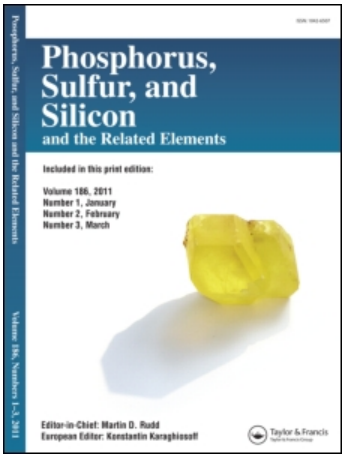


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

DIASTEREOSELECTIVITY IN THE ALKYLATION OF CHIRAL 2-AMINOMETHYL-1,3,2-DIOXAPHOSPHORINANE 2-OXIDES

Paul A. Bartlett[a]; Kevin L. McLaren[a]
[a] Department of Chemistry, University of California, Berkeley, California

To cite this Article Bartlett, Paul A. and McLaren, Kevin L.(1987) 'DIASTEREOSELECTIVITY IN THE ALKYLATION OF CHIRAL 2-AMINOMETHYL-1,3,2-DIOXAPHOSPHORINANE 2-OXIDES', Phosphorus, Sulfur, and Silicon and the Related Elements, 33: 1, 1 — 14
To link to this Article: DOI: 10.1080/03086648708074276
URL: http://dx.doi.org/10.1080/03086648708074276

Phosphorus and Sulfur, 1987, Vol. 33, pp. 1–14
Photocopying permitted by license only

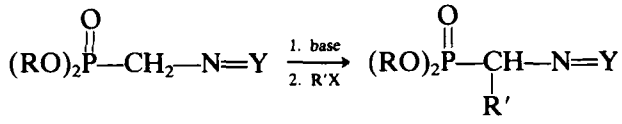
DIASTEREOSELECTIVITY IN THE ALKYLATION OF CHIRAL 2-AMINOMETHYL-1,3,2-DIOXAPHOSPHORINANE 2-OXIDES

PAUL A. BARTLETT and KEVIN L. McLAREN
Department of Chemistry, University of California, Berkeley, California 94720

(Received September 15, 1986; in final form December 27, 1986)

The alkylation of chiral cyclic diesters of α-aminomethyl-phosphonate derivatives was investigated as a potential route to the asymmetric synthesis of phosphonic acid analogs of α-amino acids. The 1,3,2-dioxaphosphorinanes derived from *d,l*-2,4-pentanediol (**1D-c** and **1D-d**), which adopt primarily the C-equatorial conformation, were compared to the homologs **1T-c** and **1T-e** derived from 2-methyl-2,4-pentanediol, in which the aminomethyl moiety is fixed in the axial configuration. While neither series shows high stereoselectivity ($de \leq 50\%$), it was shown that the two chiral auxiliaries produce asymmetric induction of the opposite sense.

Phosphonic acid analogs of α-amino acids have numerous applications in organic and biochemistry.[1] Since the specific activity of chiral α-aminophosphonic acids is largely dependent upon their absolute configuration, there is interest in an efficient means of obtaining them in optically pure form, either through resolution[2] or asymmetric synthesis.[3] A general preparation of amino acid analogs involves alkylation of derivatives of glycine,[4] a strategy which has been applied to phosphonic analogs as well (Equation (1).[5] To effect such an alkylation in an asymmetric sense, we hoped to take advantage of the higher valency of phosphorus and incorporate a chiral auxiliary in the form of a cyclic ester. Hanessian has described a related approach to chiral alkylphosphonic acids involving a bicyclic diamide derivative.[6]

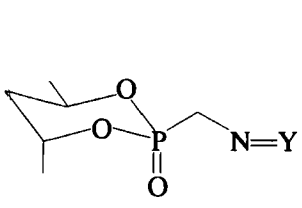


(Eq. 1)

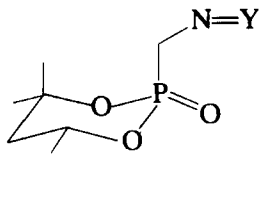
In this report, we describe our results with the cyclic esters of 2,4-pentanediol and 2-methyl-2,4-pentanediol, **D** and **T**, respectively. We envisaged advantages for each system. Synthesis of the former is simplified because of the C2 symmetry of optically active 2,4-pentanediol. On the other hand, in the C-axial isomer of **T**, the carbanion is fixed in an axial configuration where, we reasoned, the asymmetry of the ring would exert the most effect.† An additional element in our planning was potential coordination of the counterion between the phos-

† Crystallographic studies indicate that related 1,3,2-dioxaphosphorinanes adopt a chair-like conformation, although compounds with two axial substituents (e.g., **T**) are likely to be flattened to some extent.[7]

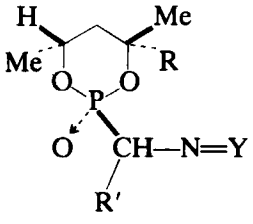
phoryl oxygen and the α-amino substituent, thus restricting the available conformations of the P—C_α bond (see structure **7**).



D

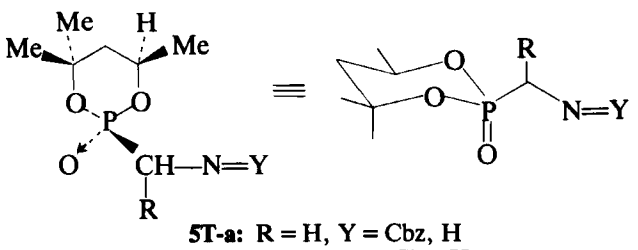


T

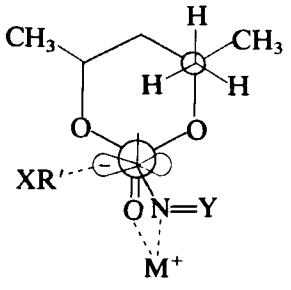


	R = H ("**D**" series)				R = CH_3 ("**T**" series)			
Y =	Cbz, H	CHO, H	C:	CHPh	Cbz, H	CHO, H	C:	CPh_2
R′ = H	**1D-a**	**1D-b**	**1D-c**	**1D-d**	**1T-a**	**1T-b**	**1T-c**	**1T-e**
R′ = CH_3			**2D-c**	**2D-d**			**2T-c**	**2T-e**
R′ = *i*Bu				**3D-d**				**3T-e**
R′ = $PhCH_2$	**4D-a**			**4D-d**	**4T-a**		**4T-c**	**4T-e**

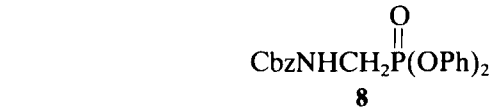
Diphenyl N-(carbobenzoxy)aminomethylphosphonate **8**[8] undergoes ester exchange with the dilithium salts of *dl*-2,4-pentanediol and 2-methyl-2,4-pentanediol to give the cyclic esters **1D-a** and **1T-a** respectively.[9] Racemic diols were employed for the purposes of initial evaluation. The dimethyl derivative **1D-a** was obtained in 73% yield; in the case of the trimethyl analog **1T-a**, comparable amounts of the *cis* and *trans* isomers **1T-a** and **5T-a** were produced in 84% total yield and separated by preparative HPLC. The carbobenzoxy protecting groups were removed from **1D-a** and **1T-a** by catalytic hydrogenolysis, and the resulting amines were converted via the formamides to the corresponding isocyanides **1D-c** (74%) and **1T-c** (91%),[10] the benzaldehyde imine **1D-d** (68%),[11] and the benzophenone imine **1T-e** (83%)[12] by standard methods.



5T-a: R = H, Y = Cbz, H
6T-a: R = Bz, Y = Cbz, H
6T-e: R = Bz, Y = CPh_2



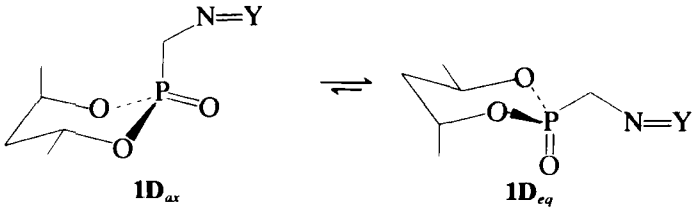
7



8

The P=O-equatorial isomer **1T-a** was identified on the basis of the upfield position of its ^{31}P NMR resonance relative to that of the P=O-axial isomer **5T-a**.[13] Throughout the series of compounds **1T** and **5T**, with Y = (H, CHO), C:, and CPh_2, the ^{31}P NMR correlation proved to be more consistent than that based on the relative positions of the phosphoryl IR stretching frequencies (Table I).[14] The assigned configurations of **1T-a** and **5T-a** were confirmed by two-dimensional phase-sensitive NOESY NMR spectroscopy.[15] For axial isomer **1T-a**, nuclear Overhauser interaction is found between one of the hydrogens α to the phosphorus (δ 3.75), and both the axial methyl group at C-4 (δ 1.5) and the axial hydrogen at C-6 (δ 4.6) (Figure 1). In contrast, no such interaction is seen in the corresponding NMR spectrum of the equatorial isomer **5T-a** (Figure 2). From ^{31}P NMR comparison with the conformationally fixed isomers **1T** and **5T**, it appears that the predominant conformers of the mobile derivatives **1D** are those in which the aminomethyl substituents adopt the equatorial position (Table I).

