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Alkylation of Chiral Phosphonoglycine Equivalents: Asymmetric Synthesis of Diethyl α-Amino-α-Alkyl-Phosphonates

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Abstract: A model was developed to rationalize the experimental results of the alkylation of chiral phosphonoglycine equivalents yielding α-amino-α-alkyl-phosphonates. The model studies, carried out using semiempirical calculations, have emphasized the role of the chelating effects in influencing the diastereoselectivity of the alkylation step. Chelation can be optimized by tuning the functionality of the substituent at carbon C-1 of the camphor skeleton. By employing **2d**, as suggested by the modelling, a major improvement in the enantiomeric excesses of compounds **5** (R=CH_3, C_2H_5) was obtained.

INTRODUCTION

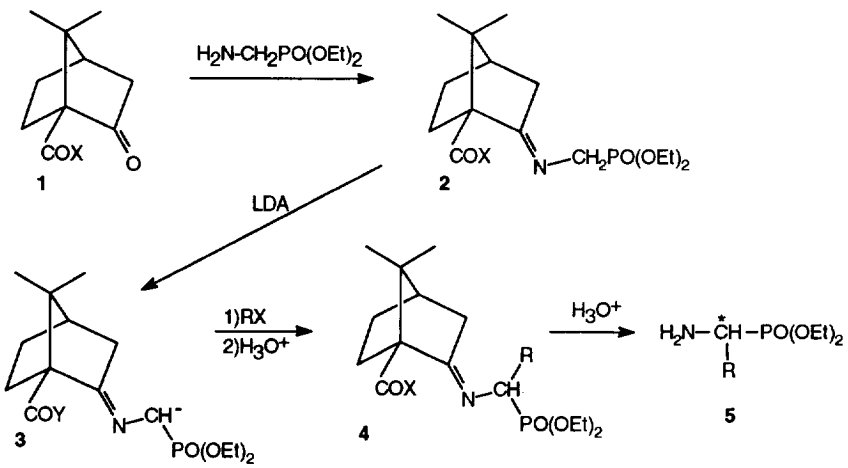
α-aminophosphonic acids and their derivatives are attracting considerable attention because of their wide ranging biological activity.[1] Due to their structural analogy to α-aminoacids, they may function as inhibitors of enzymes involved in the metabolism of proteins and aminoacids. For example, the phosphonic analogue of phenylalanine is an inhibitor of phenylalanyl-5-RNA-synthetase[2]; phosphonodipeptide alafosfalin is an antimicrobial agent.[3] It has also been shown that the bioactivity of α-aminophosphonic acids depends on their absolute configuration[4], hence the development of an efficient asymmetric synthesis of these compounds is desirable.[5]

Our research group has already reported the asymmetric synthesis of diethyl α-amino-α-alkyl-phosphonates by alkylation of chiral phosphonoglycine equivalents.[6] The alkylation of the Schiff bases derived from condensation of diethyl aminomethylphosphonate and (+)-ketopinic acid,[6a] or (+)-ketopinic acid derivatives,[6b] proceeds with high endo-diastereoselectivity when the electrophilic centre is adjacent to a π-system, as already observed for the alkylation of imines derived from natural camphor and glycine esters.[7] On the contrary when employing methyl or ethyl halides the results, in terms of diastereoselectivity of the alkylation step, depend on the nature of the functionality of the substituent at carbon C-1 of the camphor skeleton.[6b] A modelling study was therefore undertaken to rationalize the experimental results and to obtain suggestions on possible structural modifications of the chiral auxiliary, the aim being to improve the diastereoselectivity of the alkylation step. In this communication we report the modelling studies and the experimental results.

MODELLING STUDIES

For sake of clarity, we report here the synthetic scheme we followed together with the experimental results in terms of enantiomeric excess of compounds **5**

Scheme 1



a. X = OH Y = O^-

b. X =  Y = 

c. X =  Y = 

d. X = $Me_2C(OH)CH_2NH$ Y = $Me_2C(O^-)CH_2N^-$

e [a]. X = $CH_2C(OH)Me_2NH$

f [b]. X = $Ph_2C(OH)CH_2NH$

g [a]. X = $CH_2C(OH)Ph_2NH$

[a] Compounds 2e and 2g were not used according to negative modelling results. [b] For compound 2f see note 10.

