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Preparation of α-Aminobenzylphosphonic Acids with a Stereogenic Quaternary Carbon Atom via Microscopically Configurationally Stable α-Aminobenzyllithiums

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Abstract: The enantiomers of 1-phenylethylamine were phosphorylated with diethyl chlorophosphate/Et_3N and then Boc-protected (Boc = *tert*-butoxycarbonyl) at the nitrogen atom. These phosphoramidates were metalated by using *s*BuLi/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to give α-aminobenzyllithiums that isomerised to α-aminophosphonates in yields of up to 80% with retention of the configuration at the carbon atom. The intermediate tertiary organolithiums were found to be microscopically configurationally stable from −78 to 0°C in Et_2O. The protected α-aminophosphonates were deblocked by using boiling 6 M HCl or preferably Me_3SiBr/(allyl)$SiMe_3$. When the Boc group was replaced by the diethoxyphosphinyl group, the α-aminobenzyllithium intermediate partially enantiomerised even at −78°C and rearranged to yield an α-aminophosphonate with 50% *ee* (*ee* = enantiomeric excess). Similarly, N-Boc-protected phosphoramidates derived from racemates and/or enantiomers of 1-(1-naphthyl)ethyl-, 1-indanyl- and 1,2,3,4-tetrahydro-1-naphthylamine or 1-azidoindan- and 1-azido-1,2,3,4-tetrahydronaphthalene were converted to aminophosphonates in good yields. Deblocking gave α-aminophosphonic acids of excellent enantiomeric excess (97–99%), as determined by means of HPLC on a chiral ion-exchange stationary phase based on quinine carbamate. When racemic Boc-protected diethyl phosphoramidate derived from 1,2,3,4-tetrahydro-1-naphthylamine was metalated with LiTMP/TMEDA (TMP = 2,2,6,6-tetramethylpiperidine), 1-hydroxyethylphosphonamidates resulted. The configuration of the main isomer was determined by means of a single-crystal X-ray structure analysis.

Keywords: aminophosphonic acids · carbanions · configurational stability · lithium · rearrangement

Introduction

Proteinogenic and non-proteinogenic amino acids, primarily the α ones, play vital roles in biological systems. To interfere with their metabolism and to block biosynthetic pathways, a variety of analogues have been prepared and tested. As the phosphonic acid group is considered an isosteric replacement for the carboxyl group and it mimics the tetrahedral intermediate of reactions of carboxylic acid derivatives, α-aminophosphonic acids are an attractive group of analogues for amino acids.[1] Therefore, racemic and preferably chiral, non-racemic α-aminophosphonic acids and peptides containing them have been synthesised to address various biological effects.[2] *N*-Benzyl α-aminobenzylphosphonic acids were found to be potent inhibitors of human prostatic acid phosphatase.[3] (*R*)-Phosphatyrosine (the phosphonic acid analogue of L-tyrosine) is a component of naturally occurring hypotensive tripeptides.[4]

Not surprisingly, the widespread interest in aminophosphonic acids gave rise to the development of many methods for their asymmetric preparation, but a limited number for quaternary ones. For the first time, enantiomerically pure quaternary α-aminophosphonic acids were prepared by chemical resolution of racemic esters by using tartaric acid or its dibenzoyl derivative as resolving agents.[5a] One absolute configuration was assigned on the basis of a single-crystal X-ray structure analysis.[5b] Methods are known for the preparation of chiral, non-racemic individual compounds, such as α-methylphosphaphenylalanine,[6] α-aminocyclopropylphosphonic acids[7] and those obtainable by means of catalytic asymmetric allylation of α-aminophosphonates[8] and rhodium-catalysed enantioselective Michael addition[9] of diethyl α-cyanoethylphosphonate to vinyl ketones. More gen-

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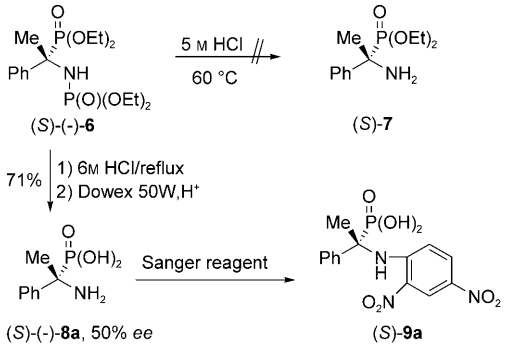
erally applicable accesses are based on the diastereoselective alkylation[10] of homochiral imidazolinylphosphonates and the highly diastereoselective addition[11] of lithium diethyl phosphite to α-ketosulfinimines.

We have found that N-protected *N*-benzylphosphoramidates undergo a phosphoramidate–α-aminophosphonate rearrangement induced by *s*BuLi or lithium amides at −78 °C to give chiral, non-racemic α-aminobenzylphosphonates.[12] The intermediary α-aminocarbanions are in part configurationally stable. These are reminiscent of those obtained by Beak et al. from N-Boc-protected pyrrolidines (Boc = *tert*-butoxycarbonyl) and benzylamines by (−)-sparteine-mediated lithiation.[13] We reasoned that this method could serve as a platform for the preparation of quaternary α-aminobenzylphosphonic acids. These are potential inhibitors of the phenylalanine ammonia-lyase.[14]

Results and Discussion

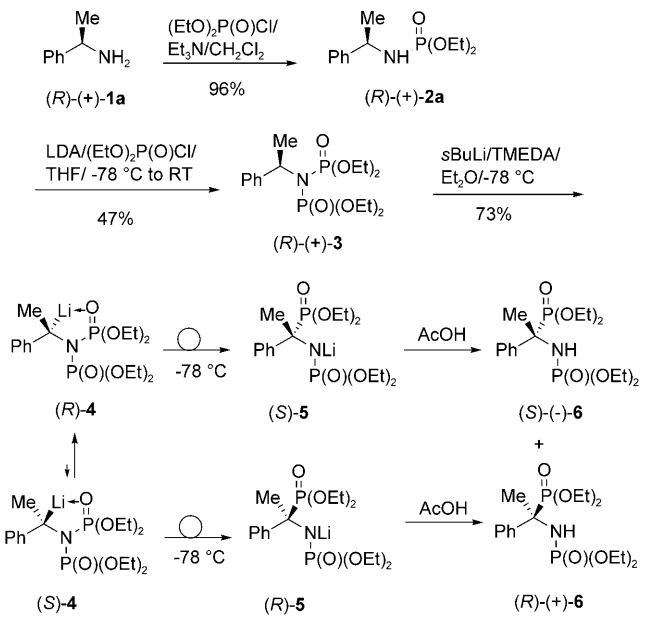
The commercially available (*R*)-1-phenylethylamine of 96% *ee* (*ee* = enantiomeric excess) was selected to study the feasibility of the approach. It seemed to be convenient to use a diethoxyphosphinyl group as a protecting group at the nitrogen atom for the respective phosphoramidate (Scheme 1). As the phosphorylation could not be performed in one step, it had to be effected in two.[12] (*R*)-1-Phenylethylamine ((*R*)-(+)-**1a**) was phosphorylated first with diethyl chlorophosphate/Et_3N and then with lithium diisopropylamide (LDA)/diethyl chlorophosphate in THF to yield the N-protected phosphoramidate (*R*)-(+)-**3**, the analytical sample of which could be obtained only by means of preparative HPLC. When it was treated with *s*BuLi/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in Et_2O at −78 °C, it rearranged smoothly to phosphonate (*S*)-(−)-**6** in 73% yield. To determine its enantiomeric excess, we tried to deblock the nitrogen atom and react it with α-methoxy-α-trifluoromethyl phenylacetyl chloride ((*S*)-MTPACl). Even harsh conditions (5 M HCl, 60 °C; Scheme 2) did not cleave



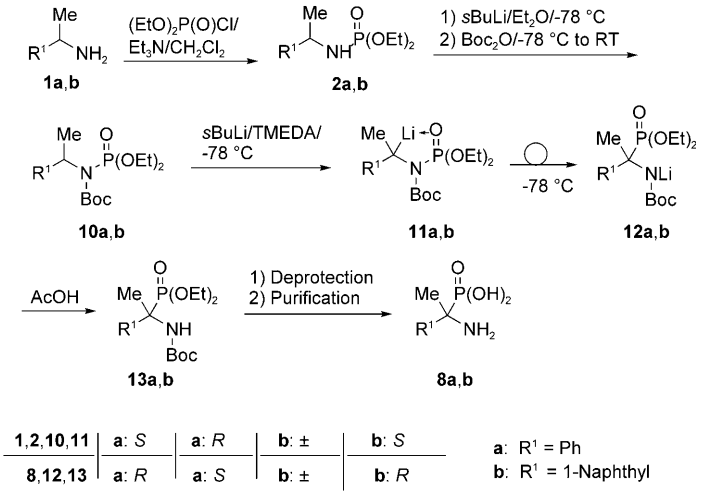
Scheme 2. Deblocking of quaternary α-aminophosphonate (*S*)-(−)-**6**.

the very stable N−P bond in (*S*)-(−)-**6**. Consequently, all protecting groups were removed by heating the solution at reflux in 6 M HCl to get the free α-aminophosphonic acid (*S*)-(−)-**8a** to determine its enantiomeric excess by using HPLC[15] on a chiral stationary phase based on quinine carbamate, after pre-column derivatisation with the Sanger reagent (2,4-dinitrofluorobenzene) to yield the *N*-2,4-dinitrophenyl (DNP) derivative (*S*)-**9a**. Surprisingly, its enantiomeric excess was found to be 50% compared with 96% for the starting (*R*)-1-phenylethylamine. We assigned the *S* configuration to α-aminophosphonic acid (−)-**8a** on the basis that 1) its levorotatory *p*-methyl and *p*-nitro analogues have the *S* configuration,[11] 2) the binding model for DNP derivatives of chiral α-aminophosphonic acids gives the *S* configuration[15] for chiral stationary phases based on quinine carbamate and 3) migration of the dialkoxyphosphinyl group from the oxygen or nitrogen atom to the carbon atom followed, so far, a retentive course[16] consistently. Evidently, the intermediate α-aminocarbanion (*R*)-**4** was configurationally unstable and partly enantiomerised (23%) resulting in phosphonate (*S*)-(−)-**6** with 50% *ee*, in which the *S* enantiomer predominated. This result, in combination with the tedious purification of the analytical sample of the starting phosphoramidate by means of HPLC, convinced us to probe the N-Boc-protected phosphoramidate next.

Thus, (*S*)-1-phenylethylamine ((*S*)-(−)-**1a**, 98% *ee*) was phosphorylated to give phosphoramidate (*S*)-(−)-**2a** in 85% yield, which was metalated at the nitrogen atom with *s*BuLi in Et_2O at −78 °C. This was followed by addition of Boc_2O and then the reaction mixture was allowed to warm up to room temperature (Scheme 3). The N-Boc-protected phosphoramidate (*S*)-(−)-**10a** isolated in 82% yield was metalated with *s*BuLi/TMEDA (1.5 equiv) in THF at −78 °C at the benzylic position to induce a phosphoramidate–α-aminophosphonate rearrangement. The reaction mixture was



Scheme 1. Conversion of (*R*)-1-phenylethylamine to aminophosphonate (*S*)-(−)-**6**.



Scheme 3. Conversion of 1-phenyl- and 1-(1-naphthyl)ethylamines into quaternary α-aminophosphonic acids **8a**,**b**.

quenched with AcOH after 1 h and worked up by using standard procedures. The crude product contained a small amount of phosphoramidate (*S*)-(−)-**2a** (determined by using TLC), formed by deprotection of starting material at the nitrogen atom with *s*BuLi, and α-aminophosphonate (*R*)-(+)-**13a** obtained by means of flash chromatography in 80% yield. The free acid (*R*)-(−)-**8a** was obtained by fully deprotecting (*R*)-**13a** by heating the solution in 6 M HCl at reflux and purification by means of ion-exchange chromatography using Dowex 50W,H^+ as before. The HPLC data showed it to have 97% *ee* and to be of the opposite configuration to the α-aminophosphonic acid prepared from the N-phosphorylated analogue (*S*)-(−)-**6**. As the enantiomeric excess of the starting (*R*)-1-phenylethylamine (96% *ee*) and that of the phosphonic acid agreed within experimental error, the dipole-stabilised tertiary intermediate α-aminobenzyllithium **11a** had to be microscopically configurationally stable at −78 °C. We assume that it is a short-lived species that isomerised with migration of the diethoxyphosphinyl group from the nitrogen atom to the carbon atom with retention of configuration.

To study the configurational stability of lithium-complexed carbanion **11a**, the phosphoramidate–α-aminophosphonate rearrangement was also performed in Et_2O and at various temperatures (−78, −30 and 0 °C; Table 1, which also contains the above-described reaction in THF for comparison). The isomerisation could be effected nearly equally well in Et_2O and in THF at −78 °C in 45 min. At a longer reaction time (3 h), side reactions such as removal of an ethyl group by excess *s*BuLi from the phosphorus atom by E2 elimination consumed product. The same effect was even more pronounced at −30 °C, where the yield doubled when the reaction time was shortened from 1 h to 10 min. The rearrangement yielded 59% of phosphonate (*R*)-(+)-**13a** at 0 °C at the very short reaction time of 3 min. In the latter two cases, the phosphonate was deblocked for the determination of the enantiomeric excess by means of HPLC.

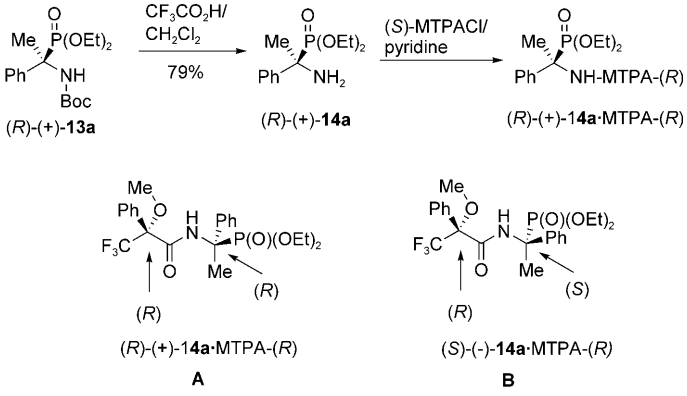
Table 1. Phosphoramidate–α-aminophosphonate rearrangement of (*S*)-(−)-**10a** under various conditions and *ee* of α-aminophosphonic acid (*R*)-(+)-**8a**.

