

## Synthesis of 1-Aminoalkylphosphinic Acids. Part 2.<sup>1</sup> An Alkylation Approach

Patrick P. McCleery\* and Brian Tuck†

Central Research Laboratories, Ciba-Geigy plc, Tenax Road, Trafford Park, Manchester M17 1WT

Aminomethylphosphinic acid (**7**), protected at nitrogen as the imine derived from benzophenone and at phosphorus as the diethylacetal and ethyl ester [*i.e.* (**6**)], undergoes facile LDA-induced alkylation. Treatment with primary alkyl halides affords, on product hydrolysis, a versatile route to phosphinic analogues of  $\alpha$ -amino carboxylic acids. Analogues of alanine, valine, leucine, phenylalanine, tyrosine, histidine, and aspartic and glutamic acids are thus prepared; the phosphonic histidine analogue (**23b**) can be prepared similarly from the imine phosphonate diester (**21**). Intra- and inter-molecular dialkylation reactions provide analogues of 1-aminocyclopropanecarboxylic acid (**14**) and 2,6-diaminoheptanedioic acid (**16**). Benzyl bromide alkylation of (**25a**) and (**30a**), where the nitrogen is protected as the imine of the 2-hydroxypinan-3-one chiral auxiliary (**24**) or (**29**), is diastereospecific leading to asymmetric synthesis of either (+)- or (-)-phenylalanine analogues; this selectivity is compared to that shown by the corresponding chiral imine phosphonate (**25b**) and imine carboxylate (**25c**).

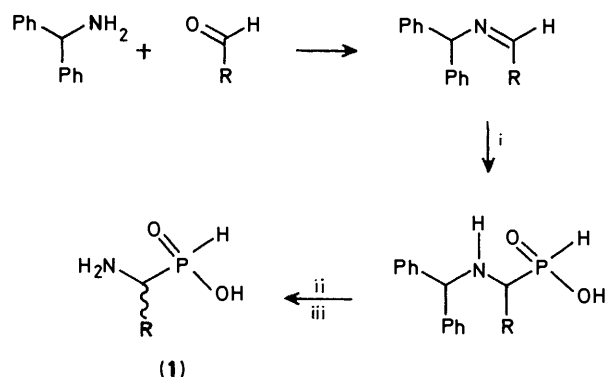
In a previous paper from these laboratories,<sup>1</sup> the synthesis of  $\alpha$ -amino phosphinic acids (**1**)<sup>‡</sup> was described by addition of phosphinic acid to the imine derived from an aldehyde and benzhydramine followed by hydrolysis (Scheme 1). It was rationalised that this class of compound would be the closest phosphorus analogue to the  $\alpha$ -amino carboxylic acids.

The previous method depends upon the availability of a suitable precursor aldehyde, and these compounds are not always readily prepared. An alternative synthetic strategy can be envisaged by alkylation of a suitably protected aminomethylphosphinic acid. This method is well known for synthesis of  $\alpha$ -amino carboxylic acids<sup>2</sup> and  $\alpha$ -amino phosphonic acids,<sup>3-6</sup> and we now demonstrate that it can also be applied to synthesizing  $\alpha$ -amino phosphinic acids (**1**).

### Results and Discussion

**Preparation of the Aminomethylphosphinate Synthone (**6**).**—In the synthesis of  $\alpha$ -amino acids by alkylation of the corresponding glycine, both acid and amine functions are generally protected, the former as an ester and the latter as for example, an imine<sup>7</sup> or isocyanide.<sup>8</sup> In this approach to  $\alpha$ -amino phosphinic acids (**1**), the acidity of the PH function must also be taken into account. We have found the 1,1-diethoxymethyl group to be a versatile and convenient protecting group, being readily introduced and cleanly removed by dilute mineral acid.<sup>9,10</sup> Furthermore, this protecting group is stable under the conditions of lithium di-isopropylamide (LDA)-induced alkylation reactions.

The required iminomethylphosphinate (**6**) was prepared as shown in Scheme 2. Addition of ethyl diethoxymethylphosphinate<sup>11</sup> (**2**) to the triazine (**3**) to give compound (**4**), followed by selective hydrogenolysis of the benzhydryl group, gave the intermediate amine (**5a**). This was condensed with benzophenone in toluene solution to yield the imine phosphinate ester (**6**). Complete removal of all protecting



Scheme 1. Reagents: i, H<sub>3</sub>PO<sub>2</sub>; ii, 6M aq. HCl, 100 °C; iii, propylene oxide, EtOH, 20 °C

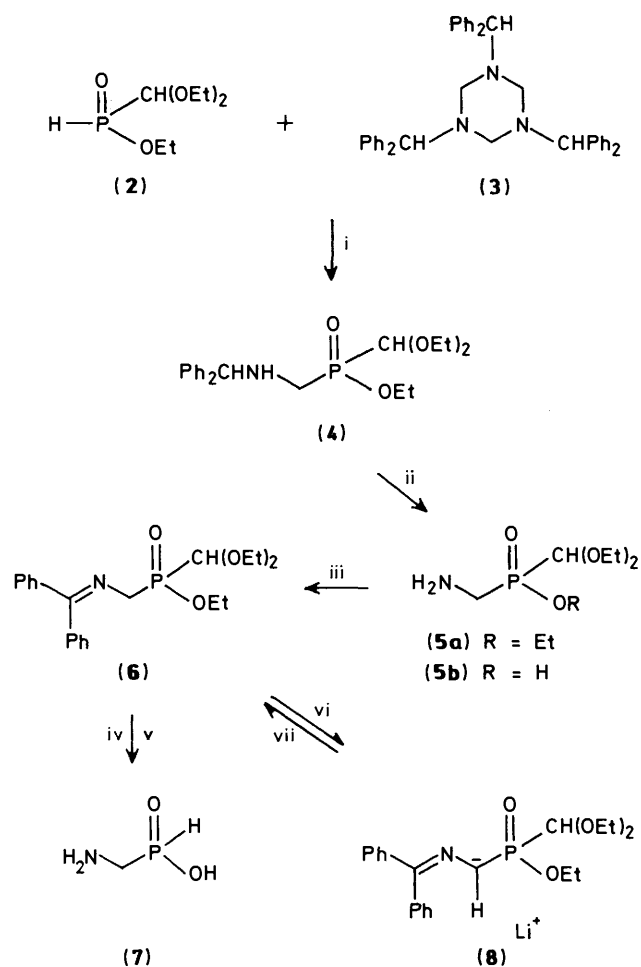
groups by dilute aqueous mineral acid gave the glycine analogue<sup>12</sup> (**7**) (**1**; R = H) in high yield. The formation and stability of the anion (**8**) were also investigated. Addition of (**6**) to a solution of LDA in THF at -78 °C gave an intense orange-red colour and a downfield shift of the phosphorus signal in the <sup>31</sup>P n.m.r. spectrum from 38.7 to 45.0 p.p.m. Storage of the anion solution at room temperature for several hours followed by proton quenching and work-up gave excellent recovery of (**6**), indicating no significant decomposition of the anion (**8**).

**Alkylation Reactions.**—Alkylation of the anion (**8**) by primary alkyl halides in the temperature range of -78 to +20 °C over 3–24 h (Scheme 3) was rapid with excellent yields of products (**9**) (Table 1), though in cases where the alkyl group was branched at the  $\beta$ -position the reaction was slower and gave lower yields. Benzyl halides were efficient electrophiles in this reaction and a range of substituted phenylalanine analogues (**1f–k**), including that of tyrosine<sup>1</sup> (**1k**), were prepared. Allyl bromide and prop-2-ynyl bromide also reacted readily, giving excellent yields of (**9l**) and (**9m**). Secondary alkyl halides were less reactive and tertiary halides failed to react at all.

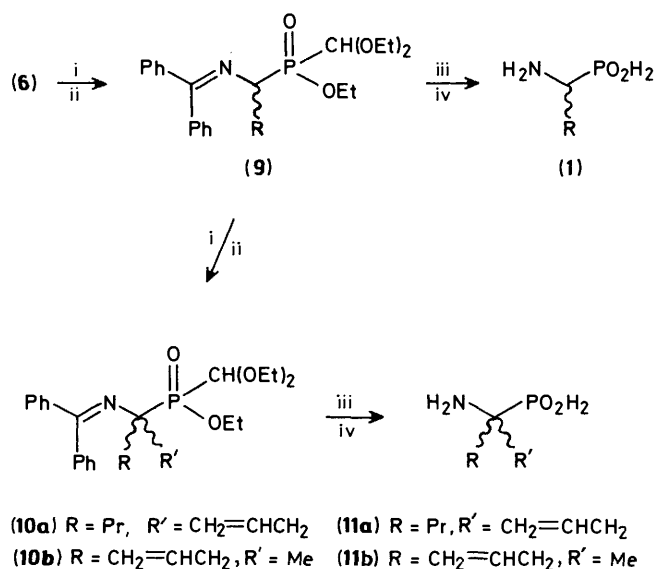
Deprotection of the products (**9**) to give the free  $\alpha$ -amino phosphinic acid was readily achieved by 1.5M aqueous hydrochloric acid at reflux. The acids (**1**) (Table 2) were obtained in high yield as the racemates.

† Present address: Ciba-Geigy Pigments, Hawkhead Road, Paisley, Renfrewshire PA2 7BG.

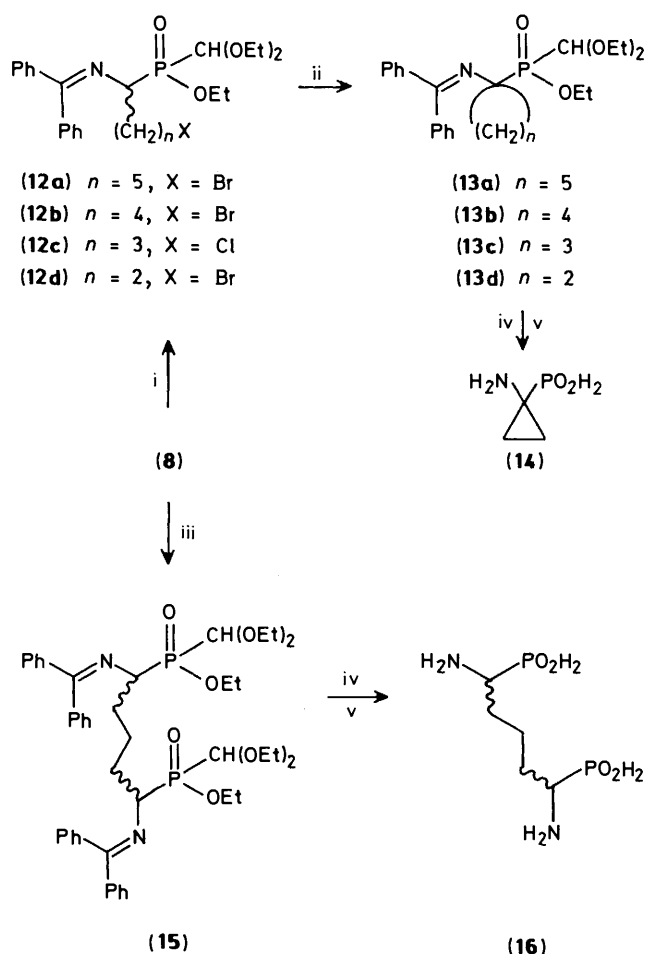
‡ These compounds were named in reference 1 as  $\alpha$ -amino phosphonous acids. Since the term 'phosphonous' implies phosphorus in the trivalent state, compounds of structure (**1**) are more correctly referred to as phosphinic acids, in accord with I.U.P.A.C. nomenclature.



