133. Nucleophilic Additions to *N*-Glycosylnitrones

Part IV[1])

Asymmetric Synthesis of *N*-Hydroxy-α-aminophosphonic and α-Aminophosphonic Acids

by **Rolf Huber** and **Andrea Vasella***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH–8057 Zürich

(2.VI.87)

The addition of phosphite anions and of tris(trimethylsilyl)phosphite ($P(OSiMe_3)_3$) to *N*-glycosyl-*C*-arylnitrones was examined. While these nitrones proved inert towards the phosphite anions, they reacted with $P(OSiMe_3)_3$ under catalysis by *Lewis* acids. Thus, $P(OSiMe_3)_3$ reacted with the crystalline *(Z)*-*N*-glycosylnitrones **2** and **8** to give the optically active *N*-hydroxy-α-aminophosphonic acids **4** and **10**, respectively, and hence the α-aminophosphonic acids **5** and **11** in yields up to 92% and with an enantiomeric excess (e.e.) up to 97% *(Scheme 1)*. The absolute configuration of the phosphonates depend upon the nature and – in one case – upon the quantity of the catalyst *(Figure)*. Upon catalysis by $HClO_4$ or $Zn(OTf)_2$, $P(OSiMe_3)_3$ added to **2** to give, in both cases, the (+)-(*R*)-phenylphosphaglycine **5** (optical purity 79–84 and 90–93%, resp.). The optical purity (o.p.) was hardly influenced by the amount of these catalysts (0.02–1 equiv.). However, catalysis by $ZnCl_2$ gave, with trace quantities of the catalyst, (–)-(*S*)-**5** (o.p. 79%), while an equimolar amount of $ZnCl_2$ yielded (+)-(*R*)-**5** (o.p. 82%). The $HClO_4$-catalyzed addition of $P(OSiMe_3)_3$ to the nitrone **14** *(Scheme 2)* led to (+)-(*R*)-*N*-hydroxyphosphavaline **15** (78%) and hence to (–)-(*R*)-phosphavaline **16** (71% from **14**, e.e. 95%). Under conditions leading from the nitrones **2**, **8**, **14**, and **20** *(Schemes 1* and *2)* predominantly to (*R*)-α-aminophosphonic acids, the addition of $P(OSiMe_3)_3$ to nitrone **18**, possessing a benzyloxy substituent as an additional potential ligand for the catalyst, gave (*S*)-phosphaserine **19**. The addition of $P(OSiMe_3)_3$ to the nitrone **20**, catalyzed by $Zn(OTf)_2$, led to (+)-(*R*)-*N*-hydroxyphosphamethionine **21** (71%, e.e. 77%) and hence to (–)-(*R*)-phosphamethionine **22** (77% from **20**, e.e. 79%). Catalysis by trace quantities of $ZnCl_2$ gave (+)-(*S*)-**22** (85%, e.e. 61%). The enantiomerically pure aminophosphonic acids **5**, **11**, and **16** were obtained by recrystallization. The e.e. of the *N*-hydroxyaminosphosphonic acids **10**, **15**, and **21** and the aminophosphonic acids **5**, **11**, **16**, and **22** were determined by the HPLC analysis of the dimethyl *N*-naphthoyl-α-aminophosphonates **7**, **13**, **17**, and **23** on a chiral stationary phase.

1. Introduction. – The interest in enantiomerically pure α-aminophosphonic acids has grown with the exploration of their biological activity [4] and the awareness of their natural occurrence [5]. Both the resolution of racemates of α-aminophosphonic acids and their asymmetric syntheses have been reported ([3] [6] and lit. cit. there). We have described the asymmetric synthesis of some α-aminophosphonic acids by 1,3-dipolar cycloadditions of *N*-glycosyl-*C*-(dialkoxyphosphonoyl)nitrones [7] and by nucleophilic addition of lithium dialkyl phosphites to the *N*-glycosyl-*C*-alkylnitrones ([2] [3], *e.g.* **14** and **18** in *Scheme 2*). The nucleophilic additions proceed with a high degree of diastereoselectivity, according to the prediction of our hypothesis based upon a 'kinetic anomeric effect' ([3] [8]).

[1]) Part III, see [1]; part II, see [2]; part I, see [3].

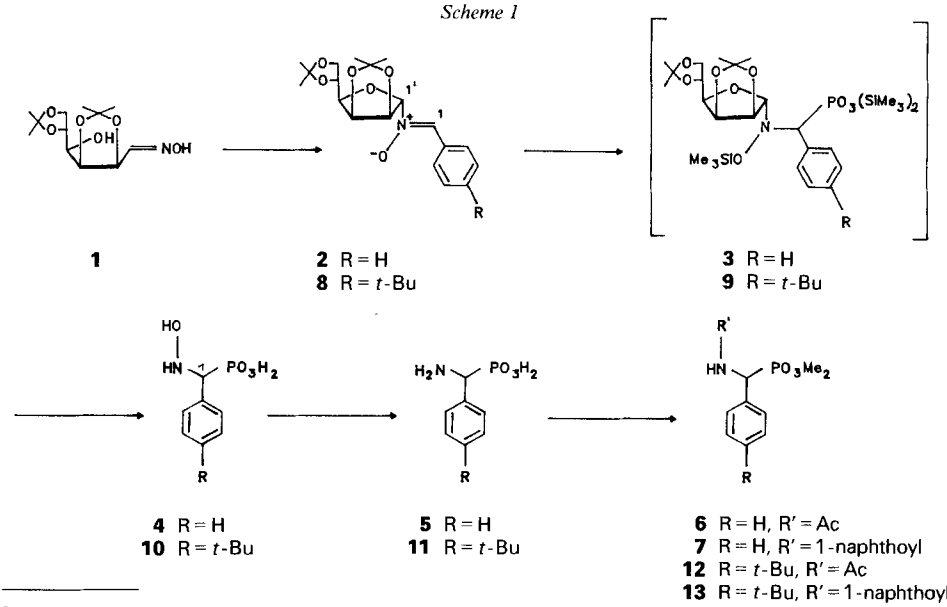
As reported in preliminary form [2], the *N*-glycosyl-*C*-arylnitrones **2** and **8** *(Scheme 1)* did not react with dialkyl phosphite anions. The $ZnCl_2$- or $HClO_4$-catalyzed additions of tris(trimethylsilyl) phosphite ($P(OSiMe_3)_3$) [9][2]) to **2** and to **8,** however, proceeded smoothly. The expected products **3** and **9** were not isolated but transformed into the *N*-hydroxy-α-aminophosphonic acids **4** and **10** and then into the α-aminophosphonic acids **5** [11] and **11,** respectively.

Whilst the enantiomeric excess (e.e.) of phenylphosphaglycine[3]) **5** could be determined by an HPLC analysis of the corresponding *N*-acetylphosphonate **6,** the e.e. of the substituted phenylphosphaglycine **11** could not be determined exactly. The enantiomers of the corresponding *N*-acetylphosphonate **12** were only partially separated by HPLC using a 'chiral column' according to *Pirkle* [12], and the specific rotation of **11** is unknown.

We now report the results of a more detailed examination of the influence of the catalyst upon the diastereoselectivity of the $P(OSiMe_3)_3$ addition to **2, 8,** and to other nitrones. We also describe the synthesis of the enantiomerically highly enriched *N*-hydroxy-α-aminophosphonic acids (*R*)- and (*S*)-**4,** (*R*)-**10,** (*R*)-**15,** and (*R*)-**21,** and of the enantiomerically pure (*R*)-α-aminophosphonic acids **5, 11,** and **16,** and **22** *(Schemes 1* and *2)*. The enantiomeric excess of the *N*-hydroxy-α-aminophosphonic and the α-aminophosphonic acids was determined by HPLC analysis of the dimethyl *N*-naphthoyl-α-aminophosphonates.

2. Results. – *Influence of the Catalyst upon the Addition of $P(OSiMe_3)_3$ to* **2**: N-*Hydroxyphenylphosphaglycine* **4** *and Phenylphosphaglycine* **5.** The crystalline nitrone **2** was

Scheme 1



1

2 R = H
8 R = *t*-Bu

3 R = H
9 R = *t*-Bu

4 R = H
10 R = *t*-Bu

5 R = H
11 R = *t*-Bu

6 R = H, R' = Ac
7 R = H, R' = 1-naphthoyl
12 R = *t*-Bu, R' = Ac
13 R = *t*-Bu, R' = 1-naphthoyl

[2]) $P(OSiMe_3)_3$ is known to add to *N*-benzylbenzylimine [10].

[3]) α-Aminophosphonic acids are named by 'replacement' nomenclature to stress their relationship to common α-amino acids; *e.g.* for 'phenylphosphaglycine', the COOH group of 'phenylglycine' has been replaced by the PO_3H_2 group. For systematic names, see *Exper. Part.*

Table 1. *Characteristic NMR Data of* N*-Hydroxy-α-aminophosphonic and α-Aminophosphonic Acids in NaOD/D_2O* (pH *ca.* 10)

		^{1}H-NMR: H–C(1)		^{13}C-NMR: C(1)		^{31}P-NMR
		J(H,P) [Hz]	δ [ppm]	*J*(C,P) [Hz]	δ [ppm]	δ [ppm]
4 R = C_6H_5	X = OH	18.8	4.30	123.3	68.6	12.8
5 R = C_6H_5	X = H	15.6[a])	3.81[a])	130.8	56.5	18.9[b])
10 R = *p*-(*t*-Bu)C_6H_4	X = OH	18.3	4.15	123.6	68.1	13.0
11 R = *p*-(*t*-Bu)C_6H_4	X = H	15.1	3.79	131.3	56.2	19.0
15 R = $(CH_3)_2CH$	X = OH	12.0	2.69	127.8	68.0	18.8
16 R = $(CH_3)_2CH$	X = H	12.5	2.42	136.9	56.7	21.9[c])
21 R = $MeS(CH_2)_2$	X = OH	12.9	2.95	132.7	60.5	17.1
22 R = $MeS(CH_2)_2$	X = H	–	2.75[d])	142.3	50.3	21.5

[a]) [19]: 4.0 ppm (*d*, *J* = 16 Hz) in $NaOD/D_2O$.
[b]) [20]: 17.9 ppm in 2M NaOD.
[c]) [20]: 21.0 ppm in 2M NaOD.
[d]) [21]: 3.44 ppm (*m*, 1 H) in D_2O.

obtained from the oxime **1** and benzaldehyde *(Scheme 1)* as a single diastereoisomer (78.9%). The expected (*Z*)-configuration [13] was confirmed by a strong (20%) nuclear *Overhauser* effect (NOE) between H–C(1) and H–C(1'). A similar NOE has been observed for the alkylnitrones **14** and **18** (see below, *Scheme 2*) [3].

A solution of **2** and $P(OSiMe_3)_3$ in CH_2Cl_2/benzene was treated at −50° with 70% $HClO_4$ (0.14 equiv.) to give the *bona fide* addition product **3** which was directly hydrolyzed with 1M HCl in MeOH (r.t., 2 h) to the crystalline (+)-(*R*)-*N*-hydroxyphenylphosphaglycine (+)-(*R*)-**4** (76.7%). The characteristic NMR data of (+)-(*R*)-**4** and other *N*-hydroxy-α-amino- and α-aminophosphonic acids are given in *Table 1*. The optical purity (o.p.) of (+)-(*R*)-**4** (87.5%) was inferred from the o.p. of (+)-(*R*)-**5** (see below)[4]). One recrystallization of (+)-(*R*)-**4** increased the o.p. to 94.8%. The *N*-hydroxy-α-aminophosphonic acid (+)-(*R*)-**4** is sparingly soluble in DMF, DMSO, pyridine, H_2O, and AcOH. It was decomposed by alkali already at pH 8–9 (r.t.) and showed a positive *Fehling* test at r.t.[5]). A solution of the product obtained after chromatography of (+)-(*R*)-**4** on *Dowex 50* (H^+) decomposed during evaporation of the solvent with the concomitant formation of benzaldehyde. Hydrogenation ($Pd(OH)_2/C$, 0.5M HCl in MeOH, 18 h) of a crystallized sample of (+)-(*R*)-**4** gave (*R*)-(=L)-phenylphosphaglycine (+)-(*R*)-**5** (90.9%) with an o.p. of 87.7%. Repeated crystallization from H_2O/EtOH gave enantiomerically pure (+)-(*R*)-**5** (63%). The e.e. was determined by HPLC analysis of the dimethyl naphthoyl derivative (+)-(*R*)-**7** (see below) and confirmed by the specific rotation of (+)-(*R*)-**5**.