The aim of the modelling studies is the rationalization of the experimental results using a very simple approach. This choice is fundamentally due to the need to first understand the differences in the behaviour of the imines **2** derived from different chiral auxiliaries **1** (scheme 1) when reacted with the same alkylating reagent, especially in cases that show appreciable differences in diastereoselectivity (thus excluding the case of the alkylating reagents with the electrophilic centre adjacent to a π-system where no appreciable differences in the diastereoselectivity are shown). For methyl and ethyl derivatives the response to the structural modifications of the chiral auxiliary is evident from the experimental result.[6b] In fact, the observed increase in selectivity obtained when employing **1c** instead of camphor and ketopinic acid **1a** must depends on the structure of the chiral auxiliary (table 1). The modelling hypothesis we used is a consequence of these findings; thus we focussed our attention on compounds **2a-c**.

Table 1. Enantiomeric excesses of compounds **5**[a]

Chiral auxiliary	R=CH3	R=CH2CH3	R=CH2-CH=CH2	R=CH2C6H5	Config.
(+)-camphor	11.0%	69.0%	95.0%	95.0%	S
1a	15.1%	62.2%	92.2%	93.0%	S
1b	22.0%	56.0%	92.0%	93.0%	S
1c	47.6%	81.0%	94.0%	99.0%	S
1d	65.0%	93.0%	91.0%	99.0%	S

[a]The enantiomeric excesses were evaluated by ^{19}F-NMR spectroscopy of the amides obtained by reacting compounds **5** with (+)-Mosher's acid chloride.

The calculations were run on the ground state structures because we hypothesized that the structure of the chiral imines **2a-c** is very similar in both the ground and reacting states, the only difference being the substitution of the acidic hydrogen atoms with the corresponding lithium ions coming from the base. Moreover we considered the effects of the steric hindrance of the two faces of the carbanion determinant for the diastereoselection. On these bases the only differentiating factor should be related to the stabilization of the intermediate through electrostatic intramolecular interactions (represented by hydrogen bonds in the starting compound, figure 1).

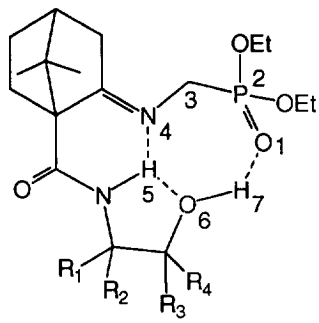


Figure 1.Imine structures used in the modelling studies

The modelling procedure consisted of the following steps: a) realization of the chiral imine structures and their minimization using AM1 program;[8] b) positioning , via rigid bond rotations, of the atoms (4-5 and 5-6, figure 1) presumably involved in the hydrogen bonds to bonding distances and further minimization; c) search for the rotational minima (through a Montecarlo-Metropolis procedure[9]) of the still free bonds. On the final optimized structures we measured the distances between the atoms potentially involved in coordinative bonds to verify their existence (Table 2). Using the previously tested compounds (camphor, **2a-2c**), we obtained results qualitatively in agreement with the experimental results (see camphor in comparison with **2a-2c**);[6b]

where the increase in the diastereoselectivity can be correlated with the increase in the number of coordinative interactions.

Table 2. Calculated distances between coordinating atoms[a]

Compound	dist. 4-5	dist. 1-5	dist. 5-6	dist 1-7
2a	2.14	3.77	-	-
2b	2.45	4.69	-	-
2c	2.43	4.71	2.50	3.79
2d	2.40	4.60	2.50	2.36
2e	2.45	4.58	2.55	3.35
2f	2.42	4.73	2.48	2.49
2g	2.40	4.74	2.34	4.03

[a]Distances are in Å

From figure 1, a third potential hydrogen bond can also be located between H-5 (or H-7) and O-1, a bond that is nevertheless not shown even by compound **2c**. This negative result is probably due to the presence of the nitrogen and oxygen atoms of the amidic residue on a rigid substructure (benzene ring). This forced us to begin a search for molecules possessing this additional hydrogen bonding and that could consequently increment the reaction diastereoselectivity.

