required for $C_{14}H_{20}NO_8P$ (*M*): 361.0927. Found: *M* = 361.0905); δ_H ($CDCl_3$, 25 °C) 1.88–2.10 (2H, m, H-6), 2.10–2.62 (2H, m, H-5), 2.63 (1H, ddd, *J* 18.2, 9.1 and 5.3, H-8), 2.69 (1H, ddd, *J* 18.2, 10.1 and 4.4, H-8′), 2.76 (1H, ddd, *J* 18.2, 9.1 and 4.4, H-9), 2.87 (1H, ddd, *J* 18.2, 10.1 and 5.3, H-9′), 3.14 (1H, t, *J* 4.0 and 4.0, H-3), 3.40 (1H, m, H-4), 3.68 (3H, s, OCH_3), 3.72 (3H, d, *J* 10.7, P-OCH_3), 3.76 (3H, d, *J* 10.7, P-OCH_3), 4.82 (1H, d, *J* 14.4, H-2); δ_C ($CDCl_3$, 25 °C) 20.4 (d, *J* 12.6, C-5), 21.5 (d, *J* 5.4, C-6), 27.7 (C-8), 28.4 (C-9), 47.3 (d, *J* 140.0, C-1), 47.7 (d, *J* 5.4, C-2), 52.7 (O*C*H_3), 52.9 (C-4), 53.4 (d, *J* 7.2, P–O*C*H_3), 53.5 (d, *J* 10.8, C-3), 54.3 (d, *J* 7.2, P–O*C*H_3), 168.9 (*C*O_2Me), 174.9 (C-7), 177.4 (C-10); X-ray diffraction (crystallisation from toluene): monoclinic crystal, *a* = 7.792 (2), *b* = 14.727 (4), *c* = 14.339 (4) Å; *α* = 90, *β* = 96.51 (2), *γ* = 90°; *V* = 1634.8 (8) $Å^3$, *Z* = 4; *d* = 1.468 g cm^{-3}.

1-Dimethoxyphosphoryl-2-succinimido-3,4-*cis*-dihydroxycyclohexane-1-carboxylic acids 11a (*endo*) and 12a (*endo*)

A mixture of 4-methylmorpholine 4-oxide monohydrate (0.12 g, 0.86 mmol), osmium tetraoxide (0.1 cm^3 of 2.5% solution in *t*-BuOH), and **3a** (0.133 g, 0.38 mmol) in CH_2Cl_2 (1 cm^3) was stirred at 20 °C for 3 days, under an argon atmosphere. After addition of $NaHSO_3$ (20 mg), the mixture was stirred for 1 h at 20 °C, then talcum powder (400 mg) and 3 drops of 6 M HCl were added, and the mixture was filtered after 15 min. The solid phase was washed with CH_2Cl_2 (15 cm^3). The organic phase was concentrated *in vacuo* and the oily residue was passed through a Dowex resin to furnish a 70 : 30 mixture of **11a** and **12a** as an hygroscopic brown oil (0.072 g, 51%); FAB-MS *m*/*z* 364 $([M - 1]^-)$ (32%); ν_{max}/cm^{-1} 3500–3000, 1738, 1704, 1651, 1462, 1372, 1219, 1183, 1050; δ_H (D_2O, 25 °C) major isomer **11a** 2.02 (m, 1H, H-6), 2.21 (2H, m, H-5 + H-5′), 2.67 (m, 1H, H-6′), 2.83 (2H, m, H-8), 2.90 (2H, m, H-9), 3.83 (3H, d, *J* 11.0, P-OCH_3), 4.48 (1H, m, H-2), 4.68 (1H, m, H-3), 4.90 (1H, m, H-4); minor isomer **12a** 2.78 (2H, m, H-8), 2.86 (2H, m, H-9), 4.46 (1H, m, H-2), 4.65 (1H, m, H-3), 4.84 (1H, m, H-4); δ_C (D_2O, 25 °C) major isomer **11a** 22.7 (C-6), 25.6 (d, *J* 12.6, C-5), 30.5 (C-8), 30.7 (C-9), 51.8 (d, *J* 165.0, C-1), 57.5 (d, *J* 7.2, P–O*C*H_3), 58.3 (C-2), 70.5 (C-3), 84.7 (C-4), 174.2 (*C*O_2H), 184.1 (C-7); minor isomer **12a** 23.11 (C-6), 25.6 (d, *J* 12.6, C-5), 57.2 (d, *J* 7.2, P–O*C*H_3), 58.5 (C-2), 70.9 (C-3), 84.4 (C-4), 175.4 (*C*O_2H), 184.4 (C-7).