The (*S*)-enantiomer of *N*-hydroxyphenylphosphaglycine, (−)-(*S*)-**4** (o.p. 88%), was obtained spectroscopically pure in 91.9% yield from the reaction of the nitrone **2** with $P(OSiMe_3)_3$ under catalysis by $ZnCl_2$ (0.01 equiv.) in refluxing benzene (16 h), followed by

[4]) Based on $[\alpha]_D^{20} = 19.4°$ for optically pure (+)-(*R*)-**5** ([14] [15]).
[5]) A similar behaviour has been described for *N*-hydroxy-α-aminocarboxylic acids [16]. These compounds are reported to be unstable [17] [18] and to disproportionate into the corresponding α-amino acid and α-ketoacid oxime when refluxed under N_2 [19].

hydrolysis and precipitation (H_2O). Hydrogenation in the presence of 20% $Pd(OH)_2/C$ of a suspension of (−)-(*S*)-**4** in aq. 1M HCl gave crystalline (*S*)-(=D)-phenylphosphaglycine (−)-(*S*)-**5** (o.p. 88.7%) in 75.4% yield. Chromatography on *Dowex 50* (H^+) of the mother liquor gave further (−)-(*S*)-**5** (o.p. 46.4%).

We next examined the dependence of the diastereoselectivity of the addition of $P(OSiMe_3)_3$ to the nitrone **2** on the nature and amount of the catalyst and the solvent. The diastereoisomeric excess (d.e.) of the addition was again inferred from the o.p. of phenylphosphaglycine **5** *(Figure)* into which **2** was transformed without isolation of either the addition product **3** or the *N*-hydroxy-α-aminophosphonic acid **4**; **5** was purified by chromatography (H_2O) on *Dowex 50* (H^+) without crystallization, collecting all relevant fractions [23][6]). Traces of $ZnCl_2$ (0.01 equiv.) in boiling benzene led to (−)-(*S*)-**5** (o.p. 78.9%)[6]); but increasing amounts of $ZnCl_2$ led first to a lower diastereoselectivity until, in the presence of 0.18 equiv. of $ZnCl_2$, an almost racemic mixture was obtained *(Figure)*. In the presence of *ca.* 1 equiv. of $ZnCl_2$[7]) in benzene at r.t., the enantiomeric (+)-(*R*)-**5** was produced with an o.p. of 82.5%[6]). A similar dependence of the diastereoselectivity upon the amount of $ZnCl_2$ was observed in THF solution. The best (*R*)-selectivity (o.p. of (+)-(*R*)-**5** 91.3%[6]), e.e. of the corresponding sample of (+)-(*R*)-**7** 97%) was obtained in the presence of zinc bis(trifluoromethanesulfonate) ($Zn(OTf)_2$) in THF at −40°. In this case, the diastereoselectivity hardly depended upon the amount of the catalyst *(Figure)*. A very weak dependence of the diastereoselectivity

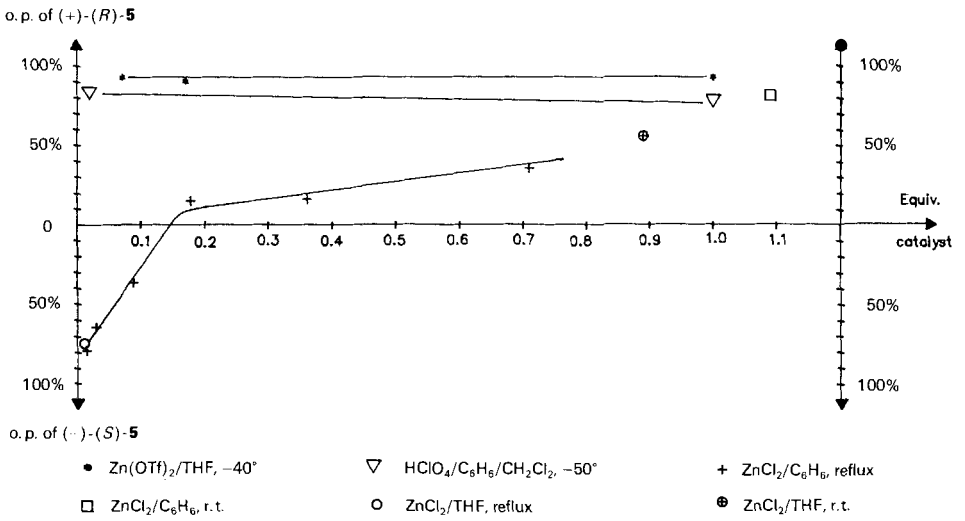


Figure. *The dependence of the diastereoisomeric excess of the $P(OSiMe_3)_3$ addition to the nitrone* **2** *upon nature and amount of the catalyst deduced from the o.p. of phenylphosphaglycine* **5**. See *Scheme 1* and *Table 3 (Exper. Part)*.

[6]) Chromatographed *(Dowex)* **5** still contained impurities (salts?). If this material was crystallized, its o.p. and the e.e. of its naphthoyl derivative **7** (see below) agreed within a limit of 1%. If crystallization was omitted, the e.e. of **7** obtained from such a sample was consistingly 3–6% higher then the o.p. of **5**.

[7]) In this case, $ZnCl_2$ was not completely dissolved in the reaction mixture. The undissolved $ZnCl_2$ might influence the diastereoselectivity; *Berlan et al.* [24] described different diastereoselectivities for the addition of dissolved or partially dissolved lithium dimethylcuprates to unsaturated oxazolidines.

upon the amount of the catalyst was also observed for $HClO_4$ *(Figure)*. No reaction occurred between $P(OSiMe_3)_3$ and **2** in the presence of fluoride (tris(dimethylamino)sulfonium difluorotrimethylsilicate [25] or tetrabutylammonium fluoride).

One of the factors responsible for the dependence of the diastereoselectivity upon the catalyst may be a stabilisation of different conformers of the nitrone (obtained by rotation around the C(1')–N bond) by selective complexation. One would then expect a similar behaviour for the aryl nitrones **2** and **8** *(Scheme 1)* and the alkyl nitrone **14** (see below, *Scheme 2*), while the alkylnitrone **18** (see below, *Scheme 2*) may behave differently, since the C-substituent of the nitrone may participate in the complexation of the catalyst.

Addition of $P(OSiMe_3)_3$ to **8**: N-*Hydroxy-[4-(*tert-*butyl)phenyl]phosphaglycine* **10** *and [4-(*tert-*Butyl)phenyl]phosphaglycine* **11**. The nitrone **8** *(Scheme 1)* was obtained from *4-(tert*-butyl)benzaldehyde[8]) and **1** as a crystalline, diastereoisomerically pure (^{13}C-, ^1H-NMR) compound (70.6%). The (*Z*)-configuration was assumed based upon the analogy with **2**.

The $HClO_4$-catalyzed addition of $P(OSiMe)_3$ to **8** in CH_2Cl_2/benzene at −50° gave after hydrolysis (1M HCl in MeOH, r.t., 2 h) and precipitation, the *N*-hydroxy-α-aminophosphonic acid (+)-(*R*)-**10** (82%), with an e.e. of 90.2%[9]). Hydrogenation of (+)-(*R*)-**10** (20% $Pd(OH)_2$ in 1M HCl in MeOH, 16 h) gave, after two recrystallizations, enantiomerically pure[9]) [4-(*tert*-butyl)phenyl]phosphaglycine (+)-(*R*)-**11** in 55% yield. Hydrogenation of a sample of not precipitated (+)-(*R*)-**10**, followed by chromatography (1M HCO_2H) on *Dowex 50* (H^+), gave (+)-(*R*)-**11** with an e.e. of 90.7%[9]). We have taken this value as a measure for the diastereoselectivity of the $P(OSiMe_3)_3$ addition. The yield of (+)-(*R*)-**11** was 85% after crystallization.

The $ZnCl_2$(0.02 equiv.)-catalyzed $P(OSiMe_3)_3$ addition to **8** (benzene, reflux, 18 h), followed by hydrolysis and hydrogenolysis, gave the enantiomer (−)-(*S*)-**11** (82%) with an e.e. of 74.7%[9]). As expected, the nitrone **2** and **8** behave very similarly in these additions.

The assignment of the absolute configuration of [4-(*tert*-butyl)phenyl]phosphaglycine **11** is based upon a comparison of its specific rotation with the one of the structurally related phenylphosphaglycine **5** of known absolute configuration [26]. This assignment accords with *Pirkle*'s chiral recognition model [12] as applied to the relative retention times of the enantiomers of the naphthoyl derivative **13**. According to this model, enantiomeric pairs of structurally similar compounds show the same relative retention times on a 'chiral column'. The presumed (*R*)-enantiomer of **11** shows the same relative retention times as (+)-(*R*)-**7** and (−)-(*R*)-**17**.

Addition of $P(OSiMe_3)_3$ to **14**: N-*Hydroxyphosphavaline* **15** *and Phosphavaline* **16**. The $HClO_4$-catalyzed $P(OSiMe_3)_3$ addition to the nitrone **14** [3] *(Scheme 2)* gave, after hydrolysis, crystalline *N*-hydroxyphosphavaline (+)-(*R*)-**15** (77.7%). Hydrogenation of crude (+)-(*R*)-**15** gave the (*R*)-configurated phosphavaline (−)-(*R*)-**16**[10]) (71%) with an e.e. of 95.4%[9]). Two recrystallizations from H_2O/EtOH gave enantiomerically pure (−)-(*R*)-**16**[9]). Catalysis by $ZnCl_2$ (0.01 equiv.) led to (+)-(*S*)-**16** (85.4%, e.e. 43.8%[9])).

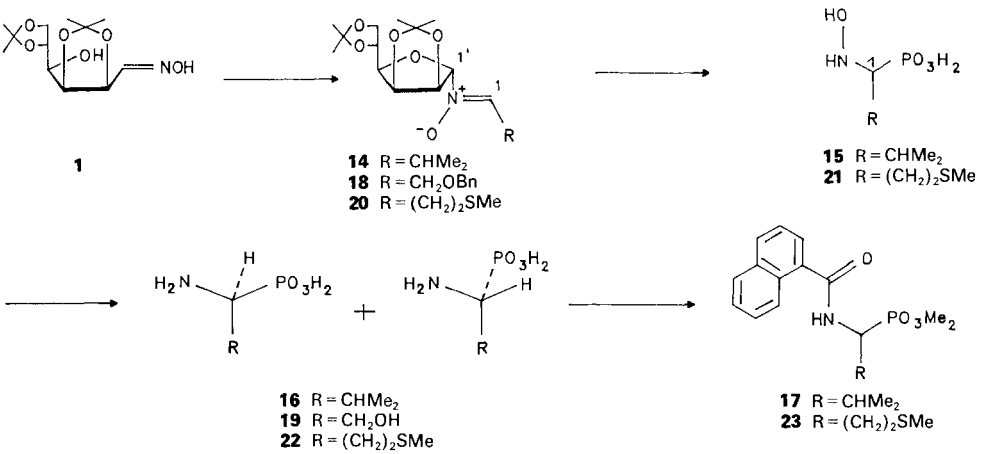
---

[8]) We thank Dr. *G. Fráter, Givaudan AG*, Dübendorf, for a generous gift of this aldehyde.

[9]) The e.e. was determined by the HPLC analysis of the corresponding dimethyl *N*-naphthoyl-α-aminophosphonate (no isolation of intermediates, see below).

[10]) For the analogous preparation of optically pure (+)-(*S*)-**16** and (+)-(*S*)-**19**, see [3].

Scheme 2



Addition of P(OSiMe$_3$)$_3$ to **18**: *Phosphaserine* **19**. The $HClO_4$-catalyzed $P(OSiMe_3)_3$ addition to the nitrone **18** (*Scheme 2*) led, with low selectivity (o.p. 30%)[11]), to phosphaserine (+)-(*S*)-**19**[10]) (81.6%). The $HClO_4$-catalyzed $P(OSiMe_3)_3$ additions to all the other nitrones which have been examined so far led predominantly to (*R*)-aminophosphonic acids, indicating the expected influence of the benzyloxy substituent in **18** on the diastereoselectivity. A nearly racemic mixture of (+)-(*S*)-**19** (88%, o.p. 2%) was obtained in the presence of equimolar amounts of $ZnCl_2$. The best (*S*)-selectivity (trace quantities of $ZnCl_2$) led to (+)-(*S*)-**19** (90%) with an o.p. of 87.7%. Weakly enriched (–)-(*R*)-**19** (83.3%, o.p. 17%) resulted upon catalysis by $Zn(OTf)_2$ (1 equiv., not completely dissolved) in THF. The uncatalyzed addition of $P(OSiMe_3)_3$ (r.t., C_6H_6) led to (+)-(*S*)-**19** (72.9%, o.p. 66%). In all these cases, yields and optical purity refer to spectroscopically homogeneous material which was purified by chromatography.