The presence of the substructure HO-CR_1R_2-CR_3R_4-NH-, capable of at least two intramolecular hydrogen bonds, is a fundamental requisite of our auxiliaries; therefore we looked at alkyl derivatives containing it, obtained by variation of R_1-R_4, in order to test their coordinative potential. In particular, we studied compounds with R_1=R_2=Me or Ph and R_3=R_4=H and compounds with R_1=R_2=H and R_3=R_4=Me or Ph that show different geometric effects that can be easily understood.

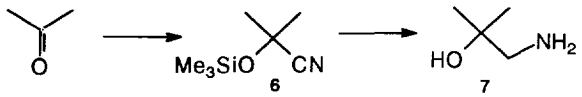
The results (table 2) indicate the best auxiliaries to be those compounds bearing R_1=R_2≠H and R_3=R_4=H. The use of one of them (R_1=R_2=Me) furnished the results shown in table 1, resulting in a significant increase in diastereoselectivity, particularly with methyl iodide.[10]

It is interesting to note that it is only for compounds of this class (R1=R2≠H) that the Montecarlo-Metropolis sampling of the rotational space assigns a high probability to a structure that has also the O_1-H_7 bond formed. The increase in intermediate rigidity amplifies the differences in the two approaching sides of the molecule, thus increasing the selectivity.

Finally it should be emphasized that a simple model like the one described here correctly rationalizes the experimental results and leads to further suggestions for an improvement in the selectivity.

EXPERIMENTAL RESULTS

1-amino-2-methyl-2-propanol **7** was prepared by reacting acetone with trimethylsilyl cyanide followed by lithiumaluminum hydride reduction of the trimethylsilylcyanidrin **6** (70% overall yields).[11]



The chiral auxiliaries **1b-d**, obtained from (+)-ketopinic acid chloride (1, X=Cl)[12] and the appropriate amine,[13] were transformed into the corresponding imines by reaction with diethyl aminomethylphosphonate in the presence of boron trifluoride as Lewis catalyst and with azeotropical removal of water. Compounds **2c** and **2d** were obtained in 90% yield and 95% yield respectively after purification by silica gel chromatography; compound **2b** underwent the next step without purification due to its instability to chromatographic systems. The absolute stereochemistry of compounds **2b-2d** was determined by hydrolysis to (+)-ketopinic acid with unchanged optical purity.[14]

The stereochemistry of the imine double bond in **2b-d** was supposed to be E by analysis of the ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra where only one diastereoisomer is detectable.[15]

The alkylation of the dianion **3b** and trianions **3c** and **3d** (obtained by treating **2b** and **2c-d** with two and three equivalents of lithium diisopropylamide respectively at -78 °C) afforded compounds **4b-d**. The subsequent hydrolysis was performed by heating a tetrahydrofuran solution of **4b-d** with 0.1M aqueous hydrochloric acid at 70 °C for 4-5h. The overall yields of diethyl α-amino-α-alkyl-phosphonates **5** were 40-50% from **2b** and 65-75% from **2c** and **2d** after bulb to bulb distillation.

Table 1 reports the enantiomeric excesses of compounds **5** by utilizing **1a-d** and (+)-camphor as chiral auxiliaries. The absolute configuration of compounds **5** was determined to be S by chiroptical comparison with reported values.[6a]

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer 457 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured in deuterochloroform with a Bruker AC 200 (200MHz and 50.3MHz respectively), ^{31}P-NMR spectra with a Varian XL-200 (81.0MHz), ^{19}F-NMR spectra with a Bruker AC 300 (282.4MHz). Mass spectra were obtained with a VG 7070 EQ spectrometer. Optical rotations were measured at 25 °C using a 1dm cell on a Perkin Elmer 241 polarimeter. Microanalyses were carried out in the microanalytical laboratory of our Department using a Perkin Elmer 240 instrument. Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F254. Tetrahydrofuran and toluene were distilled under nitrogen from lithiumaluminum hydride and sodium respectively. Melting points (mp) were determined with a hot plate microscope and are uncorrected. Organic solutions were dried over sodium sulphate and the products isolated by filtration and evaporation of the filtrate using a rotatory evaporator operating at 15 torr.