**Scheme 2.** Reagents: i, toluene, 120 °C; ii, Pd-C, H<sub>2</sub>, EtOH; iii, Ph<sub>2</sub>C=O, toluene, 120 °C; iv, 1.5M aq. HCl, 100 °C; v, propylene oxide, EtOH or Dowex 50W-X2 H<sup>+</sup> form; vi, LDA, THF, -78 °C  $\rightarrow$  0 °C; vii, saturated aq. NH<sub>4</sub>Cl



**Scheme 3.** Reagents: i, LDA, THF, -78 °C, 10 min; ii, R-X or R'-X, THF, -78 °C  $\rightarrow$  +20 °C, 3-24 h; iii, 1.5M aq. HCl, 100 °C, 3 h; iv, propylene oxide, EtOH or Dowex 50W-X2 (H<sup>+</sup> form)



**Scheme 4.** Reagents: i, excess X(CH<sub>2</sub>)<sub>n</sub>X, THF, 20 °C; ii, n-BuLi, THF, -78 °C  $\rightarrow$  +20 °C; iii, 0.5 equiv. Br(CH<sub>2</sub>)<sub>3</sub>Br, THF, -78 °C  $\rightarrow$  +20 °C; iv, 1.5M aq. HCl, 100 °C; v, Dowex 50W-X2 (H<sup>+</sup> form)

$\alpha, \omega$ -Disubstituted aminophosphinic acids (11) could be prepared by alkylation of the carbanions derived from intermediates (9) followed by acid hydrolysis. In the cases investigated [(9c)  $\rightarrow$  (10a) and (9l)  $\rightarrow$  (10b)] this second alkylation was very sluggish, and the overall yield was improved by isolation of intermediate (9) rather than a one-pot sequential procedure.

The products obtained by reaction of the anion (8) with  $\alpha, \omega$ -dihalogeno-n-alkanes depended both on chain length of the dihalide and on the reaction conditions. 'Inverse' addition of the anion to a three-fold excess of dihalide at room temperature gave the 1:1 products (12a) and (12b) in the case of 1,5-dibromopentane and 1,4-dibromobutane (Scheme 4). Shorter chain dihalides under the same conditions gave mixtures of products, although the 1:1 product (12c) was effectively produced from 1-chloro-3-iodopropane. Deprotonation of (12a) and (12b) with butyl-lithium in tetrahydrofuran (THF) resulted in conversion into the cyclic amino acid derivatives, (13a) and (13b) respectively. In contrast, under identical conditions the product (12c) failed to cyclise; this mirrors the behaviour of the analogous carboxylic derivative.<sup>13</sup> 1,2-Dibromoethane reacted with anion (8) to give a mixture which was found to be composed of both 1:1 open-chain product (12d) and cyclic material (13d). Complete conversion into the cyclic product was effected by removal of excess of dihalide and treatment with butyl-lithium, with subsequent hydrolysis leading to (14). Addition of 1,3-dibromopropane to a molar excess of the imine anion (8) resulted in clean conversion into the 1:2 product (15),

Table 1. Ethyl [1-(benzhydrylideneamino)alkyl]diethoxymethylphosphinates (6), (9), (12), (17), (19), and (22)

Compound and formula	R in compound (9)	X in RX	Yield (%)	M.p. (°C) or b.p. (°C) (mmHg)	$\delta_p(\text{CDCl}_3)^a$ (p.p.m)	Found (%) <sup>b</sup> (required)				
						C	H	N	P	
(6)	H			205—210 (0.02)	38.69	64.95 (64.77)	7.05 (7.25)	3.6 (3.60)	8.0 (7.55)	
C <sub>21</sub> H <sub>28</sub> NO <sub>4</sub> P (9a)	Me	I	84	245—250 (0.02)	40.02	65.65 (65.49)	7.35 (7.49)	3.3 (3.47)	7.65 (7.85)	
C <sub>22</sub> H <sub>30</sub> NO <sub>4</sub> P (9b)	Et	OTos	81	250—252 (0.02)	39.04	66.1 (66.17)	7.60 (7.73)	3.25 (3.26)	7.3 (7.42)	
C <sub>23</sub> H <sub>32</sub> NO <sub>4</sub> P (9c)	Pr <sup>n</sup>	Br	82	220—225 (0.02)	39.09	66.5 (66.80)	7.85 (7.94)	3.2 (3.25)	7.25 (7.18)	
C <sub>24</sub> H <sub>34</sub> NO <sub>4</sub> P (9d)	Me(CH <sub>2</sub> ) <sub>17</sub>	Br	95	Oil	39.16	72.15 (72.74)	10.05 (10.33)	2.05 (2.17)	4.8 (4.81)	
C <sub>39</sub> H <sub>64</sub> NO <sub>4</sub> P (9e)	PhCH <sub>2</sub> CH <sub>2</sub>	Br	93	Oil	38.65	65.2 (70.57)	6.75 (7.35)	2.60 (2.84)	5.80 (6.27)	
C <sub>29</sub> H <sub>36</sub> NO <sub>4</sub> P (9f)	PhCH <sub>2</sub>	Br	95	123.0—125.0	38.33	69.9 (70.13)	7.3 (7.15)	3.0 (2.92)	6.4 (6.46)	
C <sub>28</sub> H <sub>34</sub> NO <sub>4</sub> P (9g)	<i>p</i> -FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Br	92	86.5—88.0	38.84	67.5 (67.59)	6.8 (6.69)	2.75 (2.19)		
C <sub>28</sub> H <sub>33</sub> FNO <sub>4</sub> P (9h)	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Br	93	84.0—86.0	38.00	64.6 (65.43)	6.4 (6.47)	2.75 (2.72)	6.1 (6.03)	
C <sub>28</sub> H <sub>33</sub> ClNO <sub>4</sub> P (9i)	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Br	85	86.0—89.0	37.95	60.05 (60.22)	5.85 (6.00)	2.4 (2.51)	5.45 (5.55)	
C <sub>28</sub> H <sub>33</sub> BrNO <sub>4</sub> P (9j)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Br	95	Oil	38.41	38.46				
C <sub>29</sub> H <sub>36</sub> NO <sub>4</sub> P (9k)	<i>p</i> -PhCH <sub>2</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Cl	34 <sup>c</sup>	Oil	38.86	38.51	66.05 (71.77)	6.1 (6.88)	2.35 (2.39)	3.9 (5.29)
C <sub>35</sub> H <sub>40</sub> NO <sub>5</sub> P (9l)	CH <sub>2</sub> =CHCH <sub>2</sub>	Br	92	240—244 (0.02)	38.91	38.55	67.15 (67.12)	7.4 (7.51)	3.3 (3.26)	7.05 (7.21)
C <sub>24</sub> H <sub>32</sub> NO <sub>4</sub> P (9m)	HC≡CCH <sub>2</sub>	Br	94	Oil	38.96	36.83				
C <sub>24</sub> H <sub>30</sub> NO <sub>4</sub> P (9n)	Me <sub>2</sub> CHCH <sub>2</sub>	Br	86 <sup>d</sup>	Oil	37.33	39.55	66.4 (67.40)	8.35 (8.14)	3.25 (3.14)	6.75 (6.95)
C <sub>25</sub> H <sub>36</sub> NO <sub>4</sub> P (9o)	C <sub>6</sub> H <sub>11</sub> CH <sub>2</sub>	Br	90 <sup>d</sup>	Oil	39.73	39.66				
C <sub>28</sub> H <sub>40</sub> NO <sub>4</sub> P (9p)	Me <sub>2</sub> CH	Br	40 <sup>c</sup>	Oil	39.90	39.44	67.25 (66.80)	7.25 (7.94)	3.5 (3.25)	6.35 (7.18)
C <sub>24</sub> H <sub>34</sub> NO <sub>4</sub> P (9q)	Cyclopentyl	Br	35 <sup>c</sup>	Oil	39.62	39.27				
C <sub>26</sub> H <sub>36</sub> NO <sub>4</sub> P (12a)	Br(CH <sub>2</sub> ) <sub>5</sub>	Br	65	Oil	39.27	38.97	(—)			
C <sub>26</sub> H <sub>37</sub> BrNO <sub>4</sub> P (12b)	Br(CH <sub>2</sub> ) <sub>4</sub>	Br	55	Oil	39.25	39.25	58.2 (58.00)	6.7 (6.93)	2.5 (2.60)	5.55 (5.75)
C <sub>25</sub> H <sub>35</sub> BrNO <sub>4</sub> P (12c)	Cl(CH <sub>2</sub> ) <sub>3</sub>	I	66	Oil	38.74	39.12				
C <sub>24</sub> H <sub>33</sub> ClNO <sub>4</sub> P (17)	EtOCOCH <sub>2</sub>	Br	84	225—230 (0.05)	38.49	38.73	59.25 (61.86)	7.0 (7.14)	2.75 (3.01)	5.9 (6.65)
C <sub>25</sub> H <sub>34</sub> NO <sub>6</sub> P (19a)	EtOCO(CH <sub>2</sub> ) <sub>2</sub>	<i>e</i>	67	<i>ca.</i> 350 (0.02)	37.03	37.69	63.1 (63.15)	7.1 (7.21)	2.85 (2.94)	6.5 (6.51)
C <sub>26</sub> H <sub>36</sub> NO <sub>6</sub> P (19b)	(EtO) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>2</sub>	<i>e</i>	75	Oil	38.15	38.23	63.65 (63.79)	7.2 (7.41)	2.6 (2.86)	6.35 (6.33)
C <sub>27</sub> H <sub>41</sub> NO <sub>7</sub> P <sub>2</sub> (22a)	1-Tosylimidazol-4-ylmethyl	OBz	67	Oil	38.23	31.12, 38.29 <sup>f</sup>	56.3 (58.58)	7.25 (7.46)	2.25 (2.53)	10.7 (11.9)
C <sub>32</sub> H <sub>38</sub> N <sub>3</sub> O <sub>6</sub> PS					37.67	38.10				

<sup>a</sup> <sup>1</sup>H N.m.r. spectra of all compounds were consistent with that of the parent (6) substituted at the  $\alpha$ -C with the introduced alkyl group R. The chiral  $\alpha$ -C and P atoms give rise to diastereoisomers causing the acetal CH doublet to undergo shift splitting of *ca.* 0.1—0.25 p.p.m. <sup>b</sup> In some cases, slightly low % C and P analyses were due to incomplete removal of chloroform from these viscous oils. <sup>c</sup> % Yields not optimised. <sup>d</sup> Yield determined from the <sup>31</sup>P n.m.r. spectrum; unoptimised yields of pure (9n) and (9o) from chromatography were 40 and 48% respectively. <sup>e</sup> Alkylation carried out by Michael addition. <sup>f</sup>  $J_{\text{PCCCP}}$  6.83 Hz. <sup>g</sup>  $J_{\text{PCCCP}}$  6.34 Hz.

subsequent hydrolysis providing the bis(aminophosphinic) acid (16).