Addition of P(OSiMe$_3$)$_3$ to **20**: N-*Hydroxyphosphamethionine* **21** *and Phosphamethionine* **22**. Condensation of the oxime **1** and 3-(methylthio)propanal in boiling $CHCl_3$ gave the crystalline nitrone **20** (50%, *Scheme 2*) which decomposed in contact with silica gel. The diastereoisomeric purity of **20** was confirmed by its ^{1}H-NMR spectrum (single *t* (J = 5.5 Hz) at 7.05 ppm for H–C(1) and *s* for H–C(1') at 5.32 ppm). Only one signal was found in the ^{13}C-NMR spectrum for C(1) and C(1') at 136.6 and 102.2 ppm, respectively.

The addition of $P(OSiMe_3)_3$ to a THF solution of **20** in the presence of 0.03 equiv. of $Zn(OTf)_2$ at –40°, followed by hydrolysis and precipitation (H_2O), gave the *N*-hydroxy-α-aminophosphonic acid (+)-(*R*)-**21** with a low specific rotation (+0.8° in 1M NaOH). Hydrogenation of precipitated (+)-(*R*)-**21** gave phosphamethionine (–)-(*R*)-**22**[12]) in 87.8% yield, with an e.e. of 76.8%[9]), after chromatography (H_2O) on *Dowex 50* (H^+) and lyophilisation. Hydrogenation of not isolated (not precipitated) (+)-(*R*)-**21** gave (–)-(*R*)-

[11]) Based upon $[\alpha]_D^{25} = 30°$ (c = 1.0, H_2O) for optically pure (+)-(*S*)-**19** [3].

[12]) The assignment of the absolute configuration is again based on *Pirkle*'s chiral recognition model. The assignment is in agreement with the proposal of *Kupczyk-Subotkowska* and *Mastalerz* [27] who obtained optically pure (–)-(*S*)-**21** ([α] = –40.4°, c = 1.0, 0.25M NaOH) by the resolution of the enantiomers and examined the chromatographic behaviour on silica gel of diastereoisomeric dipeptides, obtained from (–)-(*S*)-**21**.

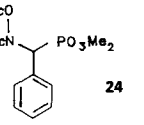
22 in 76.7% yield (from **20**) with an e.e. of 78.5%[9]). Crystallization (H_2O/EtOH) of (−)-(*R*)-**22** decreased the o.p.

The $HClO_4$- and $ZnCl_2$(1 equiv.)-catalyzed $P(OSiMe_3)_3$ addition to **20** led to (−)-(*R*)-**22** with lower e.e. (44.9% and 39.4%, resp.), whereas small amounts of $ZnCl_2$ (0.01 equiv.) led to (+)-(*S*)-**22** in 85% yield with an e.e. of 60.8%[9]).

Determination of the Enantiomeric Purity of Aminophosphonic Acids (HPLC). The diastereoisomeric excess (d.e.) of the $P(OSiMe_3)_3$ addition to the nitrone **8** could not be derived from the ^{31}P-NMR spectrum of the concentrated reaction mixture containing the product **9**. The specific rotation of the enantiomers of [4-(*tert*-butyl)phenyl]-phosphaglycine **11** is not known, and the enantiomeric acetyl derivatives (*R*)- and (*S*)-**12** were not base-line separated on a 'π-complex-hydrogen bonding' chiral stationary phase introduced by *Pirkle et al.* [12][13]). Enantiomeric dimethyl *N*-naphthoyl-α-amino-phosphonates, however, were in general well separated on this chiral stationary phase. These derivatives were prepared by silylation and acylation [28] of the aminophosphonic acids, followed by esterification (CH_2N_2). In this way, **7** (79%), **13** (81%), **17** (89%), and **23** (86%) were obtained from the racemic aminophosphonic acids **5** [21], **11**, **16** [21], and **22** [22] (*Schemes 1* and *2*). The e.e. of the non-racemic mixtures of aminophosphonic acids was determined by the HPLC analysis of the corresponding dimethyl *N*-naphthoyl-α-aminophosphonates which were prepared without isolation of the intermediates and by collecting all relevant fractions [23] after chromatography on silica[14]).

3. Discussion. – Factors determining the diastereoselectivity of the $P(OSiMe_3)_3$ addition are: (*i*) (E/Z) *equilibration of the nitrones.* No indication (^{1}H-NMR, TLC) for an equilibration was observed.

(*ii*) *Equilibrium of the conformers obtained by rotation around the C(1′)−N bond.* In the 1,3 dipolar cycloaddition [8] [1] of *N*-glycosylnitrones [3] [1], a specific conformation ('O-*endo*' conformation, *Scheme 2* in [3]) appears to be the most reactive one. This conformation has also been found for the nitrone **18** in the solid state and for the nitrones **2** and **18** in solution (NOE, $CDCl_3$, r.t.). It appears likely that the conformational equilibrium is influenced by the catalyst[15]). The addition of $ZnCl_2$ (*ca.* 0.4 equiv.) to a solution (C_6D_6) of the nitrone **2** increases the chemical shifts of H−C(1) (0.35 ppm), H−C(1′) (0.28 ppm), H−C(2′) (0.53 ppm), H−C(3′) (0.23 ppm), and H−C(4′) (0.09 ppm),



24

[13]) The determination of the diastereoselectivity of the $P(OSiMe_3)_3$ addition with the help of the *N,O*-diacetylated phosphonate **24** failed, since **24** decomposed on the column.

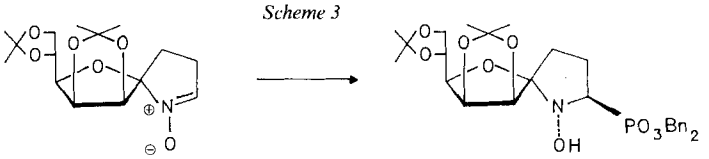
[14]) In the case of **17**, the first fraction of a chromatographed, non-racemic mixture (e.e. of the crude product 61.7%, e.e. of the chromatographed product 61.3%) contained an enantiomeric mixture with an e.e. of 79%, whilst the last fraction contained one with an e.e. of 57%.

[15]) *Helmchen et al.* [29] reported an asymmetric *Diels-Alder* reaction of the acrylate of (*S*)-ethyl lactate and cyclopentadiene (or isoprene) showing a diastereofacial selectivity of the dienophile, depending on the type of catalyst ($TiCl_4$ or $EtAlCl_2$) and the ratio of the catalyst to the acrylate. They isolated a 1:1 chelate complex of the acrylate with $TiCl_4$ and established its structure by X-ray analysis. The Ti-ion is coordinated to both carbonyl O-atoms favouring a synperiplanar conformation of the enoate group. In the presence of $EtAlCl_2$ which is expected to coordinate with a single carbonyl group, an antiperiplanar conformation of the enoate group was postulated. *Bloch* and *Gilbert* [30] reported a diastereofacial selectivity depending on the solvent (THF or Et_2O) in the addition of alkylmagnesium bromides to a chiral aldehyde (5-hydroxymethyl-7-oxa-bicyclo[2.2.1]hept-2-en-6-carbaldehyde).

respectively; the addition of $HClO_4$ (1 equiv.) to a $CDCl_3$ solution of **2** at −50° increases only the shifts of H–C(1) (0.63 ppm) and H–C(1′) (0.28 ppm). This indicates a complexation of $ZnCl_2$ with both the *N*-oxide function and O–C(2′) and a complexation of $HClO_4$ mainly with the *N*-oxide function. The results with the nitrone **18**, containing the benzyloxy substituent as an additional potential ligand, stresses the importance of chelation phenoma in determining the diastereoselectivity of the addition reactions. However, the conformational equilibrium may not only be influenced by chelation, but also by the greater steric demand of the complexed O-atom of the nitrone function.

(*iii*) *The direction of attack of the nucleophile.* The high diastereoselectivity of the addition of lithium dialkyl phosphites to the *N*-glycosyl-*C*-alkylnitrones **14** and **18** [3] was rationalized with the postulate of a 'kinetic anomeric effect' ([3] [8]). These nitrones are conformationally flexible (rotation around the C(1′)–N bond). The direction of attack of the nucleophile relative to the C(1′)–OC(4′) bond has been studied for the addition of lithium dibenzyl phosphite to the conformationally defined (*E*)-spironitrone **25** [1] *(Scheme 3)*. The phosphite added exclusively from the side opposite to the C(1′)–OC(4′)

Scheme 3



25 **26**

bond leading to the (*R*)-configurated phosphonate **26**. The analogous direction of attack of phosphites to the *si*-side of the 'O-*endo*' conformers of the conformationally flexible (*Z*)-*N*-glycosylnitrones **2**, **8**, **14**, **18**, and **20** should lead to (*S*)-configurated aminophosphonic acids. This was found to be the case for the addition of lithium dialkyl phophites to the nitrones **14** and **18** and for the uncatalyzed addition of $P(OSiMe_3)_3$ to the nitrone **18** *(Scheme 2, Table 2)*; catalysis by trace quantities of $ZnCl_2$ gave also the (*S*)-configurated aminophosphonic acids.

The (*R*)-enantiomers *(Table 2)* were obtained from the addition of $P(OSiMe_3)_3$ to the nitrones **2**, **8**, **14**, and **20** upon catalysis by $HClO_4$ and $Zn(TfO)_2$ (rather independently of the concentration of the catalyst, see the *Figure*) or in the presence of equimolar $ZnCl_2$. In

Table 2. *Relation between the Absolute Configuration of the Predominant Aminophosphonates and the Catalyst Used in the $P(OSiMe_3)_3$ Addition*

Catalyst	Nitrone				
	2	**8**	**14**	**18**	**20**
$HClO_4$	*R*	*R*	*R*	*S*	*R*
$Zn(TfO)_2$	*R*	–	–	*R*[c])	*R*
$ZnCl_2$ (1 equiv.)	*R*	–	–	*S*[d])	–
$ZnCl_2$ (*ca.* 0.01 equiv.)	*S*	*S*	*S*	*S*	*S*
–	–[a])	–[a])	–[b])	*S*	–

[a]) No $P(OSiMe_3)_3$ addition was observed in boiling benzene (48 h).
[b]) The nitrone decomposed.
[c]) Very low selectivity (17%).
[d]) Very low selectivity (2%).

this case, the nucleophile attacked on the *re*-side of the nitrone function; the change of the direction of attack might originate from the influence of the catalyst on the equilibrium of the conformers and/or the influence of the catalyst on the direction of attack of the nucleophile.

We thank the *Swiss National Science Foundation*, *Sandoz AG*, Basel, and *Givaudan AG*, Dübendorf, for generous support.

Experimental Part

General. See [3]. $ZnCl_2$ was slowly melted in the reaction flask under high vacuum (h.v.). $Zn(OTf)_2$ was dried over P_2O_5 under h.v. Methanolic HCl (1M) was prepared by diluting a 32% aq. HCl soln. (114 ml) with MeOH to 1 l. For chromatography, the mixtures *A* (BuOH/EtOH/NH_3/H_2O 3:3:3:1) and *B* (CH_2Cl_2/AcOEt) were used. TLC: *N*-hydroxy-α-aminophosphonic acids were revealed by spraying the plates with *Ehrlich*'s reagent or $KMnO_4$ soln. (0.5 g in 100 ml 1M NaOH). HPLC: the chiral stationary phase consists of (*R*)-dinitrobenzoylphenylglycine (DBPNG) covalently bonded to silica gel (5 μ, column size 250 × 21.2 mm); the integrals of the peaks of pairs of enantiomers are given in brackets behind the retention times. FC = flash chromatography.