Preparation of the amides **1b-d**. To a solution of compound **1** (X=Cl) (obtained by reacting (+)-ketopinic acid with an excess of thionyl chloride at 80 °C for 5h)[12] (4.010g, 20.0mmol) in anhydrous methylene chloride (15ml), a solution of triethyl amine (2.77ml, 20.0mmol) and the appropriate amine[13] (20.0mmol) in anhydrous methylene chloride (15ml) was added at 0 °C. After 15', the mixture was allowed to reach room temperature and left to react for 4h (TLC methylene chloride/methanol 9:1 as eluant). Aqueous 0.1N hydrochloric acid (15ml) was added, the organic layer was separated and the aqueous one extracted with methylene chloride (3x15ml). The combined organic extracts were washed with water (2x15ml), dried and

evaporated under vacuum. Compounds **1b-d** were purified by flash chromatography on silica gel (light petroleum/ethyl acetate 2:8 as eluant).

1b: yield 70%; oil; $[\alpha]_D^{20}$= +71.26 (c=14.4, $CHCl_3$); IR ($CHCl_3$) 3330, 1730, 1650, 1540; ^{1}H-NMR ($CDCl_3$) 7.25 (m, 1H), 4.22-4.00 (m, 1H), 2.65-2.42 (m, 2H), 2.25-2.05 (m, 2H), 2.02-1.92 (d, ^{2}J=18.6 Hz, 1H), 1.67-1.32 (m, 2H), 1.26 (s, 3H), 1.15 (2d, ^{3}J=6.3 Hz, 6H), 0.97 (s, 3H); ^{13}C-NMR ($CDCl_3$) 187.9 (C), 167.6 (C), 64.0 (C), 49.7 (C), 43.4 (CH_2), 42.8 (CH), 40.3 (CH), 27.7 (CH_2), 27.4 (CH_2), 22.7 (CH_3), 22.2 (CH_3), 20.7 (CH_3), 20.0 (CH_3); MS (70 eV) 224 (M^+ +1), 223 (M^+), 208, 180, 165, 137. Anal.Calcd for $C_{13}H_{21}NO_2$: C, 69.95; H, 9.42; N, 6.28. Found: C, 69.80; H, 9.31; N, 6.35.

1c: yield 80%; mp=143-145 °C; $[\alpha]_D^{20}$= +24.02 (c=6.3, $CHCl_3$); IR ($CHCl_3$) 3250, 1730, 1650, 1610, 1550; ^{1}H-NMR ($CDCl_3$) 10.05 (m, 1H), 9.15 (m, 1H), 7.25-6.80 (m, 4H), 2.81-2.42 (m, 2H), 2.39- 1.98 (m, 3H), 1.89-1.61 (m, 1H), 1.63-1.45 (m, 1H), 1.35 (s, 3H), 1.15 (s, 3H); ^{13}C-NMR ($CDCl_3$) 187.5 (C), 169.2 (C), 148.8 (C), 127.2 (CH), 125.5 (C), 122.6 (CH), 120.1 (CH), 119.9 (CH), 64.2 (C), 51.0 (C), 43.5 (CH_2), 43.0 (CH), 28.2 (CH_2), 27.8 (CH_2) , 21.0 (CH_3), 20.2 (CH_3); MS (70eV) 273 (M^+), 165, 123, 109. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.23; H, 6.88; N, 5.05.

1d: yield 80%; mp =116-118 °C; $[\alpha]_D^{20}$= +55.11 (c=7.5, $CHCl_3$); IR ($CHCl_3$) 3300, 1730, 1650, 1540, 1200; ^{1}H-NMR ($CDCl_3$) 8.00 (m, 1H), 3.49-3.35 (dd, ^{2}J=13.8Hz, ^{3}J=5.0 Hz, 1H), 3.33-3.20 (dd, ^{2}J= 13.8 Hz, ^{3}J=5.0 Hz, 1H), 2.85 (m, 1H), 2.66-2.47 (m, 2H), 2.35- 2.07 (m, 2H), 1.74-1.40 (m, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.02 (s, 3H); ^{13}C-NMR ($CDCl_3$) 187.6 (C) , 170.6 (C), 70.9 (C), 64.6 (C), 50.2 (CH_2), 50.1 (C), 43.7 (CH_2), 43.1 (CH), 28.3 (CH_2), 27.6 (CH_2), 27.3 (CH_3), 27.1 (CH_3), 20.8 (CH_3), 20.4 (CH_3); MS (70eV) 254 (M^+ +1), 236, 195, 165. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.40; H, 9.09; N, 5.53. Found: C, 66.28; H, 9.15; N, 5.60.