The carbanions of the aminomethyl derivatives **1D-c**, **1D-d**, **1T-c**, and **1T-e** were generated in THF or HMPA/THF at −78°C with 1.0 eq. of *n*-butyllithium and treated with the alkylating agent (1.5 eq.) under the same conditions for a period of two to six hours. The results are summarized in Table II. The isocyanides gave significant amounts of dialkylation, presumably as a result of the strongly acidifying influence of the isocyano moiety and the intervention of proton transfer processes. In contrast, no dialkylation was seen with the less strongly activated imines **1D-d** and **1T-e**. In the case of aldimine **1D-d**, however, THF/HMPT was used as solvent in order to facilitate deprotonation.



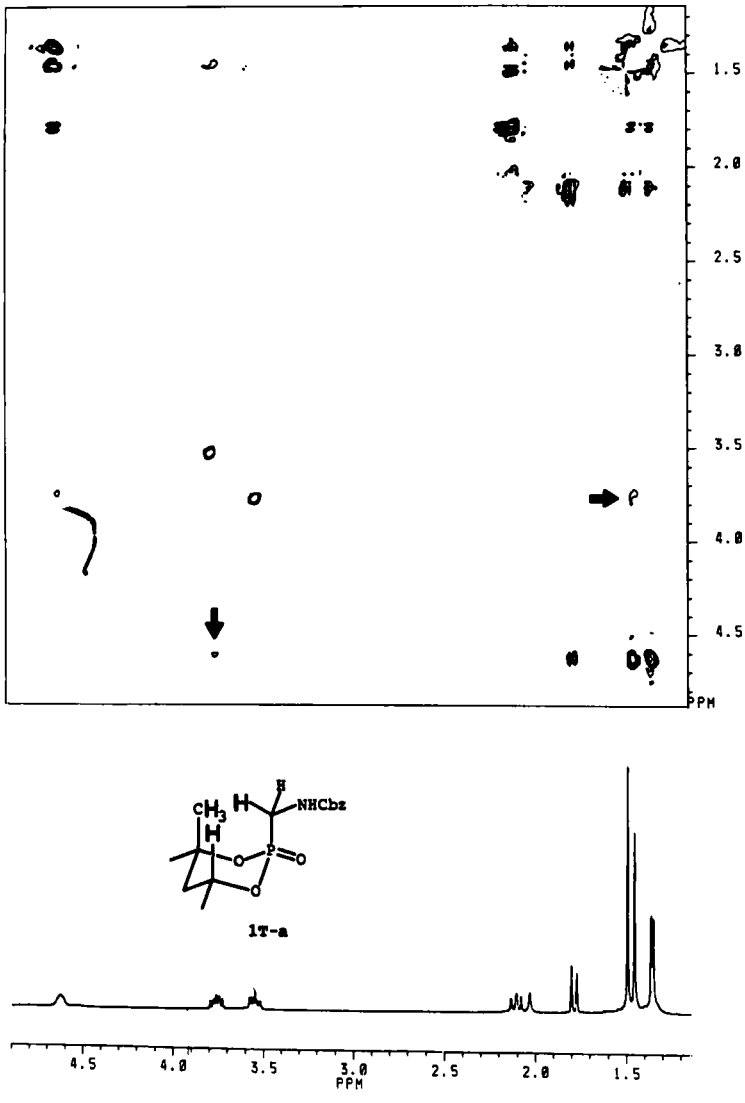
$1D_{ax}$ **$1D_{eq}$**

TABLE I

Assignment of phosphorus configuration: ^{31}P NMR (δ, ppm) and P=O IR (ν, cm^{-1}) correlations[a]

	1T		5T		1D	
Y	δ	ν	δ	ν	δ	ν
a H,Cbz	15.4	1235	17.1	1266	17.6	1235
b H,CHO	14.8	1270	16.1	1245	16.6	1270
c C:	7.3	1255	8.0	1250	7.7	1220
d CHPh		—		—	16.7	1235
e CPh_2	17.1	1230	17.2	1220		—

[a] Spectra were obtained in $CDCl_3$ (NMR) or $CHCl_3$ (IR) solution.



FIGURES 1 and 2 Negative-level contour plots of symmetrized, absorption-mode 500-MHz ^1H NOESY spectrum of **1T-a** (Figure 1) and **5T-a** (Figure 2) (obtained in $CDCl_3$, 20°C, $\tau_m = 2s$). The arrows in Figure 1 indicate the cross-peaks that result from the interactions discussed in the text.

Although the yields of alkylated product are for the most part good, the stereoselectivity of the process is modest; in the best example uncovered, the diastereomeric excess is 50%, corresponding to a 3:1 ratio of isomers. Selectivity is seen to increase with the bulk of the alkylating agent, and it is higher for the trimethyl-substituted analog **1T-e** than the lower homolog **1D-d**.

The sense of asymmetric induction was determined in the case of isomers **4D-d** by independent synthesis from optically active components, (2*R*,4*R*)-2,4-pentanediol[14] and (*S*)-phosphophenylalanine **9**. The latter compound ($[\alpha]_D^{21} = +46.3°$) was obtained by resolution according to Kafarski,[15] protected as the

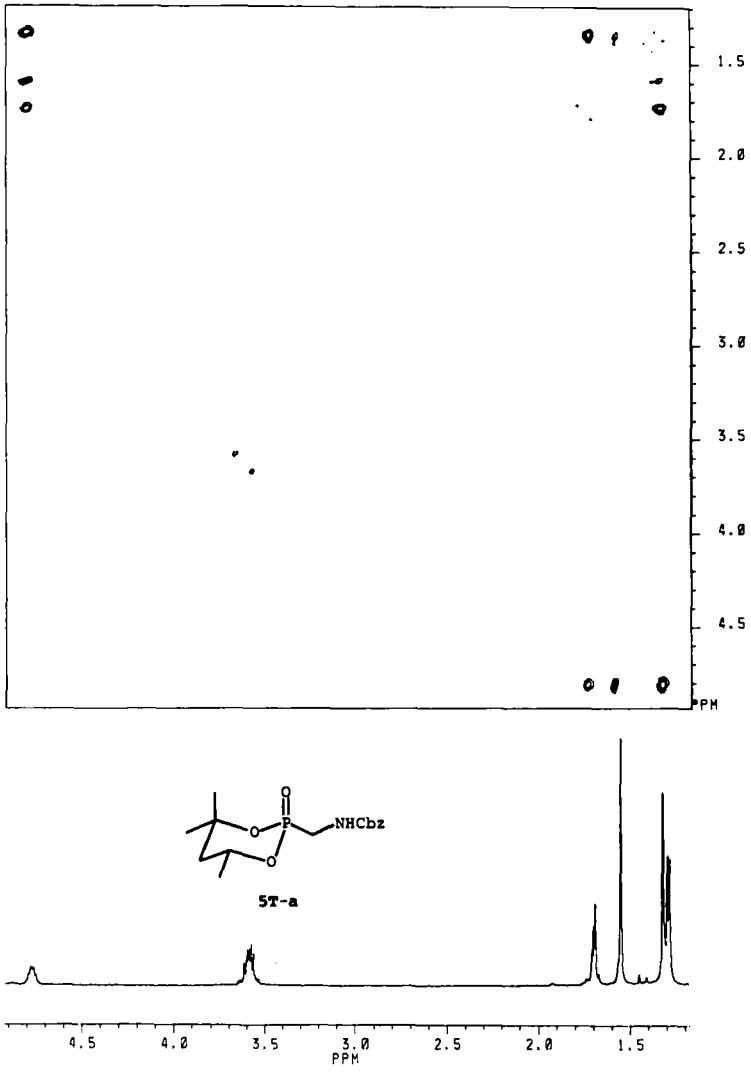


FIGURE 2

N-carbobenzoxy derivative (*S*)-**10**,[16] and converted to the acid chloride (*S*)-**11** with thionyl chloride. Reaction with optically active diol in the presence of triethylamine gave (4*R*,6*R*)-**4D-a** in 95% yield. Hydrogenolysis and conversion to the benzaldehyde imine afforded isomer (4*R*,6*R*)-**4D-d**, which proved to be the same as that formed in preponderance on alkylation of the glycine analog **1D-d**, according to ^{1}H and ^{31}P NMR spectroscopy. Approach of the alkylating agent thus occurs preferentially from the *si* face of the carbanion.

Condensation of the (*S*)-acid chloride **11** with (4*R*)-2-methyl-2,4-pentanediol[17] gave almost entirely the C-equatorial isomer **6T-a**.[18] The synthesis and alkylation of (6*R*)-**1T-e** were therefore repeated with optically active material to give (6*R*)-**4T-e** in 55% overall yield from diphenyl ester **8**. Hydrolysis of this material

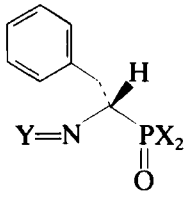
TABLE II

Alkylation of cyclic phosphonate esters[a]

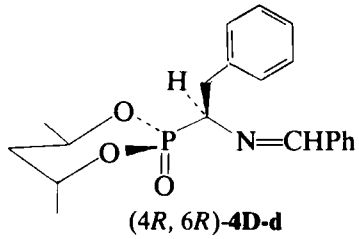
Entry	Substrate	R′ – X	Ratio, mono: dialkylation	Product	% Yield mono-alkylation[b]	Diastereomeric excess[c] (%)
1	**1D-c**	CH_3I	81:19	**2D-c**	81[d]	9
2	**1T-c**	CH_3I	77:17	**2T-c**	75[d]	23
3	**1T-c**	$PhCH_2Br$	56:24	**4T-c**	66 (69)	3
4[e]	**1D-d**	CH_3I	—	**2D-d**	77	16
5	**1D-d**	CH_3I	—	**2D-d**	48	10
6[e]	**1D-d**	*i*-BuI	—	**3D-d**	53	22
7[e]	**1D-d**	$PhCH_2Br$	—	**4D-d**	84	34
8	**1T-e**	CH_3I	—	**2T-e**	91	16
9	**1T-e**	*i*-BuI	—	**3T-e**	84	41
10	**1T-e**	$PhCH_2Br$	—	**4T-e**	79 (85)	50
11[e]	**1T-e**	$PhCH_2BR$	—	**4T-e**	89	49

[a] Reactions performed in THF at −78°C, except as noted.
[b] Yield of analytically pure material (yield based on recovered starting material), except as noted.
[c] Determined by ^{31}P NMR spectroscopy.
[d] Percent conversion by ^{1}H NMR.
[e] Reaction solvent: 10% HMPA/THF.