1. N-*(2,3:5,6-Di-*O*-isopropylidene-*α*-*D*-mannofuranosyl)phenylmethanimine* N-*Oxide* (**2**). To a soln. of **1** (8.1 g, 30 mmol) in CH_2Cl_2 (300 ml) was added benzaldehyde (6.3 g, 60 mmol), $TsOH \cdot H_2O$ (20 mg), and $MgSO_4$ (1.0 g). The suspension was vigorously stirred at r.t. for 26 h, neutralized (0.5 g of $NaHCO_3$), filtered, and evaporated. Crystallization from AcOEt (80 ml)/hexane (160 ml) at 0° gave **2** (8.6 g, 78.9%). M.p. 182–183°. R_f (hexane/AcOEt 1:1) 0.4 $[\alpha]_D^{25} = +66.4°$ (*c* = 1.9, $CHCl_3$). UV (MeOH): 293 (19511). IR (KBr): 3085*w*, 3058*w*, 2985*m*, 2928*m*, 2885*m*, 1598*w*, 1581*m*, 1518*w*, 1498*w*, 1453*s*, 1441*m*, 1380*s*, 1370*s*, 1345*m*, 1332*m*, 1327*m*, 1318*m*, 1304*m*, 1281*m*, 1270*m*, 1260*m*, 1239*m*, 1210*s*, 1158*s*, 1148*s*, 1131*s*, 1113*s*, 1089*s*, 1074*s*, 1060*s*, 1055*s*, 1038*m*, 984*m*, 948*m*, 928*m*, 907*m*, 878*m*, 862*m*, 849*s*, 833*m*, 821*m*, 795*m*, 759*m*, 740*m*, 692*s*. ^{1}H-NMR: 8.25–8.23 (*m*, 2 H); 7.57 (*s*, H–C(1)); 7.47–7.43 (*m*, 3 H); 5.48 (*s*, H–C(1′)); 5.36 (*d*, *J* = 6.0, H–C(2′)); 5.01 (*dd*, *J* = 6.0, 4.0, H–C(3′)); 4.69 (*dd*, *J* = 7.2, 3.9, H–C(4′)); 4.44–4.39 (*m*, H–C(5′)); 4.16–4.09 (*m*, 2 H–C(6′)); 1.54 (*s*, CH_3); 1.47 (*s*, CH_3); 1.39 (*s*, CH_3); 1.38 (*s*, CH_3). ^{13}C-NMR: 133.1 (*d*); 131.0 (*d*); 129.5 (*s*); 128.9 (*d*); 128.6 (*d*); 113.2 (*s*); 109.3 (*s*); 103.4 (*d*); 85.6 (*d*); 84.5 (*d*); 80.3 (*d*); 73.2 (*d*); 66.5 (*t*); 26.8 (*q*); 26.0 (*q*); 25.2 (*q*); 24.4 (*q*). Anal. calc. for $C_{19}H_{25}NO_6$ (363.41): C 62.80, H 6.93, N 3.85; found: C 63.06, H 6.73, N 4.10.

2. N-*(2,3:5,6-Di-*O*-isopropylidene-*α*-*D*-mannofuranosyl)[4-(*tert*-butyl)phenyl]methanimine* N-*Oxide* (**8**). A soln. of **1** (2.75 g, 10 mmol) in 4-(*tert*-butyl)benzaldehyde (7 ml) was treated with neutral Al_2O_3 (act. I, 700 mg) and stirred overnight at 90°. Filtration and removal of excess aldehyde (80°/10^{-5} Torr) gave an oil which was chromatographed (SiO_2, CH_2Cl_2 to *B* 17:3). Crystrallization (2 ×, hexane) gave **8** (2.96 g, 70.6%) which was stored at −20°. M.p. 92°. R_f (hexane/AcOEt 1:1) 0.54. $[\alpha]_D^{25} = +60.9°$ (*c* = 1.0, $CHCl_3$). UV (MeOH): 298 (24000). ^{1}H-NMR: 8.17 (*d*, *J* = 8.6, 2 H); 7.53 (*s*, H–C(1)); 7.45 (*d*, *J* = 8.7, 2 H); 5.46 (*s*, H–C(1′)); 5.35 (*d*, *J* = 5.9, H–C(2′)); 5.02 (*dd*, *J* = 5.9, 3.9, H–C(3′)); 4.69 (*dd*, *J* = 7.3, 3.9, H–C(4′)); 4.41 (*dt*, *J* = 7.5, 5.7, H–C(5′)); 4.12 (br. *d*, *J* ≈ 5.7, 2 H–C(6′)); 1.53 (*s*, CH_3); 1.46 (*s*, CH_3); 1.39 (*s*, CH_3); 1.38 (*s*, CH_3); 1.33 (*s*, CH_3). ^{13}C-NMR: 154.4 (*s*); 132.9 (*d*); 128.7 (*d*); 126.7 (*s*); 125.3 (*d*); 113.0 (*s*); 109.1 (*s*); 103.1 (*d*); 85.5 (*d*); 84.4 (*d*); 80.3 (*d*); 73.1 (*d*); 66.5 (*t*); 35.0 (*s*); 31.0 (*q*); 26.7 (*q*); 26.7 (*q*); 26.0 (*q*); 25.2 (*q*); 24.4 (*q*). Anal. calc. for $C_{23}H_{33}NO_6$ (419.52): C 65.85, H 7.93, N 3.34; found: C 65.69, H 7.99, N 3.16.

3. N-*(2,3:5,6-Di-*O*-isopropylidene-*α*-*D*-mannofuranosyl)-3-(methylthio)propanimine* N-*Oxide* (**20**). A soln. of **1** (956 mg, 5 mmol) and 3-(methylthio)propanal (0.6 ml, 6 mmol) in $CHCl_3$ (10 ml, filtered through acidic alox) was refluxed (5 min). $MgSO_4$ (2 g) was added and the suspension refluxed for 1 min. $NaHCO_3$ was added at r.t. and vigorously stirred (10 min). The solid was filtered off and the filtrate concentrated. The residue was dissolved in CH_2Cl_2 (0.2 ml), treated with Et_2O (2 ml) and hexane (15 ml), and left for 18 h at +4° yielding crystalline **20** (874 mg, 50%). M.p. 110–111° (sint.). R_f (AcOEt) 0.26. $[\alpha]_D^{25} = +39.8°$ (*c* = 1.0, $CHCl_3$). UV (cyclohexane): 246 (9194). IR (KBr): 3065*w*, 2995*s*, 2958*m*, 2940*m*, 2895*m*, 1592*m*, 1450*m*, 1425*m*, 1410*m*, 1389*m*, 1380*s*, 1370*s*, 1350*m*, 1338*w*, 1321*w*, 1305*m*, 1280*s*, 1265*m*, 1242*s*, 1210*s*, 1162*s*, 1142*s*, 1120*s*, 1095*s*, 1083*s*, 1070*s*, 1060*s*, 1050*s*, 1030*s*, 985*m*, 960*m*, 934*m*, 904*m*, 878*m*, 868*s*, 832*s*, 823*m*, 815*m*, 794*m*, 780*m*, 735*m*. ^{1}H-NMR: 7.05 (*t*, *J* = 5.5, H–C(1)); 5.32 (*s*, H–C(1′)); 5.25 (*d*, *J* = 6.1, H–C(2′)); 4.94 (*dd*, *J* = 5.9, 3.9, H–C(3′)); 4.57 (*dd*, *J* = 7.4, 3.9, H–C(4′)); 4.38 (br. *dt*, *J* = 7.2, 5.5, H–C(5′)); 4.2–4.0 (*m*, 2 H–C(6′)); 2.84–2.68 (*m*, 2 H–C(2), 2 H–C(3)); 2.13 (*s*, CH_3S);

1.51 (*s*, CH_3); 1.45 (*s*, CH_3); 1.38 (*s*, CH_3); 1.36 (*s*, CH_3). ^{13}C-NMR: 136.6 (*d*); 113.2 (*s*); 109.3 (*s*); 102.2 (*d*); 85.4 (*d*); 84.4 (*d*); 80.2 (*d*); 73.1 (*d*); 66.5 (*t*); 29.6 (*t*); 26.7 (*q*); 26.0 (*q*); 25.5 (*t*); 24.4 (*q*); 15.1 (*q*). Anal. calc. for $C_{16}H_{27}NO_6S$ (361.46): C 53.17, H 7.53, N 3.88; found: C 53.18, H 7.45, N 3.93.

4. *General Procedures for the Preparation of* N-*Hydroxy-α-aminophosphonic and α-Aminophosphonic Acids.* 4.1. The nitrone in the appropriate solvent (0.166M soln.) was treated at the mentioned temp. sequentially with $P(OSiMe_3)_3$ (2 equiv.) and the catalyst. After completion of the reaction, the solvent was removed, the crude product dissolved (2 ×) in MeOH and evaporated, and then treated with 1M HCl in MeOH (5 ml/mmol nitrone) at r.t. for 2 h. Crystallization or precipitation (H_2O) gave the *N*-hydroxy-α-aminophosphonic acids. MeOH (5 ml/mmol nitrone) and 20% $Pd(OH)_2/C$ (120 mg/mmol nitrone) were added to the soln. of the crude *N*-hydroxy-α-aminophosphonic acid, followed by hydrogenation (14–18 h). Filtration (MeOH) through *Celite* and evaporation gave the crude α-aminophosphonic acid which was chromatographed on *Dowex 50* (H^+), lyophilized, and dried over P_2O_5 under h. v.

4.2. The above procedure was modified in that the catalyst was dissolved by adding a soln. of the nitrone (refluxing if necessary) and then treated with $P(OSiMe_3)_3$.

The conditions for investigation of the dependence of the diastereoselectivity in the addition of $P(OSiMe_3)_3$ to **2** are given in *Table 3* (see the *Figure*).

Table 3. *Reaction Conditions of the P(SiOMe$_3$)$_3$ Addition to* **2** (150 mg, 413 μmol, see *Exper. 4.1* and *4.2*), *and Yield and Specific Rotation of the Resulting* **5**. See the *Figure*.

Catalyst	Solvent	Temp.	Time	Yield of **5**	$[\alpha]_D^{20}$ of **5** (c = 1.0–1.2 1M NaOH)
$HClO_4$ (1μmol; 11.6 μmol)	C_6H_6/CH_2Cl_2	−48°	5 min	90.3%	+16.3°
$HClO_4$ (36 μmol; 413 μmol)	C_6H_6/CH_2Cl_2	−48°	5 min	91.8%	+15.6°
$ZnCl_2$ (0.8 mg, 6 μmol)	C_6H_6	reflux	16 h	74.0%	−15.3°
$ZnCl_2$ (1.7 mg, 12.5 μmol)	C_6H_6	reflux	16 h	75.6%	−12.4°
$ZnCl_2$ (5.0 mg, 37 μmol)	C_6H_6	reflux	16 h	75.2%	−7.0°
$ZnCl_2$ (10 mg, 73 μmol)	C_6H_6	reflux	16 h	88.6%	+2.8°
$ZnCl_2$ (20 mg, 147 μmol)	C_6H_6	reflux	2 h	80.0%	+3.2°
$ZnCl_2$ (40 mg, 293 μmol)	C_6H_6	reflux	90 min	78.5%	+7.0°
$ZnCl_2$ (62 mg, 450 μmol)[a])	C_6H_6	r.t.	30 min	89.3%	+16.0°
1.84 mM $ZnCl_2$/THF soln. (2.5 ml)		reflux	29 h	85.4%	−14.5°
147 mM $ZnCl_2$/THF soln. (2.5 ml)		r.t.	16 h	75.3%	+10.9°
13 mM $Zn(OTf)_2$/THF soln. (2.5 ml)		−40°	16 h	65.0%	+18.0°
28 mM $Zn(OTf)_2$/THF soln. (2.5 ml)		−40°	4 h	72.9%	+17.6°
$Zn(OTf)_2$ (75 mg, 413 μmol)[b])	THF	−40°	20 min	85.0%	+18.1°
sat. $Zn(OTf)_2/C_6H_6$ soln. (2.5 ml)		r.t.	17 h	83.4%	+16.2°

[a]) Not completely dissolved.
[b]) Completely dissolved during the reaction.

5. *(+)-(*R*)- and (−)-(*S*)-[(Hydroxyamino)(phenyl)methyl]phosphonic Acid* ((+)-(*R*)- and (−)-(*S*)-**4**, resp.). (+)-(*R*)-**4**: According to *4.1*, with **2** (1.00 g, 2.87 mmol), $P(OSiMe_3)_3$ (2 ml, 6.4 mmol), CH_2Cl_2 (7.5 ml)/C_6H_6 (7.5 ml), and 70% $HClO_4$ soln. (36 μl, 0.4 mmol) at −50° for 5 min. The crude **3** was transformed into **4** which was dissolved in 2% aq. NH_3 soln., acidified with 2N HCl to pH 1, and left at r.t. for 16 h. The precipitate was filtered off and washed with H_2O (3 × 5 ml) and CH_2Cl_2 (3 × 5 ml) yielding (+)-(*R*)-**4** (448 mg, 76.7%). An anal. sample was obtained by dissolving **4** in 2N NaOH, acidifying with 2N HCl to pH 1, and crystallization. M.p. 182° (sint.) −190° (dec.). R_f (*A*) 0.34. $[\alpha]_D^{25}$ = +56.0° (*c* = 1.1, 1M NaOH); 60.7° (*c* = 1.2, 1M NaOH), after recrystallization. IR (KBr): 3600–3300*m*, 3300–2200*s*, 1632*s*, 1500*s* (br.), 1455*m*, 1305*w*, 1280*m*, 1237*s*, 1224*s*, 1180*s*, 1160*s*, 1138*s*, 1073*s*, 1030*s*, 1020*s*, 1005*s*, 991*s*, 932*s*, 915*m*, 786*w*, 745*w*, 732*w*, 694*s*. ^{1}H-NMR (ND_3/D_2O): 7.5–7.3 (*m*, Ph); 4.3 (*d*, *J*(H,P) = 18.8, H–C(1)). ^{13}C-NMR (DCl/D_2O): 135.6 (*d*, *J*(C,P) = 4.2); 128.4 (*d*); 127.8 (*d*); 66.7 (*dd*, *J*(C,P) = 131.8). ^{31}P-NMR (DCl/D_2O): 13.1. Anal. calc. for $C_7H_{10}NO_5P$ (203.13): C41.39, H 4.96, N 6.90, P 15.25; found: C 41.12, H 4.88, N 7.12, P 15.11.