Preparation of the Schiff bases **2b-d**. To a solution of the appropriate amide **1b-d** (3.7mmol) and diethyl aminomethylphosphonate (0.620g, 3.7mmol) in dry toluene (30ml) a catalytic amount of boron trifluoride etherate was added. The mixture was refluxed for 5h with azeotropical removal of water (TLC ethyl acetate/methanol 9:1). After evaporation of the solvent under vacuum, crude compounds **2c** and **2d** were purified by flash chromatography on silica gel (ethyl acetate/light petroleum 8:2 as eluant for compound **2c** and ethyl acetate/methanol 9:1 as eluant for compound **2d**). Compound **2b** could not be purified due to its instability in the chromatographic systems; the spectroscopic analyses were run on the crude product obtained by distillation under reduced pressure of the reaction mixture.

2b: oil; IR ($CHCl_3$) 3340, 1740, 1640, 1530, 1230, 1200, 1050, 1040; ^{1}H-NMR ($CDCl_3$) 8.95 (m, 1H), 4.28-4.05 (m, 5H), 3.81 (d, $^2J_{H\text{-}P}$=16.6 Hz, 2H), 2.68-2.43 (m, 2H), 2.24-1.91 (m +d, ^{2}J=18.6 Hz, 3H), 1.65-1.10 (m, 17H), 0.98 (s, 3H); ^{13}C-NMR ($CDCl_3$) 185.1 (C),[15] 184.7 (C),[15] 169.5 (C), 64.3 (C), 62.2 (CH_2, $^2J_{C\text{-}P}$=25.4 Hz), 62.0 (CH_2, $^2J_{C\text{-}P}$=25.6 Hz), 48.7 (CH_2, $^1J_{C\text{-}P}$=627.2 Hz), 50.0 (C), 43.9 (CH), 43.7 (CH_2), 40.6 (CH), 28.0(CH_2), 27.6 (CH_2), 22.9 (CH_3), 22.3 (CH_3), 20.9 (CH_3), 20.2 (CH_3), 16.4 (CH_3), 16.3 (CH_3); ^{31}P- NMR ($CDCl_3$) 23.65; MS (70eV) 372 (M^+), 357, 314, 286, 270, 165.

2c: yield 90%; oil; $[\alpha]_D^{20}$= +28.71 (c=6.4, $CHCl_3$); IR ($CHCl_3$ 3250, 1680, 1650, 1600, 1560, 1490, 1470, 1390, 1200, 1050, 1020; ^{1}H- NMR ($CDCl_3$) 11.90 (m, 1H), 9.80 (m, 1H), 7.18-6.72 (m, 4H), 4.24-4.06 (m, 4H), 3.86 (d, $^2J_{H-P}$ =17.1 Hz, 2H), 2.72-2.50 (m, 2H), 2.26-1.97 (m, 4H), 1.75-1.58 (m, 1H), 1.31 (t, ^{3}J=7.0 Hz, 3H), 1.29 (s, 3H), 1.27 (t, ^{3}J=7.0 HZ, 3H), 0.96 (s, 3H); ^{13}C-NMR ($CDCl_3$) 184.8 (C),[15] 184.5 (C),[15] 170.7 (C), 148.9 (C), 126.7 (CH), 126.1 (C), 122.4 (CH), 119.8 (CH), 119.7 (CH), 62.4 (CH_2, $^2J_{CP}$=20.8 Hz), 62.2 (CH_2, $^2J_{C-P}$=22.9 Hz), 61.1 (C), 51.6 (C), 48.6 (CH_2, $^1J_{C-P}$=629.0 Hz), 43.9 (CH), 35.8 (CH_2), 30.9 (CH_2), 29.1 (CH_2), 20.9 (CH_3), 19.9 (CH_3), 16.3 (CH_3), 16.2 (CH_3); ^{31}P-NMR ($CDCl_3$) 23.10; MS (70eV) 422 (M^+), 314, 286, 176, 165, 148. Anal.Calcd for $C_{21}H_{31}N_2O_5P$: C, 59.71; H, 7.34; N, 6.63. Found: C, 59.59; H, 7.22; N, 6.57.