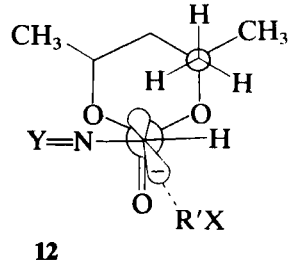
in 12 N HCl provided the free amino acid **9** (88% yield, $[\alpha]_D^{21} = -22.6°$), enriched in the *R*-enantiomer.[15] Thus, the sense of induction on alkylation of **1T-e** is reversed in comparison with that of **1D-d**, as well as inconsistent with our initial vision of the transition state (**7**).[19]



9: X = OH, Y = H_2
10: X = OH, Y = Cbz, H
11: X = Cl, Y = Cbz, H



(4*R*, 6*R*)-**4D-d**



12

The failure of model **7** to predict the sense of asymmetric induction in the alkylation of the C-axial compound **1T-e** argues against chelation of the counterion by the iminophosphonate. Absence of chelation as an element in determining the stereochemistry is also suggested by the fact that use of 10% HMPA/THF as a more dissociating solvent does not lead to a decrease in the diastereoselectivity or change in sense of asymmetric induction in these alkylations (Table II, entries 4, 6, 7, 11). A more appropriate view of the transition state for alkylation of **1T-e** may therefore be represented by structure **12**, in which steric interaction with the axial methyl group is minimized by approach of the alkylating agent *syn* to the phosphoryl oxygen. Alternatively, in view of the steric bulk developed at the α-carbon atom during the alkylation process, it is possible that the transition state may adopt a twist-boat conformation, as has been observed for highly congested 1,3,2-dioxa- and 1,3,2-oxazaphosphorinanes.[20]

EXPERIMENTAL

General. Solvents were dried by distillation from sodium/benzophenone ketyl (Et_2O and THF), CaH_2 (CH_2Cl_2, CH_3CN, and triethylamine), BaO (pyridine), or sodium metal (benzene). Alkyl halides were distilled or passed through a short column of basic alumina. The optically active diols were obtained from Aldrich Chemical Company. Unless otherwise indicated, column chromatography was performed on silica according to the method of Still[21] using the eluting solvent indicated. Reaction workups usually culminated in drying the organic layer over Na_2SO_4, filtering, and evaporating the solvent under reduced pressure on a rotary evaporator and finally under vacuum.

Unless otherwise indicated, NMR and IR data were obtained in $CDCl_3$ and $CHCl_3$ solutions, respectively. ^1H NMR data (250 MHz) are reported as: chemical shift on the δ scale, relative to internal tetramethylsilane (multiplicity, number of hydrogens, coupling constant(s) in hertz). The 2-D NOESY spectra were obtained on a Bruker 500-MHz instrument. ^{31}P NMR chemical shifts (121.5 or 81.8 MHz) are reported relative to trimethyl phosphate (internal capillary) as 3.086 ppm (downfield positive).

(4RS,6RS)-4,6-Dimethyl-1,3,2-dioxathiane-2-oxide (*i*). The cyclic sulfite esters i were prepared from the mixture of 2,4-pentanediol isomers as described by Pritchard and Vollmer,[8] and the *d,l*-isomer was separated by spinning band distillation: bp 90°C/15 mm Hg [lit.[8] 82°C/12 mm Hg]; ^1H NMR δ 1.39 (d, 3, $J = 6.4$), 1.60 (d, 3, $J = 6.7$), 1.95 (ddd, 1, $J = 4.4$, 5.9, 14.0), 2.09 (ddd, 1, $J = 5.3$, 8.9, 14.1), 4.46 (tq, 1, $J = 6.6$, 5.8), 5.06 (ddq, 1, $J = 4.5$, 9.0, 6.4).

(4RS,6RS)-2-[N-(Phenylmethoxycarbonyl)aminomethyl]-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1D-a**). A solution of the dilithium salt of (2*RS*,4*RS*)-2,4-pentanediol ws prepared by addition of 17.8 mL (26.7 mmol) of 1.5 *M* methyllithium in ether to a solution of 2.0 g (13.3 mmol) of the cyclic sulfite i[8] in 50 ml of THF at 0°C. After ca. 30 min, this solution was added to a stirred solution of 5.30 g (13.3 mmol) of the phosphonate **6** in THF at 21°C. The mixture was stirred for 10 h at 21°C, the solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 and a 2% aqueous NaOH solution. The organic layer was removed and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine and worked up to give 3.6 g of a brown oil. Purification by HPLC (92:8 EtOAc/hexanes) yielded 3.05 g (86% yield) of **1D-a** as a clear oil which crystallized on standing as white needles: mp 89–89.5°C; IR 3450 (br), 3000, 1720, 1515, 1305, 1265, 1235, 1095, 995, 975 cm^{-1}; ^1H NMR δ 1.38 (d, 3, $J = 6.2$), 1.45 (d, 3, $J = 6.5$), 1.89 (m, 2), 3.66 (ddd, 1, $J = 5.7$, 10.9, 16.1), 3.68 (ddd, 1, $J = 6.5$, 11.1, 16.1), 4.62 (m, 1), 4.82 (ddq, 1, $J = 6.3$, 5.4, 6.3), 5.12 (s, 2), 5.24 (br s, 1), 7.34 (m, 5); 31P NMR δ 17.55.

Analysis. Calculated for $C_{14}H_{20}NO_5P$: C, 53.67; H, 6.44; N, 4.47; P, 9.89. Found: C, 53.60; H, 6.37; N, 4.45; P, 9.89.

(4RS,6RS)-2-Formylaminomethyl-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1D-b**). The carbobenzoxy group was removed from 925 mg (2.95 mmol) of the dioxaphosphorinane **1D-a** by hydrogenolysis in 30 mL CH_3OH over 591 mg of 5% Pd/C for 1 h. The catalyst was removed by filtration through Celite and the solvent was evaporated to yield 528 mg (99 + % yield) of the free amine as a clear oil. This material was dissolved in 15 mL (14 g, 186 mmol) of ethyl formate and heated at reflux for 10 h. The volatile material was removed under reduced pressure to give 637 mg (99 + % yield) of a greenish oil. Purification by chromatography (89:11 EtOAc/CH_3OH) gave 600 mg (98% yield) of **1D-b** as white needles: mp 76–84°C: IR 3440 (br), 3280, 3010, 1690, 1270, 1125, 1105, 1005, 985 cm^{-1}; ^1H NMR δ 1.455 (dd, 3, $J = 1.5$, 6.5), 1.464 (dd, 3, $J = 1.0$, 6.4), 2.01 (m, 2), 3.59 (ddd, 1, $J = 5.3$, 12.0, 15.9), 3.869 and 3.871 (2 ddd, $\Sigma = 1$, $J = 6.9$, 11.7, 15.7 and 6.9, 11.7, 15.7), 4.79 (m, 2), 7.35 (br s, 1), 8.23 (s, 1); ^{31}P NMR δ 16.57.

Analysis. Calculated for $C_7H_{14}NO_4P$: C, 40.59; H, 6.81; N, 6.76; P, 14.95. Found: C, 40.27; H, 6.93; N, 6.54; P, 14.59.

(4RS,6RS)-2-Isocyanomethyl-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1D-c**). A solution of 480 mg (2.32 mmol) of formamide **1D-b** and 1.5 mL (1.1 g, 11 mmol) of triethylamine in 20 mL of CH_2Cl_2 was treated with 320 μL (530 mg, 3.4 mmol) of $POCl_3$ at 0°C. After stirring for 3 h at 0°C, the solution was filtered and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layer was worked up to yield 450 mg (99 + % yield) of a brown oil. Chromatography (90:10 EtOAc/hexanes) of this material gave 333 mg (76% yield) of **1D-c** as a clear oil: IR 3690, 3615, 3460 (br), 3030, 2990, 2410, 1525, 1390, 1220, 950, 935 cm^{-1}; ^1H NMR δ 1.51 (dd, 3, $J = 1.8$, 6.4), 1.56 (d, 3, $J = 6.6$), 2.01 (dddd, 1, $J = 1.9$, 3.9, 5.0, 14.9), 2.19 (dddd, 1, $J = 1.5$, 4.7, 8.1, 14.8), 3.85 (d, 2, $J = 16.1$), 4.93 (m, 2); ^{31}P NMR δ 7.68.

HRMS (EI). Calculated for $C_7H_{12}NO_3P$: m/z 189.0555. Found: m/z 189.0558.

Analysis. Calculated for $C_7H_{12}NO_3P$: C, 44.45; H, 6.39; N, 7.40; P, 16.38. Found: C, 44.09; H, 6.57; N, 7.10; P, 16.13.