Entry	Solvent[a]	*T* [°C]	*t*	Yield of (*R*)-**13a** [%]	*ee* of (*R*)-**8a** [%]
1	THF	−78	1 h	80	98
2	Et_2O	−78	3 h	65	[b]
3	Et_2O	−78	45 min	76	[b]
4	Et_2O	−30	1 h	39	[b]
5	Et_2O	−30	10 min	75	97
6	Et_2O	0	3 min	59	98

[a] *s*BuLi/TMEDA (1.5 equiv) was used. [b] Not determined.

Surprisingly, the enantiomeric excesses for entries 5 and 6 were 97 and 98%, respectively. This result reflects the microscopic configurational stability of the short-lived α-aminobenzyllithium (*S*)-**11a**, even at 0 °C, relative to the diethoxyphosphinyl analogue (*R*)-**4**. If the methyl group is replaced by a hydrogen atom as reported previously, the respective secondary benzyllithiums were much less configurationally stable.[12] At −78 °C they yielded phosphonates of 4 and 43% *ee*, respectively. It is well known that α-aminocarbanions[17] are less stable than α-oxyanions and that the configurational stability increases from secondary to tertiary.

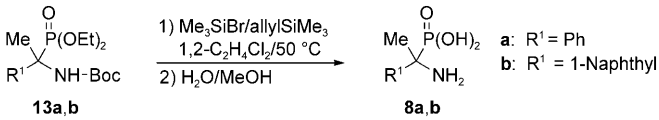
Finally, we tried to secure the absolute configuration of (*R*)-(+)-**13a** by an additional independent method, that is, by use of ^{1}H NMR spectroscopy of the Mosher amide. Its Boc group was selectively removed with CF_3CO_2H and the amine (*R*)-(+)-**14a** was derivatised with (*S*)-MTPACl[18] to give amide (*R*)-(+)-**14a**·MTPA-(*R*) (Scheme 4). The ^{1}H NMR spectrum showed four significant resonances, two strong ones ($\delta = 3.45$ (q, $J(H,F) = 1.6$ Hz; OMe), 2.06 ppm (d, $J(H,P) = 16.2$ Hz; CH_3)) and two weak ones ($\delta = 3.57$ (q, $J(H,F) = 1.6$ Hz; OMe), 2.13 ppm (d, $J(H,P) = 16.2$ Hz; CH_3)) in a ratio of 98:2, respectively. This corresponds to an enantiomeric excess of 96% for the underlying amine (*R*)-(+)-**14a**. When racemic **14a** was prepared and derivatised similarly to the enantiomer, the two sets of signals were of equal intensity. The determination of absolute configurations of alcohols and amines with a quaternary centre is not well established and is problematic, especially for the



Scheme 4. Transformation of (*R*)-**13a** into (*R*)-Mosher amide.

latter.[18] Assuming that the predominant conformations of the two diastereomeric Mosher amides are **A** and **B** (Scheme 4) with the methyl and the carbonyl groups being *syn* periplanar, the methoxy group of the (*R*)-MTPA portion should be shielded in **A**, but deshielded in **B**, which is in agreement with the shifts found ($\delta = 3.45$ vs. 3.57 ppm). Therefore, this finding also supported the assigned *R* configuration, which necessitates a retentive course for the phosphoramidate–α-aminophosphonate rearrangement. On the other hand, the phosphorus atom is shielded in **A**, but deshielded in **B**. However, the shift difference is too small to be of relevance and opposite to expectation (^{31}P NMR: major diastereomer: $\delta = 24.98$ ppm, with a shoulder at 24.96 ppm for the minor one).

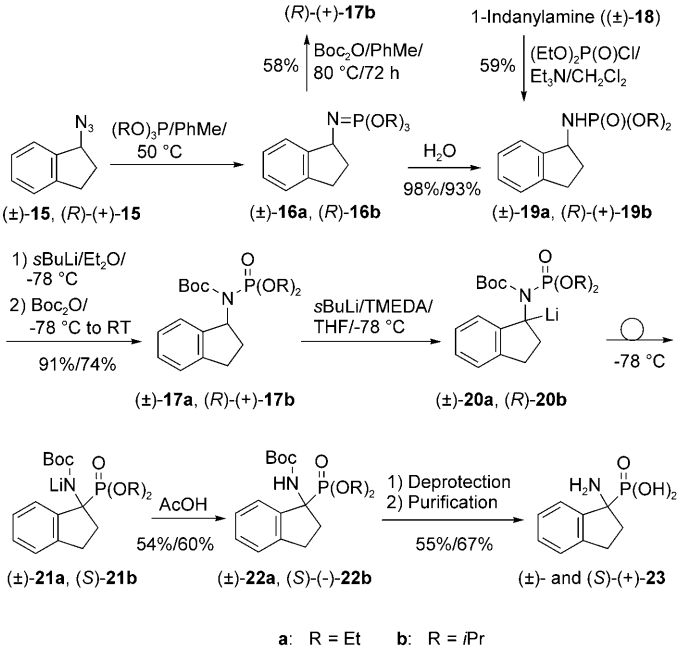
Similarly, the (*R*)-1-phenylethylamine ((*R*)-(+)-**1a**) and its racemic and *S*-configured 1-naphthyl analogue **1b** were converted to the corresponding α-aminophosphonic acids **8a** and **8b** (see Scheme 3). The rearrangements were performed under the optimised conditions, that is, by using *s*BuLi/TMEDA in THF at −78 °C. A small amount of the N-Boc-protected phosphoramidate was deprotected at the nitrogen atom by removal of Boc. All protecting groups (Boc; ethyl at the phosphorus atom) could be removed by heating the solution at reflux in 6 M HCl followed by ion-exchange chromatography (Dowex 50W,H$^+$) or under milder conditions using bromotrimethylsilane/allylsilane at 50 °C in 1,2-dichloroethane (Scheme 5).[19] After removal of volatile components under reduced pressure, hydrolysis of the silyl esters furnished the free acids **8a**,**b**, which were crystallised from water. The enantiomeric excesses were determined by means of HPLC from samples taken from the crude products. The yields of the individual steps and the enantiomeric excesses of the free acids are compiled in Table 2. The two steps, the conversion of **2** to **13** via **10**, can also be performed as a one-pot reaction in 66% yield.



13a,**b** **8a**,**b**

Scheme 5. Deblocking of N-Boc-protected aminophosphonates **13a**,**b**.

To show that cyclic benzylic amines can be similarly transformed into α-aminophosphonic acids, we selected 1-indanyl- and 1,2,3,4-tetrahydro-1-naphthylamine. In the case of the 1-indanyl derivatives we demonstrate that the corresponding alcohols can be used as starting materials as well as the amines. Thus, (±)-1-azidoindan ((±)-**15a**) prepared by using Ph_3P/diisopropyl azodicarboxylate (DIAD)/HN_3[20] was treated with triethyl phosphite (Staudinger reaction) in toluene (Scheme 6). The iminophosphorane (±)-**16a** was hydrolysed[21] to give phosphoramidate (±)-**19a**, which was protected at the nitrogen atom with a Boc group in high yield (91%). N-Boc-protected phosphoramidate (±)-**17a** was then subjected to the phosphoramidate–α-aminophosphonate rearrangement under our standard conditions (*s*BuLi/TMEDA/THF/−78 °C) to furnish aminophosphonate (±)-**22a** in 54% yield, which was deprotected. The low yield for the rearrangement, in part caused by removal of the Boc group, induced us to probe the more bulky isopropyl group as protecting groups at the phosphorus atom in the optically active series. (*S*)-1-Indanol (98% *ee*)[22] was converted to azide (*R*)-(+)-**15** by using diphenylphosphoryl azide/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[23] giving a higher enantiomeric excess than the Mitsunobu method. The azide was reacted with triisopropyl phosphite and then with water to give phosphoramidate (*R*)-(+)-**19b** in high yield. The remaining steps were similar to those with the racemic compounds. Alternatively, we tried to directly use the iminophosphorane (*R*)-**16b** for the protection at the nitrogen atom with Boc by reaction with Boc_2O. As the yield was merely 58% after heating for 72 h at 80 °C, this approach was abandoned in favour of the method via **19b**. The yield for the rearrangement was only marginally higher (60%) compared with the ethyl analogue in the racemic series. The enantiomeric excess of α-aminophosphonic acid (*S*)-(+)-**23**, the first quaternary cyclic one known, was 96%, which reflects complete inversion of configuration at the benzylic position for the introduction of the azide group



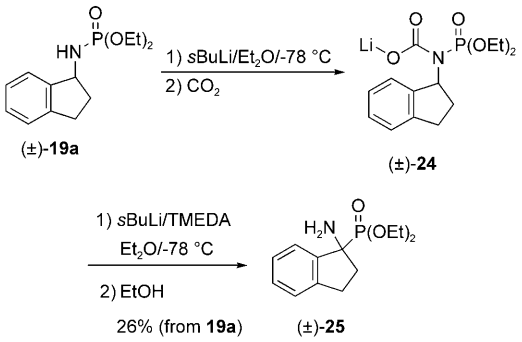
Scheme 6. Conversion of (±)- and (*R*)-1-azidoindan to α-aminophosphonic acids (±)- and (*S*)-(+)-**23**.

Table 2. Conversion of amines **1a**,**b** into α-aminophosphonic acids **8a**,**b**.

Amine/*ee* [%]	**2**/Yield [%]	**10**/Yield [%]	**13**/Yield [%]	**8**/Yield/*ee* [%]
(*R*)-**1a**/96	(*R*)-**2a**/96	(*R*)-**10a**/96	(*S*)-**13a**/79	(*S*)-**8a**/74/92
(±)-**1b**/–	(±)-**2b**/89	(±)-**10b**/96	(±)-**13b**/75	(±)-**13b**/90/–
(*S*)-**1b**/99	(*S*)-**2b**/90	(*S*)-**10b**/95	(*R*)-**13b**/61	(*R*)-**13b**/53/99

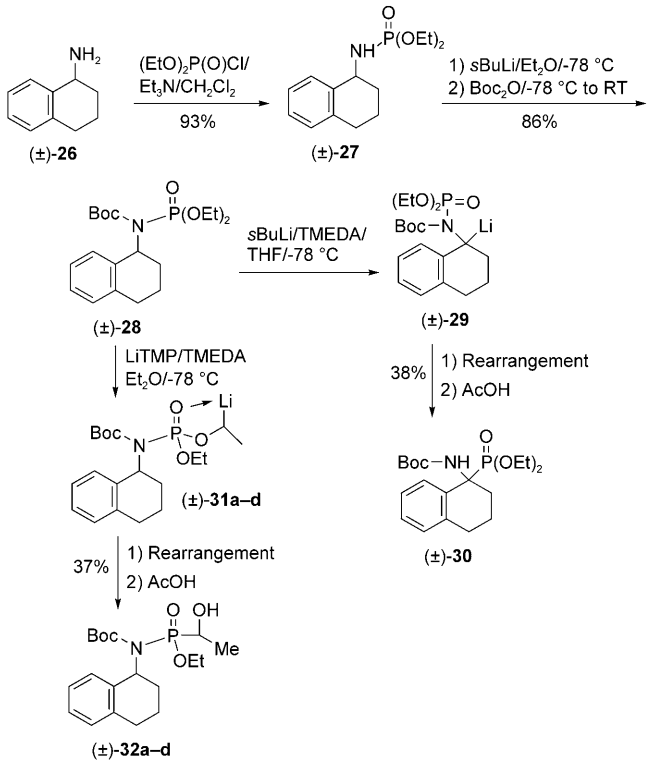
(S_N2 reaction) and stereospecificity for the rearrangement, for which we assume a retentive course by analogy to the open-chain amines.

As the Boc protecting group proved insufficiently stable towards *s*BuLi used for metalation, there were two options: 1) replacing it by the lithiocarboxyl group or 2) using a strong and sterically demanding lithium amide as a base. We reasoned that the former group should be more stable to alkyllithiums than Boc, although possibly less activating for metalation. Phosphoramidate (±)-**19a** was lithiated and reacted with CO_2 to give lithium salt (±)-**24** (Scheme 7). Removal of excess CO_2 under reduced pressure and addition of *s*BuLi/TMEDA to effect rearrangement and workup after 1 h furnished the desired phosphonate (±)-**25**, but in low yield (26%).



Scheme 7. Use of N-lithiooxycarbonyl-protected phosphoramidate (±)-**24** for phosphoramidate–α-aminophosphonate rearrangement.

As we wanted to prepare the α-aminophosphonic acid derived from 1,2,3,4-tetrahydro-1-naphthylamine ((±)-**26**) as well, we used LiTMP/TMEDA (TMP = 2,2,6,6-tetramethylpiperidine) as base and compared it with *s*BuLi/TMEDA. The amine was protected to furnish N-Boc-protected phosphoramidate (±)-**28**, which was metalated and rearranged to give α-aminophosphonate (±)-**30** in 38% yield, so far the lowest for the rearrangement (Scheme 8). To minimise removal of the Boc group, (±)-**28** was also metalated with LiTMP/TMEDA at −78 °C in Et_2O and the progress of the reaction was followed by TLC analyses. As expected, removal of the Boc group was insignificant, but surprisingly no α-aminophosphonate was formed. Instead, a new spot appeared, increasing with reaction time. After 4 h the TLC results obtained from withdrawn samples did not change any more. The crude product was a complex mixture of compounds. Flash chromatography furnished starting material (37%) and a product (37%), which seemed to be nearly homogeneous according to the TLC data, but was heterogeneous according to the spectroscopy data (^{1}H, ^{31}P NMR). On the basis of the ^{31}P NMR spectrum, it was determined to be a mixture of four phosphonamidates (δ = 34.1, 32.9, 32.5, and 31.7 ppm) in a ratio of 3:2:27:68. The ^{1}H NMR spectrum showed that one of the CH_3 groups of the ethyl groups resonated as a doublet of a doublet (J = 7.1, 18.7 Hz), which indicated a P-CH-CH_3 group. The signal of the benzylic



Scheme 8. Conversion of racemic 1,2,3,4-tetrahydro-1-naphthylamine to α-aminophosphonate (±)-**30** and hydroxyphosphonates (±)-**32a–d**.