The importance of aspartic and glutamic acids in the central nervous system is well known.<sup>14</sup> This stimulated us to use our synthetic method to make phosphorus analogues of a number of  $\alpha$ -amino carboxylic acids active in this field (Scheme 5). Reaction of the LDA-generated anion (8) with ethyl bromoacetate proved straightforward, the aspartic acid analogue<sup>15</sup> (18) being obtained in high yield after hydrolysis of (17).

To synthesize analogues of glutamic acid [*e.g.*, (20a) and (20b)], alternative conditions in a protic solvent mixture were established for conjugate addition of the anion of (6) to ethyl acrylate and diethyl vinylphosphonate. Thus deprotonation of (6) by potassium ethoxide in THF–ethanol and reaction of the anion with the Michael acceptor gave, after hydrolysis of the intermediates (19a) and (19b), glutamic acid analogues (20a) and (20b) respectively.

The phosphonic acid analogue of histidine (23b) has recently

Table 2. 1-Aminoalkylphosphinic acids (1)

Compound and formula	R	Yield (%)	M.p. (°C) (decomp.)	N.m.r. (D <sub>2</sub> O) <sup>a</sup>			(Required)			
				δ <sub>P</sub>	δ <sub>H</sub> (PH)	J <sub>PH</sub> (Hz)	C	H	N	P
(7) <sup>b</sup>	H	85	254—256	14.03	7.11	542.5				
CH <sub>6</sub> NO <sub>2</sub> P (1a) <sup>b</sup>	Me	82	223—224	21.22	6.90	532.0				
C <sub>2</sub> H <sub>8</sub> NO <sub>2</sub> P (1b)	Et	95	229—230	20.10	6.95	532.4	29.1 (29.27)	8.2 (8.19)	10.6 (11.38)	24.1 (25.16)
C <sub>3</sub> H <sub>10</sub> NO <sub>2</sub> P (1c)	Pr	77	232—233	20.46	6.96	532.0	34.5 (35.04)	8.8 (8.82)	9.95 (10.21)	22.2 (22.59)
C <sub>4</sub> H <sub>12</sub> NO <sub>2</sub> P (1d)	Me(CH <sub>2</sub> ) <sub>17</sub>	78	228—230	Insufficiently soluble			64.7 (65.67)	12.4 (12.18)	3.83 (4.03)	9.4 (8.91)
C <sub>19</sub> H <sub>42</sub> NO <sub>2</sub> P (1e)	PhCH <sub>2</sub> CH <sub>2</sub>	55 <sup>c</sup>	244—246	19.80	7.00	537	54.5 (54.27)	6.9 (7.08)	6.85 (7.03)	15.65 (15.55)
C <sub>9</sub> H <sub>14</sub> NO <sub>2</sub> P (1f) <sup>b</sup>	PhCH <sub>2</sub>	91	227—228	18.63	7.03	537				
C <sub>8</sub> H <sub>12</sub> NO <sub>2</sub> P (1g)	<i>p</i> -FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	93	238	18.52	7.03	538.6	47.15 (47.30)	5.6 (5.46)	6.8 (6.89)	15.0 (15.25)
C <sub>8</sub> H <sub>17</sub> FNO <sub>2</sub> P (1h)	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	92	237—238	18.51	7.02	537.6	43.8 (43.75)	5.05 (5.05)	6.25 (6.38)	14.1 (14.10)
C <sub>8</sub> H <sub>17</sub> ClNO <sub>2</sub> P (1i)	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	88	236—237	18.46	7.03	539.1	36.3 (36.39)	4.4 (4.20)	5.55 (5.30)	11.65 (11.73)
C <sub>8</sub> H <sub>17</sub> BrNO <sub>2</sub> P (1j)	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	75	235—236	18.74	7.06	538.7	54.5 (52.27)	7.1 (7.08)	7.0 (7.03)	15.45 (15.55)
C <sub>9</sub> H <sub>14</sub> NO <sub>2</sub> P (1k)	<i>p</i> -HOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	73	252	18.75	6.99	538.6	43.1 (43.84)	6.25 (6.44)	6.25 (6.39)	14.1 (14.13)
C <sub>8</sub> H <sub>12</sub> NO <sub>3</sub> P·H <sub>2</sub> O (1l)	CH <sub>2</sub> =CHCH <sub>2</sub>	84	235	18.79	7.02	538.6	35.0 (35.56)	7.15 (7.46)	9.95 (10.37)	22.45 (22.93)
C <sub>4</sub> H <sub>10</sub> NO <sub>2</sub> P (1m)	HC≡CCH <sub>2</sub>	78	215—218	16.89	7.06	543	36.1 (36.10)	6.3 (6.06)	10.3 (10.52)	22.7 (23.27)
C <sub>4</sub> H <sub>8</sub> NO <sub>2</sub> P (1n) <sup>b</sup>	Me <sub>2</sub> CHCH <sub>2</sub>	69	222—223	21.03	6.97	532.9				
C <sub>5</sub> H <sub>14</sub> NO <sub>2</sub> P (1o)	C <sub>6</sub> H <sub>11</sub> CH <sub>2</sub>	53	227—229	21.16	6.95	533.5	50.4 (50.25)	9.35 (9.49)	7.05 (7.33)	16.15 (16.20)
C <sub>8</sub> H <sub>18</sub> NO <sub>2</sub> P (1p) <sup>b</sup>	Me <sub>2</sub> CH	71	186	18.39	6.96	534.2				
C <sub>4</sub> H <sub>12</sub> NO <sub>2</sub> P (1q)	Cyclopentyl	81	235—237	19.68	7.02	536.5	43.4 (44.17)	8.3 (8.65)	8.35 (8.58)	19.1 (18.98)
C <sub>6</sub> H <sub>14</sub> NO <sub>2</sub> P (18)	HO <sub>2</sub> CH <sub>2</sub>	67	209—212	17.11	7.04	546.9	23.4 (23.54)	5.4 (5.27)	8.6 (9.15)	19.75 (20.33)
C <sub>3</sub> H <sub>8</sub> NO <sub>4</sub> P (20a)	HO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub>	45	ca. 122	19.28	6.94	538.1	30.0 (28.75)	6.25 (6.03)	6.95 (8.38)	
C <sub>4</sub> H <sub>10</sub> NO <sub>4</sub> P (20b)	H <sub>2</sub> O <sub>3</sub> P(CH <sub>2</sub> ) <sub>2</sub>	40	232	19.17 26.98	6.97	539.7	18.05 (17.74)	5.45 (5.46)	6.5 (6.90)	29.4 (30.51)
C <sub>3</sub> H <sub>11</sub> NO <sub>5</sub> P (23a)	Imidazol-4-ylmethyl	77	242	21.77	6.79	526.3	34.2 (34.29)	5.75 (5.76)	22.1 (23.99)	15.8 (17.69)

<sup>a</sup> <sup>1</sup>H N.m.r. spectra of all compounds were consistent with that of the parent (7)<sup>1</sup> substituted at the α-C with the appropriate alkyl group R.

<sup>b</sup> Compounds have previously been described. <sup>c</sup> Yield overall from (6).

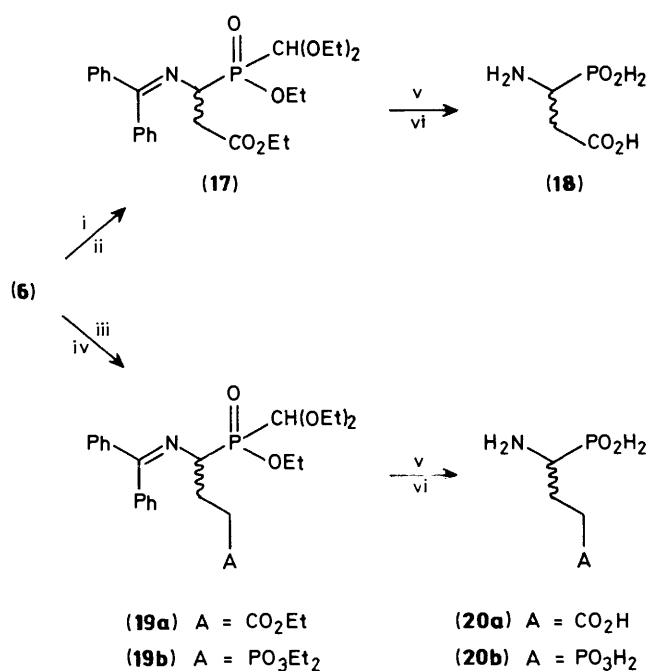
been prepared by a route involving construction of the imidazole ring from the carboxy group of α-phosphono aspartic acid.<sup>16</sup> The authors of this work reported that they were unable to synthesize phosphonohistidine from substituted imidazole precursors. In contrast we have found that the protected phosphinic analogue (22a) may be prepared by condensation of (8) and 4-(benzoyloxymethyl)imidazole, provided the imidazole NH is protected as the tosyl derivative<sup>17</sup> (Scheme 6). Hydrolysis gave the free acid (23a). Similarly, phosphonohistidine (23b) itself was readily prepared from the imine-phosphonate diester (21) by alkylation with 4-benzoyloxymethyl-1-tosylimidazole<sup>17</sup> to give (22b) and subsequent hydrolysis. Compound (21) was synthesized from diethyl aminomethylphosphonate<sup>3,8</sup> and benzophenone, in similar fashion to the preparation of (6).

Although tryptophan has been prepared by the alkylation of ethyl nitroacetate<sup>18</sup> or methyl isocyanoacetate<sup>19</sup> anions with

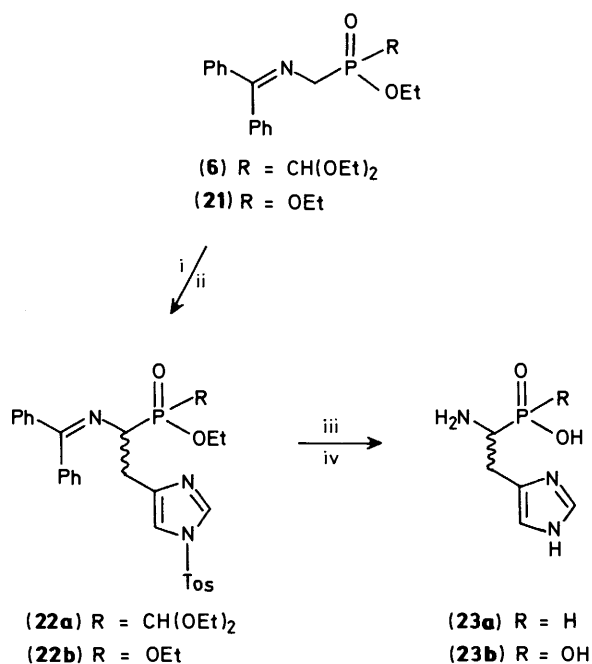
gramine [3-(dimethylaminomethyl)indole],<sup>20</sup> our attempts to adopt this approach to the phosphinic derivative (1; R = indol-3-ylmethyl)<sup>1</sup> were unsuccessful.