2d: yield 95%; oil; $[\alpha]_D^{20}$= +52.91 (c=7.1, $CHCl_3$); IR ($CHCl_3$) 3350, 1670, 1640, 1550, 1215, 1190, 1050, 1020; ^{1}H-NMR ($CDCl_3$) 9.40 (m, 1H), 4.30-4.04 (m, 4H), 3.81 (d, $^2J_{H-P}$=16.2 Hz, 2H), 3.51-3.35 (dd, ^{2}J=14.3 Hz, ^{3}J=5.2 Hz, 1H), 3.26-3.10 (dd, ^{2}J=14.3 Hz, ^{3}J=5.1 Hz, 1H), 2.42-2.27 (m, 2H), 2.23-1.88 (m, 3H), 1.70-1.48 (m, 2H), 1.33 (t, ^{3}J=7.0 Hz, 6H), 1.27 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 0.94 (s, 3H); ^{13}C-NMR ($CDCl_3$) 184.9 (C),[15] 184.6 (C),[15] 171.6 (C), 70.2 (C), 62.4 (CH2, $^2J_{C-P}$=25.9 Hz), 62.1 (CH2, $^2J_{C-P}$ P=26.2 Hz), 61.6 (C), 50.7 (C), 48.7 (CH_2, $^1J_{C-P}$=627.8Hz), 43.9 (CH), 35.8 (CH_2), 30.8 (CH_2), 29.5 (CH_2), 27.9(CH_2), 27.1 (CH_3), 26.9 (CH_3), 20.8 (CH_3), 20.0 (CH_3), 16.4 (CH_3), 16.3 (CH_3); ^{31}P- NMR (DMSO-d_6) 24.77; MS (70eV) 403 (M^+ +1), 344, 314, 286, 176, 148. Anal.Calcd. for $C_{19}H_{35}N_2O_5P$: C, 56.71; H, 8.70; N, 6.96. Found: C, 56.62; H, 8.80; N, 6.85.

General procedure for the alkylation of the Schiff bases **2b-d**. To a solution of lithium diisopropylamide (2.10 mmol for **2b**, 3.15 mmol for **2c** and **2d**) in anhydrous tetrahydrofuran (3ml/mmol) a solution of the appropriate Schiff base (1.00mmol) in anhydrous tetrahydrofuran (3ml) was added at -78 °C under argon atmosphere. After 30' at -78 °C, a precooled(-78 °C) solution of the alkylating agent (1.1mmol) in anhydrous tetrahydrofuran (2ml) was added. The reaction mixture was kept at -78° C for 5h, quenched with aqueous 1N hydrochloric acid (3.5ml) and allowed to reach room temperature. After evaporation of the tetrahydrofuran under vacuum at room temperature, the mixture was extracted with methylene chloride (4X8ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate, water, dried over sodium sulphate and evaporated under vacuum. When using benzyl bromide as alkylating agent, the residue was chromatographed on silica gel (ethyl acetate as eluant for **4b** and **4c** and ethyl acetate/methanol 95:5 as eluant for **4d**) in order to remove the excess of benzyl bromide.
Compounds **4b-d** were submitted to the following hydrolytic step without purification; therefore the spectroscopic analyses were run on the diastereoisomeric mixtures. The yields refer to the crude products **4b-d**.

4b, R=CH_3: 70%, oil; ^{1}H-NMR($CDCl_3$)4.30-4.00 (m, 5H), 3.90-3.60 (m, 1H), 2.70-1.90 (m, 7H), 1.70-1.11 (m, 18H), 0.99 (s, 3H); MS (70eV) 386 (M^+), 371, 358, 328, 284, 249, 190, 179, 160, 109.

4b, R=CH_2CH_3: 72%, oil; ^{1}H-NMR($CDCl_3$) 4.30-3.96(m, 5H), 3.70-3.51 (m, 1H), 2.71-1.79 (m, 7H), 1.70-1.45 (m, 2H), 1.45-1.10 (m, 18H), 0.98 (s, 3H); MS(70eV) 400 (M^+), 372, 344, 314, 286, 235, 176, 148.