CHN (δ = 5.20 ppm) was still present. These characteristic features are in agreement with the tentatively assigned structures (±)-**32a–d** of isomeric α-hydroxyphosphonates with three stereogenic centres. When the sample was kept for a while, crystals of isomer (±)-**32a** formed that corresponded to the predominant phosphonamidate in the mixture (δ = 31.7 ppm). Its ^{1}H and ^{13}C NMR spectrum supported the assignment, but did not give the configuration at the stereogenic centres. Single-crystal X-ray structure analysis secured the proposed structure (±)-**32a** with the relative configurations (Figure 1, Table 3). Clearly, LiTMP did not metalate (±)-**28** in the position α to the nitrogen atom at the benzylic position, but instead in the position α to the oxygen atom at the ethyl group. The α-oxyethyllithium intermediates (±)-**31a–d** isomerised to α-hydroxyphosphonamidates (±)-**32a–d** (phosphate–α-hydroxyphosphonate rearrangement). This result shows that the sterically encumbered base LiTMP removed the more easily accessible hydrogen atom from the methylene group rather than from the benzylic position, which should be of roughly equal acidity. For the first time, this allows the acidity of hydrogen atoms in the position α to the oxygen atom in phosphoramidates (and phosphates) and in the position α to the nitrogen atom in *N*-benzyl phosphoramidates to be estimated. Their pK_a should be about 37, the pK_a of 2,2,6,6-tetramethylpiperidine.[24] The low yield of (±)-**32a–d** is very likely caused by elimination of ethylene from the phosphoramidate (±)-**28** by LiTMP, giving water-soluble salts. It was therefore not surprising that *N*-alkyl phosphoramidates could not yet be

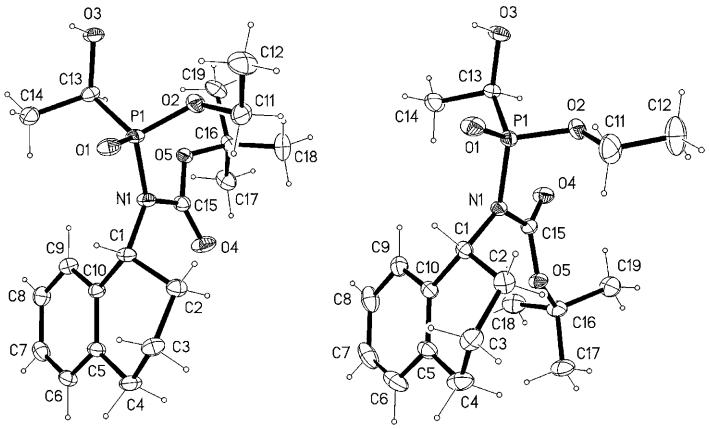


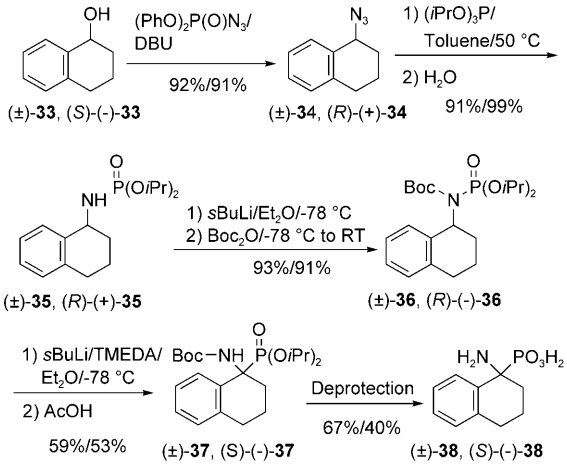
Figure 1. Structural views of two of the four independent molecules in the solid-state structure of (±)-**32a** (50% thermal ellipsoids). Note the difference in the orientation of the Boc group of the two molecules.

Table 3. Selected bond lengths [Å] and angles [°] for (±)-**32a**. The values given are averages of the four independent molecules.

P1−O1	1.475(2)	N1-C1	1.495(2)
P1−O2	1.575(2)	N1−C15	1.397(2)
P1−N1	1.697(2)	O2−C11	1.455(3)
P1−C13	1.824(2)	O3−C13	1.418(2)
O3−(H)···O1′	2.731(2)		
P1-N1-C1	119.8(1)	O1-P1-O2	115.0(1)
P1-N1-C15	120.0(1)	P1-O2-C11	119.8(2)
C1-N1-C15	119.3(1)	P1-C13-O3	109.0(2)

metalated at the position α to the nitrogen atom to get α-aminophosphonates, because the pK_a of the hydrogen atoms in the position α to the nitrogen atom will be significantly higher than those in the position α to the oxygen atom. When the experiment was repeated, except that the temperature was kept between −50 and −45 °C, only 4% of starting material was recovered and the yield (39%) of the mixture of the α-hydroxyphosphonates with minor changes in their ratio was virtually the same as before (37%). The higher reaction temperature increased elimination relative to rearrangement. This reaction could form the basis for the preparation of optically active α-hydroxyphosphonates starting from phosphoramidates derived from optically active amines.

To improve the yield for the phosphoramidate–aminophosphonate rearrangement in the 1,2,3,4-tetrahydro-1-naphthylamine series, we switched from the ethyl to the isopropyl protecting groups (Scheme 9). The racemic and (*S*)-1-tetralol[22] **33** were first converted in high yield via azides **34** into phosphoramidates **35** and then into N-Boc-protected amides **36**. Base-induced rearrangement furnished α-aminophosphonates **37** in acceptable yields of 59 and 53%, respectively. Complete removal of protecting groups gave the free α-aminophosphonic acids (±)- and (*S*)-(−)-**38**, the latter with an enantiomeric excess of 97% as determined by using HPLC after pre-column derivatisation with the Sanger reagent. The configuration was assigned on the basis of assuming retention for the rearrangement.



Scheme 9. Conversion of (±)- and (*S*)-1,2,3,4-tetrahydro-1-naphthol to α-aminophosphonic acids (±)- and (*S*)-(−)-**38**.

Conclusion

We have shown that secondary benzylic amines and azides can be transformed easily first into *N*-benzyl phosphoramidates and then into N-Boc-protected derivatives. These could then be lithiated with *s*BuLi/TMEDA in THF or Et_2O to give at −78 °C microscopically configurationally stable tertiary α-amino carbanions. These carbanion intermediates were stable up to 0 °C as proven for the reaction in Et_2O before rearranging to α-aminophosphonates (phosphoramidate–aminophosphonate rearrangement), as demonstrated for 1-phenylethylamine. Removal of protecting groups with bromotrimethylsilane/allytrimethylsilane followed by hydrolysis, gave crystalline quaternary benzylic α-aminophosphonic acids. In one case, when LiTMP was used as base to induce the rearrangement of the diethyl phosphoramidate derived from (±)-1,2,3,4-tetrahydro-1-naphthylamine, a hydrogen atom in the position α to the oxygen atom in the ethyl protecting group was removed. The ensuing phosphoramidate–α-hydroxyphosphonate rearrangement furnished a mixture of four α-hydroxyphosphonates. The predominating diastereomer was isolated as a crystalline product amenable to X-ray structure analysis. This enabled us to secure the relative configurations of the three stereogenic centres. This product allowed the pK_a of the respective hydrogen atoms in the position α to the oxygen atom in phosphates to be estimated to be below 37.

Experimental Section

General: Reactions were carried out under argon in oven-dried glassware. ^{1}H, ^{13}C and ^{31}P NMR spectra were usually measured in $CDCl_3$ at 300 K on a Bruker Avance DRX 400 at 400.1, 100.6 and 162 MHz, respectively, or on a Bruker DPX 250 (^{1}H: 250.1 MHz; ^{13}C: 62.9 MHz) in rare cases. Chemical shifts were referenced to residual $CHCl_3$ (δ_H = 7.24 ppm), $CDCl_3$ (δ_C = 77.00 ppm) or H_3PO_4 (external). Additional ^{1}H and ^{13}C (*J* modulated) spectra were measured at 360 K in [D_8]toluene on a DRX 400 at 400.1 and 100.6 MHz, respectively, and referenced to the

CHD_2 ($\delta_H = 2.09$ ppm) and the CD_3 group ($\delta_C = 21.04$ ppm). IR spectra were run as films on a silicon disc on a Perkin-Elmer 1600 FTIR spectrometer.[25] IR spectra of the ground aminophosphonic acids were recorded on an attenuated total internal reflection (ATR) diamond on a Perkin-Elmer Spektrum 2000 IR spectrometer. Optical rotations were measured at 20 °C on a Perkin-Elmer 351 polarimeter in a 1 dm cell. TLC analyses were carried out on 0.25 mm-thick Merck plates of silica gel 60 F_{254}. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualised by using UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (23.0 g) and of $Ce(SO_4)_2\cdot 4H_2O$ (1.0 g) in 10% aqueous H_2SO_4 (500 mL), followed by heating with a heat gun. Melting points were determined on a Reichert Thermovar instrument and are uncorrected.

TMEDA, Et_3N and pyridine were heated at reflux over powdered CaH_2 and toluene was heated at reflux over sodium/benzophenone; they were then distilled and stored over molecular sieves (4 Å). Et_2O was heated at reflux over $LiAlH_4$ and THF was heated at reflux over potassium under argon; they were then distilled prior to use. CH_2Cl_2 was dried by being passed through aluminium oxide 90 (active, neutral, 0.063–0.200 mm, activity I) and stored over molecular sieves (3 Å). TMP was used as supplied.

HPLC control for enantiomeric excess determination of α-aminophosphonic acids was performed as reported[15] by using pre-column derivatisation with the Sanger reagent to yield DNP derivatives and a chiral ion-exchange stationary phase based on quinine carbamate (CSP I in ref. [15], 150×4 mm i.d.): mobile phase: 80% MeOH/20% 50 mM NaH_2PO_4; pH_{app} 5.6; $T = 40$ °C; flow rate: 1 mL min^{-1}; compound/retention factor: (*R*)-(+)-**8a**/3.49, (*S*)-(−)-**8a**/4.81, (*R*)-(+)-**8b**/4.00, (*S*)-(−)-**8b**/6.94, (*R*)-(−)-**23**/2.88, (*S*)-(+)-**23**/3.90, (*R*)-(+)-**38**/3.37, (*S*)-(−)-**38**/4.28.

Phosphorylation of benzyl amines with diethyl chlorophosphate—General Procedure A: Diethyl chlorophosphate (3.45 g, 2.89 mL, 20 mmol) was added dropwise to a solution of amine (20 mmol) und triethylamine (3.04 g, 4.20 mL, 30 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C. Stirring was continued at 20 °C until the starting material was consumed (TLC, 8 h). Water (10 mL) and HCl (6 mL, 2 M) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by bulb-to-bulb distillation or flash chromatography.

Phosphorylation of benzyl amines with diisopropyl bromophosphate—General Procedure B: A solution of bromine (18.0 mL, 18.0 mmol, 1 M in dry CH_2Cl_2) was added dropwise to a solution of triisopropyl phosphite (3.75 g, 4.44 mL, 18.0 mmol) in dry CH_2Cl_2 (10 mL) under argon at −50 °C. The mixture was stirred for 30 min at 0 °C, re-cooled to −50 °C and benzyl amine (15 mmol) and Et_3N (3.04 g, 4.18 mL, 30 mmol) were added. After stirring the mixture at 20 °C until the starting material was consumed (TLC, several hours), HCl (12 mL, 2 M) und water (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by means of flash chromatography.

Preparation of N-Boc-protected phosphoramidates from phosphoramidates by using *s*BuLi/Boc_2O—General Procedure C: *s*BuLi (5.14 mL, 7.2 mmol, 1.4 M in cyclohexane) was added to a stirred solution of phosphoramidate (6 mmol) in dry Et_2O or THF (10 mL) under argon at −78 °C. After 15 min di-*t*-butyl dicarbonate (1.48 g, 6.6 mmol, Boc_2O) dissolved in dry Et_2O (5 mL) was added. The mixture was allowed to warm up in the cooling bath and was stirred until the starting material was consumed (18 h). After addition of AcOH (3 mL, 2 M in Et_2O) and water (10 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of flash chromatography.

Phosphoramidate–α-aminophosphonate rearrangement of N-Boc-protected phosphoramidates with *s*BuLi/TMEDA—General Procedure D: TMEDA (0.17 g, 0.23 mL, 1.5 mmol) and *s*BuLi (1.1 mL, 1.5 mmol, 1.4 M in cyclohexane) were added to a solution of an N-Boc-protected phosphoramidate (1.0 mmol) in dry Et_2O (or THF) (5 mL) under argon at −78 °C. When the product did not increase anymore (monitored by TLC, up to 1 h), AcOH (2 mL, 4 mmol, 2 M in Et_2O) and water (5 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of flash chromatography.

Deprotection of N-protected α-aminophosphonates with hot HCl (6 M)—General Procedure E: A mixture of aminophosphonate (1.0 mmol) and concentrated HCl (4 mL) und water (4 mL) was heated at reflux for 16 to 18 h. After concentration under reduced pressure, the residue was dried in a vacuum desiccator (KOH) and then purified by means of ion exchange chromatography (Dowex 50W,H^+, 50–100 mesh). Fractions (TLC: *i*PrOH/H_2O/NH_3 6:3:1) containing aminophosphonic acid were pooled, lyophilised and crystallised from water.