(−)-(*S*)-**4**: According to *4.2*, with $ZnCl_2$ (2.2 mg, 16 μmol), **2** (600 mg, 1.65 mmol), C_6H_6 (10 ml), and $P(OSiMe_3)_3$ (1 ml, 3.2 mmol) for 16 h. Evaporation gave an oil which was taken in H_2O (4 ml) and left at r.t. for 20 h. Filtration and washing (see (+)-(*R*)-**4**) gave (−)-(*S*)-**4** (308 mg, 91.9%). R_f and ^{1}H-NMR: as for (+)-(*R*)-**4**. $[\alpha]_D^{25} = -56.3°$ (*c* = 1.3, 1M NaOH). ^{13}C-NMR (NaOD/D_2O): 139.5 (*s*); 128.5 (*d*); 128.0 (*d*); 126.5 (*d*); 68.6 (*dd*, *J*(C,P) = 123.3). ^{31}P-NMR (NaOD/D_2O): 12.8.

6. *(+)-(R)- and (−)-(S)-[Amino(phenyl)methyl]phosphonic Acid* ((+)-(*R*)- and (−)-(*S*)-**5**, resp.). (−)-(*S*)-**5**: A suspension of (−)-(*S*)-**4** (100 mg, 0.49 mmol; $[\alpha]_D^{25} = -56.3°$) and 20% $Pd(OH)_2$/C (50 mg) in 1M aq. HCl (7 ml) was hydrogenated overnight. Filtration through *Celite*, evaporation and crystallization[16]) ($EtOH/H_2O$) gave (−)-(*S*)-**5** (69 mg, 75.4%). M.p. 275°. R_f (*A*) 0.2. $[\alpha]_D^{20} = -17.2°$ (*c* = 0.9, 1M NaOH). IR (KBr): 3450*m* (v. br.), 3150*s*, 2935*s*, 2850*m* (v. br.), 2620*s* (br.), 1715*m* (v. br.), 1625*s*, 1608*m*, 1508*m*, 1454*w*, 1389*m*, 1379*m*, 1351*w*, 1273*s*, 1256*m*, 1218*s*, 1194*s*, 1158*m*, 1110*m*, 1082*s*, 1070*s*, 1041*m*, 1026*m*, 1004*w*, 922*s*, 898*m*, 828*w*, 780*m*, 772*m*, 712*m*, 700*s*, 613*w*, 600*m*. ^{1}H-NMR (NaOD/D_2O): 7.40–7.23 (*m*, Ph), 3.81 (*d*, *J* = 15.6, H–C(1)). ^{13}C-NMR (NaOD/D_2O): 143.36 (*d*, *J*(C,P) = 2.2); 128.9 (*d*); 128.5 (*d*); 127.1 (*d*); 56.5 (*dd*, *J*(C,P) = 130.8). ^{31}P-NMR (NaOD/D_2O): 18.9. Anal. calc. for $C_7H_{10}NO_3P$ (187.14): C 44.93, H 5.39, N 7.48, P 16.55; found: C 44.92, H 5.51, N 7.53, P 16.30.

Similarly, (+)-(*R*)-**4** (160 mg, 0.79 mmol; $[\alpha]_D^{25} = +56.0°$) was transformed into (+)-(*R*)-**5** which was purified by chromatography (H_2O) on *Dowex 50* (H^+) (134 mg, 90.9%; $[\alpha]_D^{20} = +17.0°$ (*c* = 1.1, 1M NaOH)). Crystallization (3 ×, H_2O/EtOH, +4°) gave (+)-**5** (63.3%) with an $[\alpha]_D^{20} = +19.5°$ (*c* = 1.3, 1N NaOH).

7. *(+)-(R)-[(Hydroxyamino)(4-(*tert*-butyl)phenyl)methyl]phosphonic Acid* ((+)-**10**). According to *4.1*, with **8** (346 mg, 0.826 mmol), CH_2Cl_2 (2.5 ml), C_6H_6 (2.5 ml), $P(OSiMe_3)_3$ (0.5 ml, 1.6 mmol), and 70% $HClO_4$ soln. (15 μl, 0.175 mmol) at −45° for 10 min. A part (47.0% *v/v*) of crude **10** was purified by crystallization from MeOH/H_2O 1:1 (12 h at r.t.); the crystals were washed (2 × 3 ml H_2O, 2 × 2 ml MeOH, 3 × 2 ml CH_2Cl_2) and dried at 10^{-6} Torr to give (+)-(*R*)-**10** (82.5 mg, 82%). For elemental analysis, a sample was crystallized by acidifying (HCl) a NaOH soln. of **10** ($[\alpha]_D^{25} = +63.6°$ (*c* = 1.4, 1M NaOH)). The rest of crude **10** (53% *v/v*, 0.438 mmol) was transformed to (+)-(*R*)-**11**, as detailed in *Exper. 8*. **10:** M.p. 192–194 (dec.). R_f (*A*): dec. $[\alpha]_D^{25} = +56.3°$ (*c* = 1.3, 1M NaOH). IR (KBr): 3420*w* (v. br.), 3060*m* (br.), 2960*s*, 2905*s*, 2900–2100*m*, 1603*m*, 1512*m*, 1460*w* (br.), 1390*w* (br.), 1362*w*, 1247*w*, 1228*m*, 1203*s*, 1190*m*, 1178*m*, 1156*m*, 1032*s*, 1020*s*, 1003*s*, 933*s*, 854*w*, 838*m*, 621*m*. ^{1}H-NMR (D_2O/NaOD): 7.53–7.40 (*m*, Ph); 4.15 (*d*, *J*(H,P) = 18.3, H–C(1)); 1.32 (*s*, 3 CH_3). ^{13}C-NMR (D_2O/NaOD): 150.1 (*s*); 136.4 (*s*); 128.4 (*dd*, *J*(C,P) = 4.5); 124.8 (*d*); 68.1 (*dd*, *J*(C,P) = 123.6); 33.7 (*s*); 30.6 (*q*). ^{31}P-NMR (D_2O/NaOD): 13.0. Anal. calc. for $C_{11}H_{18}NO_4P$ (259.22): C 50.97, H 6.94, N 5.40, P 11.95; found: C 51.20, H 6.85, N 5.38, P 11.71.

8. *(RS)-, (+)-(R)- and (−)-(S)-[Amino(4-(*tert*-butyl)phenyl)methyl]phosphonic Acid* ((*RS*)-, (+)-(*R*)-, and (−)-(*S*)-**11**, resp.). 8.1. *From* **8**. (−)-(*S*)-**11**: According to *4.2* with $ZnCl_2$ (1.4 mg, 10 μmol), **8** (173.2 mg, 0.413 mmol), C_6H_6 (5 ml), $P(OSiMe_3)_3$ (0.25 ml, 0.8 mmol) at reflux overnight. Chromatography (1M HCO_2H) on *Dowex 50* (H^+) and evaporation gave a mixture (155 mg; $[\alpha]_D^{25} = -6.1°$ (*c* = 1.4, 1M NaOH)) of (−)-(*S*)-**11** and HCO_2Na after drying at h.v. Crystallization (HCO_2H/H_2O) gave pure (−)-(*S*)-**11** (85.3 mg, 85%). M.p. 251–253°. R_f (*A*) 0.62. $[\alpha]_D^{25} = -13.4°$ (*c* = 1.4, 1M NaOH). IR (KBr): 3420*w* (v. br.), 3300–2000*s*, 1643*m*, 1593*m*, 1513*s*, 1521*s*, 1475*w*, 1460*w*, 1421*w*, 1392*w*, 1365*m*, 1343*w*, 1328*w*, 1251*m*, 1216*s*, 1190*s*, 1073*m*, 1042*s*, 1020*s*, 1009*m*, 916*s*, 836*s*, 821*m*, 746*w*, 723*w*, 670*w*, 639*w*. ^{1}H-NMR: 7.50–7.34 (*m*, Ph); 3.79 (*d*, *J*(H,P) = 15.1, H–C(1)); 1.32 (*s*, 3 CH_3). ^{13}C-NMR: 150.8 (*s*); 140.2 (*s*); 128.7 (*dd*, *J*(C,P) = 4.8); 126.0 (*d*); 56.2 (*dd*, *J*(C,P) = 131.3); 34.8 (*s*); 31.7 (*q*). ^{31}P-NMR: 19.0. Anal. calc. for $C_{11}H_{18}NO_3P$ (243.24): C 54.32, H 7.46, N 5.76, P 12.73; found: C 54.47, H 7.50, N 5.76, P 12.73.

8.2. *From (+)-(R)-***10**. A suspension of (+)-(*R*)-**10** (117.5 mg, 0.45 mmol; $[\alpha]_D^{25} = +56.3°$) and 20% $Pd(OH)_2$/C (50 mg) in 1M HCl/MeOH (8 ml) was hydrogenated (18 h). Filtration through *Celite*, evaporation, and crystallization (1 × from AcOH/EtOH/H_2O, 2 × from AcOH/EtOH) gave (+)-(*R*)-**11** (60 mg, 54.8%). $[\alpha]_D^{25} = +15.8°$ (*c* = 1.1, 1N NaOH).

(+)-(*R*)-**11**: Crude (+)-(*R*)-**10** (0.438 mmol, see *Exper. 7*) was transformed (see *Exper. 8.1*) into a mixture (151 mg; $[\alpha]_D^{25} = +8.4°$ (*c* = 1.7, 1M NaOH)) of (+)-(*R*)-**11** and HCO_2Na. Crystallization (HCO_2H/H_2O) gave 87.4 mg (82%) of (+)-(*R*)-**11**. $[\alpha]_D^{25} = +14.5°$ (*c* = 1.7, 1M NaOH). R_f, ^{1}H-, ^{31}P-NMR: as for (−)-(*S*)-**11**.

8.3. *(RS)-***11**: Following [21], 4-(*tert*-butyl)benzaldehyde (4.05 g, 25 mmol) was transformed into (*RS*)-**11** (950 mg, 19.7%). R_f and ^{1}H-NMR: as for (−)-(*S*)-**11**.

---

[16]) The mother liquor showed an $[\alpha]_D^{20} = -9°$ (*c* = 1.0, 1M NaOH), after chromatography (H_2O) on *Dowex 50* (H^+).

9. *(+)-(R)-(1-Hydroxyamino-2-methylpropyl)phosphonic Acid* ((+)-(*R*)-**15**). According to *4.1*, with **14** (548 mg, 1.66 mmol), CH_2Cl_2 (8.3 ml), C_6H_6 (8.3 ml), $P(OSiMe_3)_3$ (1 ml, 3.2 mol), 70% $HClO_4$ soln. (40 mg, 0.28 mmol) at −50° for 10 min. A part (12 ml, 1.11 mmol) of crude **15** was precipitated with H_2O (3 ml). The solid was filtered off, dissolved in 2N NaOH, acidified to pH *ca.* 1 (2N HCl), and stored overnight in the refrigerator. The crystals were washed (2 × 2 ml H_2O, 2 × 2 ml MeOH, 2 × 2 ml CH_2Cl_2) and dried to give (+)-(*R*)-**15** (145.5 mg, 77.7%). The rest (6 ml, 0.55 mmol) of crude **15** was transformed to (−)-(*R*)-**16**, as detailed in *Exper. 10*. (+)-(*R*)-**15**: M.p. dec. above 175°. R_f (*A*) 0.33. $[\alpha]_D^{25}$ = +26.7° (*c* = 1.2, 1M NaOH). IR (KBr): 3510*m* (br.), 3200–2000*s*, 1604*s*, 1510*m*, 1478*m*, 1460*m*, 1440*m*, 1393*m*, 1350*w*, 1291*w*, 1228*s*, 1205*s*, 1169*s*, 1146*s*, 1108*s*, 1000*s* (br.), 950*s*, 833*m*, 805*w* (br.), 756*m*, 643*m*. ^{1}H-NMR (NaOD/D_2O): 2.69 (*dd*, *J* = 5.1, *J*(H,P) = 12.0, H–C(1)); 2.14–2.00 (*m*, H–C(2)), 1.11 (*d*, *J* = 6.9, CH_3); 1.01 (*d*, *J* = 6.9, CH_3). ^{13}C-NMR: 68.0 (*dd*, *J*(C,P) = 127.8); 28.4 (*d*); 22.6 (*dq*, *J*(C,P) = 8.0); 19.6 (*dq*, *J*(C,P) = 4.8). ^{31}P-NMR (NaOD/D_2O): 18.8. Anal. calc. for $C_4H_{12}NO_4P$ (169.12): C 28.41, H 7.15, N 8.28, P 18.32; found: C 28.46, H 7.40, N 8.48, P 18.32.