Methyl 1-dimethoxyphosphoryl-2-succinimido-3,4-*cis*-dihydroxycyclohexane-1-carboxylate 14b (*exo*)

A mixture of 4-methylmorpholine 4-oxide monohydrate (0.25 g, 1.86 mmol), osmium tetraoxide (0.1 cm^3 of 2.5% solution in *t*-BuOH), and **3b** (0.323 g, 0.933 mmol) in CH_2Cl_2 (1 cm^3) was stirred at 20 °C for 2 days under an argon atmosphere. Work-up gave **14b** as an hygroscopic green oil (0.285 g, 86%); δ_H (D_2O, 25 °C) 1.85 (1H, m, H-5), 1.98 (1H, m, H-6), 2.25 (1H, m, H-6′), 2.46 (1H, m, H-5′), 2.77 (2H, dd, H-8), 2.86 (2H, dd, H-9), 3.75 (3H, s, OCH_3), 3.75 (3H, d, *J* 11.0, P-OCH_3), 3.81 (3H, d, *J* P-OCH_3), 4.20 (1H, m, H-4), 4.62 (1H, ddd, *J* 11.3, 3.1 and 0.9, H-3), 4.80 (1H, dd, *J* 11.3 and 10.1, H-2); δ_C (D_2O, 25 °C) 26.4 (d, *J* 5.4, C-6), 29.6 (d, *J* 12.6, C-5), 30.3 (C-8), 30.7 (C-9), 52.7 (d, *J* 7.2, C-2), 54.7 (d, *J* 145.0, C-1), 56.0 (O*C*H_3), 56.6 (d, *J* 7.2, P-O*C*H_3), 58.0 (d, *J* 7.2, P-O*C*H_3), 68.7 (d, *J* 12.6, C-3), 71.6 (C-4), 173.6 (*C*O_2Me), 183.5 (C-10), 184.0 (C-7).

2-Succinimido-3-methoxycarbonyl-3-phosphonohexane-1,6-dioic acids 13a (*endo*) and 13b (*exo*)

A 65 : 35 mixture of **3b** (*exo*) and **3a** (*endo*) (0.27 g, 0.79 mmol) in methanol (10 cm^3) was saturated, at −78 °C, with ozone. After 10 min, the solvent was evaporated at 20 °C *in vacuo*. The

residue was treated at −78 °C with H_2O_2 (0.5 cm^3, 20% solution in water) and HCO_2H (1 cm^3), then heated at 100 °C for 25 min. After concentration and washing with diethyl ether (2 × 20 cm^3) the white precipitate was dried *in vacuo*. A 65 : 35 mixture of **13b** and **13a** was recovered (0.3 g, 95%); mp 77–78 °C; FAB-MS *m*/*z* 380 ([M − 1]$^-$) (20%), 348 (28%), 304 (32%); ν_{max}/cm^{-1} 3426 (br), 1718, 1393, 1257, 1182, 1060; δ_H (D_2O, 67 °C) **13a** (*endo*) 2.34 (1H, m, H-4), 2.44 (1H, m, H-4′), 2.77 (1H, ddd, *J* 17.1, 11.3 and 5.8, H-5), 3.01 (4H, s, H-8), 3.03 (1H, ddd, *J* 17.1, 11.3 and 5.8, H-5′), 3.92 (3H, s, OCH_3), 5.80 (1H, d, *J* 9.1, H-2); **13b** (*exo*) 2.4–2.7 (4H, m, H-4 + H-5), 3.73 (3H, s, OCH_3), 5.30 (1H, d, *J* 7.0, H-2); δ_C (D_2O, 67 °C) **13a** (*endo*) 28.5 (C-4), 31.2 (C-8), 33.4 (C-5), 56.3 (O*C*H_3), 57.3 (d, *J* 118.0, C-3), 57.9 (C-2), 172.9 (d, *J* 11.5, *C*O_2Me), 174.9 (d, *J* 6.0, C-1), 180.7 (C-6), 183.2 (C-7); **13b** (*exo*) 29.6 (C-4), 30.6 (C-8), 32.8 (C-5), 55.7 (O*C*H_3), 56.6 (d, *J* 133.0, C-3), 58.1 (C-2), 172.5 (d, *J* 7.7, *C*O_2Me), 174.8 (d, *J* 2.8, C-1), 179.9 (C-6), 182.6 (C-7).