4b, R=CH_2-CH=CH_2 : 70%, oil; ^{1}H-NMR ($CDCl_3$) 5.78-5.50 (m, 1H), 5.25-4.94 (m, 2H), 4.30-3.92 m, 5H), 3.82-3.62 (m, 1H), 2.70- 2.42 (m, 4H), 2.25-1.82 (m, 4H), 1.70-1.10 (m, 16H), 0.98 (s, 3H); MS (70eV) 412 (M^+), 397, 326, 310, 275, 233, 216, 191, 172, 135.

4b, R=$CH_2C_6H_5$: 75%, oil; ^{1}H-NMR ($CDCl_3$) 7.50-7.10 (m, 5H), 4.35- 4.05 (m, 5H), 3.95-3.70 (m, 1H), 3.46-3.30 (m, 1H), 3.10-2.90 (m, 1H), 2.63-1.63 (m, 7H), 1.33-1.10 (m, 15H), 0.99 (s, 3H); MS (70eV) 462 (M^+), 447, 393, 371, 325,266, 256, 238, 234, 208, 148, 91.

4c, R=CH_3: 90%, oil; ^{1}H-NMR($CDCl_3$) 7.22-6.93 (m, 3H), 6.93-6.77 (m, 1H), 4.31-3.78 (m, 5H), 2.90-1.92 (m, 7H), 1.50-1.11 (m, 12H), 1.10 (s, 3H); MS (70eV) 436 (M^+), 328, 300, 230, 190, 162, 148, 121, 109.

4c, R=CH_2CH_3: 87%, oil; ^{1}H-NMR($CDCl_3$) 7.19-6.90 (m, 3H), 6.90- 6.73 (m, 1H), 4.27-4.00 (m, 4H), 3.78-3.58 (m, 1H), 2.80-2.52(m, 2H), 2.32-1.58 (m, 7H), 1.48-1.18 (m, 9H), 1.03 (s, 3H), 0.92 (t, ^{3}J=7.1 Hz,3H); MS (70eV) 450 (M^+), 342, 314, 286, 204, 176, 165, 123, 109.

4c, R=CH_2-CH=CH_2: 87%, oil; ^{1}H-NMR($CDCl_3$) 7.18-6.98 (m, 3H), 6.92-6.78 (m, 1H), 5.80-5.55 (m, 1H), 5.20-5.00 (m, 2H), 4.29- 4.01 (m, 4H), 3.91-3.71 (m, 1H), 2.98-2.50 (m, 2H), 2.32-1.54 (m, 7H), 1.43-1.21 (m, 9H), 1.02 (s, 3H); MS (70eV) 462 (M^+), 354, 326, 216, 176, 141, 121.

4c, R=$CH_2C_6H_5$, 90%, oil; ^{1}H-NMR ($CDCl_3$) 7.60-6.90 (m, 9H), 4.39- 4.10 (m, 4H), 4.02-3.80 (m, 1H), 3.52-3.35 (m, 1H), 3.21-3.00 (m, 1H), 2.50-1.70 (m, 7H), 1.42-1.10 (m, 9H), 0.90 (s, 3H); MS (70eV) 512 (M^+), 422, 404, 376, 314, 286, 176, 148, 91.

4d, R=CH_3: 85%, oil; ^{1}H-NMR($CDCl_3$) 4.33-4.04 (m, 4H), 3.94-3.74 (m, 1H), 3.55 (dd, ^{2}J=14.6 Hz, ^{3}J=6.8 Hz, 1H), 3.10 (dd, ^{2}J=14.6 Hz, ^{3}J=4.6 Hz, 1H), 2.70-1.60 (m, 7H), 1.55-1.20 (m, 18H), 1.02 (s, 3H); MS (70eV) 417 (M^+ +1), 399, 358, 279, 254, 236, 154.

4d, R=CH_2CH_3: 92%, oil; ^{1}H-NMR($CDCl_3$) 4.30-3.92 (m, 4H), 3.68- 3.53 (m, 1H), 3.48 (dd, ^{2}J=12.9 Hz, ^{3}J=6.5 Hz, 1H), 3.11 (dd, ^{2}J=12.9 Hz, ^{3}J=4.6 Hz, 1H), 2.70-1.75 (m, 7H), 1.70-1.45 (m, 2H), 1.40-1.10 (m, 15H), 0.96 (s, 3H), 0.88 (t, ^{3}J=7.0 Hz, 3H); MS (70eV) 431 (M^+ +1), 413, 379, 293, 254, 236, 154.