(4RS,6RS)-2-(Benzylideneamino)methyl-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1D-d**). Nitrogen was bubbled through a solution of 1.89 g (6.03 mmol) of **1D-a** in 30 mL of MeOH containing 0.60 g of 10% Pd/C for ca. 15 min. The flask was then purged with hydrogen gas several times. The mixture was stirred vigorously under a hydrogen atmosphere for 1 h. The solution was purged with nitrogen for ca. 5 min and the catalyst was removed by vacuum filtration through Celite. The solvent was removed *in vacuo* to yield 1.09 g (99 + % yield) of the free amine as a clear oil. The residue was immediately dissolved in 20 mL of benzene containing ca. 2 g of Na_2SO_4 and 4 Å molecular sieves. The mixture was cooled to 0°C, 1.8 mL (1.9 g, 18 mmol) of benzaldehyde was added dropwise, and the mixture was allowed to warm to 21°C with stirring over 11 h. The supernatant was evaporated to give 2.4 g of a yellow oil. Rapid purification[22] by chromatography on silica gel (2:98 MeOH/EtOAC) gave 1.09 g (68% yield) of **1D-d** as a clear oil. By ^1H NMR this material appears to be a 1:1 mixture of E and Z imine isomers: IR (CH_2Cl_2) 2990, 2940, 2880, 1645, 1280, 1235, 1120, 1100, 995, 975cm^{-1}; ^1H NMR δ 1.33 (dd, 3, J = 1.4, 6.4), 1.45 (dd, 3, J = 0.7, 6.5), 1.88 (m, 2), 4.125 and 4.129 (2 dd, Σ = 1, J = 14.3, 17.3 and 14.2, 17.3), 4.209 and 4.214 (2 dd, Σ = 1, J = 14.2, 18.2 and 14.3, 18.2), 4.71 (m, 1), 4.81 (m, 1), 7.46 (m, 3), 7.76 (m, 2), 8.28 and 8.30 (2 s, Σ = 1); ^{31}P NMR δ 16.73.

Analysis. Calculated for $C_{13}H_{18}NO_3P$: C, 58.42; H, 6.79; N, 5.24; P, 11.59. Found: C, 58.05; H, 6.82; N, 5.07; P, 11.27.

(2RS,6RS)- and (2SR,6RS)-2-[(N-Phenylmethoxycarbonyl)aminomethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1T-a** *and* **4T-a**). A solution of the dilithium salt of (4*RS*)-2-methyl-2,4-pentanediol was prepared by addition of 21.2 mL (28.8 mmol) of 1.36 *M* *n*-butyllithium in hexane to a solution of 1.70 g (14.4 mmol) of the diol in 120 mL of THF at 0°C. This solution was added over 45 min to a stirred solution of 5.72 g (14.4 mmol) of phosphonate **8** in 110 mL of THF heated at 42–45°C. The mixture was stirred at 45°C for 1 h, then at 21°C for 12 h. The solvent was evaporated and the residue was partitioned between EtOAc and 1% aq. NaOH. The aqueous layer was extracted twice with EtOAc and the combined organic layer was worked up to yield 4.8 g of a white powder. ^{31}P NMR showed the compound to be a 1.5/1 mixture of *trans/cis* diastereomers. Purification by HPLC (85:15 EtOAc/hexanes) gave 1.35 g (29% yield) of **1T-a**, 440 mg (9% yield) of a mixture of the two isomers, and 2.18 g (46% yield) of **5T-a**, all as white powders.

1T-a. mp 100.5–101°C; IR 3450 (br), 2990, 1720, 1515, 1305, 1275, 1235, 1150, 1130, 1050, 995, 960 cm^{-1}; ^1H NMR δ 1.35 (dd, 3, J = 1.2, 6.1), 1.45 (s, 3), 1.49 (s, 3), 1.78 (ddd, 1, J = 2.1, 2.1, 14.7), 2.11 (dd, 1, J = 11.7, 14.4), 3.54 (ddd, 1, J = 5.2, 10.5, 15.8), 3.75 (ddd, 1, J = 6.8, 10.7, 16.0), 4.61 (m, 1), 5.10 (br s, 1), 5.13 (s, 2), 7.36 (m, 5); ^{31}P NMR δ 15.42.

Analysis. Calculated for $C_{15}H_{22}NO_5P$: C, 55.04; H, 6.77; N, 4.28; P, 9.46. Found: C, 55.12; H, 6.85; N, 4.30; P, 9.58.

5T-a. mp 124–125°C; IR 3460 (br), 3000, 1725, 1520, 1315, 1266, 1240, 1153, 1133, 1052, 995 cm^{-1}; ^1H NMR δ 1.33 (dd, 3, J = 1.5, 6.2), 1.36 (d, 3, J = 1.5), 1.59 (s, 3), 1.74 (d, 2, J = 5.9), 3.62 (ddd, 1, J = 6.0, 11.2, 15.3), 3.63 (ddd, 1, J = 6.1, 11.5, 16.4), 4.80 (m, 1), 5.05 (br s, 1), 5.13 (s, 2), 7.35 (m, 5); ^{31}P NMR δ 17.14.

Analysis. Calculated for $C_{15}H_{22}NO_5P$: C, 55.04; H, 6.77; N, 4.28; P, 9.46. Found: C, 54.98; H, 6.81; N, 4.32; P, 9.50.

(2R,6R)- and (2S,6R)-2-[(N-Phenylmethoxycarbonyl)aminomethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide ((6*R*)-**1T-a** *and* (6*R*)-**5T-a**). Prepared from 0.92 g of (4*R*)-2-methyl-2,4-pentanediol as described above for the racemic material. (6*R*)-**1T-a**: mp 88–90°C; $[\alpha]_D^{21}$ + 13.1° (c 10, $CHCl_3$). (6*R*)-**5T-a**. mp 130–131°C; $[\alpha]_D^{21}$ + 9.4° (c 10, $CHCl_3$).

(2RS,6RS)-2-Formylaminomethyl-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1T-b**). Prepared in 89% yield from 433 mg of **1T-a** as described above for **1D-b**: mp 142–144°C; IR 3440 (br), 3270 (br), 3010, 3000, 1680, 1385, 1270, 1152, 1130, 1050, 995, 962 cm^{-1}; ^1H NMR δ 1.38 (dd, 3, J = 1.7, 6.1), 1.49 (d, 3, J = 0.8), 1.53 (s, 3), 1.79 (ddd, 1, J = 2.1, 2.1, 14.7), 2.05 (dd, 1, J = 11.5, 14.6) 3.49 (ddd, 1, J = 5.0, 11.9, 15.6), 4.01 (ddd, 1, J = 7.3, 10.9, 15.5), 4.74 (dddq, 1, J = 2.2, 2.2, 11.4, 6.1), 7.56 (br s, 1), 8.23 (s, 1); ^{31}P NMR δ 14.77.

Analysis. Calculated for $C_8H_{16}NO_4P$: C, 43.44; H, 7.29; N, 6.33; P, 14.00. Found: C, 43.19; H, 7.30; N, 6.34; P, 13.99.

(2RS,6RS)-2-Isocyanomethyl-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1T-c**). Prepared in 80% yield from 223 mg of **1T-b** as described above for **1D-c**: mp 112.5–113°C; IR 3450 (br), 3010,

2990, 2160, 1300, 1255, 1155, 1130, 1052, 1005, 965 cm^{-1}; ^1H NMR δ 1.46 (dd, 3, J = 1.9, 6.2), 1.58 (s, 3), 1.60 (s, 3), 1.94 (ddd, 1, J = 2.2, 2.2, 15.0), 2.23 (dd, 1, J = 11.4, 15.0), 3.83 (d, 2, J = 16.0), 4.88 (dddq, 1, J = 2.3, 2.3, 11.3, 6.2); ^{31}P NMR δ 7.29.

Analysis. Calculated for $C_8H_{14}NO_3P$: C, 47.29; H, 6.95; N, 6.89; P, 15.24. Found: C, 47.38; H, 7.03; N, 6.77; P, 14.99.

(2RS,6RS)-2-[N-(Diphenylmethylene)aminomethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**1T-e**). Nitrogen was bubbled through a solution of 680 mg (2.08 mmol) of **1T-a** in 70 mL of MeOH containing 440 mg (2.31 mmol) of $TsOH \cdot H_2O$ and 210 mg of 10% Pd/C for ca. 15 min. The flask was then purged with hydrogen gas several times. The mixture was stirred vigorously under a hydrogen atomosphere for 3 h. The solution was purged with nitrogen for ca. 5 min and the catalyst was removed by vacuum filtration through Celite. The solvent was removed *in vacuo* to yield 790 mg (99% yield) of the salt as a clear glass.

The oil was dissolved in 17 mL of CH_2Cl_2 followed by dropwise addition of 0.75 g (4.14 mmole) of benzophenone imine.[23] A white precipitate formed immediately. The mixture was stirred at 21 °C for 4 h, then washed with saturated NH_4Cl solution and with brine. The organic layer was worked up and the crude product was purified by chromatography (silica gel, 95:5 EtOAc/hexanes) to give 610 mg (83% yield) of the imine **1T-e** as a colorless oil. This material was recrystallized in two crops from CH_2Cl_2/hexanes to yield 58 mg (78% yield) of clear prisms: mp 87–88°C; IR 3000, 1620, 1450, 1390, 1380, 1320, 1300, 1280, 1230, 1160, 1130, 1050, 1000 cm^{-1}; ^1H NMR δ 1.41 (dd, 3, J = 1.6, 6.2), 1.46 (s, 3), 1.52 (s, 3), 1.79 (ddd, 1, J = 2.1, 2.1, 14.6), 2.12 (dd, 1, J = 11.4, 14.6), 3.98 (d, 2, J = 17.5), 4.83 (dddq, 1, J = 2.2, 2.2, 10.7, 6.1), 7.17 (dd, 2, J = 1.9, 7.5), 7.3–7.5 (m, 6), 7.63 (dd, 2, J = 1.4, 7.9); ^{31}P NMR δ 17.12.