*Asymmetric Synthesis.*—2-Hydroxypinan-3-one<sup>21,22</sup> (24) or (29) has been reported by several groups to be an accessible, efficient chiral auxiliary in the alkylation of imine glycinates for asymmetric synthesis of both mono-<sup>23–26</sup> and di-substituted<sup>27,28</sup> α-amino carboxylic acids and also as a resolution reagent for α-amino carboxylates.<sup>29</sup>

Condensation of (1*R*,2*R*,5*R*)-(+)-2-hydroxypinan-3-one<sup>24</sup> (24) with the aminomethylphosphinate (5a) (Scheme 7) readily provided a 1:1 diastereoisomeric mixture of the imine phosphinate (25a) which underwent diastereospecific alkylation with LDA [2 molar equiv. to generate the dianion (26)] and benzyl bromide. Hydrolysis of the product (27a) led exclusively to (*R*)-(-)-α-aminophenethylphosphinic acid<sup>1</sup>



**Scheme 5.** Reagents: i, LDA, THF,  $-78^\circ\text{C}$ , 20 min; ii, BrCH<sub>2</sub>CO<sub>2</sub>Et, THF,  $-78^\circ\text{C} \rightarrow +20^\circ\text{C}$ ; iii, KH, THF-EtOH (3:1 v/v),  $0^\circ\text{C}$ , 10 min; iv, CH<sub>2</sub>=CH<sub>2</sub>A, THF,  $0^\circ\text{C} \rightarrow 20^\circ\text{C}$ ; v, 6M aq. HCl,  $100^\circ\text{C}$ , 6 h; vi, Dowex 50W-X2 (H<sup>+</sup> form)



**Scheme 6.** Reagents: i, 2 LDA, THF,  $-78^\circ\text{C}$ , 10 min; ii, 4-benzoyloxymethyl-1-tosylimidazole, THF,  $-78^\circ\text{C} \rightarrow +20^\circ\text{C}$ ; iii, 6M aq. HCl,  $100^\circ\text{C}$ , 6 h; iv, Dowex 50W-X2 (H<sup>+</sup> form)

(28a) (e.e. >99%).\* Similarly, the imine phosphinate ester (30a), prepared from (5a) and (1*S*,2*S*,5*S*)-(-)-2-hydroxypinan-3-one<sup>22</sup> (29), underwent diastereospecific alkylation on deprotonation and treatment with benzyl bromide to give (31); hydrolysis of this gave exclusively the (*R*)-(+)-phenylalanine analogue (32).

Alkylation of (25a) with LDA and methyl iodide proved less diastereoselective and, after hydrolysis of the intermediates (27b), (*R*)-(-)-1-aminoethylphosphinic acid<sup>1</sup> (28b) was

obtained in only 46% e.e. In the case of the corresponding diethyl phosphonate (25b) the diastereoselectivity of the benzylation reaction was reduced to 83% d.e. Hydrolysis of the separable intermediates (27c) led to *R*-(-)- $\alpha$ -aminophenethylphosphonic acid (28c) in 72% e.e. For the dianion of the imine (25c), derived from (24) and ethyl glycinate, the benzylation proved even less diastereoselective, product hydrolysis of (27d) giving (*S*)-(-)-phenylalanine (28d) in 74% e.e.

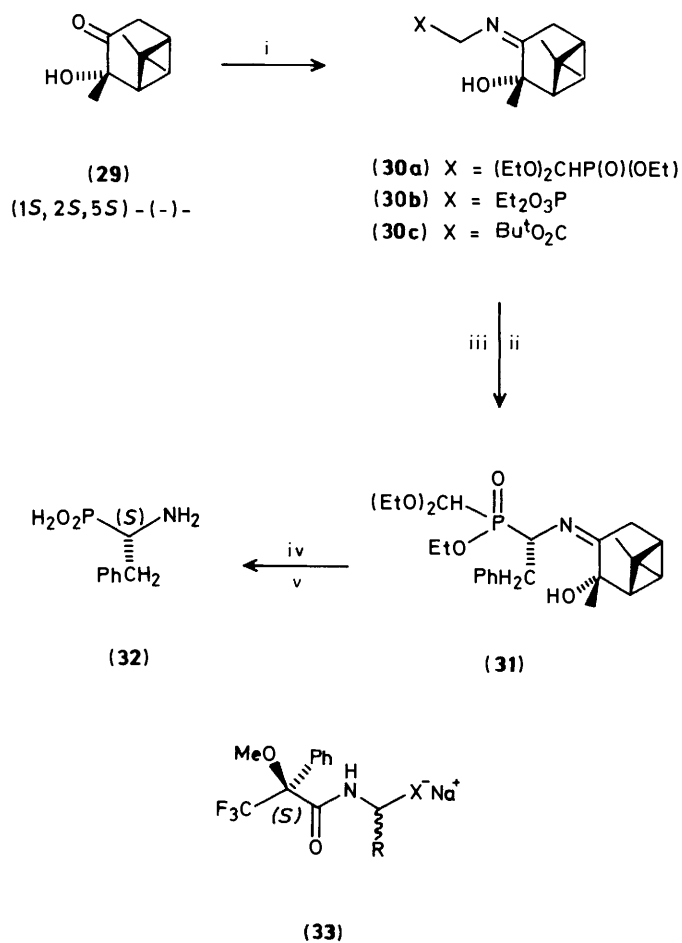
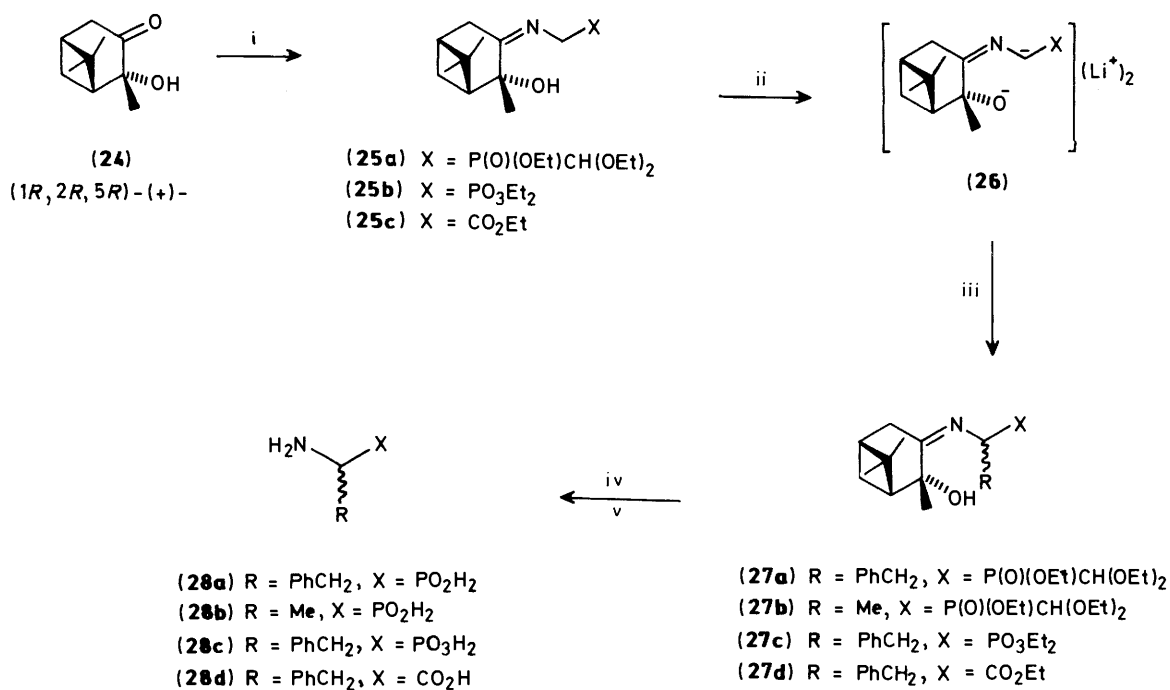
These results compare favourably with related imine alkylations reported in the literature also using this terpenoid auxiliary (29); the corresponding diethyl phosphonate<sup>31</sup> (30b) gave a product with a diastereoisomeric excess of 97% when alkylated with LDA and 3,4-dimethoxybenzyl bromide,<sup>31</sup> and the *t*-butyl glycinate (30c) to d.e.s of 72 and 66% with LDA then benzyl bromide or 3,4-dimethoxybenzyl bromide respectively.<sup>23</sup> It thus appears here that the tetrahedral nature of the ester function  $\alpha$  to the carbanion undergoing alkylation and the degree of oxygenation associated with it enhance the diastereoselectivity of the benzylation, *i.e.*, CO<sub>2</sub>Et < PO<sub>3</sub>Et<sub>2</sub> < P(=O)(OEt)CH(OEt)<sub>2</sub>.

## Experimental

**General.**—All compounds for which analytical and spectroscopic data are quoted were homogeneous to t.l.c. and <sup>31</sup>P n.m.r. T.l.c. was carried out on Merck high performance silica gel 60F<sub>254</sub> pre-coated plates (10 × 5 cm) which were developed in chloroform-ethanol (19:1 v/v) for imines or in acetic acid-water-acetone-propan-2-ol (2:5:7.5:5.5) for  $\alpha$ -amino phosphinic acids.<sup>1</sup> Preparative chromatography was performed on silica gel 60 (70–230 mesh ASTM) (Merck) with chloroform-ethanol (99:1 v/v) as eluant for imines, and on Dowex 50W-X2 ion exchange resin (200–400 mesh; H<sup>+</sup> form) (Bio-Rad) with water as eluant for  $\alpha$ -amino phosphinic acids. <sup>1</sup>H N.m.r. spectra were recorded on a Jeol FX-90Q spectrometer operating at 89.55 MHz [referenced internally to SiMe<sub>4</sub> (for CDCl<sub>3</sub> solutions) and externally to sodium 3-(trimethylsilyl)propane-sulphonate (for D<sub>2</sub>O solutions)], as were <sup>31</sup>P n.m.r. spectra (operating at 36.21 MHz, and referenced externally to H<sub>3</sub>PO<sub>4</sub> for both CDCl<sub>3</sub> and D<sub>2</sub>O solutions), <sup>13</sup>C n.m.r. spectra (operating at 22.49 MHz and referenced internally to <sup>13</sup>CDCl<sub>3</sub> at 77.10 p.p.m.), and <sup>19</sup>F n.m.r. spectra (operating at 84.25 MHz and referenced externally to CFCl<sub>3</sub>); chemical shifts are reported in p.p.m. with positive values being downfield from the reference. I.r. spectra were measured on Perkin-Elmer 157, 457, and 881 grating spectrophotometers. M.p.s were determined on a Buchi Type S and are uncorrected, as are b.p.s. Microanalyses were made on a Perkin-Elmer 240 Elemental Analyser. Di-isopropylamine was distilled from solid potassium hydroxide, and tetrahydrofuran (THF) was dried and distilled from sodium benzophenone ketyl immediately before use. Butyl-lithium (1.6M solution in hexane) was used as supplied (Fluka). All reactions were carried out under dry nitrogen, which was purified by successive passage through Fieser's deoxygenating solution, saturated aqueous lead(II) acetate, concentrated sulphuric acid, and potassium hydroxide pellets. Unless stated otherwise, all reactions were carried out at room temperature, which refers to 18–24 °C.