Deprotection of N-protected α-aminophosphonates with bromotrimethylsilane/allyltrimethylsilane—General Procedure F: Allyltrimethylsilane (0.46 g, 0.64 mL 4.0 mmol) and bromotrimethylsilane (0.77 g, 0.65 mL, 5.0 mmol) were added to a stirred solution of α-aminophosphonate (1 mmol) in dry 1,2-$C_2H_4Cl_2$ (6 mL) at 0 °C under argon. Then, the mixture was heated for 5 h at 50 °C (bath temperature). After cooling, volatile components were removed (5 mm Hg). The residue was dissolved in dry CH_2Cl_2 (5 mL) and concentrated under reduced pressure three times, the last time at 0.5 mbar. Methanol (10 mL) and water (5 mL) were added to the residue and stirred for 30 min. The mixture was concentrated under reduced pressure. Water was added and removed again under reduced pressure. After addition of water (20 mL) the mixture was lyophilised. The crude product was crystallised from water or water/EtOH.

(*R*)-(+)- and (*S*)-(−)-Diethyl *N*-(1-phenylethyl)phosphoramidate ((*R*)-(+)- and (*S*)-(−)-2a): (*R*)-(+)-1-Phenylethylamine (0.727 g, 6.0 mmol, 0.77 mL, 96% *ee*) was converted to (*R*)-(+)-**2a** by using General Procedure A. The residue was purified by bulb-to-bulb distillation (140 °C, 0.08 mbar) to give phosphoramidate (*R*)-(+)-**2a** (1.479 g, 96%) as a colourless oil; $[\alpha]_D^{20} = +40.9$ ($c = 2.37$, acetone). Similarly, (*S*)-(−)-1-phenylethylamine (20 mmol, 2.42 g, 2.54 mL, 98% *ee*) was converted to (*S*)-(−)-**2a** (4.35 g, 85%); $[\alpha]_D^{20} = -43.1$ ($c = 1.61$, acetone). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.07$ (dt, $J = 0.8$, 7.1 Hz, 3H), 1.28 (dt, $J = 0.5$, 7.1 Hz, 3H), 1.44 (dd, $J = 0.5$, 6.8 Hz, 3H), 3.22 (br t, $J = 8.8$ Hz), 3.69 (m, 1H), 3.90 (m, 1H), 4.02 (m, 2H), 4.28 (dquint, $J = 6.8$, 7.1 Hz, 1H), 7.20 ppm (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 15.8$ (d, $J = 6.9$ Hz), 16.1 (d, $J = 6.9$ Hz), 25.2 (d, $J = 6.1$ Hz), 51.4, 62.0 (d, $J = 4.6$ Hz), 62.2 (d, $J = 5.4$ Hz), 125.8 (2C), 127.0, 128.4 (2C), 145.1 ppm (d, $J = 4.6$ Hz); IR (Si): $\tilde{\nu} = 3212$, 2978, 2904, 1457, 1232, 1031, 966 cm^{-1}; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 8.7$ ppm; elemental analysis calcd (%) for $C_{12}H_{20}NO_3P$ (257.3): C 56.02, H 7.84, N 5.44; found: C 56.19, H 7.37, N 5.06.

(*R*)-(+)-Tetraethyl *N*-(1-phenylethyl)bis(phosphoramidate) ((*R*)-(+)-3): Phosphoramidate (*R*)-(+)-**2a** (1.30 g, 5.0 mmol) was phosphorylated at the nitrogen atom (flash chromatography: CH_2Cl_2/EtOAc 1:8, $R_f = 0.28$) to give (*R*)-(+)-**3** (0.94 g, 47%) as a colourless oil by using General Procedure B.[12] The analytical sample was additionally purified by using HPLC (Superspher Si 60: 4 μm; 237 mm×32 mm i.d.; 80 mL min^{-1}; hexanes/EtOAc 3:7; **2a**: $t_R = 26.7$ min; **3**: $t_R = 32$ min); $[\alpha]_D^{20} = +8.8$ ($c = 1.06$, acetone). ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 1.20$ (t, $J = 7.1$ Hz, 6H), 1.27 (t, $J = 7.1$ Hz, 6H), 1.81 (d, $J = 7.1$ Hz, 3H), 5.12 (tq, $J = 7.1$, 19.9 Hz, 1H), 7.26 (m, 3H), 7.55 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.8$ (d, $J = 3.7$ Hz), 15.88 (d, $J = 4.1$ Hz, 2C), 15.93 (d, $J = 4.1$ Hz), 19.2, 56.5, 62.85 (d, $J = 2.6$ Hz), 62.89 (d, $J = 2.6$ Hz), 63.1 (d, $J = 2.6$ Hz), 63.2 (d, $J = 2.6$ Hz), 127.0, 127.6 (2C), 128.0 (2C), 141.7 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 4.9$ ppm; IR (Si): $\tilde{\nu} = 3491$, 2983, 2934, 2909, 1497, 1478, 1449, 1392, 1370, 1260, 1210, 1166, 1028, 982 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{29}NO_6P_2$ (393.3): C 48.86, H 7.43, N 3.56; found: C 48.92, H 7.44, N 3.43.

(*S*)-(−)-Diethyl 1-(diethoxyphosphinylamino)-1-phenylethylphosphonate ((*S*)-(−)-6): Phosphoramidate (*R*)-(+)-**3** (0.39 g, 1 mmol) was rearranged by using General Procedure D (Et_2O, 3.5 h; flash chromatography: CH_2Cl_2/EtOAc 1:8, $R_f = 0.08$) to give phosphonate (*S*)-(−)-**6** (0.288 g,

73%) as a colourless oil. $[\alpha]_D^{20}=-24.6$ ($c=0.57$, acetone); ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta=1.00$ (dt, $J=0.9$, 7.1 Hz, 3H), 1.12 (dt, $J=0.5$, 7.1 Hz, 3H), 1.20 (dt, $J=0.5$, 7.1 Hz, 6H), 1.27 (dt, $J=0.9$, 7.1 Hz, 3H), 1.94 (d, $J=17.1$ Hz, 3H), 3.67 (m, 2H), 3.98 (m, 7H), 7.29 (m, 3H), 7.58 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=15.7$ (d, $J=7.4$ Hz), 15.9 (d, $J=7.8$ Hz), 16.1 (d, $J=6.0$ Hz), 16.2 (d, $J=5.5$ Hz), 20.0 (dd, $J=1.8$, 5.5 Hz), 56.7 (d, $J=155.3$ Hz), 62.1 (d, $J=5.5$ Hz), 62.3 (d, $J=5.5$ Hz), 63.2 (d, $J=7.4$ Hz), 63.4 (d, $J=7.4$ Hz), 127.0 (d, $J=5.1$ Hz, 2C), 127.4 (d, $J=2.7$ Hz), 127.8 (d, $J=2.3$ Hz, 2C), 140.7 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=26.1$ (d, $J=46.6$ Hz), 7.0 ppm (d, $J=46.6$ Hz); IR (Si): $\tilde{\nu}=3480$, 3240, 2982, 1444, 1393, 1243, 1164, 1029, 970 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{29}NO_6P_2$ (393.3): C 48.86, H 7.43, N 3.56; found: C 48.83, H 7.22, N 3.39.

Deblocking of (*S*)-(−)-diethyl 1-(diethoxyphosphinylamino)-1-phenylethylphosphonate ((*S*)-(−)-6): The phosphonate (250 mg, 0.64 mmol) was deblocked by using General Procedure E (ion-exchange chromatography: water as eluent; TLC: *i*PrOH/H_2O/NH_3 6:3:1, $R_f=0.62$) to give aminophosphonic acid (*S*)-(−)-**8a** (0.091 g, 71%, 50% *ee*). $[\alpha]_D^{20}=-24.6$ ($c=0.94$, 1 M NaOH).

(*S*)-(−)- and (*R*)-(+)-Diethyl *N*-(*t*-butoxycarbonyl)-*N*-(1-phenylethyl)-phosphoramidate ((*S*)-(−)- and (*R*)-(+)-10a): Compounds **10a** were prepared by using General Procedure C. The crude products were purified by means of flash chromatography (hexanes/EtOAc 1:2, $R_f=0.61$) to give colourless oils. Phosphoramidate (*S*)-(−)-**2a** (1.54 g, 6.0 mmol) gave (*S*)-(−)-**10a** (1.75 g, 82%); $[\alpha]_D^{20}=-10.3$ ($c=0.81$, acetone). Similarly, diethyl *N*-(1-phenylethyl)phosphoramidate ((*R*)-(+)-**2a**) (0.50 g, 1.9 mmol) gave phosphoramidate (*R*)-(+)-**10a** (0.65 g, 96%); $[\alpha]_D^{20}=+10.1$ ($c=2.51$, acetone). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta=1.29$ (s, 9H), 1.29 (dt, $J=1.0$, 7.1 Hz, 3H), 1.32 (dt, $J=1.0$, 7.1 Hz, 3H), 1.76 (d, $J=6.8$ Hz, 3H), 4.09 (m, 4H), 5.42 (dq, $J=6.8$, 13.9 Hz, 1H), 7.19 (m, 1H), 7.28 (m, 2H), 7.39 ppm (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=16.1$ (d, $J=6.9$ Hz), 16.2 (d, $J=6.9$ Hz), 18.2, 27.9 (3C), 54.8 (d, $J=3.1$ Hz), 63.2 (d, $J=6.1$ Hz), 63.7 (d, $J=6.1$ Hz), 82.2, 126.6, 126.8 (2C), 127.9 (2C), 142.3 (d, $J=3.6$ Hz), 153.2 ppm (d, $J=6.9$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=17.5$ ppm; IR (Si): $\tilde{\nu}=2980$, 1721, 1292, 1162, 1028 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{28}NO_5P$ (357.4): C 57.13, H 7.90, N 3.92; found: C 56.93, H 7.62, N 3.84.

(*R*)-(+)- and (*S*)-(−)-Diethyl 1-(*t*-butoxycarbonylamino)-1-phenylethylphosphonate ((*R*)-(+)- and (*S*)-(−)-13a): Phosphoramidate (*S*)-(−)-**10a** (0.73 g, 2 mmol) was rearranged in dry THF at −78°C in 1 h according to General Procedure D. Flash chromatography (EtOAc/hexanes 1:1, $R_f=0.28$) furnished phosphonate (*R*)-(+)-**13a** (0.58 g, 80%) as a colourless oil; $[\alpha]_D^{20}=+2.9$ ($c=1.50$, acetone). Analogously, (*S*)-(−)-**10a** (0.357 g, 1 mmol) was transformed in dry Et_2O at −78°C (3 h) into phosphonate (*R*)-(+)-**13a** (0.26 g, 65%). (*R*)-(+)-**13a** (0.26 g, 76%) was furnished from (*S*)-(−)-**10a** (0.357 g, 1 mmol) in dry Et_2O at −78°C in 45 min. After 1 h, (*S*)-(−)-**10a** (0.357 g, 1 mmol) yielded 0.139 g (39%) (*R*)-(+)-**13a** in dry Et_2O at −30°C, but after 10 min, also at −30°C, 0.26 g (73%) of product were obtained; $[\alpha]_D^{20}=+3.4$ ($c=0.83$, acetone). (*S*)-(−)-**10a** (0.71 g, 2 mmol) gave (*R*)-(+)-**13a** (0.42 g, 59%) in dry Et_2O at 0°C in 3 min; $[\alpha]_D^{20}=+2.4$ ($c=2.31$, acetone). Phosphoramidate (*R*)-(+)-**10a** (0.50 g, 1.4 mmol) was rearranged by means of General Procedure D in dry Et_2O at −78°C in 45 min to aminophosphonate (*S*)-(−)-**13a** (0.39 g, 79%); $[\alpha]_D^{20}=-2.9$ ($c=1.52$, acetone). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta=1.15$ (t, $J=7.1$ Hz, 3H), 1.21 (t, $J=7.1$ Hz, 3H), 1.31 (br s, 9H), 2.02 (d, $J=16.2$ Hz, 3H), 3.69 (m, 1H), 3.86 (m, 3H), 5.61 (br s, 1H), 7.22 (m, 1H), 7.30 (m, 2H), 7.45 ppm (m, 2H); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=25.9$ ppm; ^{1}H NMR (400.1 MHz, $C_6D_5CD_3$, 350 K): $\delta=0.90$ (t, $J=7.1$ Hz, 3H), 0.95 (t, $J=7.1$ Hz, 3H), 1.28 (s, 9H), 2.14 (dd, $J=1.5$, 15.9 Hz, 3H), 3.53 (m, 1H), 3.72 (m, 3H), 5.75 (br d, $J=10.6$ Hz, 1H), one H_{ar} overlapped with signals of [D_8]toluene, 7.13 (m, 2H), 7.57 ppm (m, 2H); ^{13}C NMR (100.6 MHz, $C_6D_5CD_3$, 350 K, 137.5): $\delta=16.2$ (d, $J=6.1$ Hz), 16.2 (d, $J=5.4$ Hz), 21.7 (d, $J=4.6$ Hz), 28.4 (3C), 58.5 (d, $J=147.6$ Hz), 63.1 (d, $J=6.9$ Hz), 63.1 (d, $J=6.9$ Hz), 79.3, 127.1 (d, $J=3.1$ Hz), 127.7 (d, $J=4.6$ Hz, 2C), 127.9 (d, $J=3.1$ Hz, 2C), 141.0 (d, $J=4.6$ Hz), 154.4 ppm; ^{31}P NMR (162 MHz, $C_6D_5CD_3$, 350 K): $\delta=26.2$ ppm; IR (Si): $\tilde{\nu}=3401$, 2979, 2930, 1734, 1495, 1250, 1165, 1047, 1023, 965 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{28}NO_5P$ (357.4): C 57.13, H 7.90, N 3.92; found: C 56.91, H 7.74, N 4.14.