Analysis. Calculated for $C_{20}H_{24}NO_3P$: C, 67.22; H, 6.77; N, 3.92; P, 8.67. Found: C, 67.44; H, 6.77; N, 3.93; P, 8.58.

(2R,6R)-2[N-(Diphenylmethylene)aminomethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide ((*6R*)-**1T-e**). Prepared in 87% yield from 375 mg of optically active (6*R*)-**1T-a** as described above for racemic material; recrystallized from EtOAc/pentane as clear plates: mp 87–88°C; $[\alpha]_D^{21}$ + 11.6° (c 15, $CHCl_3$).

Analysis. Calculated for $C_{20}H_{24}NO_3P$: C, 67.22; H, 6.77; N, 3.92; P, 8.67. Found: C, 67.38; H, 6.86; N, 3.79; P, 8.52.

(4RS,6RS)-2-[1-(Benzylideneamino)ethyl]-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (**2D-d**); *general alkylation procedure A.* The anion of dioxaphosphorinane **1D-d** was prepared by addition of 0.54 mL (0.81 mmol) of 1.5 *M* *n*-butyllithium in hexane to a stirred solution of 196 mg (0.733 mmol) of **1D-d** in 7.5 mL of THF and 0.7 mL (0.7 g, 4 mmol) of HMPA at −78°C. After 1 h, 92 μL (210 mg, 1.5 mmol) of methyl iodide was added and the mixture was stirred at −78°C for 3 h. The reaction was quenched with a saturated KH_2PO_4 solution, the mixture was partitioned between EtOAc and water, and the organic layer was worked up to give 155 mg of a pale oil. ^1H NMR analysis showed the mixture to be a 11:89 mixture of the starting material **1D-d** and the desired alanine analog **2D-d**: ^{31}P NMR showed a diastereomeric ratio of 58:42 (16% de). This material proved to be difficult to purify by chromatography due to the hydrolytic sensitivity of the imine moiety: IR 3010, 2950, 1645, 1277, 1130, 1105, 1000, 984.

Major diastereomer. ^1H NMR δ 1.36 (dd, 3, J = 0.5, 6.3), 1.494 (dd, 3, J = 1.3, 6.4), 1.60 (dd, 3, J = 7.0, 18.0), 1.7–2.1 (m, 2), 3.95 (dq, 1, J = 6.6, 7.1), 4.52 (m, 1), 4.83 (m, 1), 7.45 (m, 1), 7.48 (m, 2), 7.76 (m, 2), 8.33 & 8.35 (2s, Σ = 1); ^{31}P NMR δ 19.08.

Minor diastereomer. ^1H NMR δ 1.15 (dd, 3, J = 1.5, 6.3), 1.492 (d, 3, J = 6.4), 1.62 (dd, 3, J = 7.1, 18.2), 1.7–2.1 (m, 2), 3.89 (dq, 1, J = 5.6, 6.9), 4.74 (m, 1), 4.83 (m, 1), 7.45 (m, 1), 7.48 (m, 2), 7.76 (m, 2), 8.30 and 8.32 (2s, Σ = 1); ^{31}P NMR δ 19.90.

HRMS (FAB). Calculated for $C_{14}H_{20}NO_3P$: m + 1/z 282.1259. Found: m + 1/z 282.1267.

(2RS,6RS)-2-[1-[N-(Diphenylmethylene)amino]ethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**2T-e**); *general alkylation procedure B.* The anion of dioxaphosphorinane **1T-e** was prepared by addition of 97 μL (0.13 mmol) of 1.3 *M* *n*-butyllithium in hexanes to a stirred solution of 45 mg (0.13 mmol) of **1T-e** in 1 ml of THF at −78°C. After 1 h, 16 μL (36 mg, 0.26 mmol) of CH_3I was added to the lemon yellow anion. The reaction was stirred at −78°C for 3 h, followed by quenching with saturated NH_4Cl solution. After warming to 21°C, the mixture was partitioned between CH_2Cl_2 and brine, the organic layer was removed, and the aqueous layer was washed once with CH_2Cl_2. The combined organic layer was worked up to yield 51 mg of a brown glass. ^{31}P NMR spectroscopy showed the compound to be a 58:42 mixture of diastereomers (16% de). Purification by chromatography (98:2 CH_2Cl_2/MeOH) gave 43 mg (91% yield) of a colorless glass, which crystallized on

standing: mp 115–121°C; IR ($CDCl_3$) 3010, 2270, 1665, 1455, 1290, 1240, 1165, 1150, 1060, 1000 cm^{-1}.

Major diastereomer. ^1H NMR δ 1.48 (s, 3), 1.45 (dd, 3, J = 1.6, 6.0), 1.39 (dd, 3, J = 3.1, 6.9), 1.70 (s, 3), 1.77 (ddd, 1, J = 1.9, 1.9, 14.6), 2.07 (dd, 1, J = 4.8, 14.4), 4.04 (m, 1), 4.87 (m, 1), 7.17 (dd, 3, J = 2.1, 7.2), 7.3–7.6 (m, 6), 7.64 (dd, 2, J = 1.4, 6.4); ^{31}P NMR δ 20.76.

Minor diastereomer. ^1H NMR δ 1.21 (s, 3), 1.26 (dd, 3, J = 1.6, 6.2), 1.45 (dd, 3, J = 1.6, 6.0), 1.55 (s, 3), 1.77 (ddd, 1, J = 1.9, 1.9, 14.6), 2.11 (dd, 1, J = 4.8, 14.6), 4.04 (m, 1), 4.62 (m, 1), 7.17 (dd, 3, J = 2.1, 7.2), 7.3–7.6 (m, 6), 7.64 (dd, 2, J = 1.4, 6.4); ^{31}P NMR δ 19.28.

Analysis. Calculated for $C_{21}H_{26}NO_3P$: C, 67.91; H, 7.06; N, 3.77; P, 8.34. Found: C, 67.54; H, 7.15; N, 3.71; P, 8.21.

(2RS,6RS)-2-(Isocyanoethyl)-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**2T-c**). Following procedure B, the anion was prepared from 50 mg (0.25 mmol) of dioxaphosphorinane **1T-c** and treated with 34 μL of methyl iodide for 4.5 h at −78°C. The crude product (64 mg) was shown to be a mixture of 80:15:5 **2T-c**/dialkylation product/**1T-c**, with 23% de in **2T-c**, by ^{31}P NMR. Purification by chromatography (80:20 EtOAc/hexanes) gave 50 mg of essentially the same mixture (75% yield) of **2T-c** by ^1H and ^{31}P NMR: IR 3680 (br w), 3450 (br m), 3000, 2950, 2150, 1455, 1380, 1275, 1235, 1155, 1130, 1095, 1045, 995, 990, 985, 960, 890 cm^{-1}.

Major diastereomer. ^1H NMR δ 1.45 (dd, 3, J = 1.8, 6.2), 1.58 (s, 6), 1.64 (dd, 3, J = 7.3, 16.2), 1.93 (ddd, 1, J = 2.0, 2.0, 15.0), 2.22 (dd, 1, J = 11.5, 14.8), 3.94 (m, 1), 4.86 (m, 1); ^{31}P NMR δ 10.63.

Minor diastereomer. ^1H NMR δ 1.46 (dd, 3, J = 1.7, 6.2), 1.58 (s, 6), 1.66 (dd, 3, J = 7.3, 16.3), 1.94 (ddd, 1, J = 2.0, 2.0, 15.0), 2.23 (dd, 1, J = 11.5, 14.7), 3.94 (m, 1), 4.86 (m, 1); ^{31}P NMR δ 11.30.

(4RS,6RS)-2-[1-(Benzylideneamino)-3-methylbutyl]-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (**3D-d**). Following procedure A, the anion was prepared from 58 mg (0.217 mmol) of dioxaphosphorinane **1D-d** and treated with 28 μL (44 mg, 0.242 mmol) of isobutyl iodide for 4 h at −78°C. The crude product (69 mg) was purified by chromatography (alumina, EtOAc) to give 37 mg (53% yield) of the leucine analog **3D-d**, as a white powder. ^{31}P NMR analysis showed the compound to be a 61:39 mixture of diastereomers (24% de): mp 126–128°C; IR 3000, 2970, 1640, 1265, 1125, 1105, 1005, 982 cm^{-1}.

Major diastereomer. ^1H NMR δ 0.852 (d, 3, J = 6.5), 0.93 (d, 3, J = 6.6), 1.33 (d, 3, J = 6.5), 1.50 (dd, 3, J = 1.2, 6.2), 2.2–1.7 (m, 5), 3.85 (ddd, 1, J = 2.7, 11.4, 14.0), 4.43 (ddq, 1, J = 5.5, 6.3, 12.6), 4.79 (m, 1), 7.46 (m, 3), 7.77 (m, 2), 8.30 and 8.32 (2s, Σ = 1); ^{31}P NMR δ 18.99.

Minor diastereomer. ^1H NMR δ 0.847 (d, 3, J = 6.5), 0.93 (d, 3, J = 6.6), 1.11 (dd, 3, J = 1.5, 6.3), 1.48 (d, 3, J = 6.4), 2.2–1.7 (m, 5), 3.85 (ddd, 1, J = 2.7, 11.4, 14.0), 4.76 (m, 1), 4.79 (m, 1), 7.46 (m, 3), 7.77 (m, 2), 8.26 and 8.28 (2s, Σ = 1); ^{31}P NMR δ 19.75.