### Ethyl Benzhydrylaminoethyl(diethoxymethyl)phosphinate<sup>15</sup> (4).—A solution of 2,4,6-tris(benzhydryl)hexahydro-1,3,5-tria-

\* Enantiomeric purity of the free  $\alpha$ -amino phosphinic acid was determined by preparation of the Mosher-reagent derivatives<sup>30</sup> and <sup>31</sup>P and <sup>19</sup>F n.m.r. analysis of their resultant *N*-[(*S*)-(-)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl] sodium salts (33) (Table 4). Diastereoisomeric purity of the alkylated pinane-imine precursors was determined by intensity comparison of their <sup>31</sup>P n.m.r. shift signals.



**Scheme 7.** Reagents: i, H<sub>2</sub>NCH<sub>2</sub>X, toluene, 120 °C; ii, 2 LDA, THF, -78 °C, 10 min; iii, R-Hal, THF, -78 °C → +20 °C, 3–24 h; iv, 1.5M aq. HCl, 100 °C; v, propylene oxide, EtOH or Dowex 50W-X2 (H<sup>+</sup> form)

zine (3) (14.06 g, 24.0 mmol) and ethyl diethoxymethylphosphinate<sup>11</sup> (2) (14.12 g, 72.0 mol) in dry toluene (120 ml) was heated under reflux for 2 h and then the solvent removed under reduced pressure to afford the product (28.13 g) in quantitative yield. Chromatography on silica gel with chloroform as eluant gave pure (4) as a colourless viscous oil;  $v_{\max}$  (neat) 3 258w (NH), 1 224s (P=O), and 1 060vs (P-O-C)  $\text{cm}^{-1}$ ;  $\delta_{\text{P}}(\text{CDCl}_3)$  40.89;  $\delta_{\text{H}}(\text{CDCl}_3)$  1.1–1.4 (9 H, m, 3 × Me), 2.15 (1 H, br s, exchanges with D<sub>2</sub>O, NH), 3.01 (2 H, d,  $J_{\text{PCH}}$  10.3 Hz, CH<sub>2</sub>P), 3.5–4.0 [4 H, m, PCH(OCH<sub>2</sub>Me)<sub>2</sub>], 4.23 (2 H, m, POCH<sub>2</sub>Me), 4.86 [1 H, d,  $J_{\text{PCH}}$  7.7 Hz, PCH(OEt)<sub>2</sub>], 4.89 (1 H, s, Ar<sub>2</sub>CH), and 7.1–7.4 (10 H, m, ArH).

**Ethyl Aminomethyl(diethoxymethyl)phosphinate (5a).**—The crude *N*-benzhydryl amine (4) was dissolved in absolute ethanol (400 ml) containing 5% palladium on activated carbon (3.0 g), and hydrogenated at 50–60 °C and 50–60 atm pressure until the uptake of hydrogen had ceased (20 h). The catalyst was removed by filtration and the filtrate evaporated. The residual oil was co-evaporated with chloroform (2 × 50 ml) and then kept at –10 °C for 48 h. The suspension was filtered neat and the crystalline residue was washed with diethyl ether (2 × 10 ml) and dried to give aminomethyl(diethoxymethyl)phosphinic acid (5b) (1.05 g, 7.4%) as a colourless solid, m.p. 205–207 °C (Found: C, 36.08; H, 8.12; N, 7.03; P, 15.51. C<sub>6</sub>H<sub>16</sub>NO<sub>4</sub>P requires C, 36.55; H, 8.18; N, 7.10; P, 15.71%);  $v_{\max}$  (Nujol) 3 400m, 3 215m, 2 730m, 2 620m, 2 130w, 1 545m, 1 180s, 1 128m, 1 060s, and 1 012m  $\text{cm}^{-1}$ ;  $\delta_{\text{P}}(\text{D}_2\text{O})$  22.17;  $\delta_{\text{H}}(\text{D}_2\text{O})$  1.20 (6 H, t, 2 × Me), 3.04 (2 H, d,  $J_{\text{PCH}}$  10.04 Hz, PCH<sub>2</sub>), 3.6–4.0 (4 H, m, OCH<sub>2</sub>), and 4.62 (1 H, d,  $J_{\text{PCH}}$  3.93 Hz, PCH). The solution from which the phosphinic acid (34) had been separated was evaporated to afford the crude product. This was purified by chromatography on silica gel with CHCl<sub>3</sub>–EtOH (19:1 v/v) eluant and then distilled *in vacuo* (b.p. 160–162 °C at 0.2 mmHg) to provide the free amine (5a) (12.0 g, 74%) as a colourless oil (Found: C, 42.95; H, 9.25; N, 6.6; P, 13.75. C<sub>8</sub>H<sub>20</sub>NO<sub>4</sub>P requires C, 42.66; H, 8.95; N, 6.22; P, 13.75%);  $v_{\max}$  (neat) 3 380w, 3 304w, 2 980m, 2 935w, ca. 2 890w br, 1 218s, 1 110m, 1 060s, 1 040s, and 954m  $\text{cm}^{-1}$ ;  $\delta_{\text{P}}(\text{CDCl}_3)$  40.95;  $\delta_{\text{H}}(\text{CDCl}_3)$  1.20–1.45 (9 H, m, 3 × Me), 1.56 (2 H, s, exchanges with D<sub>2</sub>O, NH<sub>2</sub>), 3.09 (2 H, d,  $J_{\text{PCH}}$  7.20 Hz, PCH<sub>2</sub>), 3.60–4.00 [4 H, m, PCH(OCH<sub>2</sub>Me)<sub>2</sub>], 4.23 (2 H, m, POCH<sub>2</sub>Me), and 4.82 [1 H, d,  $J_{\text{PCH}}$  6.12 Hz, PCH(OEt)<sub>2</sub>].

**Ethyl Benzhydrylideneaminomethyl(diethoxymethyl)phosphinate (6).**—The amine (5a) (17.17 g, 76.23 mmol) and benzophenone (15.30 g, 83.96 mmol) in toluene (200 ml) were heated under reflux for 4 h with removal of water (Dean–Stark apparatus). Upon removal of the solvent, the residual oil was chromatographed and then further purified by bulb-to-bulb (Kugelrohr) distillation *in vacuo* (b.p. 205–210 °C at 0.02 mmHg) to afford (6) as a near-colourless, viscous oil (24.40 g, 82%) (Found: C, 64.95; H, 7.05; N, 3.6; P, 8.0. C<sub>21</sub>H<sub>28</sub>NO<sub>4</sub>P requires C, 64.77; H, 7.25; N, 3.60; P, 7.95%);  $v_{\max}$  (neat) 3 025w, 2 952m, 2 870m, 1 620m, 1 445m, 1 392w, 1 315m, 1 292m, 1 225s, 1 160m, 1 113s, 1 056vs, and 950m  $\text{cm}^{-1}$ ;  $\delta_{\text{P}}(\text{CDCl}_3)$  38.69;  $\delta_{\text{H}}(\text{CDCl}_3)$  1.16–1.41 (9 H, m, 3 × Me), 3.64–4.04 [4 H, m, PCH(OCH<sub>2</sub>Me)<sub>2</sub>], 4.00 (2 H, d,  $J_{\text{PCH}}$  13.78 Hz, CH<sub>2</sub>P), 4.24 (2 H, m, POCH<sub>2</sub>Me), 4.98 [1 H, d,  $J_{\text{PCH}}$  8.31 Hz, PCH(OEt)<sub>2</sub>], 7.17–7.48 (8 H, m, ArH), and 7.58–7.62 (2 H, m, ArH of one benzene ring *ortho* to C=N);  $\delta_{\text{C}}(\text{CDCl}_3)$  14.10 [s, CH(OCH<sub>2</sub>Me)<sub>2</sub>], 15.50 (d,  $J_{\text{POC}}$  5.59 Hz, POCH<sub>2</sub>Me), 50.47 (d,  $J_{\text{PC}}$  101.63 Hz, CH<sub>2</sub>P), 60.62 (d,  $J_{\text{POC}}$  6.87 Hz, POCH<sub>2</sub>), 63.45–64.12 [2 d, CH(OCH<sub>2</sub>Me)<sub>2</sub>], 98.82 [d,  $J_{\text{PC}}$  144.17 Hz, PCH(OEt)<sub>2</sub>], 126.76–127.55 [4 s, C-2,2' and C-3,3', =CH], 129.02 and 134.26 [2s, C-4,4', =CH], 138.10 and 138.22 [2s, C-1,1', =CH], and 170.30 (d,  $J_{\text{CNP}}$  15.10 Hz, C=NCH<sub>2</sub>P).

**Ethyl [1-(Benzhydrylideneamino)alkyl]diethoxymethylphosphinates (9) and (17) by Alkylation: General Procedure.**—Lithium di-isopropylamide (LDA) was prepared under nitrogen by the addition of butyl-lithium (12.0 mmol) in hexane (7.5 ml) to di-isopropylamine (1.21 g, 12.0 mmol) in THF (12 ml) at –78 °C. After 10 min a solution of the imine (6) (3.89 g, 10.0 mmol) in THF (10 ml) was added, followed 10 min later by a solution of the appropriate alkylating reagent (*e.g.* alkyl halide, tosylate, benzoate) (24.0 mmol) in THF (25 ml). The mixture was allowed to warm to room temperature (18–24 °C), and left for 4–16 h; it was then shaken with saturated aqueous ammonium chloride (100 ml) and extracted with diethyl ether (2 × 15 ml). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated to yield a viscous orange oil, which was chromatographed on silica gel (150 g) with CHCl<sub>3</sub> as eluant to afford the alkylated imine (9) as a mixture of diastereoisomers. Further purification could be achieved either by bulb-to-bulb (Kugelrohr) distillation *in vacuo* [*e.g.* (9a), (9l), (17)] affording a pale yellow viscous oil or by crystallisation from hexane [*e.g.* (9f–i)] which gave colourless prisms. Analytical and spectroscopic data for the products are collected in Table 1.

**Ethyl 1-(Benzhydrylideneamino)alkyl(diethoxymethyl)phosphines (19) by Conjugate (Michael) Addition.**—(a) Potassium ethoxide was prepared under nitrogen by adding dry ethanol (10 ml) dropwise during 5 min to a stirred suspension of anhydrous potassium hydride (0.54 g, 13.44 mmol) in THF (10 ml) at 0 °C. After 10 min the imine (6) (4.36 g, 11.20 mmol) dissolved in THF (10 ml) was added, followed 10 min later by a solution of ethyl acrylate (1.35 g, 13.44 mmol) in THF (10 ml). The mixture was then allowed to warm to room temperature. After 16 h, the solvent was evaporated at <40 °C under reduced pressure and the residue was shaken with saturated aqueous ammonium chloride and extracted with ether (2 × 150 ml). Work-up, chromatography, and distillation as described for compounds (9) provided ethyl 1-(benzhydrylideneamino)-3-ethoxycarbonylpropyl(diethoxymethyl)phosphinate (19a) (3.66 g, 67%) as a viscous yellow oil (b.p. ca. 350 °C at 0.02 mmHg).