Deblocking of (*R*)-(+)-13a and derivatisation of (*R*)-(+)-14a with (*S*)-MTPACl: Phosphonate (*R*)-(+)-**13a** (0.11 g, 0.30 mmol) was dissolved in dry CH_2Cl_2 (1 mL). After addition of CF_3CO_2H (1 mL) the mixture was stirred for 3 h at 20°C (TLC: CH_2Cl_2/MeOH 10:1) and then concentrated under reduced pressure. CH_2Cl_2 (10 mL), water (3 mL) and concentrated ammonia (5 drops) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with water (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (CH_2Cl_2/MeOH 15:1, TLC: 10:1, $R_f=0.72$) gave aminophosphonate (*R*)-(+)-**14a** (65 mg, 84%) as a colourless oil. $[\alpha]_D^{20}=+26.4$ ($c=1.23$, dry ethanol); ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta=1.12$ (dt, $J=0.5$, 6.9 Hz, 3H), 1.23 (dt, $J=0.5$, 6.9 Hz, 3H), 1.69 (d, $J=15.8$ Hz, 3H), 1.88 (br s, 2H), 3.85 (m, 4H), 7.30 (m, 3H), 7.61 ppm (m, 2H); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=29.10$ ppm; IR (Si): $\tilde{\nu}=3455$, 2986, 1682, 1556, 1447, 1207, 1140, 1025 cm^{-1}.

A mixture of aminophosphonate (*R*)-(+)-**14a** (26 mg, 0.10 mol), (*S*)-MTPACl (63 mg, 0.25 mmol), dry CH_2Cl_2 (0.5 mL), and dry pyridine (1 mL) was stirred for 16 h at 20°C. Water (a few drops) were added and the mixture was concentrated under reduced pressure. CH_2Cl_2 (10 mL) and HCl (5 mL, 2 M) were added. The organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of flash chromatography (hexanes/EtOAc 1:5, $R_f=0.70$) to give the (*R*)-Mosher amide of (*R*)-(+)-**14a** (40 mg, 85%, 96% *ee*) as a colourless oil. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta=1.11$ (t, $J=7.1$ Hz; CH_3, minor diastereomer), 1.15 (t, $J=7.1$ Hz; CH_3, major), 1.17 (t, $J=7.1$ Hz; CH_3, major), 1.21 ($J=7.1$ Hz; CH_3, minor), 2.06 (d, $J=16.2$ Hz; CH_3, 98%), 2.13 (d, $J=16.2$ Hz; CH_3, 2%), 3.45 (q, $J=1.6$ Hz; OCH_3, 98%), 3.57 (q, $J=1.6$ Hz; OCH_3, 2%), 3.69–4.00 (m, 4H), 7.21–7.58 (m, 10H), 7.86 ppm (br d, $J=10.7$ Hz, 1H; NH, major); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=24.96$ (minor diastereomer), 24.98 ppm (major).

(*R*)-(+)- and (*S*)-(−)-1-Amino-1-phenylethylphosphonic acid ((*R*)-(+)- and (*S*)-(−)-8a) as monohydrates: Phosphonate (*R*)-(+)-**13a** (0.13 g, 0.37 mmol) was deprotected according to General Procedure E (Dowex 50W,H^+; TLC: *i*PrOH/H_2O/NH_3 6:3:1, $R_f=0.37$; eluent: at first water, then aqueous AcOH (10%)) to yield aminophosphonic acid (*R*)-(+)-**8a** (0.05 g, 67%) as colourless crystals: m.p. 221–223°C (H_2O); $[\alpha]_D^{20}=+43.6$ ($c=0.81$, 1 M NaOH); *ee* of crude product: 97% (*ee* of crude product of rearrangement at −30°C: 98%). Phosphonate (*R*)-(+)-**13a** (0.31 g, 0.85 mmol, from rearrangement at 0°C) gave aminophosphonic acid (*R*)-(+)-**8a** (0.11 g, 56%) according to General Procedure F and crystallisation from water: *ee* of crude product: 98%; $[\alpha]_D^{20}=+49.5$ ($c=0.48$, 1 M NaOH). Phosphonate (*S*)-(−)-**13a** (0.454 g, 1.27 mmol) yielded aminophosphonic acid (*S*)-(−)-**8a** (0.21 g, 74%) according to General Procedure F and crystallisation from water; m.p. 222–223°C (ref. [26]: 235°C for monohydrate of racemate); *ee* of crude product: 92% (prepared from (*R*)-1-phenylethylamine ((*R*)-(+)-**1a**, 96% *ee*)); $[\alpha]_D^{20}=-50.2$ ($c=0.45$, 1 M NaOH). ^{1}H NMR (400.1 MHz, D_2O/NaOD, HDO = 4.67): $\delta=1.62$ (d, $J=12.1$ Hz, 3H), 7.23 (m, 1H), 7.32 (m, 2H), 7.43 ppm (m, 2H); ^{13}C NMR (100.6 MHz, D_2O/NaOD): $\delta=24.1$, 57.7 (d, $J=130.0$ Hz), 126.4 (d, $J=3.1$ Hz, 2C), 126.9 (d, $J=1.5$ Hz), 128.4 (d, $J=1.5$ Hz, 2C), 142.9 ppm; ^{31}P NMR (162 MHz, D_2O/NaOD): $\delta=8.1$ ppm; IR (ATR): $\tilde{\nu}=3113$, 2929, 1614, 1538, 1500, 1446, 1380, 1177, 1056, 1028, 924 cm^{-1}; elemental analysis calcd (%) for $C_8H_{14}NO_3P\cdot H_2O$ (219.2): C 43.84, H 6.44, N 6.39; found: C 43.56, H 5.83, N 5.86.

(±)- and (*S*)-(−)-Diethyl *N*-[1-(1-naphthyl)ethyl]phosphoramidate ((±)- and (*S*)-(−)-2b): 1-(1-Naphthyl)ethylamine ((±)-**1b**) (1.00 g, 5.84 mmol) was phosphorylated by using General Procedure A. Flash chromatography (EtOAc, $R_f=0.25$) gave phosphoramidate (±)-**2b** (1.59 g, 89%) as colourless crystals; m.p. 82–83°C (hexanes). Similarly, 1-(1-naphthyl)-ethylamine ((*S*)-(−)-**1b**) (0.51 g, 3.0 mmol, 99% *ee*) furnished phosphoramidate (*S*)-(−)-**2b** (0.83 g, 90%); m.p. 85–88°C (hexanes); $[\alpha]_D^{20}=-16.9$ ($c=0.80$, acetone). ^{1}H NMR (400.1 MHz, $CDCl_3$): $\delta=1.03$ (t, $J=7.1$ Hz, 3H), 1.24 (t, $J=7.1$ Hz, 3H), 1.28 (t, $J=7.1$ Hz, 6H), 1.62 (d, $J=6.8$ Hz, 3H), 3.19 (br s, 1H), 3.74 (m, 1H), 3.93 (m, 1H), 4.05 (m, 2H), 5.16 (sext, $J=6.8$ Hz, 1H), 7.50 (m, 4H), 7.75 (d, $J=8.1$ Hz, 1H), 7.85 (dd, $J=1.3$,

8.1 Hz, 1H), 8.14 ppm (d, J=8.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.9 (d, J=7.7 Hz), 16.2 (d, J=6.9 Hz), 24.9 (d, J=4.6 Hz), 47.4, 62.3 (d, J=5.4 Hz), 62.4 (d, J=5.4 Hz), 122.3, 123.0, 125.4, 125.6, 126.1, 127.8, 128.9, 130.3, 133.9, 140.8 ppm (d, J=5.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ=18.1 ppm; IR (Si, racemate): $\tilde{\nu}$=3215, 2979, 1232, 1031, 967 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{22}NO_3P$ (307.3): C 62.53, H 7.22, N 4.56; found for (±)-**2b**: C 62.70, H 7.29, N 4.54.

(±)- and (*S*)-(+)-Diethyl *N*-(*t*-butoxycarbonyl)-*N*-[1-(1-naphthyl)ethyl]-phosphoramidate ((±)- and (*S*)-(+)-10b): Diethyl *N*-[1-(1-naphthyl)-ethyl]phosphoramidate ((±)-**2b**) (1.54 g, 5 mmol) was converted by using General Procedure C (THF, flash chromatography: hexanes/EtOAc 2:1, R_f=0.32) to phosphoramidate (±)-**10b** (1.96 g, 96%) as colourless crystals; m.p. 71°C (hexanes). Similarly, diethyl *N*-[1-(1-naphthyl)ethyl]phosphoramidate ((*S*)-(−)-**2b**) (0.73 g, 2.36 mmol) was converted to phosphoramidate (*S*)-(+)-**10b** (0.91 g, 95%); m.p. 63–64°C (hexanes); $[\alpha]_D^{20}$=+16.1 (c=1.12, acetone). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.94 (dt, J=0.5, 7.1 Hz, 3H), 1.26 (dt, J=1.0, 7.1 Hz, 3H), 1.40 (s, 9H), 1.95 (d, J=7.1 Hz, 3H), 3.38 (m, 1H), 3.57 (m, 1H), 4.00 (m, 1H), 4.10 (m, 1H), 6.14 (dq, J=7.1, 17.7 Hz, 1H), 7.45 (m, 3H), 7.76 (brt, J=7.8 Hz, 2H), 7.82 (dd, J=1.5, 7.8 Hz, 1H), 8.18 ppm (d, J=8.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.7 (d, J=7.6 Hz), 16.1 (d, J=6.9 Hz), 19.1, 28.0 (3C), 52.1 (d, J=3.1 Hz), 62.5 (d, J=5.4 Hz), 63.2 (d, J=6.1 Hz), 82.3, 123.9, 124.8, 125.1, 125.9, 127.2, 128.1, 128.7, 131.8, 133.6, 136.1 (d, J=2.3 Hz), 153.8 ppm (d, J=5.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ=2.2 ppm; IR (Si, racemate): $\tilde{\nu}$=2980, 1708, 1298, 1163, 1027, 978 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{30}NO_5P$ (407.4): C 61.90, H 7.42, N 3.44; found for (±)-**10b**: C 62.12, H 7.36, N 3.43.

(±)- and (*R*)-(−)-Diethyl 1-(*t*-butoxycarbonylamino)-1-(1-naphthyl)ethylphosphonate ((±)- and (*R*)-(−)-13b): Phosphoramidate (±)-**10b** (1.10 g, 2.70 mmol) was transformed (General Procedure D, flash chromatography: hexanes/EtOAc 1:1, R_f=0.28) into phosphonate (±)-**13b** (0.83 g, 75%) as colourless crystals; m.p. 76–78°C (hexanes). Similarly, phosphoramidate (*S*)-(+)-**10b** (0.66 g, 1.61 mmol) gave aminophosphonate (*R*)-(−)-**13b** (0.49 g, 75%); $[\alpha]_D^{20}$=−68.3 (c=1.06, acetone). ^{1}H NMR (400.1 MHz, $C_6D_5CD_3$, 353 K): δ=0.77 (t, J=7.1 Hz, 3H), 0.92 (t, J=7.1 Hz, 3H), 1.09 (brs, 9H), 2.27 (d, J=14.9 Hz, 3H), 3.51 (m, 1H), 3.66 (m, 2H), 3.81 (m, 1H), 5.78 (brd, J=9.9 Hz, 1H), 7.21 (m, 2H), 7.33 (ddd, J=1.5, 6.8, 8.6 Hz, 1H), 7.53 (brd, J=8.1 Hz, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.65 (dd, J=3.0, 7.6 Hz, 1H), 9.07 ppm (d, J=8.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $C_6D_5CD_3$, 353 K): δ=16.2 (d, J=5.4 Hz), 16.4 (d, J=5.4 Hz), 25.7 (brs), 28.3 (3C), 30.4 (d, J=148.4 Hz), 63.1 (d, J=6.9 Hz), 63.2 (d, J=6.1 Hz), 79.3, 125.0, 127.2 (d, J=6.1 Hz), 128.0, 129.3, 133.0 (d, J=4.6 Hz), 135.4, 137.1 (d, J=4.6 Hz), 154.1 ppm (d, J=15.3 Hz); ^{31}P NMR (162 MHz, $C_6D_5CD_3$, 353 K): δ=26.1 ppm; IR (Si, racemate): $\tilde{\nu}$=3436, 3271, 2979, 1697, 1367, 1248, 1165, 1048, 1165, 1048, 1025 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{30}NO_5P$ (407.4): C 61.90, H 7.42, N 3.44; found for (±)-**13b**: C 61.94, H 7.43, N 3.22.