Analysis. Calculated for $C_{17}H_{26}NO_3P$: C, 63.14; H, 8.10; N, 4.33; P, 9.58. Found: C, 63.42; H, 8.19; N, 4.12; P, 9.30.

(2-RS,6RS)-2-[1-[N-(Diphenylmethylene)amino]-3-methylbutyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**3T-e**). Following procedure B, the anion was prepared from 150 mg (0.42 mmol) of dioxaphosphorinane **2d** and treated with 0.10 mL (0.16 mg, 0.87 mmol) of *i*-BuI for 14 h at −78°C. The crude product (199 mg) was purified by chromatography (70:30 EtOAc/hexanes) to yield 147 mg (84% yield) of the leucine analog **4d** (R = *i*-Bu) as a clear glass which crystallized on standing to clear rosettes. ^{31}P NMR analysis showed the compound to be a 71:29 mixture of diastereomers (41% de): mp 153–156°C; IR 3010, 2980, 1625, 1605, 1475, 1455, 1395, 1265, 1240, 1160, 1135, 1055, 1000, 990, 965 cm^{-1}.

Major diastereomer. ^1H NMR δ 0.44 (d, 3, J = 6.5), 0.85 (d, 3, J = 6.6), 1.13 (s, 3), 1.43 (dd, 3, J = 1.4, 6.2), 1.40 (m, 1), 1.50 (s, 3), 1.73 (m, 2), 1.96 (m, 1), 2.10 (m, 1), 4.10 (ddd, 1, J = 2.4, 11.9, 11.9), 4.79 (m, 1), 7.2–7.5 (m, 8), 7.64 (dd, 2, J = 0.6, 7.3); ^{31}P NMR δ 20.73.

Minor diastereomer. ^1H NMR δ 0.49 (d, 3, J = 6.5), 0.86 (d, 3, J = 6.6), 1.53 (s, 3), 1.23 (dd, 3, J = 1.6, 6.2), 1.40 (m, 1), 1.66 (s, 3), 1.73 (m, 2), 1.96 (m, 1), 2.10 (m, 1), 4.13 (ddd, 1, J = 2.6, 11.5, 11.5), 4.53 (m, 1), 7.2–7.5 (m, 8), 7.64 (dd, 2, J = 0.6, 7.3); ^{31}P NMR δ 18.43.

Analysis. Calculated for $C_{24}H_{32}NO_3P$: C, 69.71; H, 7.80; N, 3.39; P, 7.49. Found: C, 69.95; H, 7.81; N, 3.41; P, 7.56.

(4R,6R)-2-[(1S)-2-Phenyl-1-[N-(phenylmethoxycarbonyl)amino]ethyl]-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide ((*4R,6R*)-**4D-a**), *via condensation.* The phosphonic dichloridate (*S*)-**11** was prepared by addition of 0.45 mL (0.73 g, 6.2 mmol) of $SOCl_2$ to a stirred slurry of 502 mg (1.50 mmol) of (*S*)-**10** in 5 mL of CH_2Cl_2 at 21°C in a dry nitrogen atmosphere, causing the diacid to go into solution within 5 min. After 4 h, all volatile material was removed *in vacuo*. The yellow sticky residue

was dissolved in 15 mL of CH_2Cl_2, and 190 mg (1.82 mmol) of (2*R*,4*R*)-2,4-pentanediol and 1.7 mL (1.2 g, 12.2 mmol) of Et_3N were added to the stirring solution. After 1 h, the mixture was diluted with 50 mL of CH_2Cl_2 and was washed with 1 *N* HCl, saturated $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered and evaporated *in vacuo* to yield 0.60 g of a white powder. Purification by chromatography (2:98 CH_3OH/CH_2Cl_2) gave 0.57 g (95% yield) of (4*R*,6*R*)-**4D-a**, as a white powder: mp 166–167°C; $[\alpha]_D^{21} + 40.7°$ (c = 0.5, $CHCl_3$); IR 3430, 3000, 1725, 1715, 1515, 1505, 1455, 1390, 1265, 1255, 1245, 1235, 1100, 995, 975 cm^{-1}; ^1H NMR δ 1.32 (d, 3, $J = 6.3$), 1.36 (d, 3, $J = 6.5$), 1.85 (t, 2, $J = 5.1$), 2.91 (ddd, 1, $J = 9.7$, 10.6, 14.5), 3.26 (ddd, 1, $J = 5.6$, 9.2, 14.5), 4.36 (m, 2), 4.78 (m, 1), 4.99 (d, 1, $J = 12.5$), 5.05 (d, 1, $J = 12.5$), 5.14 (br d, 1, $J = 10.1$), 7.25 (m, 6), 7.29 (m, 4); ^{31}P NMR δ 18.31.

Analysis. Calculated for $C_{21}H_{26}NO_5P$: C, 62.52; H, 6.50; N, 3.47; P, 7.68. Found: C, 62.70; H, 6.47; N, 3.42; P, 7.57.

(4RS,6RS)-2-[1-(Benzylideneamino)2-phenylethyl]-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (**4D-d**), *via alkylation.* Following procedure A, the anion was prepared from 54 mg (0.20 mmol) of dioxaphosphorinane **1D-d** and treated with 26 μL (0.219 mmol) of benzyl bromide for 6 h at −78°C. The crude product (65 mg) was purified by chromatography (alumina, EtOAc) to give 60 mg (84% yield) of the phenylalanine analog **4D-d**, as a clear oil. ^{31}P NMR analysis showed the compound to be a 67:33 mixture of diastereomers (34% de): IR 1640, 1125, 1105, 1000, 980 cm^{-1}.

Major diastereomer. ^1H NMR δ 1.34 (dd, 3, $J = 0.5$, 6.5), 1.56 (dd, 3, $J = 1.2$, 6.4), 1.89 (m, 1), 2.00 (m, 1), 3.20 (m, 1), 3.50 (m, 1), 3.87 (ddd, 1, $J = 2.2$, 11.3, 11.3), 4.50 (ddq, 1, $J = 6.1$, 12.3, 6.1), 4.89 (m, 1), 7.14 (m, 5), 7.43 (m, 3), 7.65 (m, 2), 7.76 and 7.78 (2s, $\Sigma = 1$); ^{31}P NMR δ 17.70.

Minor diastereomer. ^1H NMR δ 1.12 (dd, 3, $J = 1.1$, 6.3), 1.52 (dd, 3, $J = 0.5$, 6.5), 1.89 (m, 1), 2.00 (m, 1), 3.20 (m, 1), 3.50 (m, 1), 3.87 (ddd, 1, $J = 2.2$, 11.3, 11.3), 4.78 (m, 1), 4.89 (m, 1), 7.14 (m, 5), 7.43 (m, 3), 7.65 (m, 2), 7.72 and 7.74 (2s, $\Sigma = 1$); ^{31}P NMR δ 18.52.

Analysis. Calculated for $C_{20}H_{24}NO_3P$: C, 67.22; H, 6.77; N, 3.92; P, 8.67. Found: C, 67.24; H, 6.90; N, 3.72; P, 8.46.

(2RS,6RS)-2-[1-(Isocyanoamino)-2-phenylethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**4T-c**). Following procedure B, the anion was prepared from 30 mg (0.15 mmol) of dioxaphosphorinane **1T-c** and treated with 35 μL (50 mg, 0.29 mmol) of benzyl bromide for 6 h at −78°C. ^{31}P NMR analysis showed the crude product to be a 56:24:20 mixture of **4T-c**/dialkylation product/**1T-c**, with a 3% de in **4T-c**. Purification by chromatography (50:50 EtOAc/hexanes) gave 12 mg of the dialkylation product, 4 mg of starting material, and 26 mg (60% yield, 69% yield based on recovery of starting material) of **4T-c** as a glass: IR 3020, 2960, 2160, 1505, 1465, 1385, 1275, 1160, 1135, 1055, 990 cm^{-1}; ^1H NMR δ 1.43 and 1.44 (2dd, $\Sigma = 3$, $J = 2.0$, 6.2 and 2.7, 6.1), 1.58 (s, 6), 1.93 (dd, 1, $J = 2.0$, 15.0), 2.24 (ddd, 1, $J = 2.8$, 11.5, 14.6), 2.99 and 3.03 (2ddd, $\Sigma = 1$, $J = 6.3$, 8.1, 14.3 and 6.4, 8.3, 14.2), 3.37 (m, 1), 3.99 and 4.06 (2ddd, $\Sigma = 1$, $J = 3.1$, 10.7, 10.7 and 3.0, 11.0, 11.0), 4.87 (m, 1), 7.32 (m, 5); ^{31}P NMR δ 9.38 (major diastereomer), 9.93.

Analysis. Calculated for $C_{15}H_{20}NO_3P$: C, 61.43; H, 6.87; N, 4.78; P, 10.56. Found: C, 61.27; H, 6.99; N, 4.73; P, 10.80.

(2RS,6RS)-2-[1-[N-(Diphenylmethylene)amino]-2-phenylethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**4T-e**). Following procedure B, the anion was prepared from 31 mg (0.87 μmol) of dioxaphosphorinane **1T-e** and treated with 21 μL (30 mg, 0.18 mmol) of benzyl bromide for 4 h at −78°C. The crude product (34 mg) was purified by chromatography (70:30 EtOAc/hexanes) to give 31 mg (79% yield) of **4T-e** as a white powder and 2 mg of **1T-e** (85% yield based on recovery of starting material). ^{31}P NMR analysis showed the compound to be a 75:25 mixture of diastereomers (50% de): mp 126–131°C; IR 3010, 2960, 1625, 1610, 1585, 1455, 1395, 1385, 1325, 1265, 1160, 1135, 1045, 980 (vs) cm^{-1}.