(b) In the same way, the addition of diethyl vinylphosphonate (1.97 g, 12.01 mmol) to the potassium ethoxide-generated anion of (6) (3.90 g, 10.01 mmol) gave, after chromatography, ethyl 1-(benzhydrylideneamino)-3-(diethylphosphonyl)propyl (diethoxymethyl)phosphinate (19b) (4.16 g, 75%) as a viscous orange oil.

**$\alpha$ -Amino Phosphinic Acids (1) by Hydrolysis of Alkylated Imines (9): General Procedure.**—A mixture of the alkylated imine (9) and 1.5M hydrochloric acid (20 ml per mmol) [or concentrated hydrochloric acid (12M; 15 ml per mmol) for the hydrolyses of (9k), (19b), and (27c)] were heated together under reflux for 2–4 h (or for 6–8 h as required) until completion of the hydrolysis, as determined from the <sup>31</sup>P n.m.r. spectrum. The excess of acid was removed by evaporation under reduced pressure and, to complete the removal, water (3 × 10 ml) was added and removed in the same way. The residual hydrochloride gum was dissolved in water (20 ml), washed with ether (2 × 20 ml), and evaporated. The free amino acid was isolated in one of two ways: (i) ion exchange chromatography, followed by evaporation of those eluates homogeneous to <sup>31</sup>P n.m.r. and to t.l.c. (developed with ninhydrin/butan-1-ol solution). The residue was triturated (where necessary) with hexane, diethyl ether, or acetone, and the resulting solid dried *in vacuo* over phosphorus pentoxide; or (ii) dissolution in hot ethanol (twice the minimum volume required), cooling of the solution to room temperature and then addition of propylene oxide dropwise with stirring to precipitate the desired acid. This was separated, washed with ethanol (2 × 10 ml) and then diethyl ether (2 × 10 ml), and dried as in (i) above. Physical and

spectroscopic data for the  $\alpha$ -amino phosphinic acids prepared are collected in Table 2.

*$\alpha,\alpha$ -Disubstituted Aminophosphinic Acids: 2-Aminopent-4-en-2-ylphosphinic Acid (11b).*—Alkylation of the allyl-imine-phosphinate (**9l**) (4.31 g, 10.37 mmol) with LDA and methyl iodide as described in the General Procedure above afforded, on work up, ethyl 1-(benzhydrylideneamino)pent-4-en-2-yl-(diethoxymethyl)phosphinate (**10b**) (1.40 g, 30%);  $\nu_{\max.}$ (neat) 2974s, 1656m (C=N), 1484m, 1230s (P=O), 1052s, and 1030s (P—O—C)  $\text{cm}^{-1}$ ;  $\delta_{\text{p}}(\text{CDCl}_3)$  40.57 and 40.99;  $\delta_{\text{H}}(\text{CDCl}_3)$  0.88—1.5 (12 H, m, 4  $\times$  Me), 2.4—3.3 (2 H, m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.54—4.11 [4 H, m,  $\text{PCH}(\text{OCH}_2\text{Me})_2$ ], 4.32 (2 H, m,  $\text{POCH}_2\text{Me}$ ), 4.91—5.31 (3 H, m, = $\text{CH}_2$  and PCH), 5.60—6.14 (1 H, m, CH=), and 7.22—7.68 (10 H, m, ArH). Hydrolysis of (**10b**) by the General Procedure gave the acid (**11b**) (0.33 g, 71%) (Found: C, 39.6; H, 8.1; N, 9.2; P, 20.6.  $\text{C}_5\text{H}_{12}\text{NO}_2\text{P}$  requires C, 40.27; H, 8.11; N, 9.39; P, 20.77%) as a colourless solid, m.p. 210 °C (decomp.);  $\nu_{\max.}$ (Nujol) 2310m and 2150m (P—H), 1177s (P=O), and 1068s (P—O)  $\text{cm}^{-1}$ ;  $\delta_{\text{p}}(\text{D}_2\text{O})$  24.49;  $\delta_{\text{H}}(\text{D}_2\text{O})$  1.34 (3 H, d,  $J_{\text{PCH}}$  14.4 Hz, Me), 2.48 (2 H, t,  $J_{\text{CH}}$  9.3 Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.14—5.42 (2 H, m, = $\text{CH}_2$ ), 5.65—6.16 (1 H, m, CH=), and 6.92 (1 H, d,  $J_{\text{PH}}$  532 Hz, P—H).

Under the same conditions, alkylation of the LDA-derived anion of imine (**9c**) with allyl bromide failed to proceed to completion (ca. 60% reaction), but here the dialkylated product (**10a**) [ $\delta_{\text{p}}(\text{CDCl}_3)$  40.86 and 41.21] could not be separated from one of the diastereoisomers of (**9c**) [ $\delta_{\text{p}}(\text{CDCl}_3)$  39.32]. Hydrolysis of the chromatographed product [ratio of (**10a**):(**9c**) = 3:1] gave 4-aminohept-1-en-4-ylphosphinic acid (**11a**);  $\delta_{\text{p}}(\text{D}_2\text{O})$  23.95;  $\delta_{\text{H}}(\text{CDCl}_3)$  7.00 (1 H, d,  $J_{\text{PH}}$  533 Hz, P—H); contaminated with ca. 25% of 1-aminobutylphosphinic acid (**1c**),  $\delta_{\text{p}}(\text{D}_2\text{O})$  20.49.

*1-Aminocyclopropylphosphinic Acid (14).*—Butyl-lithium (172 mmol) in hexane (108 ml) was added to di-isopropylamine (9.35 g, 92.40 mmol) in THF (90 ml) at  $-78^\circ\text{C}$ . After 10 min, the imine (**6**) (16.35 g, 41.98 mmol) in THF (40 ml) was added, followed 10 min later by 1,2-dibromoethane (58.52 g, 311 mmol) in THF (50 ml). The solution was stirred for 2 h at  $-78^\circ\text{C}$  and then allowed to warm to room temperature overnight (14 h). Work-up of the mixture as described above followed by chromatography with chloroform as eluant removed the excess of dibromoethane to provide a product containing the desired imine intermediate (**13d**) ( $\delta_{\text{p}}$  37.61) and its mono-alkylated precursor (**12d**) ( $\delta_{\text{p}}$  37.81—only one diastereoisomer) in the ratio ca. 3:2. Eluates of (**13d**) and (**12d**) homogeneous to t.l.c. were combined, evaporated under reduced pressure, taken up in THF (50 ml), and cooled to  $-78^\circ\text{C}$ . Further butyl-lithium (20 mmol) in THF (12.5 ml) was added during 5 min, after which the mixture was allowed to warm to room temperature over 3 h. The product was isolated and purified chromatographically as above to afford ethyl 1-(benzhydrylideneamino)cyclopropyl-(diethoxymethyl)phosphinate (**13d**) (9.90 g, 57%) as a viscous orange oil;  $\nu_{\max.}$ (neat) 2930m, 1601w sh, 1265m, 1590w, 1435w, 1378w, 1300w sh, 1265m, 1225m, 1196m, 1096m, 1040s sh, 1024s, 942m, 838m, 744s, and 690s  $\text{cm}^{-1}$ ;  $\delta_{\text{p}}(\text{CDCl}_3)$  37.61;  $\delta_{\text{p}}(\text{CDCl}_3)$  1.20—1.50 (13 H, m,  $\text{CH}_2\text{CH}_2$  and 3  $\times$  Me), 3.70—4.10 [4 H, m,  $\text{PCH}(\text{OCH}_2\text{Me})_2$ ], 4.32 (2 H, m,  $\text{POCH}_2\text{Me}$ ), 5.28 (1 H, d,  $J_{\text{PCH}}$  10.0 Hz, PCH), and 7.20—7.70 (10 H, m, ArH).

The above imine (**13d**) (4.60 g, 11.07 mmol), on hydrolysis with 1.5M hydrochloric acid (200 ml) according to the general procedure described above, provided, after treatment with propylene oxide, 1-aminocyclopropylphosphinic acid hemihydrate (**14**) (1.08 g, 75%) as a cream coloured solid, m.p. 226 °C (decomp.) (Found: C, 28.2; H, 6.6; N, 10.4; P, 22.95.  $\text{C}_3\text{H}_8\text{NO}_2\text{P}\cdot 0.5\text{H}_2\text{O}$  requires C, 27.70; H, 6.97; N, 10.77; P,

23.81%);  $\nu_{\max.}$ (Nujol) 3331m, 2335m, 2115m, 1622m, 1568m, 1540m, 1462m, 1424w, 1378m, 1258m, 2185s, 1108m, 1054s, 1012m, 986s, 945m, and 852s  $\text{cm}^{-1}$ ;  $\delta_{\text{p}}(\text{D}_2\text{O})$  15.90;  $\delta_{\text{H}}(\text{D}_2\text{O})$  1.05—1.30 (4 H, m,  $\text{CH}_2\text{CH}_2$ ) and 7.08 (1 H, d,  $J_{\text{PH}}$  550 Hz, PH).

*1,5-Diaminopentane-1,5-diylidiphosphinic Diacid (16).*—To a stirred solution of the lithiated anion generated from the imine (**6**) (3.69 g, 9.48 mmol) and LDA (11.37 mmol) in THF at  $-78^\circ\text{C}$ , as described in the general procedure above, was added a half molar equivalent of 1,3-dibromopropane (1.15 g, 5.66 mmol) and the mixture then allowed to warm to 20 °C. After 16 h, work-up and chromatography gave the four diastereoisomers of diethyl [1,5-bis(benzhydrylideneamino)pentane-1,5-diylbis-(diethoxymethyl)phosphinate] (**15**) (2.76 g, 71%) as a viscous orange oil;  $\delta_{\text{p}}(\text{CDCl}_3)$  38.81, 38.65, 38.53, and 38.45. Hydrolysis of the bis-imine (**15**) (2.72 g, 3.32 mmol) with boiling 1.5M hydrochloric acid (75 ml) as described above, followed by ion exchange chromatography and trituration with ethanol provided the diacid (**16**) (0.67 g, 62%) as a hygroscopic colourless solid, m.p. 281—283 °C (decomp.) (Found: C, 26.55; H, 7.05; N, 11.05.  $\text{C}_5\text{H}_{16}\text{N}_2\text{O}_4\text{P}_2$  requires C, 26.10; H, 7.01; N, 12.17%);  $\nu_{\max.}$ (Nujol) 3350m, 2730m, 2358m, 1632m, 1550m, 1180s, 1046s, 968m, and 726m  $\text{cm}^{-1}$ ;  $\delta_{\text{p}}(\text{D}_2\text{O})$  19.68;  $\delta_{\text{H}}(\text{D}_2\text{O})$  1.40—2.16 [6 H, m,  $(\text{CH}_2)_3$ ], 2.88—3.28 (2 H, m, NCHP), and (1 H, d,  $J_{\text{PH}}$  538 Hz, PH).