10. *(−)-(R)- and (+)-(S)-(1-Amino-2-methylpropyl)phosphonic Acid* ((−)-(*R*)- and (+)-(*S*)-**16**, resp.). (−)-(*R*)-**16**: According to *4.1*, crude (+)-(*R*)-**15** (0.55 mmol, see *Exper. 9*) was transformed into (−)-(*R*)-**16** (60.4 mg, 71%). $[\alpha]_D^{25}$ = −2.1° (*c* = 1.6, H_2O). Anal. data: see [3].

(+)-(*S*)-**16**: According to *4.2*, with $ZnCl_2$ (0.8 mg, 5.9 μmol), **14** (272 mg, 0.826 mmol), and C_6H_6 (5 ml) at reflux for 5 min. $P(OSiMe_3)_3$ (0.5 ml, 1.6 mmol; after 16 h further 0.1 ml) was added at r.t. After 40 h, (+)-(*S*)-**16** (108 mg, 85.4%) was obtained. $[\alpha]_D^{25}$ = +0.74° (*c* = 1.8, H_2O).

11. *(+)-(S)-(1-Amino-2-hydroxyethyl)phosphonic acid* ((+)-(*S*)-**19**). See *Table 4*.

Table 4. *Reaction Conditions of the $P(OSiMe_3)_3$ Addition to* **18** (340 mg, 0.834 μmol, see *Exper. 4.1* and *4.2*), *and Yield and Specific Rotation of the Resulting* **19**

Catalyst	Solvent	Temp.	Time	Yield of **19**	$[\alpha]_D^{25}$ of **19** in H_2O
$HClO_4$ (40 mg, 280 mmol)	CH_2Cl_2/C_6H_6 1:1	−50°	10 min	81.6%	+9.0° (*c* = 1.5)
$ZnCl_2$ (1.4 mg, 10 μmol)	C_6H_6	r.t.	20 min	90.0%	+26.3° (*c* = 1.1)
$ZnCl_2$ (114 mg, 836 μmol)	C_6H_6	r.t.	20 min	88.6%	+0.5° (*c* = 1.5)
–	C_6H_6	r.t.	90 h	72.9%	+19.8° (*c* = 1.1)
$Zn(OTf)_2$ (303 mg, 836 μmol)	THF	−40°	20 min	83.3%	−5.1° (*c* = 1.2)

12. *(+)-(R)-[1-Hydroxyamino-3-(methylthio)propyl]phosphonic Acid* ((+)-(*R*)-**21**). According to *4.2*, with **20** (478 mg, 1.39 mmol) and 13 mM $Zn(OTf)_2$/THF soln. (8.4 ml) at −40° and $P(OSiMe_3)_3$ (0.6 ml, 1.8 mmol). The crude product was taken up in 1M HCl in MeOH (2 ml) and left at r.t. for 2 h and at +4° for 16 h. The crystals were washed (2 × 1.5 ml MeOH, 2 × 1.5 ml H_2O, 2 × 1.5 ml MeOH/CH_2Cl_2) and dried (10^{-6} Torr) to give pure (+)-(*R*)-**21** (32 mg, 11.3%). The filtrate and washings were evaporated and treated with H_2O (10 ml). The solid was filtered off and washed (as described); repetition of this procedure gave further (+)-(*R*)-**21** (total 198 mg, 71.4%). M.p. 185° (quick heating, dec.). R_f (*A*) 0.9 (dec.). $[\alpha]_D^{25}$ = +0.8° (*c* = 1.1, 1M NaOH). IR (KBr): 3430*m* (v. br.), 3200–2000*m*, 1613*s*, 1512*m*, 1445*m*, 1433*m*, 1260*m*, 1218*s*, 1198*s*, 1155*m*, 1113*s*, 1081*s*, 1045*s*, 875*w*, 726*w*, 705*w*, 630*m*. ^{1}H-NMR (D_2O/NaOD): 2.95 (*ddd*, *J* = 8.2, 4.8, *J*(H,P) = 12.9, H–C(1); irrad. at 2.7 gave *d*, *J* = 12.9); 2.8–2.6 (*m*, 2 H–C(3)); 2.14 (*s*, CH_3); 2.1–1.9 (*m*, 2 H–C(2)). ^{13}C-NMR (D_2O/NaOD): 60.5 (*dd*, *J*(C,P) = 132.7); 32.0 (*dt*, *J*(C,P) = 9.4); 28.0 (*t*); 14.9 (*q*). ^{31}P-NMR: 17.1. Anal. calc. for $C_{14}H_{12}NO_4PS$ (201.18): C 23.88, H 6.01, N 6.96, P 15.40; found: C 23.84, H 6.25, N 6.85, P 15.21.

13. *(−)-(R)- and (+)-(S)-[1-Amino-3-(methylthio)propyl]phosphonic Acid* ((−)-(*R*)- and (+)-(*S*)-**22**, resp.). 13.1. *From Nitrone* **20**. See *Table 5*. Data of (−)-(*R*)-**22**: M.p. 265–266° (dec.; EtOH/H_2O). R_f (*A*) 0.42. $[\alpha]_D^{25}$ = −11.5° (*c* = 1.1, H_2O). IR (KBr): 3420*m* (v. br.), 3250–2500*s*, 2500–1900*m*, 1650*m*, 1605*m*, 1538*s*, 1450*w*, 1435*w*, 1423*w*, 1322*w*, 1273*w*, 1250*m* (br.), 1183*s*, 1135*m*, 1090*w* (br.), 1030*s*, 1006*s*, 951*s*, 929*s*, 880*w*, 682*m*, 652*w*. ^{1}H-NMR (D_2O): 3.27 (*ddd*, *J* = 5.3, 8.4, *J*(H,P) = 13,6, H–C(1); irrad. at 1.9 gave *d*, *J* = 13.6); 2.7–2.5 (*m*, 2 H–C(2)); 2.2–1.8 (*m*, 2 H–C(3)); 1.97 (*s*, CH_3). ^{13}C-NMR (D_2O): 49.1 (*dd*, *J*(C,P) = 142.3); 30.7 (*dt*, *J*(C,P) = 9.8); 28.6 (*t*); 14.8 (*q*). ^{31}P-NMR: 13.5. Anal. calc. for $C_4H_{12}NO_3PS$ (185.12): C 25.94, H 6.53, N 7.56, P 16.73; found: C 25.70, H 6.70, N 7.35, P 16.44.

Table 5. *Reaction Conditions of the $P(OSiMe_3)_3$ Addition to* **20** (see *Exper. 4.1* and *4.2*), *and Yield and Specific Rotation of the Resulting* **22**

Nitrone **20**	Catalyst	Solvent	Time	Temp.	Yield of **22**	$[\alpha]_D^{25}$ of **22** (H_2O)
102 mg (292 µmol)	$HClO_4$ (40 mg, 280 µmol)	C_6H_6/CH_2Cl_2 1:1 (4 ml)	10 min	−70°	55.9%	−11.5° (*c* = 1.0)
871 mg (2.49 mmol)	13 mM Zn (=Tf)$_2$/THF soln. (15 ml)		1 h	−40°	76.7%	−20.1° (*c* = 1.1)
144 mg (413 µmol)	$ZnCl_2$ (0.6 mg, 4.4 µmol)	C_6H_6 (2.5 ml)	2 h	r.t.	84.5%	+14.6° (*c* = 1.0)
144 mg (413 µmol)	$ZnCl_2$ (56 mg, 413 µmol)	C_6H_6 (2.5 ml)	15 min	r.t.	77.1%	−10.1° (*c* = 1.1)

13.2. *From* **21**. (+)-(*S*)-**21** (56.2 mg, 0.28 mmol; $[\alpha]_D^{25}$ = +0.8) was hydrogenated in 1M HCl (5 ml)/MeOH (3 ml) for 18 h. Chromatography on *Dowex 50* (H^+) and lyophilizing gave (−)-(*R*)-**22** (44.9 mg, 87.8%). $[\alpha]_D^{25}$ = −17.2° (*c* = 1.1, H_2O); $[\alpha]_D^{20}$ = 30.5° (*c* = 1.1, 0.25M NaOH).

14. *General Procedure for the Preparation of Dimethyl [1-(Naphthalene-1-carboxamido)alkyl]phosphonates.* The aminophosphonic acid (0.1 mmol) was treated with pyridine (1 ml) and Me_3SiCl (0.12 ml, 1.0 mmol) at r.t. to give a clear soln. CH_2Cl_2 (2 ml) was added after 30–60 min. The mixture was cooled to − 25° and 1-naphthoyl chloride (0.15 ml, 1.2 mmol) added dropwise. After 2 h, MeOH (1 ml) was given to the mixture which, after 30 min, was taken up in cold 2M HCl (15 ml) and extracted with CH_2Cl_2 (8 × 25 ml). The org. layer was concentrated to *ca.* 10 ml, MeOH (2 ml) was added and the mixture treated with CH_2N_2 in Et_2O (excess CH_2N_2 was destroyed with AcOH.) Evaporation (h.v.) and FC gave the products.

15. *(RS)-, (−)-(S)-, and (+)-(R)-Dimethyl [(Naphthalene-1-carboxamido)(phenyl)methyl]phosphonate* ((*RS*)-, (−)-(*S*)-, and (+)-(*R*)-**7**, resp.). (*RS*)-**7**: According to *Exper. 14*, with (*RS*)-**5** (77 mg, 0.41 mmol), pyridine (2 ml), Me_3SiCl (0.5 ml, 0.4 mmol), and 1-naphthoyl chloride (0.4 ml, 2.7 mmol). FC (SiO_2, *B* 1:1) gave (*RS*)-7 (120 mg, 78.9%). For elemental analysis, m.p., and UV, a sample was crystallized from CH_2Cl_2/cyclohexane. M.p. (CH_2Cl_2/cyclohexane) 185.5–186.5°. R_f (*B* 2:1) 0.25. HPLC (DNBPG column, hexane/i-PrOH/MeOH 16:3:1, 1 ml/min, 290 nm): (*R*)-**7** at 20.5 min (100.0), (*S*)-**7** at 23.1 min (100.8). UV (cyclohexane): 223 (55270). IR (KBr): 3600–3200*w*, 3255*s*, 3170*w*, 3080*w*, 3070–3010*w*, 2958*m*, 2852*w*, 1955*w* (br.), 1895*w* (br.), 1820*w* (br.), 1650*s*, 1672*w*, 1593*w*, 1575*w*, 1530*s* (br.), 1500*m*, 1455*m* (br.), 1352*w*, 1335*w*, 1294*m*, 1253*m*, 1236*s*, 1212*m*, 1194*m*, 1182*m*, 1150*m*, 1065*s*, 1038*s*, 922*w*, 896*w*, 867*w*, 833*m*, 820*w*, 810*w*, 788*s*, 767*m*, 751*m*, 742*m*, 700*s*. ^{1}H-NMR: 8.27–8.22 (*m*, 1 H); 7.96–7.85 (*m*, 2 H); 7.68–7.35 (*m*, 9 H); 7.07 (br. *dd*, $J \approx 9$, J(H,P) ≈ 3, NH); 5.88 (*dd*, J = 9.6, J(H,P) = 20.8, H–C(1)); 3.79 (*d*, J(H,P) = 10.8, CH_3); 3.56 (*d*, J(H,P) = 10.7, CH_3). ^{13}C-NMR: 168.6 (*d*, J(C,P) = 6.9); 134.8 (*s*); 133.6 (*s*); 130.8 (*d*); 130.2 (*s*); 128.8 (*d*); 128.2 (*d*); 128.1 (*d*); 127.1 (*d*); 126.3 (*d*); 125.33 (*d*); 125.25 (*d*); 124.5 (*d*); 53.7 (*dq*, J(C,P) = 6.5); 53.3 (*dq*, J(C,P) = 6.8); 50.1 (*dd*, J(C,P) = 154.4). ^{31}P-NMR: 24.3. Anal. calc. for $C_{20}H_{20}NO_4P$ (369.36): C 65.04, H 5.45, N 3.79, P 8.39; found: C 64.97, H 5.71, N 3.95, P 8.50

(−)-(*S*)-**7**: According to *Exper. 14*, uncrystallized (−)-(*S*)-**5** (18.7 mg, 0.1 mmol, $[\alpha]_D^{20}$ = −11.2°) gave (−)-**7** (21.4 mg, 57.9%). $[\alpha]_D^{20}$ = − 8.9° (*c* = 1.4, $CHCl_3$). HPLC (conditions, see (*RS*)-**7**): (*R*)-**7** at 15.1 min (1.00), (*S*)-**7** at 16.7 min (4.15).