Major diastereomer. ^1H NMR δ 1.16 (s, 3), 1.48 (dd, 3, $J = 1.5$, 6.3), 1.50 (s, 3), 1.74 (ddd, 1, $J = 2.0$, 2.1, 14.4), 2.12 (dd, 1, $J = 11.2$, 14.4), 3.21 (ddd, 1, $J = 6.3$, 11.0, 13.0), 3.33 (ddd, 1, $J = 2.4$, 7.3, 13.1), 4.09 (ddd, 1, $J = 2.4$, 10.5, 11.0), 4.86 (dddq, 1, $J = 1.7$, 2.2, 11.2, 6.2), 6.3 (br s, 2), 6.97 (m, 2), 7.1–7.5 (m, 9), 7.56 (d, 2, $J = 6.9$); ^{31}P NMR δ 19.05.

Minor diastereomer. ^1H NMR δ 1.25 (dd, 3, $J = 1.3$, 6.2), 1.58 (s, 3), 1.73 (ddd, 1, $J = 2.4$, 2.4, 14.4), 1.76 (s, 3), 2.10 (dd, 1, $J = 14.1$, 14.4), 3.19 (m, 1), 3.32 (m, 1), 4.12 (ddd, 1, $J = 2.4$, 10.6, 11.0), 4.57 (m, 1), 6.3 (br s, 2), 6.97 (m, 2), 7.1–7.5 (m, 9), 7.56 (d, 2, $J = 6.9$); ^{31}P NMR δ 17.16.

Analysis. Calculated for $C_{27}H_{30}NO_3P$: C, 72.47; H, 6.76; N, 3.13; P, 6.92. Found: C, 72.43; H, 6.73; N, 3.10; P, 6.90.

(2RS,6SR)-2-[N-(Diphenylmethylene)aminomethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**5T-e**). The carbobenzoxy group was hydrogenolyzed from **5T-a** by treating 203 mg (0.620 mmol) of **5T-a** and 130 mg (0.683 mmol) of *p*-TsOH·H_2O with 62 mg of 10% Pd/C under H_2 for 1 h. After

isolation, the salt was converted into the benzophenone imine by treatment with 260 mg (1.44 mmol) of benzophenone imine. Purification by chromatography (silica gel, 90:10 EtOAc/hexanes) gave 213 mg (96% yield) of **5T-e** as a white powder: mp 128.5–129.5°C; IR 3390 (br), 2290, 1620, 1220, 1130, 1050, 995 cm^{-1}; ^1H NMR δ 1.38 (dd, 3, $J = 1.7, 6.2$), 1.44 (d, 3, $J = 1.8$), 1.59 (s, 3), 1.67 (ddd, 1, $J = 2.2, 2.2, 14.3$), 2.00 (dd, 1, $J = 11.7, 14.0$), 3.93 (d, 2, $J = 17.7$), 4.81 (dddq, 1, $J = 2.3, 2.3, 11.8, 6.1$), 7.2–7.7 (m, 10); ^{31}P NMR δ 17.20.

Analysis. Calculated for $C_{20}H_{24}NO_3P$: C, 67.22; H, 6.77; N, 3.92; P, 8.67. Found: C, 67.31; H, 6.82; N, 3.89; P, 8.70.

(2RS,6SR)-2-[1-(Diphenylmethylene)amino-2-phenylethyl]-4,4,6-trimethyl-1,3,2-dioxaphosphorinane-2-oxide (**6T-e**, *via alkylation*). Following procedure B, the anion was prepared from 107 mg (0.30 mmol) of dioxaphosphorinane **5T-e** and treated with 80 μL (120 mg, 0.67 mmol) of benzyl bromide for 3.5 h at −78°C. The crude product (240 mg) was purified by chromatography (80:20 EtOAc/hexanes) to give 122 mg (91% yield) of **6T-e** as a clear glass, which crystallized on standing to white rosettes, and 10 mg of **5T-e** (100% yield based on recovery of starting material). ^{31}P NMR analysis showed the compound to be a 55:45 mixture of diastereomers (9% de): mp 135–137°C; IR 3400 (br w), 2990, 2940, 1620, 1495, 1455, 1450, 1385, 1375, 1320, 1280, 1255, 1155, 1130, 1050, 995, 960 cm^{-1}; 1H NMR δ 1.17 and 1.56 (2dd and m, $\Sigma = 3$, $J = 1.8, 6.2$), 1.20 and 1.69 (2d, $\Sigma = 3$, $J = 2.0$ and 1.4), 1.57 and 1.59 (2s, $\Sigma = 3$), 1.62 (m, 1), 1.96 (ddd, 1, $J = 0.9, 12.0, 12.3$), 3.15 (m, 1), 3.31 (ddd, 1, $J = 2.3, 7.0, 13.1$), 4.02 (m, 1), 4.80 and 4.85 (2m, $\Sigma = 1$), 6.3 (br s, 2), 6.99 (m, 2), 7.15 (m, 4), 7.2–7.4 (m, 5), 7.57 (m, 2); ^{31}P NMR δ 17.72, 17.81 (major diastereomer).

Analysis. Calculated for $C_{27}H_{30}NO_3P$: C, 72.47; H, 6.76; N, 3.13; P, 6.92. Found: C, 72.29; H, 6.82; N, 3.09; P, 7.14.

Diphenyl N-(Phenylmethoxycarbonyl)aminomethyl Phosphonate (**8**). Prepared in 42% yield by the procedure of Oleksyszyn and Subotkowska,[7] with recrystallization of the product from methanol: mp 114–116°C [lit.[7] 114–116°C].

(S)-1-[N-(Phenylmethoxycarbonyl)amino]-2-phenylethyl Phosphonic Acid ((*S*)-**10**). A slurry of 1.36 g (6.8 mmol) of **10**, 1.2 g (14 mmol) of $NaHCO_3$, and 1.5 g (14 mmol) of Na_2CO_3 in 7 mL of 2 *N* NaOH was prepared. This was treated at 0°C with four aliquots of 1.0 mL (4.8 g, 28 mmol) of benzylchloroformate at 1-h intervals followed by stirring at 21°C for 20 h. The slurry was partitioned between 0.5 *N* NaOH at Et_2O. The aqueous layer was acidified with 12 *N* HCl and washed with CH_2Cl_2. The organic layer was worked up to give 2.2 g of a brown glass which was recrystallized (EtOAc/hexanes) to give 2.11 g (92% yield) of a white powder: mp 142–144°C; $[\alpha]_D^{21} + 36.3°$ (c = 1, CH_3OH); IR 3380 (br), 3010, 2800 (br), 2300 (br), 1710, 1510, 1495, 1450, 1340, 1305, 1230, 1010, 950, 945 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 2.79 (m, 1), 3.24 (m, 1), 4.17 (br s, 2), 4.84 (br d, 1, $J = 12.8$), 4.87 (d, 1, $J = 12.7$), 5.00 (d, 1, $J = 12.3$), 7.21 (m, 10); ^{31}P NMR ($CDCl_3/CD_3OD$) δ 23.64 (br).

Analysis. Calculated for $C_{16}H_{18}NO_5P$: C, 57.32; H, 5.41; N, 4.18; P, 9.24. Found: C, 57.06; H, 5.42; N, 3.99; P, 8.99.

(4R,6R)-2-[(1S)-1-(Benzylideneamino)-2-phenylethyl]-4,6-dimethyl-1,3,2-dioxaphosphorinane-2-oxide ((*4R,6R*)-**4D-a**). A solution of 538 mg (1.33 mmol) of optically active (*4R,6R*)-**4D-a** (prepared by condensation) in 5 mL of MeOH containing 270 mg of 5% Pd/C was purged with a stream of nitrogen for 5 min. The nitrogen atmosphere was replaced with hydrogen, and the suspension was allowed to stir for 4 h. The catalyst was removed by filtration through Celite and the solvent was removed under reduced pressure to yield 357 mg (99% yield) of the free amine as a clear oil.

The oil was dissolved immediately in 5 mL of benzene with 1 g of Na_2SO_4. Rapid dropwise addition of 0.27 mL (0.28 g, 2.66 mmol) of benzaldehyde was followed by stirring at 21°C for 12 h. The solution was diluted with CH_2Cl_2 and filtered, and the solvent was removed under reduced pressure. Purification by chromatography[21] (80:20 EtOAc/hexanes) gave 326 mg (69% yield) of (*4R,6R*)-**4D-d** as a colorless glass. The crude product was recrystallized from EtOAc/hexanes to give (*4R,6R*)-**4D-d** as white needles: mp 72–76°C; $[\alpha]_D^{21} + 81.5°$ (c 1, $CHCl_3$); IR 3430 (br w), 3080, 3010, 2950, 2890, 2860, 1645, 1610, 1585, 1505, 1460, 1390, 1260, 1125, 1100, 1000, 985, 925, 900 cm^{-1}; ^1H NMR δ 1.35 (dd, 3, $J = 0.6, 6.5$), 1.57 (dd, 3, $J = 1.2, 6.4$), 1.86 (m, 1), 2.02 (dddd, 1, $J = 1.3, 4.6, 7.6, 13.7$), 3.19 (ddd, 1, $J = 6.1, 11.1, 13.6$), 3.49 (ddd, 1, 2.1, 7.8, 13.6), 3.87 (ddd, 1, $J = 2.2, 11.3, 11.3$), 4.50 (ddq, 1, $J = 5.7, 12.0, 6.4$), 4.88 (m, 1), 7.16 (m, 5), 7.42 (m, 3), 7.64 (m, 2), 7.77 (d, 1, $J = 4.8$); ^{31}P NMR δ 17.66.