(±)- and (*R*)-(+)-1-Amino-1-(1-naphthyl)ethylphosphonic acid ((±)- and (*R*)-(+)-8b)) as hemihydrate and monohydrate, respectively: Phosphonate (±)-**13b** (0.33 g, 0.81 mmol) was converted (General Procedure E, Dowex 50W,H$^+$, H_2O; TLC: *i*PrOH/H_2O/NH_3 6:3:1, R_f=0.32) to 1-aminophosphonic acid (±)-**8b** (0.03 g, 14%) as brownish crystals. Phosphonate (±)-**13b** (0.15 g, 0.38 mmol) was also converted (General Procedure F) to aminophosphonic acid (±)-**8b**·0.5 H_2O (0.09 g, 90%) as colourless crystals; m.p. 205–208°C (water, low solubility even in hot water). Aminophosphonate (*R*)-(−)-**13b** (0.30 g, 0.74 mmol) analogously gave aminophosphonic acid (*R*)-(+)-**8b**·H_2O (0.11 g, 53%); m.p. 212°C (water); $[\alpha]_D^{20}$=+101.1 (c=0.44, 1M NaOH) (*ee* of crude product: 99%, *R* configuration). ^{1}H NMR (400.1 MHz, D_2O/NaOD, δ=4.67): δ=1.74 (d, J=12.4 Hz, 3H), 7.41 (m, 3H), 7.62 (dd, J=0.5, 6.3 Hz, 1H), 7.72 (d, J=8.1 Hz, 1H), 7.83 (m, 1H), 8.89 ppm (m, 1H); ^{13}C NMR (100.6 MHz, D_2O/NaOD): δ=27.3, 58.2 (d, J=130.8 Hz), 124.8, 125.5, 125.5 (d, J=6.1 Hz), 125.7 (d, J=2.3 Hz), 127.7, 129.1, 130.4, 131.7 (d, J=3.1 Hz), 134.8 (d, J=1.5 Hz), 142.6 ppm; ^{31}P NMR (162 MHz, D_2O): δ=22.2 ppm; IR (ATR, racemate): $\tilde{\nu}$=3049, 1615, 1515, 1445, 1390, 1138, 1108, 913 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{14}NO_3P$·0.5 H_2O (260.2): C 55.39, H 5.81, N 5.38; found for (±)-**8b**: C 55.35, H 5.1, N 5.36; elemental analysis calcd (%) for $C_{12}H_{14}NO_3P$·H_2O (269.2): C 53.53, H 5.99, N 5.20; found for (*R*)-(+)-**8b**: C 53.50, H 5.95, N 5.18.

(±)-1-Azidoindan ((±)-15) by Mitsunobu reaction: HN_3 (5.60 mmol, 7.30 mL, 0.77M in toluene, HN_3) was added to a stirred solution of triphenylphosphane (1.26 g, 4.80 mmol) and (±)-1-indanol (0.537 g, 4 mmol) in dry THF (5 mL) at 0°C under argon; this was followed immediately by addition of DIAD (0.97 g, 0.95 mL, 4.80 mmol). The mixture was stirred for 18 h at 20°C. After the addition of MeOH (5 drops) it was concentrated under reduced pressure and heated with hexanes. After cooling, the mother liquor was removed, concentrated under reduced pressure and purified by means of flash chromatography (hexanes/CH_2Cl_2 2:1, R_f=0.48) to give (±)-1-azidoindan ((±)-**15**) (0.56 g, 88%) as a colourless liquid.

Preparation of (*R*)-(+)-1-azidoindan ((*R*)-(+)-15) by use of diphenylphosphoryl azide/DBU: DBU (0.93 g, 0.92 mL, 6.12 mmol) and $(PhO)_2P(O)N_3$ (1.68 g, 1.31 mL, 6.10 mmol) were added to a stirred solution of (*S*)-(+)-1-indanol (0.68 g, 5.10 mmol, >98% *ee*) in dry toluene (8 mL) at 0°C under argon. After stirring for 2 h at 0°C and 5 h at 20°C, water (10 mL) and 5% HCl (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of flash chromatography (hexanes/CH_2Cl_2 5:1, R_f=0.77) to give (*R*)-(+)-**15** (0.57 g, 70%, 94.1% *ee*) as a colourless liquid. $[\alpha]_D^{20}$=+29.3 (c=1.61, hexane) (ref. [22]: $[\alpha]_D^{20}$=+25.3 (c=1.10, hexane)).

(±)-Diethyl *N*-(1-indanyl)phosphoramidate ((±)-19a) from amine: 1-Indanamine ((±)-**18**) (0.240 g, 1.80 mmol) was converted (General Procedure A, flash chromatography: EtOAc, R_f=0.40) to phosphoramidate (±)-**19a** (0.29 g, 59%) as colourless crystals. M.p. 65°C (hexanes).

(±)-Diethyl *N*-(1-indanyl)phosphoramidate ((±)-19a) from azide: A stirred solution of triethyl phosphite (0.997 g, 1.03 mL, 6 mmol) and 1-azidoindan ((±)-**15**) (5 mmol) in dry toluene (10 mL) was heated for 4 h at 50°C. The cooled mixture was diluted with THF and water (5 mL each) and concentrated under reduced pressure. Flash chromatography (EtOAc/hexanes 1:2, R_f=0.39) of the crude product gave phosphoramidate (±)-**19a** (1.32 g, 98%). M.p. 65°C (hexanes); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.34 (dt, J=0.8, 7.1 Hz, 3H), 1.35 (dt, J=0.8, 7.1 Hz, 3H), 1.77 (m, 1H), 2.55 (ddt, J=2.8, 7.6, 12.6 Hz, 1H), 2.76 (m, 1H), 2.78 (t, J=10.9 Hz, 1H), 2.91 (ddd J=2.8, 8.6, 15.7 Hz, 1H), 4.11 (m, 4H), 4.65 (m, 1H), 7.20 (m, 3H), 7.39 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.2 (d, J=6.9 Hz), 16.3 (d, J=6.9 Hz), 29.8, 36.7 (d, J=2.3 Hz), 57.0, 62.4 (d, J=6.1 Hz), 62.4 (d, J=6.1 Hz), 123.9, 124.7, 126 6, 127.7, 142.7, 144.5 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): δ=9.4 ppm; IR (Si): $\tilde{\nu}$=3207, 2980, 1459, 1232, 1058, 1032, 999 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{20}NO_3P$ (269.3): C 57.98, H 7.49, N 5.20; found: C 57.93, H 7.44, N 5.14.

(±)-Diethyl *N*-(*t*-butoxycarbonyl)-*N*-(1-indanyl)phosphoramidate ((±)-17a): Reaction of phosphoramidate (±)-**19a** (1.06 g, 3.94 mmol) gave (General Procedure C; flash chromatography: EtOAc/hexanes 1:1, R_f=0.51) phosphoramidate (±)-**17a** (1.32 g, 91%) as a colourless oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.20 (s, 9H), 1.33 (dt, J=0.8, 7.1 Hz, 3H), 1.36 (dt, J=1.0, 7.1 Hz, 3H), 2.33 (m, 1H), 2.47 (m, 1H), 2.84 (m, 1H), 3.03 (ddd, J=2.8, 9.9, 15.9 Hz, 1H), 4.18 (m, 4H), 5.68 (dt, J=8.3, 11.4 Hz, 1H), 7.15 ppm (s, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.1 (d, J=6.8 Hz), 16.3 (d, J=7.6 Hz), 27.7 (3C), 30.3, 30.7 (d, J=1.5 Hz), 62.2 (d, J=3.8 Hz), 63.4 (d, J=6.1 Hz), 63.8 (d, J=5.4 Hz), 82.0, 122.5, 124.7, 126.2, 127.0, 142.2, 143.3 (d, J=3.8 Hz), 153.0 ppm (d, J=7.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ=4.3 ppm; IR (Si): $\tilde{\nu}$=2980, 1718, 1457, 1394, 1368, 1295, 1160, 1028, 979 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{28}NO_5P$ (369.4): C 58.53, H 7.64, N 3.79; found: C 58.29, H 7.68, N 3.84.

(±)-Diethyl 1-(*t*-butoxycarbonylamino)-1-indanylphosphonate ((±)-22a): Phosphoramidate (±)-**17a** (0.37 g, 1.0 mmol) was rearranged (General Procedure D; *s*BuLi/TMEDA, THF; flash chromatography: EtOAc/hexanes 1:1, R_f=0.35) to give phosphonate (±)-**22a** (0.20 g, 54%) as colourless crystals. M.p. 100–101°C (hexanes); ^{1}H NMR (400.1 MHz, $C_6D_5CD_3$, 353 K): δ=0.84 (t, J=7.1 Hz, 3H), 1.04 (t, J=7.1 Hz, 3H), 1.27 (s, 9H), 2.78–3.01 (m, 4H), 3.56 (m, 1H), 3.75 (m, 1H), 3.88 (m, 2H), 5.52 (brd,

J=6.6 Hz, 1H), 7.01 (m, 3H), 7.46 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $C_6D_5CD_3$, 353 K): δ=16.3 (d, J=5.4 Hz), 16.5 (d, J=4.6 Hz), 28.5 (3C), 31.2 (d, J=1.5 Hz), 34.2, 53.5 (d, J=186.6 Hz), 62.8 (d, J=7.7 Hz), 63.2 (d, J=6.9 Hz), 79.4, 124.9 (d, J=2.3 Hz), 125.3 (d, J=3.1 Hz), 126.6 (d, J=2.3 Hz), 128.5 (d, J=3.1 Hz), 141.9 (d, J=3.8 Hz), 145.2 (d, J=6.9 Hz), 153.5 ppm; ^{31}P NMR (162 MHz, $C_6D_5CD_3$, 353 K): δ=25.8 ppm; IR (Si): $\tilde{\nu}$=3271, 2979, 2930, 1718, 1490, 1457, 1391, 1367, 1249, 1163, 1062, 1024, 966 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{28}NO_5P$ (369.4): C 58.53, H 7.64, N 3.79; found: C 58.27, H 7.61, N 3.80.

(*R*)-(+)-Diisopropyl *N*-(1-indanyl)phosphoramidate ((*R*)-(+)-19b): (*R*)-(+)-1-Azidoindan ((*R*)-(+)-**15**) (0.88 g, 5.5 mmol) and triisopropyl phosphite were transformed (flash chromatography: EtOAc/hexanes 1:1; R_f= 0.55) according to the procedure used for the preparation of (±)-diethyl *N*-(1-indanyl)phosphoramidate from the azide to phosphoramidate (*R*)-(+)-**19b** (1.51 g, 93%) as colourless crystals. M.p. 46–51°C (hexanes); $[\alpha]_D^{20}$=+51.3 (c=0.94, hexanes); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.34 (d, J=6.3 Hz, 3H), 1.35 (d, J=6.3 Hz, 9H), 1.76 (m, 1H), 2.56 (ddt, J= 2.6, 7.6, 12.6 Hz, 1H), 2.70 (brt, J=10.6 Hz, 1H), 2.76 (m, 1H), 2.90 (ddd, J=2.6, 8.6, 15.9 Hz, 1H), 4.67 (m, 3H), 7.21 (m, 3H), 7.43 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=23.9 (d, J=5.3 Hz), 23.9 (d, J= 4.6 Hz), 24.0 (d, J=4.6 Hz), 24.0 (d, J=4.6 Hz), 29.9, 36.8 (d, J=3.8 Hz), 57.1, 70.9 (d, J=6.1 Hz), 70.9 (d, J=6.1 Hz), 124.0, 124.6, 126.6, 127.7, 142.8, 144.8 ppm (d, J=7.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ= 7.6 ppm; IR (Si): $\tilde{\nu}$=3210, 2977, 2935, 1460, 1385, 1232, 1109, 1017, 986 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{24}NO_3P$ (297.3): C 60.59, H 8.14, N 4.71; found: C 60.55, H 7.93, N 4.70.

(*R*)-(+)-Diisopropyl *N*-(*t*-butoxycarbonyl)-*N*-(1-indanyl)phosphoramidate ((*R*)-(+)-17b): Phosphoramidate (*R*)-(+)-**19b** (1.19 g, 4.0 mmol) was transformed in dry THF according to General Procedure C (flash chromatography: hexanes/EtOAc 2:1, R_f=0.48) into phosphoramidate (*R*)-(+)-**17b** (1.18 g, 74%) as a colourless oil. $[\alpha]_D^{20}$=+8.1 (c=2.40, hexanes).

Preparation of (*R*)-(+)-17b by reaction of (*R*)-1-azidoindan ((*R*)-(+)-15) with triisopropyl phosphite, followed by reaction with Boc_2O: A solution of (*R*)-(+)-**15** (0.35 g, 2.2 mmol) and triisopropyl phosphite (0.50 g, 0.59 mL, 2.4 mmol) in dry toluene (8 mL) was stirred at 50°C for 18 h (TLC: EtOAc) under argon. After cooling, Boc_2O (0.52 g, 2.4 mmol) dissolved in dry toluene (1 mL) was added; then heating was continued for 72 h at +80°C and finally AcOH (2 mL, 2M, in Et_2O) was added. The mixture was concentrated under reduced pressure and dissolved in hexanes. The mixture was filtered to remove a small amount of urea derived from 1-aminoindan and the concentrated mother liquor was purified by means of flash chromatography (EtOAc/hexanes 1:1, R_f=0.67) to give (*R*)-(+)-**17b** (0.51 g, 58%). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.20 (s, 9H), 1.31 (d, J=6.1 Hz, 3H), 1.34 (d, J=6.1 Hz, 3H), 1.37 (d, J=6.1 Hz, 3H), 1.38 (d, J=6.1 Hz, 3H), 2.34 (m, 1H), 2.46 (m, 1H), 2.83 (dt, J= 8.6, 15.9 Hz, 1H), 3.03 (ddd, J=2.8, 9.9, 15.9 Hz, 1H), 4.67 (dsept, J= 6.2, 7.8 Hz, 1H), 4.80 (dsept, J=6.2, 7.8 Hz, 1H), 5.71 (dt, J=8.6, 11.1 Hz, 1H), 7.14 ppm (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=23.5 (d, J=5.4 Hz), 23.8 (d, J=5.4 Hz), 23.8 (d, J=5.4 Hz, 2C), 27.7 (3C), 30.3, 30.7, 62.3 (d, J=3.1 Hz), 72.1 (d, J=6.1 Hz), 72.5 (d, J=6.1 Hz), 81.7, 122.4, 124.6, 126.1, 126.9, 142.2, 143.5, 153.0 ppm (d, J=6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ=1.9 ppm; IR (Si): $\tilde{\nu}$=2980, 2934, 1724, 1293, 1270, 1161, 1001 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{32}NO_5P$ (397.5): C 60.44, H 8.12, N 3.52; found: C 60.42, H 8.08, N 3.58.