(+)-(*R*)-**7**: According to *Exper. 14*, crystallized (+)-(*R*)-**5** (18.7 mg, 0.1 mmol; $[\alpha]_D^{20}$ = +17.4° (*c* = 1.3, 1M NaOH)) gave (+)-(*R*)-**7** (23 mg, 68.5%). HPLC (conditions, see (*RS*)-**7**): (*R*)-**7** at 16.9 min (17.5), (*S*)-**7** at 19.2 min (1.00).

Similarly, uncrystallized (+)-(*R*)-**5** ($[\alpha]_D^{20}$ = +18.1°) gave (+)-(*R*)-**7** (71%). HPLC: (*R*)-**7** at 19.3 min (68.0), (*S*)-**7** at 22.7 min (1.00).

Twice recrystallized (H_2O/EtOH) (+)-(*R*)-**5** ($[\alpha]_D^{20}$ = +19.5°) gave (+)-(*R*)-**7** showing a single peak (19.2 min) in the HPLC.

16. *(RS)-, (−)-(S)-, and (+)-(R)-Dimethyl [(Naphthalene-1-carboxamido)(4-(*tert*-butyl)phenyl)methyl]-phosphonate* ((*RS*)-, (−)-(*S*)-, and (+)-(*R*)-**13**, resp.). (*RS*)-**13**: According to *Exper. 14*, (*RS*)-**11** (24.3 mg, 0.1 mmol) gave, after chromatography (SiO_2, *B* 2:1), (*RS*)-**13** (34.5 mg, 81%). For elemental analysis, m.p., and UV, a sample was crystallized from CH_2Cl_2/cyclohexane. M.p. 166–167°. R_f (hexane/AcOEt/MeOH 20:20:1) 0.25. HPLC (DNBPG column, hexane/i-PrOH 4:1, 1.5 ml/min; 290 nm): (*R*)-**13** at 11.5 min (100.0), (*S*)-**13** at 15.60 min

(100.3). UV (cyclohexane): 223 (59740). IR (KBr): 3600–3200*w*, 3230*m*, 3070–3010*w*, 2960*m*, 2925*m*, 2850*w*, 1655*s*, 1623*w*, 1592*w*, 1580*w*, 1531*s*, 1515*m*, 1460*w*, 1445*w*, 1365*w*, 1329*w*, 1310*m*, 1249*m*, 1223*s*, 1207*m*, 1185*w*, 1150*w*, 1110*w*, 1045*s*, 1020*s*, 906*w*, 807*w*, 853*m*, 840*m*, 832*m*, 825*m*, 818*m*, 810*m*. ^{1}H-NMR: 8.30–8.25 (*m*, 1 H); 7.95–7.82 (*m*, 2 H); 7.67–7.39 (*m*, 8 H); 7.05 (*dd*, J = 9.7, J(H,P) = 3.5, NH); 5.88 (*dd*, J = 9.8, J(H,P) = 20.4, H–C(1)); 3.80 (*d*, J(H,P) = 10.8, CH_3O); 3.57 (*d*, J(H,P) = 10.6, CH_3O); 1.32 (*s*, 3 CH_3). ^{13}C-NMR: 168.5 (*d*, J(C,P) = 5.0); 151.4 (*d*, J(C,P) = 2.6); 133.7 (*s*); 133.5 (*s*); 131.4 (*s*); 131.0 (*d*); 130.2 (*s*); 128.3 (*d*); 127.8 (*d*); 127.7 (*d*); 127.2 (*d*); 126.5 (*d*); 125.9 (*dd*, J(C,P) = 1.7); 125.3 (*dd*, J(C,P) = 1.9); 124.6 (*d*); 53.9 (*dq*, J(C,P) = 6.7); 53.5 (*dq*, J(C,P) = 7.2); 49.6 (*dd*, J(C,P) = 154.4); 37.3 (*s*); 31.3 (*q*). Anal. calc. for $C_{24}H_{28}NO_4P \cdot C_6H_{12}$ (509.63): C 70.70, H 7.91, N 2.75, P 6.08; found: C 70.41, H 7.69, N 2.76, P 5.81.

(–)-(*S*)-**13**: According to *Exper. 14*, uncrystallized (–)-(*S*)-**11** (45 mg, 104 μmol; $[\alpha]_D^{25} = -6.1°$) gave, after chromatography (SiO_2, hexane/AcOEt/MeOH 20:20:1), (–)-(*S*)-**13** (34 mg, 77.1%). $[\alpha]_D^{25} = -11.8°$ (c = 1.6, $CHCl_3$). HPLC (conditions, see (*RS*)-**13**): (*R*)-**13** at 14.6 min (1.00), (*S*)-**13** at 19.2 min (6.90).

(+)-(*R*)-**13**: According to *Exper. 14*, uncrystallized (+)-(*R*)-**11** (45 mg, 104 μmol; $[\alpha]_D^{25} = +8.4°$) gave (+)-(*R*)-**13** (32.4 mg, 73.5%). $[\alpha]_D^{25} = +14.4°$ (c = 2.5, $CHCl_3$). HPLC (conditions, see (*RS*)-**13**): (*R*)-**13** at 14.5 min (20.2), (*S*)-**13** at 21.8 (1.00).

Similarly, crude (+)-(*R*)-**11** (see *8.2*) gave (+)-(*R*)-**13**. HPLC: (*R*)-**13** at 12.9 min (19.6), (*S*)-**13** at 19.5 min (1.00).

From twice recrystallized (AcOH/EtOH) (+)-(*R*)-**11** resulted (+)-(*R*)-**13** showing a single peak (12.2 min) in the HPLC.

17. *(*RS*)-, (–)-(*R*)-, and (+)-(*S*)-Dimethyl [1-(Naphthalene-1-carboxamido)-2-methylpropyl]phosphonate* ((*RS*)-, (–)-(*R*)-, and (+)-(*S*)-**17**, resp.) (*RS*)-**17**: According to *Exper. 14*, with (*RS*)-**16** (75 mg, 0.49 mmol), pyridine (2 ml), Me_3SiCl (0.4 ml, 2.7 mmol), and 1-naphthoyl chloride (0.3 ml, 2.4 mmol). FC (SiO_2, *B* 1:1) gave (*RS*)-**17** (146 mg, 89%). For elemental analysis, m.p., and UV, a sample was crystallized from CH_2Cl_2/cyclohexane. M.p. 123°, R_f (*B* 1:1) 0.23. HPLC (DNBPG column, hexane/i-PrOH 4:1, 1.5 ml/min; 290 nm): (*R*)-**17** at 12.33 min (100.0), (*S*)-**17** at 15.29 min (100.4). UV (cyclohexane): 224 (53 370). IR (KBr): 3430*w* (v. br.), 3215*m*, 3200*m*, 3060*w*, 3015*w*, 2970*w*, 2955*m*, 2925*w*, 2900*w*, 2875*w*, 2850*w*, 1658*s*, 1622*w*, 1592*w*, 1580*w*, 1535*s*, 1465*w*, 1448*w*, 1390*w*, 1371*w*, 1309*m*, 1282*w*, 1253*w*, 1222*s*, 1188*w*, 1158*w*, 1145*w*, 1100*w*, 1043*s*, 1013*s*, 898*w*, 869*w*, 837*m*, 818*w*, 808*w*. ^{1}H-NMR: 8.33–8.28 (*m*, 1 H); 7.98–7.87 (*m*, 2 H); 7.66–7.45 (*m*, 4 H); 6.24 (br. *d*, J = 10, NH); 4.47 (*ddd*, J = 10.5, 4.5, J(H,P) = 18.0, H–C(1)); 3.86 (*d*, J(H,P) = 10.6, CH_3O); 3.81 (*d*, J(H,P) = 10.4, CH_3O); 2.39–2.33 (*m*, H–C(2)); 1.17 (*dd*, J = 6.8, J(H,P) = 1.0, CH_3); 1.11 (*d*, J = 6.9, CH_3). ^{13}C-NMR: 169.2 (*d*, J(C,P) = 5.2); 134.0 (*s*); 133.7 (*s*); 130.9 (*d*); 130.2 (*s*); 128.3 (*d*); 127.2 (*d*); 126.5 (*d*); 124.9 (*d*); 124.6 (*d*); 52.95 (*dq*, J(C,P) = 6.4); 52.77 (*dq*, J(C,P) = 7.1); 50.1 (*dd*, J(C,P) = 151.7); 29.0 (*dd*, J(C,P) = 3.4); 20.6 (*dq*, J(C,P) = 12.0); 18.2 (*dq*, J(C,P) = 5.0). ^{31}P-NMR: 27.4. Anal. calc. for $C_{17}H_{22}NO_4P$ (335.34): C 60.89, H 6.61, N 4.18, P 9.24; found: C 61.14, H 6.50, N 3.90, P 9.50.

(–)-(*R*)-**17**: According to *Exper. 14*, uncrystallized (–)-(*R*)-**16** (15 mg, 0.1 mmol; $[\alpha]_D^{25} = -2.1°$) gave (–)-(*R*)-**17** (21 mg, 62.6%). $[\alpha]_D^{25} = -26.1°$ (c = 0.7, $CHCl_3$). HPLC (conditions, see (*RS*) = **-17**): (*R*)-**17** at 14.4 min (42.3), (*S*)-**17** at 19.7 min (1.00).

Similarly, twice recrystallized (H_2O/EtOH) (–)-(*R*)-**16** gave (–)-(*R*)-**17** showing a single peak (13.2 min) in the HPLC.

(+)-(*S*)-**17**: According to *Exper. 14*, uncrystallized (+)-(*S*)**16** (15 mg, 0.1 mmol; $[\alpha]_D^{25} = +0.74°$) gave (+)-(*S*)-**17** (19 mg, 56.6%). HPLC (conditions, see (*RS*)-**17**): (*R*)-**17** at 18.6 min (1.00), (*S*)-**17** at 23.4 min (2.56).

18. *(*RS*)-, (–)-(*R*)-, and (+)-(*S*)-Dimethyl [1-(Naphthalene-1-carboxamido)-3-(methylthio)propyl]-phosphonate* ((*RS*)-, (–)-(*R*)-, and (+)-(*S*)-**23**, resp.). (*RS*)-**23**: According to *Exper. 14*, (*RS*)-**22** (187.1 mg, 1 mmol) gave (*RS*)-**23** (310 mg, 84.4%). HPLC (DNBPG column, hexane/i-PrOH/MeOH 16:4:1, 1 ml/min; 290 nm): (*R*)-**23** at 16.9 min (101.4), (*S*)-**23** at 18.9 min (100.0). IR, ^{1}H- and ^{13}C-NMR: as for (–)-(*R*)-**23**.