4d, R=CH_2-CH=CH_2: 90%, oil; ^{1}H-NMR($CDCl_3$) 5.77-5.50 (m, 1H), 5.19-5.00 (m, 2H), 4.30-4.00 (m, 4H), 3.82-3.67 (m, 1H), 3.47 (dd, ^{2}J=13.7 Hz, ^{3}J=6.5 Hz, 1H), 3.15 (dd, ^{2}J=13.7 Hz, ^{3}J=4.5 Hz, 1H), 2.80-2.45 (m, 4H), 2.20-1.45 (m, 5H), 1.40-1.20 (m, 15H), 0.97 (s, 3H); MS (70eV) 443 (M^+ +1), 425, 384, 254, 236, 139.

4d, R=$CH_2C_6H_5$: 90%, oil; ^{1}H-NMR($CDCl_3$) 7.40-7.15 (m, 5H), 4.35- 4.10 (m, 4H), 4.00-3.84 (m, 1H), 3.48 (m, 1H), 3.39-3.06 (m, 3H), 2.66-1.67 (m, 7H), 1.45-1.07 (m, 15H), 0.90 (s, 3H); MS (70eV) 492 (M^+), 433, 404, 355, 266, 205, 109, 91.

General procedure for the hydrolysis of the alkylated Schiff Bases **4b-d**. A mixture of the appropriate alkylated Schiff base **4b-4d** (1mmol), aqueous 0.1N hydrochloric acid (45ml) and tetrahydrofuran (30ml) was stirred at 70°C for 4h. The organic solvent was evaporated under vacuum and the aqueous layer extracted with methylene chloride (3X15ml) in order to recover the chiral auxiliary. The aqueous layer was alkalinized to pH=8.5 with a saturated aqueous sodium carbonate solution and extracted with ethyl acetate (4X15ml). The combined extracts were dried over sodium sulphate and evaporated to yield compounds **5** which were purified by bulb-to-bulb distillation under reduced pressure using a Buchi GKR-50 apparatus. The enantiomeric excesses of compounds **5** are reported in table 1. For the physical and spectroscopic characteristic of compounds **5** see ref 6a.

The yields, after purification, were 60-70% from **4b** and 80-85% from **4c** and **4d**.

In Table 3, the optical rotations of compounds **5** together with the ^{19}F-NMR chemical shifts of the corresponding Mosher's amides are reported.

Table 3. Optical rotations ($CHCl_3$) of compounds **5** and ^{19}F-NMR chemical shifts of the corresponding Mosher's amides.

	R = CH_3 $[\alpha]_D^{20}$	R = CH_2CH_3 $[\alpha]_D^{20}$	R = CH_2-CH=CH_2 $[\alpha]_D^{20}$	R = $CH_2C_6H_5$ $[\alpha]_D^{20}$
1a[a]	+2.63	+4.98	+4.17	+17.66
1b[a]	+3.65	+4.16	+4.18	+17.34
1c[a]	+7.30	+5.88	+4.17	+17.20
1d[a]	+9.63	+6.70	+3.80	+17.89
$[\alpha]_D^{20}$[b]	+14.60	+7.18	+4.31	-18.07[c]
^{19}F-NMR[d]	-69.04	-69.02	-68.66	-69.43
	-69.40	-69.24	-68.76	-69.55

[a] Chiral auxiliary employed, see scheme 1. [b] Optical rotations of compounds **5** reported in literature, see ref. 6a. [c] The reported value corresponds to the opposite enantiomer. [d] ^{19}F-NMR chemical shifts (δ, internal reference C_6F_6) of the two diastereoisomeric Mosher's amides, measured in $CDCl_3$.

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13. 1-amino-2-methyl-2-propanol: b.p.=40 °C, 12torr; ^{1}H-NMR ($CDCl_3$) 2.58 (s, 2H), 1.13 (s, 6H); MS (70eV) 90 (M^+ +1), 72.
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