(*S*)-(−)-Diisopropyl 1-(*t*-butoxycarbonylamino)-1-indanylphosphonate ((*S*)-(−)-22b): Phosphoramidate (*R*)-(+)-**17b** (0.40 g, 1.0 mmol) was rearranged in dry THF by using General Procedure D (flash chromatography: hexanes/EtOAc 2:1, R_f=0.27) to give phosphonate (*S*)-(−)-**22b** (0.24 g, 60%) as a colourless oil. $[\alpha]_D^{20}$=−1.2 (c=1.30, hexanes); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=0.77 (d, J=6.1 Hz, 3H), 1.16 (d, J= 6.1 Hz, 3H), 1.19 (s, 9H), 1.22 (d, J=6.1 Hz, 3H), 1.25 (d, J=6.1 Hz, 3H), 2.66 (m, 2H), 2.92 (m, 2H), 4.30 (dsept, J=6.1, 6.6 Hz, 1H), 4.56 (dsept, J=6.1, 6.6 Hz, 1H), 5.38 (d, J=8.8 Hz, 1H), 7.11 (m, 3H), 7.31 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=22.7 (d, J= 6.1 Hz), 23.7 (d, J=5.4 Hz), 23.8 (d, J=3.1 Hz), 24.2 (d, J=2.3 Hz), 27.9 (3C), 30.4 (2C), 65.4 (d, J=157.6 Hz), 71.3 (d, J=7.7 Hz), 72.3 (d, J= 7.7 Hz), 79.4, 124.4 (d, J=1.5 Hz), 124.5, 126.0 (d, J=3.1 Hz), 128.0 (d, J=2.3 Hz), 140.1, 144.1 (d, J=6.9 Hz), 154.0 ppm (d, J=13.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ=24.0 ppm; IR (Si): $\tilde{\nu}$=3443, 3071, 2978, 2932, 1718, 1701, 1491, 1457, 1386, 1367, 1248, 1172, 1142, 1106, 1058, 1042, 985 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{32}NO_5P$ (397.5): C 60.44, H 8.12, N 3.52; found: C 60.42, H 8.15, N 3.26.

(±)-Diethyl 1-amino-1-indanylphosphonate ((±)-24) by means of carboxylation: *s*BuLi (1.1 mL, 1.54 mmol, 1.4M, in cyclohexane) was added to a stirred solution of *N*-(1-indanyl)phosphoramidate (±)-**19a** (0.27 g, 1.0 mmol) in dry Et_2O (4 mL) at −78°C under argon. A few minutes later, the argon was replaced by CO_2 (in a balloon). After 10 min, the volatiles were removed at −30°C under reduced pressure (5 mm) and the flask was flushed three times with argon and then filled with it. Dry Et_2O (4 mL) was added to the residue. The mixture was cooled to −78°C and dry TMEDA (0.29 g, 0.38 mL, 2.5 mmol) and *s*BuLi (1.79 mL, 2.51 mmol, 1.4M, in cyclohexane) were added. After stirring for 1 h at −78°C, ethanol (5 mL) was added. The mixture was concentrated under reduced pressure. The residue was treated with water (10 mL) and extracted with CH_2Cl_2 (3×12 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of flash chromatography (CH_2Cl_2/EtOH 15:1, R_f=0.64) to give 1-amino-1-indanylphosphonate (±)-**25** (0.07 g, 26%) as a colourless oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.12 (t, J=7.1 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H), 1.87 (brs, 2H), 1.97 (ddt, J=9.1, 13.4, 21.2 Hz, 1H), 2.79 (dddd, J=4.0, 7.3, 13.4, 14.7 Hz, 1H), 2.99 (m, 2H), 3.78 (m, 1H), 3.95 (m, 1H), 4.08 (m, 2H), 7.21 (m, 3H), 7.45 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=16.3 (d, J=5.4 Hz), 16.5 (d, J=6.1 Hz), 30.4 (d, J=2.3 Hz), 38.4 (d, J=3.1 Hz), 62.5 (d, J=7.6 Hz), 63.0 (d, J=6.9 Hz), 124.7 (d, J=3.1 Hz), 124.7 (d, J=3.1 Hz), 126.7 (d, J=3.1 Hz), 128.4 (d, J=2.3 Hz), 144.1, 144.2 ppm, PC (n.d.); ^{31}P NMR (162 MHz, $CDCl_3$): δ= 28.7 ppm; IR (Si): $\tilde{\nu}$=3368, 2980, 1235, 1025, 963 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{20}NO_3P$ (269.3): C 57.98, H 7.49, N 5.20; found: C 57.76, H 7.19, N 5.13.

(±)-and (*S*)-(+)-1-Amino-1-indanylphosphonic acid ((±)- and (*S*)-(+)-23), the former as monohydrate: Phosphonate (±)-**22a** (0.45 g, 1.21 mmol) was deblocked by using General Procedure F and crystallised from water to give (±)-aminophosphonic acid (±)-**23**·H_2O (0.14 g, 55%) as colourless crystals; m.p. 213–214°C. Diisopropyl 1-(*t*-butoxycarbonylamino)-1-indanylphosphonate ((*S*)-(−)-**22b**) (0.18 g, 0.46 mmol) was deblocked by using General Procedure E and purified by means of ion-exchange chromatography (Dowex 50W,H^+, H_2O; TLC: *i*PrOH/H_2O/NH_3 6:3:1, R_f=0.43) to furnish aminophosphonic acid (*S*)-(+)-**23** (0.065 g, 67%) as colourless crystals; m.p. 232–233°C (water/ethanol), $[\alpha]_D^{20}$= +30.5 (c=0.43, water) (*ee* of crude product: 96%, *S* configuration). ^{1}H NMR (400.1 MHz, D_2O, δ=4.67): δ=2.19 (dddd, J=7.6, 8.8, 14.0, 23.0 Hz, 1H), 2.74 (dddd, J=4.6, 8.2, 14.0, 21.1 Hz, 1H), 3.03 (m, 2H), 7.30 (m, 3H), 7.49 ppm (brd, J=7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, D_2O): δ=32.9 (d, J=2.3 Hz), 36.3, 67.7 (d, J=148.4 Hz), 127.4 (d, J= 1.5 Hz), 128.2, 129.3 (d, J=1.5 Hz), 132.5 (d, J=2.3 Hz), 141.0, 147.6 ppm (d, J=6.1 Hz); ^{31}P NMR (162 MHz, D_2O): δ=15.1 ppm; IR (ATR, racemate): $\tilde{\nu}$=2926, 1630, 1602, 1531, 1479, 1459, 1180, 1141, 1090, 1030, 913 cm^{-1}; elemental analysis calcd (%) for $C_9H_{12}NO_3P$·H_2O (231.2): C 46.76, H 6.10, N 6.06; found for (±)-**23**: C 46.35, H 5.86, N 5.97; elemental analysis calcd (%) for $C_9H_{12}NO_3P$ (213.2): C 50.71, H 5.67, N 6.57; found for (*S*)-(+)-**23**: C 50.55, H 5.61, N 6.46.

(±)-Diethyl *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)phosphoramidate ((±)-27): 1-Amino-1,2,3,4-tetrahydronaphthalene ((±)-**26**) (0.88 g, 6.0 mmol) was phosphorylated by using General Procedure A (flash chromatography: hexanes/EtOAc 2:1, R_f=0.32) to furnish phosphoramidate (±)-**27** (1.58 g, 93%) as colourless crystals. M.p. 72–74°C (hexanes); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.34 (t, J=7.1 Hz, 6H), 1.78 (m, 2H), 2.07 (m, 1H), 2.74 (m, 3H), 4.11 (m, 4H), 4.34 (m, 1H), 7.05 (m, 1H), 7.15 (m, 2H), 8.74 ppm (m, 1H); ^{13}C NMR: (100.6 MHz, $CDCl_3$): δ=16.7 (d, J= 6.9 Hz), 20.2, 29.6, 33.0, 50.5, 62.9 (d, J=5.4 Hz, 2C), 126.5, 127.5, 129.0, 129.4, 137.6, 138.8 ppm (d, J=7.7 Hz); ^{31}P NMR: (162 MHz, $CDCl_3$): δ= 9.1 ppm; IR (Si): $\tilde{\nu}$=3181, 2981, 2935, 1451, 1235, 1040 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{22}NO_3P$ (283.3): C 59.35, H 7.83, N 4.94; found: C 59.14, H 7.96, N 4.90.

(±)-Diethyl *N*-(*t*-butoxycarbonyl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-phosphoramidate ((±)-28): Phosphoramidate (±)-**27** (0.57 g, 2.0 mmol) was Boc-protected by using General Procedure C (flash chromatography: EtOAc/hexanes 2:1, R_f=0.71) to give phosphoramidate (±)-**28** (0.66 g, 86%) as a colourless oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.20 (s, 9H), 1.34 (dt, J=0.8, 7.1 Hz, 3H), 1.38 (br t, J=7.1 Hz, 3H), 1.73 (ddq, J=3.0, 4.8, 13.4 Hz, 1H), 1.97 (m, 1H), 2.13 (m, 1H), 2.27 (m, 1H), 2.75 (m, 2H), 4.18 (m, 4H), 5.27 (dt, J=6.1, 11.6 Hz, 1H), 7.06 (m, 3H), 7.25 ppm (m, 1H); ^{13}C NMR: (100.6 MHz, $CDCl_3$): δ=16.1 (d, J=6.9 Hz), 16.3 (d, J=6.9 Hz), 23.0, 27.7 (3C), 29.7, 29.7, 56.9 (d, J=3.1 Hz), 63.4 (d, J=5.4 Hz), 64.1 (d, J=6.1 Hz), 82.0, 125.5, 125.9, 126.0, 128.7, 137.3, 138.1 ppm (d, J=3.8 Hz), C=O (n.d.); ^{31}P NMR: (162 MHz, $CDCl_3$): δ=4.6 ppm; IR (Si): $\tilde{\nu}$=2980, 2935, 1723, 1394, 1368, 1287, 1160, 1032 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{30}NO_5P$ (383.4): C 59.52, H 7.89, N 3.65; found: C 59.55, H 7.62, N 3.59.

(±)-Diethyl 1-(*t*-butoxycarbonylamino)-(1,2,3,4-tetrahydronaphthalen-1-yl)phosphonate ((±)-30): Phosphoramidate (±)-**28** (0.24 g, 0.64 mmol) was rearranged by using General Procedure D (THF, flash chromatography: CH_2Cl_2/EtOAc 3:1, R_f=0.58) to give phosphonate (±)-**30** (0.09 g, 38%) as a colourless oil. ^{1}H NMR: (400.1 MHz, 353 K, $C_6D_5CD_3$): δ=0.77 (t, J=7.1 Hz, 3H, CH_3), 1.05 (t, J=7.1 Hz, 3H), 1.28 (s, 9H), 1.84 (m, 1H), 2.14 (m, 1H), 2.45 (dddt, J=0.5, 3.5, 6.8, 13.7 Hz), 2.74 (m, 2H), 2.93 (dddd, J=3.8, 11.2, 13.7, 25.5 Hz, 1H), 3.35 (ddq, J=7.1, 8.9, 10.1 Hz, 1H), 3.66 (dquint, J=7.1, 10.1 Hz, 1H), 3.89 (m, 2H), 5.90 (br d, J=10.1 Hz), 6.88 (m, 1H), 6.96 (m, 2H), 7.79 ppm (dt, J=1.8, 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, 353 K, $C_6D_5CD_3$): δ=16.2 (d, J=5.4 Hz), 16.5 (d, J=5.4 Hz), 20.8 (d, J=2.3 Hz), 28.5 (3C), 30.1, 31.2 (d, J=3.1 Hz), 58.3 (d, J=148.4 Hz), 62.9 (d, J=6.9 Hz), 63.3 (d, J=6.9 Hz), 79.4, 126.0 (d, J=3.1 Hz), 127.5 (d, J=3.1 Hz), 128.5 (d, J=3.8 Hz), 129.3 (d, J=2.3 Hz), 136.2 (d, J=5.4 Hz), 139.5 (d, J=6.9 Hz), 154.4 ppm (d, J=16.1 Hz); ^{31}P NMR :(162 MHz, $C_6D_5CD_3$, 350 K): δ=27.4 ppm; IR (Si): $\tilde{\nu}$=2927, 1730, 1489, 1165, 1050, 1024, 966 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{30}NO_5P$ (383.4): C 59.52, H 7.89, N 3.65; found: C 59.61, H 7.71, N 3.60.

Rearrangement of (±)-diethyl *N*-(*t*-butoxycarbonyl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)phosphoramidate ((±)-28) with LiTMP/TMEDA as base: *n*BuLi (2.54 mL, 1.6 M in hexane, 4.06 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.574 g, 0.69 mL, 4.06 mmol) and TMEDA (0.472 g, 0.61 mL, 4.06 mmol) in dry Et_2O (6 mL) at −20 °C under argon. After stirring for 30 min, the solution was cooled to −78 °C and (±)-**28** (0.778 g, 2.03 mmol, dissolved in 5 mL of dry Et_2O) was added. Four hours later, the reaction was quenched with AcOH (5 mL, 2 M in Et_2O) and water (10 mL). The organic phase was separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to flash chromatography (hexanes/EtOAc 1:1, R_f=0.30) to give starting material (0.287 g, 37%) and a mixture of hydroxyphosphonamidates (±)-**32a–d** (0.287 g, 37%), from which isomer (±)-**32a** was obtained as colourless crystals by crystallising twice from hexanes. M.p. 116–117 °C.