(–)-(*R*)-**23**: According to *Exper. 14*, with (–)-(*R*)-**22** (95 mg, 0.51 mmol; $[\alpha]_D^{25} = -20.1°$; not crystallized), pyridine (2 ml), Me_3SiCl (0.5 ml, 4 mmol); CH_2Cl_2 (5 ml), and 1-naphthoyl chloride (0.6 ml, 4 mmol). FC (SiO_2, CH_2Cl_2/MeOH 40:1) gave (–)-(*R*)-**23** (143 mg, 75.9%) as an oil. R_f (AcOEt) 0.29. HPLC (conditions, see (*RS*)-**23**): (*R*)-**23** at 11.4 min (8.30), (*S*)-**23** at 13.1 min (1.00). $[\alpha]_D^{25} = -39.5°$ (c = 1.6, $CHCl_3$). IR: 3420*m*, 3230*w* (br.), 3040*w*, 2990*s*, 2950*m*, 2917*m*, 2850*w*, 1662*s*, 1621*w*, 1591*w*, 1578*w*, 1492*s*, 1442*m*, 1392*w*, 1341*w*, 1312*m*, 1292*s*, 1148*m*, 1040*s* (br.), 957*w*, 895*w* (br.). ^{1}H-NMR: 8.33–8.28 (*m*, 1 H); 7.96–7.85 (*m*, 2 H); 7.65–7.42 (*m*, 4 H); 6.56 (br. *d*, $J \approx 9.8$, NH, no exchange with D_2O); 4.95 (*ddt*, J = 10, 10, 4, J(H,P) = 16, H–C(1)); 3.84 (*d*, J(H,P) = 10.7, CH_3O); 3.78 (*d*, J(H,P) = 10.7, CH_3O); 2.9–2.6 (*m*, 2 H–C(3)); 2.4–1.9 (*m*, 2 H–C(2)); 2.14 (*s*, CH_3S). ^{13}C-NMR: 169.1 (*d*, J(C,P) = 4.2); 133.6 (*s*); 133.5 (*s*); 130.9 (*d*); 130.1 (*s*); 128.3 (*d*); 127.2 (*d*); 126.4 (*d*); 125.1 (*d*); 53.20 (*dq*, J(C,P) = 7.1); 53.15 (*dq*, J(C,P) = 6.0); 44.4 (*dd*, J(C,P) = 155.6); 30.6 (*dt*, J(C,P) = 14.4);

29.4 (*dt*, *J*(C,P) = 3.1); 40.2 (*q*). ^{31}P-NMR: 27.2. Anal. calc. for $C_{17}H_{22}NO_4PS$ (367.40): C 55.58, H 6.04, N 3.81, P 8.43; found: C 55.50, H 5.98, N 3.61, P 8.25.

Similarly, uncrystallized (–)-(*R*)-**22** (5 mg, 27 μmol; $[\alpha]_D^{25} = -10.1°$) gave (–)-(*R*)-**23** (6.5 mg, 65%). HPLC (conditions, see (*RS*)-**23**): (*R*)-**23** at 10.5 min (3.06), (*S*)-**23** at 11.9 min (1.00).

(–)-(*R*)-**22** ($[\alpha]_D^{25} = -17.2°$; see *13.2*) gave (–)-(*R*)-**23**. HPLC: (*R*)-**23** at 15.4 min (7.59), (*S*)-**23** at 17.9 min (1.00).

(+)-(*S*)-**23**: According to *Exper. 14*, uncrystallized (+)-(*S*)-**22** (53 mg, 0.286 mmol; $[\alpha]_D^{25} = +14.6°$) gave (+)-(*S*)-**23** (90 mg, 85.7%). HPLC (conditions, see (*RS*)-**23**): (*R*)-**23** at 11.2 min (1.00), (*S*)-**23** at 13.6 min (4.1).

19. *Dimethyl [(*N*-Acetoxyacetamido)(phenyl)methyl]phosphonate* (**24**). A stirred suspension of **4** (100 mg, 0.58 mmol) in Ac_2O (2 ml) was treated with 70% $HClO_4$ soln. (50 μl) at r.t. After 10 min, the clear soln. was evaporated. The yellow oil in Et_2O (3 ml) was treated with CH_2N_2 in Et_2O. Chromatography (SiO_2, CH_2Cl_2/hexane/MeOH 20:20:1) gave **24** (84 mg, 45.9%). Crystallization (2 ×) from benzene/hexane gave a pure sample. M.p. 88–91°. R_f (CH_2Cl_2/hexane/MeOH 10:10:1) 0.2. IR: 3090*w*, 3065*w*, 2955*w*, 2815*w*, 1807*s*, 1670*s*, 1493*w*, 1452*m*, 1435*w*, 1370*s*, 1340*w*, 1328*w*, 1168*s*, 1132*s*, 1110*s*, 1040*s* (br.), 998*m*, 883*w*. ^{1}H-NMR: 7.65–7.60 (*m*, 2 arom. H); 7.39–7.36 (*m*, 3 arom. H); 6.08 (*d*, *J*(H,P) = 22.9, H–C(1)); 3.83 (*d*, *J*(H,P) = 11.0, CH_3O); 3.48 (*d*, *J*(H,P) = 10.7, CH_3O); 2.24 (*s*, AcO); 2.09 (*d*, *J*(H,P) = 0.7, AcN). Anal. calc. for $C_{13}H_{18}NO_6P$ (315.26): C 49.53, H 5.76, N 4.44, P 9.82; found: C 49.80, H 5.85, N 4.20, P 9.54.

20. *(*RS*)-Dimethyl [(Acetamido)(phenyl)methyl]phosphonate* (**6**). Similarly to **24**, (*RS*)-**5** (100 mg, 0.53 mmol) was acylated at 100° (90 min) and treated with CH_2N_2 to give, after FC (SiO_2, AcOEt/MeOH 19:1), (*RS*)-**6** (57 mg, 41.8%). M.p. (benzene/hexane) 138–139.5°. R_f (AcOEt/MeOH 19:1) 0.17. HPLC (DNBPG column, hexane/Et_2O/*t*-BuOMe/MeOH 8:5.5:5.5:1, 2 ml/min; 250 nm): (*R*)-**6** at 9.59 min (1.00), (*S*)-**6** at 8.78 min (1.03). IR: 3430*w*, 3270*w*, 3200*w*, 3090*w*, 3060*w*, 3035*w*, 2875*m*, 2835*w*, 1678*s*, 1600*s*, 1585*s*, 1540*m*, 1533*m*, 1492*s*, 1450*m*, 1359*m*, 1340*w*, 1282*w*, 1110*w*, 1098*w*, 1040*s* (br.), 915*w*, 860*w*, 835*m*. ^{1}H-NMR: 7.5–7.3 (*m*, C_6H_5); 7.12 (br. *d*, *J* = 10, NH); 5.59 (*dd*, *J* = 10, *J*(H,P) = 21, H–C(1)); 3.81 (*d*, *J*(H,P) = 10.8, CH_3O); 3.46 (*d*, *J*(H,P) = 10.5, CH_3O); 2.03 (*d*, *J* = 0.8, Ac). Anal. calc. for $C_{11}H_{16}NO_4P$ (257.23): C 51.36, H 6.27, N 5.45, P 12.04; found: C 51.64, H 6.32, N 5.30, P 11.94.

21. *(*RS*)-Dimethyl [(Acetamido)(4-(*tert*-butyl)phenyl)methyl]phosphonate* (**12**). Similarly to **24**, (*RS*)-**11** (100 mg, 0.47 mmol) gave, after FC (SiO_2, AcOEt/MeOH 24:1) (*RS*)-**12** (75 mg, 57%). R_f (AcOEt/MeOH 24:1) 0.23. IR: 3430*w*, 3270*w* (br.), 3200*w*, 3100–3030*w*, 2960*s*, 2905*w*, 2870*w*, 2855*w*, 1675*s* (br.), 1500*s* (br.), 1368*m*, 1328*w*, 1282*m*, 1123*w*, 1110*m*, 1090*m*, 1050*s* (br.). ^{1}H-NMR: 7.38 (*s*, C_6H_4); 6.95 (br. *d*, *J* = 10, NH); 5.57 (*dd*, *J* = 9.7, *J*(H,P) = 20.5, H–C(1)); 3.80 (*d*, *J*(H,P) = 10.8, CH_3O); 3.47 (*d*, *J*(H,P) = 10.6, CH_3O); 2.02 (*d*, *J*(H,P) = 0.7, AcO); 1.30 (*s*, 3 CH_3). ^{13}C-NMR: 169.6 (*d*, *J*(C,P) = 7.3); 150.8 (*d*, *J*(C,P) = 2.9); 129.2 (*d*, *J*(C,P) = 9.2); 127.8 (*dd*, *J*(C,P) = 6.0); 125.3 (*d*, *J*(C,P) = 1.5); 53.5 (*dq*, *J*(C,P) = 7.2); 53.4 (*d*, *J*(C,P) = 7.2); 49.0 (*d*, *J*(C,P) = 155.6); 34.4 (*s*); 31.2 (*q*); 22.6 (*q*).

REFERENCES

[1] B. Bernet, E. Krawczyk, A. Vasella, *Helv. Chim. Acta* **1985,** *68,* 2299.

[2] R. Huber, A. Knierzinger, E. Krawczyck, J.-P. Obrecht, A. Vasella, in 'Organic Synthesis: an Interdisciplinary Challenge', Proceedings of the 5th IUPAC symposium on organic synthesis, Eds. J. Streith, H. Prinzbach, and G. Schill, Blackwell Scientific Publications, 1985, 255–265.

[3] R. Huber, A. Knierzinger, J.-P. Obrecht, A. Vasella, *Helv. Chim. Acta* **1985,** *68,* 1730.

[4] P. Kafarski, B. Leijczak, P. Mastalerz, 'Phosphonopeptides: Synthesis and Biological Activity', Beiträge zur Wirkstofforschung, Heft 25, Berlin, 1985.

[5] P. Kafarski, P. Mastalerz, 'Aminophosphonates: Natural Occurrence, Biochemistry and Biological Properties', Beiträge zur Wirkstofforschung, Heft 21, Berlin, 1984.

[6] U. Schöllkopf, R. Schütze, *Liebigs Ann. Chem.* **1987,** 45.

[7] A. Vasella, R. Voeffray, *Helv. Chim. Acta* **1982,** *65,* 1953.

[8] A. Vasella, *Helv. Chim. Acta* **1977,** *60,* 1273.

[9] T. Hata, M. Sekino, *J. Am. Chem. Soc.* **1974,** *96,* 7363.

[10] J. Zon, *Pol. J. Chem.* **1981,** *55,* 643.

[11] W.F. Gilmore, M.A. McBride, *J. Am. Chem. Soc.* **1973,** *94,* 4361.

[12] W. H. Pirkle, J. M. Finn, B. C. Hamper, J. Schreiner, J. R. Pribish, in 'Asymmetric Reactions and Processes in Chemistry', Eds. E. L. Eliel and S. Otsuka, ACS Symposium Series No 185, Am. Chem. Soc. 1982, pp. 245–260.
[13] a) Y. Inouye, K. Takaya, A. Katisawa, *Magn. Res. Chem.* **1985,** *23,* 101; b) Y. Inouye, J. Hara, H. Kakisawa, *Chem. Lett.* **1980,** 1407.
[14] M. Hoffman, *Pol. J. Chem.* **1978,** *52,* 851.
[15] P. Kafarski, B. Leijczak, J. Szewczyk, *Can. J. Chem.* **1963,** *61,* 2425.
[16] E. Bühler, G. B. Brown, *J. Org. Chem.* **1967,** *32,* 265.
[17] T. F. Emery, *Biochemistry* **1963,** *2,* 1041.
[18] B. L. Mollert, I. J. McFarlane, E. E. Conn, *Acta Chem. Scand., Ser. B* **1977,** *31,* 343.
[19] J. D. Spenser, A. Ahmad, *Proc. Chem. Soc.* **1961,** 375.
[20] J. W. Huber, W. F. Gilmore, *Tetrahedron Lett.* **1979,** 3049.
[21] Z. H. Kudzin, W. J. Stec, *Synthesis* **1978,** 469.
[22] C. C. Tam, K. L. Mattocks, M. Tischler, *Synthesis* **1982,** 188.
[23] W.-L. Tsai, K. Hermann, E. Hug, B. Rohde, A. S. Dreiding, *Helv. Chim. Acta* **1985,** *68,* 2238.
[24] J. Berlan, J. Besace, E. Stephan, P. Cresson, *Tetrahedr. Lett.* **1985,** *26,* 5765.
[25] R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1983,** *105,* 1598 and ref. cit. therein.
[26] T. Glowiak, W. Sawka-Dobrowolska, J. Kowalik, P. Mastalerz, M. Soraka, J. Zon, *Tetrahedron Lett.* **1977,** 3965.
[27] L. Kupczyk-Subotkowska, P. Mastalerz, *Int. J. Peptide Protein Res.* **1983,** *21,* 485.
[28] H. R. Kricheldorf, M. Fehrle, *Synthesis* **1974,** 420.
[29] a) T. Poll, G. Helmchen, B. Bauer, *Tetrahedron Lett.* **1984,** *25,* 2191; b) T. Poll, A. Sobczak, H. Hartmann, G. Helmchen, *ibid.* **1985,** 3095; c) T. Poll, J. O. Metter, G. Helmchen, *Angew. Chem.* **1985,** *97,* 116.
[30] R. Bloch, L. Gilbert, *Tetrahedron Lett.* **1987,** *28,* 423.