2-Amino-3-carboxy-3-phosphonohexane-1,6-dioic acids 16a (*endo*) and 16b (*exo*)

A 35 : 65 mixture of **13a** and **13b** (0.1 g, 0.26 mmol) was heated in 6 M aqueous HCl (5 cm^3) for 17 h at 100 °C. After concentration *in vacuo*, the residue was dissolved in H_2O (1 cm^3) and extracted several times with diethyl ether to remove succinic anhydride. Concentration of the aqueous phase gave a 35 : 65 mixture of **16a** and **16b** (hydrochlorides) as an hygroscopic beige powder (0.077 g, 92%); mp 61–62 °C; FAB-MS *m*/*z* 287 ([M − Cl + 1]$^{\cdot+}$) (15%); ν_{max}/cm^{-1} (KBr) 3420 (br), 1733, 1684, 1653, 1247, 1060; δ_H (D_2O, 25 °C) **16a** 2.26–2.66 (4H, m, H-4 + H-5), 4.74 (1H, d, *J* 8.5, H-2); **16b** 2.26–2.66 (4H, m, H-4 + H-5), 4.81 (1H, d, *J* 3.1, H-2); δ_C (D_2O, 25 °C) **16a** 25.5 (C-4), 29.8 (C-5), 52.3 (d, *J* 125.0, C-3), 59.6 (C-2), 175.4 (d, *J* 19.7, *C*O_2H), 175.7 (C-6), 178.0 (C-1); **16b** 23.4 (C-4), 29.8 (C-5), 53.4 (d, *J* 125.0, C-3), 59.7 (C-2), 175.6 (C-6), 178.0 (C-1), 180.0 (d, *J* 19.7, *C*O_2H).

1-Methoxyphosphoryl-2-amino-3,4-*trans*-dihydroxycyclohexane-1-carboxylic acid 17b

A solution of **10b** (93 mg, 0.25 mmol, containing 15% of **10a**) in CH_3CN (5 cm^3) was heated with saturated aqueous LiOH (5 cm^3) at 100 °C for 17 h. The solution was made acidic with 6 M HCl, concentrated *in vacuo* and passed through a Dowex resin. The recovered aqueous phase was extracted several times with ether, then concentrated to furnish **17b** (hydrochloride) as a yellow oil (0.073 g, 66%); APCI-MS *m*/*z* 268 ([M − Cl − 1]$^-$) (80%), 224 (18%); δ_H (D_2O, 25 °C) 1.64 (1H, m, H-5), 2.05 (1H, m, H-5′), 2.06 (1H, m, H-6), 2.18 (1H, m, H-6′), 3.86 (1H, m, *J* 9.1 and 2.2, H-2), 3.98 (1H, m, H-3), 4.01 (1H, m, H-4); δ_C (D_2O, 25 °C) 24.9 (d, *J* 5.4, C-6), 25.3 (d, *J* 10.8, C-5), 50.4 (d, *J* 118.0, C-1), 53.3 (C-2), 56.1 (d, *J* 7.2, P–O*C*H_3), 71.1 (C-4), 71.7 (d, *J* 10.8, C-3), 176.5 (*C*O_2H).

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