*1-Amino-2-[1H-imidazol-4(or 5)-yl]ethylphosphonic Acid (23b).*—Condensation of benzophenone (11.4 g, 62.5 mmol) with diethyl aminomethylphosphonate<sup>3</sup> (11.0 g, 65.8 mmol) in toluene (200 ml), as described for preparation of the imine phosphinate (**6**), provided diethyl benzhydrylideneaminomethylphosphonate (**21**) (15.3 g, 74%) as a colourless viscous oil (b.p. ca. 230 °C at 0.05 mmHg) which solidified with time, m.p. 52—54 °C (Found: C, 65.3; H, 6.7; N, 4.4; P, 9.35.  $\text{C}_{18}\text{H}_{22}\text{NO}_3\text{P}$  requires C, 65.25; H, 6.69; N, 4.23; P, 9.35%);  $\nu_{\max.}$ (neat) 3030w, 2960m, 2885w, 1620m, 1598w, 1566w, 1490w, 1478w, 1444m, 1390m, 1315m, 1294m, 1248s, 1160m, 1098m, 1044s, 1028s, 966s, 950s sh, 874w, 780s, and 696s  $\text{cm}^{-1}$ ;  $\nu_{\max.}$ (Nujol) 1622m, 1598w, 1578w, 1492w, 1446m, 1400w, 1378w, 1346w, 1320m, 1300w, 1252s, 1186w, 1164m, 1098w, 1077m, 1054s sh, 1030s, 1012s, 968s, 957s sh, 948m, and 783ms  $\text{cm}^{-1}$ ;  $\delta_{\text{p}}(\text{CDCl}_3)$  23.09;  $\delta_{\text{p}}(\text{CDCl}_3)$  1.38 (6 H, t, 2  $\times$  Me), 3.87 (2 H, d,  $J_{\text{PCH}}$  17.7 Hz,  $\text{CH}_2\text{P}$ ), 4.22 [4 H, m,  $\text{P}(\text{OCH}_2\text{Me})_2$ ], and 7.16—7.70 (10 H, m, ArH).

Alkylation of the imine phosphonate (**21**) (1.20 g, 3.63 mmol) with LDA (8.00 mmol) and 4(or 5)-benzoyloxymethyl-1-(*p*-tolylsulphonyl)imidazole<sup>17</sup> (2.59 g, 7.27 mmol) in THF at  $-78^\circ\text{C}$  and warming to 20 °C overnight, according to the general alkylation procedure above, gave, after chromatography, the product (1.27 g, 62%). Recrystallisation from ethyl acetate—hexane (ca. 4:1 v/v) afforded diethyl 1-(benzhydrylideneamino)-2-[1-(*p*-tolylsulphonyl)imidazol-4(or 5)-yl]ethylphosphonate (**22b**) (0.93 g, 45%) as cream coloured prisms, m.p. 131—133 °C (Found: C, 61.55; H, 5.55; N, 7.3.  $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_5\text{PS}$  requires C, 61.58; H, 5.70; N, 7.43%);  $\nu_{\max.}$ (Nujol) 3074w, 3058w, 1617w, 1614w sh, 1592w, 1570w, 1454m, 1443m, 1364s, 1388m, 1237s, 1189m, 1172s, 1078s, 1044s, 1010s, 960m, 940m, 933m, 806w, 768m, 700s, 696s, 678m, and 668s  $\text{cm}^{-1}$ ;  $\delta_{\text{p}}(\text{CDCl}_3)$  23.56;  $\delta_{\text{H}}(\text{CDCl}_3)$  1.31 [6 H, m(q),  $\text{P}(\text{OCH}_2\text{Me})_2$ ], 2.26 (3 H, s, ArMe), 3.31 (2 H, m,  $\text{CH}_2\text{CHP}$ ), 3.86—4.34 [5 H, m,  $\text{P}(\text{OCH}_2\text{Me})_2$  and CHP], 6.26—6.42 (2 H, m, ArH *ortho* to C=N of one Ph ring), and 6.88—7.76 (14 H, m, ArH). Hydrolysis of the alkylated imine (**22b**) (0.80 g, 1.41 mmol) with boiling concentrated hydrochloric acid (125 ml) for 7 h and work-up by ion exchange chromatography followed by trituration with acetone, according to the general hydrolysis procedure above, provided the monohydrate of phosphono-histidine (**23b**) (0.21 g, 71%) as colourless microcrystals, m.p.



**Table 3.** (2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylideneamino)alkyl-phosphinates, -phosphonates, and -carboxylates (**25**), (**27**), (**30**), and (**31**)

Compound and formula	Configuration	Yield (%)	B.p. °C (mmHg)	[ $\alpha$ ] <sub>D</sub> <sup>20</sup> (c, l, CHCl <sub>3</sub> )	$\delta_p$ (CDCl <sub>3</sub> )/p.p.m.		Intensity ratio $\delta_p(1'R):(1'S)$	D.e. (%) (1'R)	Found (%) <sup>a</sup> (Required)			
					(1'R)	(1'S)			C	H	N	P
( <b>25a</b> ) C <sub>18</sub> H <sub>34</sub> NO <sub>5</sub> P	1R,2R,5R	71	150—180 (0.1)	+6.85	{ 38.74 38.92 }		>99:1	>98	56.95 (57.58)	8.95 (9.13)	3.5 (3.73)	8.3 (8.25)
( <b>25b</b> ) C <sub>15</sub> H <sub>28</sub> NO <sub>4</sub> P	1R,2R,5R	41	150—170 (0.1)	+14.73	23.10				54.55 (46.77)	8.85 (8.89)	4.15 (4.41)	9.7 (9.76)
( <b>25c</b> ) C <sub>14</sub> H <sub>23</sub> NO <sub>3</sub>	1R,2R,5R	75	90—110 (0.03)	+7.36					64.0 (66.37)	8.75 (9.15)	5.4 (5.33)	
( <b>27a</b> ) C <sub>25</sub> H <sub>40</sub> NO <sub>5</sub> P	1R,2R,5R,1'R	53			{ 38.50 38.69 }							
( <b>27b</b> ) C <sub>19</sub> H <sub>36</sub> NO <sub>5</sub> P	1R,2R,5R,1'R	45			{ 40.06 40.24 }		78:22	56				
( <b>27c</b> ) C <sub>22</sub> H <sub>34</sub> NO <sub>4</sub> P	1R,2R,5R,1'R	56			27.31	23.63	91.3:8.7	82.6	62.45 (65.17)	8.50 (7.96)	3.55 (3.45)	7.05 (7.64)
( <b>27d</b> ) C <sub>21</sub> H <sub>29</sub> NO <sub>3</sub>	1R,2R,5R,1'S	79					87.5:12.5	75	70.55 (73.43)	8.2 (8.51)	3.45 (4.08)	
( <b>30a</b> ) C <sub>18</sub> H <sub>34</sub> NO <sub>5</sub> P	1S,2S,5S	7		-6.28	{ 38.73 38.89 }				56.15 (46.58)	9.4 (9.13)	3.4 (3.73)	7.45 (8.25)
( <b>31</b> ) C <sub>25</sub> H <sub>40</sub> NO <sub>5</sub> P	1S,2S,5S,1'S	41			{ 38.49 38.65 }		<1:99	<2				

<sup>a</sup> See Footnote b, Table 1.**Table 4.** Enantio-enriched 1-aminoalkyl-phosphinic and -phosphonic, and 1-aminoalkanecarboxylic acids (**28**) and (**32**), and their *N*-[(*S*)-(-)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl] sodium salts (**33**)

Compound and formula	R	X	$\alpha$ -Configuration	Yield (%)	[ $\alpha$ ] <sub>D</sub> <sup>20</sup> (c, H <sub>2</sub> O)	M.p. (°C) (decomp.)	$\delta_p$ (D <sub>2</sub> O) (p.p.m.)	Chemical shifts in p.p.m. for ( <b>33</b> )				Intensity ratio $\delta_F R:S$	E.e.
								$\delta_p$ (R)	$\delta_p$ (S)	$\delta_F$ (R)	$\delta_F$ (S)		
( <b>28a</b> ) C <sub>8</sub> H <sub>12</sub> NO <sub>2</sub> P	PhCH <sub>2</sub>	PO <sub>2</sub> H	1R	74	-59 (1.0)	228—229	18.64	23.30		-68.92		>99:1	99
( <b>28b</b> ) C <sub>2</sub> H <sub>8</sub> NO <sub>2</sub> P	Me	PO <sub>2</sub> H	1R	55		223—224	21.28	24.70	24.37	-68.85	-68.85	73:27	46
( <b>28c</b> ) C <sub>8</sub> H <sub>12</sub> NO <sub>3</sub> P	PhCH <sub>2</sub>	PO <sub>3</sub> H	1R	12	-35 (0.09)	274		15.1	15.1	-68.61	-68.37	86:14	72
( <b>28d</b> ) C <sub>9</sub> H <sub>11</sub> NO <sub>2</sub>	PhCH <sub>2</sub>	CO <sub>2</sub> H	2S	63	-28.5 (2.0)	273—276				-66.72		87:13	74
( <b>32</b> ) C <sub>8</sub> H <sub>12</sub> NO <sub>2</sub> P	PhCH <sub>2</sub>	PO <sub>2</sub> H	1S	46	+82 (0.08)	239	18.63		22.98		68.79	<1:99	99

218 °C (decomp.) (Found: C, 30.7; H, 5.55; N, 19.6; P, 13.45. C<sub>5</sub>H<sub>10</sub>N<sub>3</sub>O<sub>3</sub>P·H<sub>2</sub>O requires C, 28.71; H, 5.78; N, 20.09; P, 14.81%;  $\nu_{\max}$  (Nujol) 3 135m (br band at 3 600—2 200m), 1 630m, 1 550w, 1 534w, 1 170m sh, 1 120s sh, 1 078s, 1 040s sh, 972ms, 850w br, 668m, and 628m cm<sup>-1</sup>;  $\delta_p$ (D<sub>2</sub>O) 10.31;  $\delta_H$ (D<sub>2</sub>O) 2.94—3.58 (3 H, m, CH<sub>2</sub>CHP), 7.22 and 8.28 (2 H, 2 s, ArH).

*Asymmetric Synthesis of 1-Aminoalkyl-phosphinic and -phosphonic, and 1-Aminoalkanecarboxylic Acids: Preparation of Pinane-imine Building Blocks.*—A ca. 0.5M solution of (1R,2R,5R)-(+)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptane-3-one<sup>24</sup> (**24**) [b.p. 118 °C at 15 mmHg, m.p. 30—31 °C, [ $\alpha$ ]<sub>D</sub><sup>24</sup> +38.8° (c 1.0 in CHCl<sub>3</sub>), [ $\alpha$ ]<sub>D</sub><sup>20</sup> +20° (c 2.5 in EtOH)] in refluxing toluene was condensed, using a Dean-Stark apparatus, with 1.2 mol equiv. of aminomethylphosphinate (**5**), diethyl aminomethylphosphonate,<sup>3</sup> or ethyl glycinate for 4—8 h (<sup>31</sup>P n.m.r. and t.l.c.). Removal of the solvent and chromatography of the residual oils on silica gel with CHCl<sub>3</sub> gave the corresponding pinane-imines (**25a—c**), which were distilled *in vacuo* (Kugelrohr) (see Table 3).