(S_P*)-Ethyl *N*-(*t*-butoxycarbonyl)-*N*-[(*R)-1,2,3,4-tetrahydronaphthalen-1-yl)]-[(*S**)-1-hydroxyethyl]phosphonamidate ((±)-32a)**: ^{1}H NMR (400.1 MHz, 353 K, $C_6D_5CD_3$): δ=1.03 (s, 9H), 1.13 (t, J=7.1 Hz, 3H), 1.55 (m, 1H), 1.62 (dd, J=7.1, 18.4 Hz, 3H), 1.77 (m, 1H), 2.14 (m, 1H), 2.24 (m, 1H), 2.47 (m, 1H), 2.68 (m, 1H), 3.97 (m, 1H), 4.07 (m, 1H), 4.13 (t, J=6.6 Hz, 1H), 4.50 (m, 1H), 5.48 (dt, J=7.8, 10.1 Hz, 1H), 6.84 (br d, J=7.5 Hz, 1H), 6.93 (br d, J=7.5 Hz, 1H), 6.99 (br d, J=7.5 Hz, 1H), 7.36 ppm (br d, J=7.5 Hz, 1H); ^{13}C NMR: (100.6 MHz, 353 K, $C_6D_5CD_3$): δ=16.4 (d, J=6.1 Hz), 18.7, 23.4, 27.9 (3C), 30.3, 30.9, 55.8, 61.9 (d, J=8.4 Hz), 67.6 (d, J=138.44 Hz), 82.6, 126.3, 126.4, 126.5, 129.2, 138.2, 139.0 (d, J=4.6 Hz), 155.6 ppm (d, J=8.4 Hz); ^{31}P NMR (162 MHz, $C_6D_5CD_3$, 350 K): δ=31.9 ppm; IR (Si): $\tilde{\nu}$=3317, 2979, 1707, 1399, 1368, 1282, 1157, 1100, 1029 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{32}NO_5P$ (385.4): C 59.21, H 8.37, N 3.63; found: C 59.49, H 8.08, N 3.63.

Crystal structure analysis: X-ray data of (±)-**32a** were collected at 100 K on a Bruker Smart APEX CCD area detector diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation, λ=0.71073 Å, using 0.3° ω-scan frames covering a hemisphere of the reciprocal space. After data integration, corrections for absorption and $\lambda/2$ effects were applied. The structure was solved with direct methods and was then refined on F^2 with hydrogen atoms in idealised positions by using SHELXTL.[27] CCDC-668518 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*Crystal data for (±)-**32a***: $C_{19}H_{30}NO_5P$; M_r=383.41; monoclinic; space group $P2_1/c$ (no. 14); T=100(2) K; a=14.5683(9), b=11.5085(7), c=48.043(3) Å; β=91.007(1)°; V=8053.6(9) Å^3; Z=16; Z'=4; ρ_{calcd}=1.265 g cm^{-3}; μ=0.165 mm^{-1}; 69485 reflections collected up to θ_{max}=30°; 23239 independent reflections (R_{int}=0.035); 18774 observed reflections ($I>2\sigma(I)$); final R indices: R_1=0.065 ($I>2\sigma(I)$), wR_2=0.155 (all data). The structure contains four independent molecules, which are cyclically linked into two pseudocentrosymmetric pairs by means of pairs of CH-O-H···O=P hydrogen bonds. The four molecules differ significantly in conformation (P-N-(CO)-O-*t*Bu for two molecules in a *cisoid* and for two molecules in a *transoid* configuration; variations in the orientation of the (P)-O-Et groups).

(±)- and (*R*)-(+)-1-Azido-1,2,3,4-tetrahydronaphthalene ((±)- and (*R*)-(+)-34): (±)-α-Tetralol (0.15 g, 1.0 mmol) was prepared in analogy to (*R*)-(+)-1-azidoindan (flash chromatography: EtOAc/hexanes 1:19, R_f=0.80) to give (±)-**34** (0.16 g, 92%) as a colourless liquid. Similarly, (*S*)-(−)-1,2,3,4-tetrahydro-1-naphthol (1.26 g, 8.47 mmol, 99.8% *ee*, $[\alpha]_D^{20}$=−30.9 (c=4.9, $CHCl_3$)) was converted to (*R*)-(+)-**34** (1.32 g, 90%); $[\alpha]_D^{20}$=+45.0 (c=3.67, acetone). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.81 (m, 1H), 1.98 (m, 3H), 2.74 (m, 1H), 2.84 (m, 1H), 4.56 (≈t, J=4.3 Hz, 1H), 7.13 (m, 1H), 7.22 (m, 2H), 7.28 ppm (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.0, 28.8, 29.1, 59.5, 126.1, 128.1, 129.1, 129.4, 133.7, 137.3 ppm; IR (Si, racemate): $\tilde{\nu}$=2940, 2096, 1492, 1455, 1245, 1060, 944 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{11}N_3$ (173.2): C 69.34, H 6.40, N 24.26; found: C 69.40, H 6.33, N 24.45.

(±)- and (*R*)-(+)-Diisopropyl *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)phosphoramidate ((±)- and (*R*)-(+)-35): Compound (±)-**34** (0.16 g, 0.92 mmol) was reacted with triisopropyl phosphite in analogy to the preparation of diethyl *N*-(1-indanyl)phosphoramidate ((±)-**15**) from azide. The crude product was subjected to flash chromatography (hexanes/EtOAc 2:1, R_f=0.42) to yield phosphoramidate (±)-**35** (0.26 g, 91%) as colourless crystals; m.p. 76–77 °C (hexanes). Similarly, (*R*)-(+)-1-azido-1,2,3,4-tetrahydronaphthalene ((*R*)-(+)-**34**) (1.20 g, 6.91 mmol) gave phosphoramidate (*R*)-(+)-**35** (2.14 g, 99%); m.p. 65–68 °C, $[\alpha]_D^{20}$=+41.1 (c=0.95, hexane). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.32 (d, J=6.1 Hz, 6H), 1.33 (d, J=6.1 Hz, 3H), 1.34 (d, J=6.1 Hz, 3H), 1.83 (m, 3H), 2.08 (m, 1H), 2.64 (t, J=10.1 Hz, 1H), 2.75 (m, 2H), 4.34 (ddd, J=6.3, 9.6, 10.1 Hz), 4.64 (m, 2H), 7.04 (m, 1H), 7.14 (m, 2H), 7.53 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.9, 23.9 (d, J=4.6 Hz), 23.9 (d, J=5.4 Hz), 24.0 (d, J=5.4 Hz, 2C), 29.2, 32.6 (d, J=1.5 Hz), 50.1, 70.9 (d, J=6.1 Hz), 70.9 (d, J=5.4 Hz), 126.0, 127.0, 128.7, 128.9, 137.2, 138.7 ppm (d, J=8.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ=7.5 ppm; IR (Si, racemate): $\tilde{\nu}$=3201, 2976, 2930, 1458, 1221, 1100, 1020, 993 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{26}NO_3P$ (311.4): C 61.72, H 8.42, N 4.50; found: C 61.42, H 8.15, N 4.26.

(±)- and (*R*)-(−)-Diisopropyl *N*-(*t*-butoxycarbonyl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)phosphoramidate ((±)- and (*R*)-(−)-36): Phosphoramidate (±)-**35** (0.50 g, 1.60 mmol) was Boc-protected by using General Procedure C (flash chromatography: CH_2Cl_2/EtOAc 10:1, R_f=0.35) to give phosphoramidate (±)-**36** (0.61 g, 93%) as a colourless oil. Analogously, phosphoramidate (*R*)-(+)-**35** (2.03 g, 6.51 mmol) gave Boc-protected phosphoramidate (*R*)-(−)-**36** (2.43 g, 91%); $[\alpha]_D^{20}$=−26.1 (c=1.57, hexane). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ=1.19 (s, 9H), 1.30 (d, J=6.1 Hz, 3H), 1.34 (d, J=6.1 Hz, 3H), 1.37 (d, J=6.1 Hz, 3H), 1.38 (d, J=6.1 Hz, 3H), 1.73 (ddq, J=2.8, 4.6, 13.1 Hz, 1H), 1.97 (m, 1H), 2.11 (m, 1H), 2.29 (m, 1H), 2.68 (m, 1H), 2.80 (m, 1H), 4.68 (oct, J=6.1 Hz, 1H), 4.82 (oct, J=6.1 Hz, 1H), 5.29 (dt, J=6.8, 11.2 Hz, 1H), 7.00 (m, 1H), 7.04 (m, 3H), 7.24 ppm (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=23.0, 23.4 (d, J=5.4 Hz), 23.8 (d, J=5.4 Hz), 23.8 (d, J=3.8 Hz), 23.9 (d, J=4.6 Hz), 27.7 (3C), 29.7 (2C), 56.9 (d, J=3.1 Hz), 72.0 (d, J=6.1 Hz), 72.7 (d, J=6.9 Hz,), 81.6, 125.4, 125.8, 125.8, 128.7, 137.3, 138.4

(d, $J=3.8$ Hz), 153.1 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=2.2$ ppm; IR (Si, racemate): $\tilde{\nu}=2980$, 2935, 1724, 1386, 1368, 1287, 1162, 1071, 1000 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{34}NO_5P$ (411.5): C 61.30, H 8.33, N 3.40; found: C 61.38, H 8.16, N 3.39.

(±)- and (*S*)-(−)-Diisopropyl [1-(*t*-butoxycarbonylamino)-1,2,3,4-tetrahydronaphthalen-1-yl]phosphonate ((±)- and (*S*)-(−)-37): Phosphoramidate (±)-**36** (0.29 g, 0.70 mmol) was rearranged (THF; flash chromatography: CH_2Cl_2/EtOAc 3:1, $R_f=0.61$) by using General Procedure D to give phosphonate (±)-**37** (0.17 g, 59%) as a colourless oil. Analogously, phosphoramidate (*R*)-(−)-**36** (0.82 g, 2.0 mmol) yielded aminophosphonate (*S*)-(−)-**37** (0.44 g, 53%); $[\alpha]_D^{20}=-25.9$ ($c=0.64$, hexane). ^{1}H NMR (400.1 MHz, 353 K, $C_6D_5CD_3$): $\delta=0.62$ (d, $J=6.1$ Hz, 3H), 1.04 (d, $J=6.3$ Hz, 3H), 1.14 (d, $J=6.1$ Hz, 3H), 1.17 (d, $J=6.3$ Hz, 3H), 1.27 (s, 9H), 1.87 (m, 1H), 2.12 (m, 1H), 2.47 (dddt, $J=0.5$, 3.5, 6.6, 13.6 Hz, 1H), 2.70 (m, 2H), 2.96 (dddd, $J=3.8$, 11.1, 13.4, 25.4 Hz, 1H), 4.20 (oct, $J=6.1$ Hz, 1H), 4.62 (oct, $J=6.3$ Hz, 1H), 5.95 (br d, $J=10.1$ Hz, 1H), 6.97 (3H overlapped with signals of $C_6D_5CD_3$), 7.82 ppm (m, 1H); ^{13}C NMR (100.6 MHz, 353 K, $C_6D_5CD_3$): $\delta=20.9$, 22.9 (d, $J=6.1$ Hz), 23.9 (d, $J=5.4$ Hz), 24.2 (d, $J=3.1$ Hz), 24.5 (d, $J=2.3$ Hz), 28.6 (3C), 30.2, 31.3 (d, $J=4.6$ Hz), 58.4 (d, $J=149.9$ Hz), 71.4 (d, $J=7.7$ Hz), 72.5 (d, $J=7.7$ Hz), 79.3, 126.0 (d, $J=3.1$ Hz), 127.3 (d, $J=3.1$ Hz), 128.6 (d, $J=4.6$ Hz), 129.2 (d, $J=3.4$ Hz), 136.6 (d, $J=4.6$ Hz), 139.6 (d, $J=6.9$ Hz), 154.5 ppm (d, $J=16.8$ Hz); ^{31}P NMR (162 MHz, 353 K, $C_6D_5CD_3$): $\delta=25.8$ ppm; IR (Si, racemate): $\tilde{\nu}=3401$, 2978, 2934, 1730, 1488, 1367, 1248, 1167, 1103, 987 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{34}NO_5P$ (411.5): C 61.30, H 8.33, N 3.40; found: C 61.10, H 8.06, N 3.30.

(±)- and (*S*)-(−)-(1-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)phosphonic acid ((±)- and (*S*)-(−)-38), the former as a sesquihydrate: Phosphonate (±)-**37** (0.96 g, 2.3 mmol) was deblocked by using General Procedure E and purified by means of ion-exchange chromatography (Dowex 50W, H^+, water; TLC: *i*PrOH/H_2O/NH_3 6:3:1, $R_f=0.48$) to give 1-aminophosphonic acid (±)-**38** (0.40 g, 67%) as colourless crystals; m.p. 218 °C (water). Analogously, aminophosphonate (*S*)-(−)-**37**·1.5 $H_2$0 (0.50 g, 1.21 mmol) was deblocked by using General Procedure F and lyophilised crude product was crystallised from water (25 °C)/ethanol (25 °C to +4 °C; seemed to be less soluble in hot water than water of 25 °C) to give aminophosphonic acid (*S*)-(−)-**38** (0.11 g, 40%); *ee* of crude product: 97%; m.p. 230–232 °C; $[\alpha]_D^{20}=-13.9$ ($c=0.43$, water). ^{1}H NMR (400.1 MHz, D_2O): $\delta=1.75$ (m, 1H), 2.02 (m, 2H), 2.43 (m, 1H), 2.77 (m, 2H), 7.22 (m, 3H), 7.64 ppm (dt, $J=1.0$, 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, D_2O): $\delta=18.8$ (d, $J=3.8$ Hz), 29.1, 31.4, 56.8 (d, $J=142.3$ Hz), 126.7 (d, $J=1.5$ Hz), 127.7 (d, $J=3.1$ Hz), 128.9 (d, $J=1.5$ Hz), 130.3, 132.0 (d, $J=2.3$ Hz), 139.0 ppm (d, $J=5.4$ Hz); ^{31}P NMR (162 MHz, D_2O): $\delta=15.8$ ppm; IR (ATR, racemate): $\tilde{\nu}=3401$, 3198, 2859, 1614, 1525, 1494, 1448, 1182, 1024, 921 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{14}NO_3P$ (227.2): C 52.86, H 6.21, N 6.17; found for (*S*)-(−)-**38**: C 52.62, H 6.20, N 6.07; elemental analysis calcd (%) for $C_{10}H_{14}NO_3P$·1.5 H_2O (254.2): C 47.24, H 6.74, N 5.51; found for (±)-**38**): C 46.97, H 6.51, N 5.43.

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