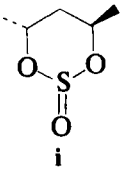
Analysis. Calculated for $C_{20}H_{24}NO_3P$: C, 67.22; H, 6.77; N, 3.92; P, 8.67. Found: C, 66.86; H, 6.66; N, 3.77; P, 8.53.

ACKNOWLEDGMENT

We would like to express our appreciation to John H. Bushweller for assistance in obtaining the NOESY spectra. Support for this work was provided by the National Institutes of Health (grant no. CA-22747).

REFERENCES

1. General: R. L. Hilderbrand, "The Role of Phosphonates in Living Systems," (CRC Press, Boca Raton, Florida, 1983); R. Engel, *Chem. Rev.*, **77,** 349–67 (1977); D. Redmore, *Topics, Phos. Chem.*, **8,** 515 (1976); Antibiotics: J. W. Huber, W. F. Gilmore, L. W. Robertson, *J. Med. Chem.*, **18,** 106 (1975); J. G. Allen, *et al., Nature,* **272,** 56–58 (1978); T. Kametani, K. Kigasawa, H. Hiiragi, K. Wakisaka, S. Haga, H. Sugi, K. Tamigawa, Y. Suski, K. Fukawa, O. Irino, O. Saita, S. Yamabe, *Heterocycles,* **16,** 1205 (1981); Insecticides or herbicides: J. Emsley, D. Hall, in "The Chemistry of Phosphorus," (Harper and Row, London, 1976), pg. 494; D. D. Baird, R. P. Upchurch, H. C. Steinruecken, N. Amrhein, *Biochem. Biophys. Res. Commun.*, **94,** 1207–12 (1980); W. B. Homesley, J. E. Franz, *Proceedings of the North Central Weed Control Conference,* **26,** 64 (1971), *in* "The Herbicide Glyphosate" E. Grossbard, and D. Atkinson, editors (Butterworth & Co. Ltd, Boston, 1985); Enzyme inhibitors: N. E. Jacobsen, P. A. Bartlett, *J. Am. Chem. Soc.*, **103,** 654–657 (1981); E. D. Thorsett, E. E. Harris, E. R. Peterson, W. J. Greenlee, A. A. Patchett, E. H. Ulm, T. C. Vassil, *Proc. Natl. Acad. Sci. U.S.A.*, **79,** 2176–90 (1982); P. A. Bartlett, C. K. Marlowe, *Biochemistry,* **22,** 4618–22 (1983); E. W. Petrillo, Jr., D. W. Cushman, M. E. Duggan, J. E. Heikes, D. S. Karanewsky, M. A. Ondetti, B. O'Reilly, G. C. Rovnyak, J. Schwartz, *et al., Peptides: Structure and Function, Proc. Natl. Pept. Symp., 8th,* (V. J. Hruby and D. H. Rich, editors (Pierce Chemical Company, 1983) pp. 541–50; P. A. Bartlett, W. B. Kezer, *J. Am. Chem. Soc.*, **106,** 4282–83 (1984); P. A. Bartlett, L. A. Lamden, *Biorg. Chem.*, **14,** 356–377 (1986).
2. P. Kafarski, B. Lejczak and J. Szewczyk,, *Can. J. Chem.*, **61,** 2425 (1983); T. Głowiak, W. Sawka-Dobrowolska, J. Kowalik, P. Mastalerz, M. Soroka, J. Zòn, *Tetrahedron Lett.*, 3965–68 (1977); J. Zòn, *Polish J. Chem.*, **55,** 643 (1981).
3. W. F. Gilmore and H. A. McBride, *J. Am. Chem. Soc.*, **94,** 4361 (1972); T. Głowiak, W. Sawka-Dobrowolska, J. Kowalik, P. Mastalerz, M. Soroka, J. Zòn, *Tetrahedron Lett.*, 3965–68 (1977); A. Kotynski, W. Stec, *J. Chem. Res. (S),* 41 (1978); J. W. Huber III, W. F. Gilmore, *Tetrahedron Lett.*, 3049–52 (1979); J. Zòn, *Polish J. Chem.*, **55,** 643 (1981); A. Vasella, R. Voeffray, *Helv. Chim. Acta,* **65,** 1953 (1982); I. Hoppe, U. Schoellkopf, M. Nieger, E. Egert, *Angew. Chem.*, **97,** 1066–67 (1985); U. Schoellkopf, I. Hoppe, A. Thiele, *J. Liebigs Ann. Chem.*, 555–59 (1985).
4. *Inter alia*: U. Schoellkopf, R. Scheuer, *J. Liebigs Ann. Chem.*, 939 (1984); U. Schoellkopf, H. J. Neubauer, *Synthesis,* 861 (1982); U. Schoellkopf, W. Hartwig, K. H. Pospischil, H. Kehne, *Synthesis,* 996 (1981); U. Schoellkopf, U. Groth, D. Chuanzheng, *Angew. Chem. Int. Ed. Eng.*, 797 (1981); M. J. O'Donnell, C. L. Barney, J. R. McCarthy, *Tetrahedron Lett.* **26,** 3067–70 (1985); M. J. O'Donnell, K. Wojciechowski, L. Ghosez, M. Navarro, F. Sainte, J. P. Antoine, *Synthesis,* 313 (1984).
5. J. Rachon, U. Schoellkopf and T. Wintel, *J. Liebigs Ann. Chem.*, 709–18 (1981).
6. S. Hanessian, D. Delorme, S. Beaudoin and Y. Leblanc, *J. Am. Chem. Soc.*, **106,** 5754–56 (1984).
7. M. G. B. Drew, J. Rodgers, D. W. White and J. G. Verkade, *J.C.S. Chem. Commun.*, 227 (1971); Mazhar-ul-Hague, C. N. Caughlan, J. H. Hargis, W. G. Bentrude, *J. Chem. Soc.* (A), 1786 (1970); R. C. G. Killean, J. L. Lawrence, I. M. Magennis, *Acta Cryst. Sect. B,* **27,** 189 (1971).
8. J. Oleksyszyn and L. Subotkowska, *Synth. Commun.*, 906 (1980).
9. In the case of *dl*-2,4-pentanediol, the dialkoxide was generated directly from methyllithium and the cyclic sulfite *i* used in purification of the diol (J. G. Pritchard, R. L. Vollmer, *J. Org. Chem.*, **28,** 1545 (1963).



i

10. U. Schoellkopf, R. Schroeder and D. Stafforst, *J. Liebigs. Ann. Chem.*, **44** (1974).
11. A. Arrieta, F. Cossio and C. Palomo, *Tetrahedron*, **41**, 1703 (1985).
12. M. J. O'Donnell and R. L. Polt, *J. Org. Chem.*, **47**, 2663–66 (1982).
13. J. A. Mosbo and J. G. Verkade, *J. Am. Chem. Soc.*, **95**, 4659–65 (1973).
14. D. W. White, G. K. McEwen, R. D. Bertrand and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971); J. G. Verkade, *Phos. and Sulfur*, 251 (1976); J. A. Mosbo, J. G. Verkade, *J. Org. Chem.*, **42**, 1549–55 (1977).
15. D. J. States, R. A. Haberkorn and D. J. Ruben, *J. Magnetic Resonance*, **48**, 286 (1982).
16. K. Ito, T. Harada, A. Tai and Y. Izumi, *Chem. Lett.*, 1049 (1979).
17. P. Kafarski, B. Lejczak and J. Szewczyk, *Can. J. Chem.*, **61**, 2425 (1983).
18. N. O. V. Sonntag, *Chem. Rev.*, **52**, 237 (1953).
19. G. Kirchner, M. P. Scollar and A. M. Klibanov, *J. Am. Chem. Soc.*, **107**, 7072–76 (1985).
20. The condensation of (*S*)-**11** with the diol provides a greater proportion of C-equatorial isomer (**6T-a**) than does the analogous condensation with **8**. That the bulkier side chain produces more of the C-equatorial diastereomer provides further support for the stereochemical assignments.
21. These results provide further evidence that the lower homolog **1D-d** undergoes alkylation from the C-equatorial conformation ($\mathbf{1D_{eq}}$). Consistent with this interpretation is the observation that alkylation of the trimethyl derivative **5T-e**, in which the carbanion is fixed in the equatorial position, shows a slight selectivity (9% de) for the diastereomer corresponding to (4*R*,6*R*)-**4D-d**, i.e., asymmetric induction of the same relative sense.
22. R. O. Day, W. G. Bentrude, K. C. Yee, W. N. Setzer, J. A. Deiters and R. R. Holmes, *J. Am. Chem. Soc.*, **106**, 103–106 (1984); W. G. Bentrude, R. O. Day, J. M. Holmes, G. S. Quin, W. N. Setzer, A. E. Sopchik, R. R. Holmes, *ibid.*, **106**, 106–111 (1984); D. G. Gorenstein, R. Rowell, *ibid.*, **101**, 4925–28 (1979); M. G. B. Drew, J. Rogers, *Acta Cryst. Sect. B*, **28**, 924 (1972).
23. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923–25 (1978).
24. The benzaldehyde imines undergo some hydrolysis during chromatography, hence they were purified as quickly as possible.
25. P. L. Pickard and T. L. Tolbert, *Organic Syntheses, Coll. Vol. V*, 520 (1973).