*Ethyl diethoxymethyl[(1R,2R,5R)-(+)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylideneamino)methyl]phosphinate* (**25a**) distilled as a viscous yellow oil;  $\nu_{\max}$  (neat) 3 400mbr (OH), 2 982s, 2 935s, 1 652m (C=N), 1 480m, 1 448m, 1 397m, 1 372m, 1 300, 1 220s (P=O), 1 164m, 1 113s, 1 064vs (P—O—C), 959m, and 757s cm<sup>-1</sup>;  $\delta_H$ (CDCl<sub>3</sub>) 0.88 (3 H, s, 2-Me), 1.2—1.4 (9 H, m, 3 × CH<sub>2</sub>Me), 1.30 and 1.46 (6 H, 2 s, 2 × 6-Me), 1.61—2.70 (6 H, m, 1-, 4-, 5-, and 7-H), 2.85 (1 H, br s, exchanges with D<sub>2</sub>O, OH), 3.6—4.1 [6 H, m, PCH(OCH<sub>2</sub>Me)<sub>2</sub> and CH<sub>2</sub>P], 4.26 (2 H, m, POCH<sub>2</sub>Me), and 4.72 and 4.74 [1 H, 2 d, *J*<sub>PCH</sub> 7.8 and 8.1 Hz, PCH(OEt)<sub>2</sub>].

*Diethyl [(1R,2R,5R)-(+)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylideneamino)methyl]phosphonate* (**25b**) distilled as a viscous yellow oil;  $\nu_{\max}$  (neat) 3 400m (OH), 2 990s, 2 922s, 1 650m (C=N), 1 478w, 1 448w, 1 393m, 1 370m, 1 245s (P=O), 1 162m, 1 060s and 1 030s (P—O—C), and 970s cm<sup>-1</sup>;  $\delta_H$ (CDCl<sub>3</sub>) 0.88 (3 H, s, 2-Me), 1.36 (6 H, t, *J* 7 Hz, 2 × CH<sub>2</sub>Me), 1.35 and 1.50 (6 H, 2 s, 2 × 6-Me), 1.61—2.68 (6 H, m, 1-, 4-, 5-, and 7-H), 2.70 (1 H, s, exchanges with D<sub>2</sub>O, OH), 3.92 (2 H, d, *J*<sub>PCH</sub> 17 Hz, CH<sub>2</sub>P), and 4.17 (2 H, dq, *J*<sub>HH</sub> = *J*<sub>PH</sub> = 7 Hz, POCH<sub>2</sub>Me).

*Ethyl (1R,2R,5R)-(+)-2-Hydroxy-2,6,6-trimethylbicyclo-*

[3.1.1]hept-3-ylideneamino)acetate (**25c**) distilled as a viscous orange coloured oil;  $\nu_{\max}$ (neat) 3458m (OH), 2992s, 2928s, 1745s (C=O), 1658m (C=N), 1475m, 1450m, 1372ms, 1346m, 1270m, 1236m, 1190s, and 1092m  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.87 (3 H, s, 2-Me), 1.29 (3 H, t,  $J$  7 Hz,  $\text{CH}_2\text{Me}$ ), 1.32 and 1.51 (6 H, 2 s, 2  $\times$  6-Me), 1.6–2.6 (6 H, m, 1-, 4-, 5-, and 7-H), 3.05 (1 H, s, exchanges with  $\text{D}_2\text{O}$ , OH), 4.16 (2 H, s,  $\text{NCH}_2$ ), and 4.20 (2 H, q,  $J$  7 Hz,  $\text{OCH}_2$ ).

In the same way, condensation of (1*S*,2*S*,5*S*)-(–)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one<sup>22</sup> (**29**) {b.p. 116 °C at 15 mmHg, m.p. 34–35 °C from pentane,  $[\alpha]_{\text{D}}^{20}$  –36.7 °C ( $c$  1.0 in  $\text{CHCl}_3$ )} with aminomethylphosphinate (**5**) in refluxing toluene gave, after chromatography, ethyl diethoxymethyl{(1*S*,2*S*,5*S*)-(–)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylideneamino)methyl}phosphinate (**30a**) as a viscous yellow oil;  $\nu_{\max}$ (neat) and  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) identical with those of its antipode (**25a**) described above.

**Diastereoselective Alkylation Reactions.**—These were carried out as described in the General Procedure above for alkylation of the achiral imine-phosphinate (**6**) except that the quantities of both di-isopropylamine and butyl-lithium were increased from 1.2 to 2.2 mol equiv. Work-up and chromatography as for (**6**) provided the following alkylated pinane-imines (see Table 3) as viscous orange yellow oils:

(i) Ethyl diethoxymethyl{(1*R*,2*R*,5*R*,1'*R*)-1-(2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-ylideneamino)-2-phenylethyl}phosphinate (**27a**) (0.51 g, 53%);  $\nu_{\max}$ (neat) 3400m br (OH), 1650m (C=N), 1218s (P=O), 1060s (P–O–C), and 754s and 704m  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.16 (3 H, s, 2-Me), 1.1–1.5 (15 H, m, 3  $\times$   $\text{OCH}_2\text{Me}$  and 2  $\times$  6-Me), 1.6–2.7 (6 H, m, 1-, 4-, 5-, and 7-H),  $c$ . 2.9 (1 H, br s, exchanges with  $\text{D}_2\text{O}$ , OH), 3.2–3.3 (2 H, m,  $\text{CH}_2\text{Ar}$ ), 3.6–4.0 [4 H, m,  $\text{PCH}(\text{OCH}_2\text{Me})_2$ ], 4.1–4.4 (3 H, m,  $\text{POCH}_2\text{Me}$  and  $\text{NCHP}$ ), 4.6–4.8 [1 H, m,  $\text{PCH}(\text{OEt})_2$ ], and 7.16 (5 H, m, ArH). Ratio (1*R*,2*R*,5*R*,1'*R*)-(27a) [ $\delta_{\text{P}}(\text{CDCl}_3)$  38.50 and 38.69]:(1*R*,2*R*,5*R*,1'*S*)-(27a) [ $\delta_{\text{P}}$  not detectable] >99:1; d.e. >99%.

(ii) Ethyl diethoxymethyl{(1*R*,2*R*,5*R*,1'*R*)-1-(2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylideneamino)ethyl}phosphinate (**27b**) (0.40 g, 45%);  $\nu_{\max}$ (neat) 3422m (OH), 1648m (C=N), 1210s (P=O), and 1060vs (P–O–C)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.84, 0.88, and 0.91 (3 H, '3s', 2-Me), 1.1–1.55 (18 H, m, 6  $\times$  Me), 1.6–2.7 (6 H, m, 1-, 4-, 5-, and 7-H), 3.25 (1 H, br s, exchanges with  $\text{D}_2\text{O}$ , OH), 3.6–4.0 (5 H, m,  $\text{NCHP-CH}(\text{OCH}_2\text{Me})_2$ ), 4.1–4.4 (2 H, m,  $\text{POCH}_2\text{Me}$ ), and 4.7–4.8 [1 H, m,  $\text{PCH}(\text{OEt})_2$ ]. Ratio (1*R*,2*R*,5*R*,1'*R*)-(27b) [ $\delta_{\text{P}}(\text{CDCl}_3)$  40.06 and 40.24]:(1*R*,2*R*,5*R*,1'*S*)-(27b) [ $\delta_{\text{P}}(\text{CDCl}_3)$  39.63 and 39.97] = 78:22; d.e. = 56%.

(iii) Diethyl {(1*R*,2*R*,5*R*,1'*R*)-1-(2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylideneamino)-2-phenylethyl}phosphonate (**27c**) (1.90 g, 56%);  $\nu_{\max}$ (neat) 3412m (OH), 1650m (C=N), 1252s (P=O), and 1058vs (P–O–C)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.17 (3 H, s, 2-Me), 1.17–1.34 (6 H, 2 s, 2  $\times$  Me), 1.36 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{Me}$ ), 1.5–2.7 (7 H, m, 1-, 4-, 5-, 7-, and O-H), 3.1–3.4 (2 H, m,  $\text{CH}_2\text{Ar}$ ), 4.0–4.4 (5 H, m,  $\text{OCH}_2$  and  $\text{CHP}$ ), and 7.16 (5 H, s, ArH). Ratio (1*R*,2*R*,5*R*,1'*R*)-(27c) [ $\delta_{\text{P}}(\text{CDCl}_3)$  23.71]:(1*R*,2*R*,5*R*,1'*S*)-(27c) [ $\delta_{\text{P}}(\text{CDCl}_3)$  23.63] = 91.3:8.7; d.e. = 82.6%.

(iv) Ethyl (1*R*,2*R*,5*R*,2'*S*)-2-(2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylideneamino)-3-phenylpropionate (**27d**) (3.0 g, 79%);  $\nu_{\max}$ (neat) 3462m (OH), 1740s (C=O), 1654m (C=N), 756s, and 702m  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.30 (3 H, s, 2-Me of 2'*S*-diastereoisomer), 0.88 (3 H, s, 2-Me of 2'*R*-diastereoisomer) (Ratio 2'*S*:2'*R* = ca. 87.5:12.5; d.e. = ca. 75%), 1.21 and 1.46 (6 H, 2 s, 2  $\times$  6-Me), 1.27 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{Me}$ ), 1.4–2.7 (7 H, m, 1-, 4-, 5-, 7-, and OH), 2.9–3.5 (2 H, m,  $\text{CH}_2\text{Ar}$ ), 4.19 (2 H, q,  $J$  7 Hz,  $\text{OCH}_2$ ), 4.44 (1 H, dd,  $J$  4 Hz,  $\text{NCH}$ ), and 7.17 (5 H, m, ArH).

(v) Ethyl {diethoxymethyl-(1*S*,2*S*,5*S*,1'*S*)-1-(2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylideneamino)-2-phenylethyl}phosphinate (**31**) (0.40 g, 41%);  $\nu_{\max}$ (neat) and  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) as described for its antipode (**27a**). Ratio (1*S*,2*S*,5*S*,1'*S*)-(31) [ $\delta_{\text{P}}(\text{CDCl}_3)$  38.49 and 38.65]:(1*S*,2*S*,5*S*,1'*R*)-(31) [ $\delta_{\text{P}}$  not detected] >99:1; d.e. >99%.

**Enantio-enriched  $\alpha$ -Amino Acid Analogues.**—These were obtained by hydrolysis of the above alkylated pinane-imines, according to the General Procedure described earlier, and the products (analytical and spectroscopic data given in Table 4) were consistent with those reported in the literature. Prepared in this way were: (1*R*)-(–)-1-amino-2-phenylethylphosphinic acid<sup>1</sup> (**28a**) (150 mg, 74%), e.e. >99%, from hydrolysis of (**27a**); (1*R*)-(–)-1-aminoethylphosphinic acid<sup>1</sup> (**28b**) (62 mg, 55%), e.e. 46%, from (**27b**); (1*R*)-(–)-1-amino-2-phenylethylphosphonic acid (**28c**) (117 mg, 12%), e.e. 72%, from (**27c**); *S*-(–)-phenylalanine (**28d**) (0.88 g, 63%), e.e. 74%, from (**27d**); and (1*S*)-(+)-1-amino-2-phenylethylphosphinic acid<sup>1</sup> (**32**) (74 mg, 46%), e.e. >99%, from (**31**).

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