Diastereo- and Enantioselective Synthesis of (+)- and (−)-*cis*-2-Aminocyclobutanols

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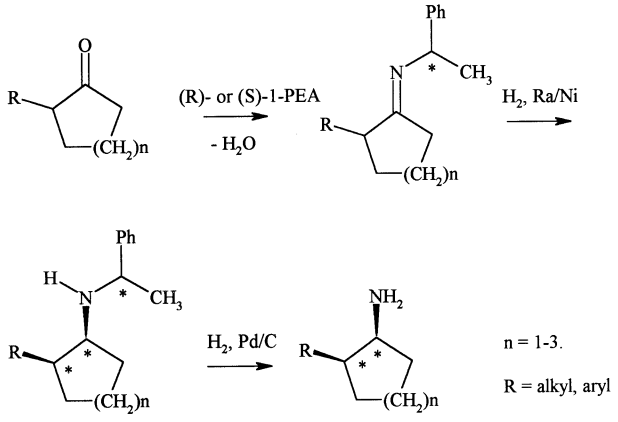
The hitherto unknown (+)- and (−)-*cis*-2-aminocyclobutanols **6a**,**b** and **7a**,**b**, as well as the corresponding benzyloxycyclobutanamines **8a**,**b**, have been synthesized by means of asymmetric reductive amination, with *de* values of 100% and *ee* values ranging from 96.9 to 99.8%. The relative *cis* configuration has been established by NO experiments, whereas the absolute stereochemistry has been deduced from the CD spectra of the corresponding salicylidene derivatives and confirms the *like* induction at C-1.

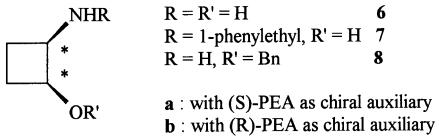
Second-generation asymmetric synthesis[1] remains one of the most popular methods for introducing chirality into potentially bioactive compounds. In pioneering work in this field, Overberger et al.[2] described the enantioselective synthesis of chiral primary amines by means of asymmetric reductive amination using (*R*)-(+)- and (*S*)-(−)-1-phenylethylamine (PEA) as the chiral auxiliaries. In previous communications from this laboratory[3a][3b][3c], we have reported on both enantio- and diastereoselective syntheses of various cyclic amines according to an analogous reaction sequence (Scheme 1).

Scheme 1. Asymmetric reductive amination sequence



Chiral α-amino alcohols have attracted much interest in recent years as substructures of very potent HIV-I protease inhibitors[4a][4b]. Furthermore, chiral cyclic *cis*-α-amino alcohols are also of particular interest as effective ligands in asymmetric catalysis[5][6a] and asymmetric synthesis[5][6b]. This prompted us to devise a convenient synthesis of the optically active (+)- and (−)-*cis*-2-aminocyclobutanols **6a**,**b**.

Figure 1. The (+)- and (−)-*cis*-2-aminocyclobutanols and corresponding benzyloxycyclobutanamines



Although multistep syntheses of both the racemic *cis*- and *trans*-2-aminocyclobutanols have been described previously[7][8a][8b], to the best of our knowledge, an enantioselective preparation of **6** has yet to be devised. We reasoned that the asymmetric reductive amination sequence should offer a suitable route to the desired optically active α-amino alcohols. Herein, we describe the first enantioselective syntheses of the (+)- and (−)-*cis*-aminocyclobutanols **6a**,**b** and **7a**,**b**, and of the corresponding benzyloxycyclobutanamines **8a**,**b** (Figure 1).

Racemic 2-benzyloxycyclobutanone **3**, the substrate for the asymmetric reductive amination sequence, was obtained from dimethyl succinate (**1**) according to a slightly modified literature procedure[9]. We improved the initial step, the condensation of **1** with chlorotrimethylsilane in molten sodium, by performing the reaction in an ultrasound bath. In this way, the intermediate 1,2-bis(trimethylsilyloxy)cyclobutene (**2**) was obtained in satisfactory yields and could then be subjected to acid-catalyzed alcoholysis to yield **3** (Scheme 2).

Subsequent imine condensation with one equivalent of either (*R*)-(+)- or (*S*)-(−)-PEA in refluxing benzene[10], containing a catalytic amount of *p*-toluenesulfonic acid, led to a mixture of four imines **4a**,**b**. Indeed, for both **4a** and **4b**, the complex ^{13}C-NMR spectra exhibited four sets of signals attributable to the diastereomeric imines, those due to the two *Z* isomers indicating that these were present at

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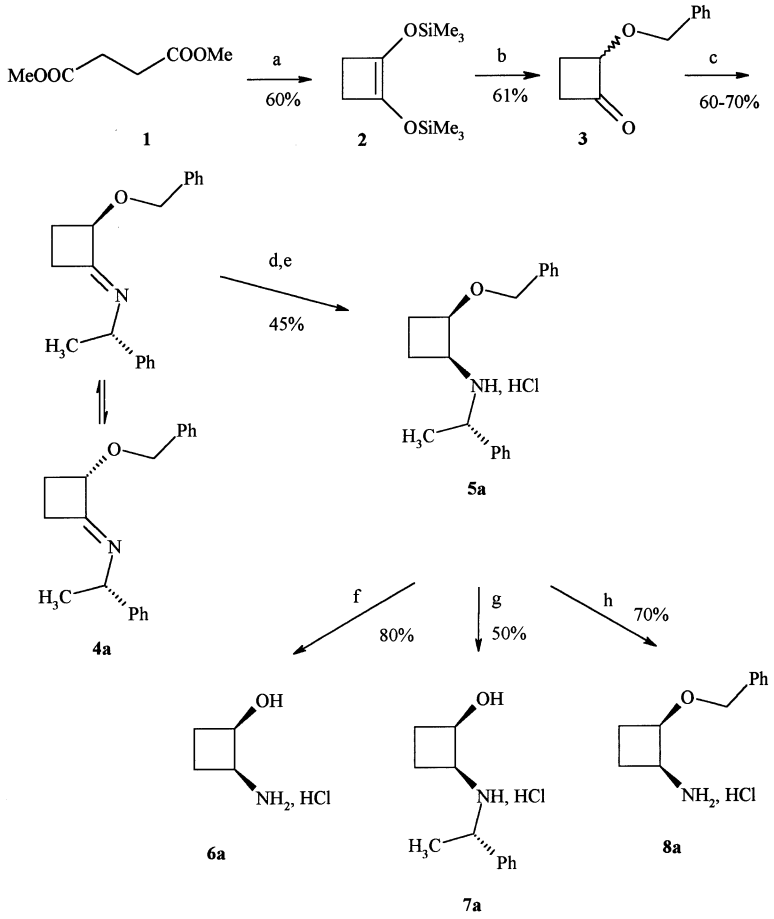
Scheme 2. Synthesis of the optically active **6a**, **7a** and **8a** (the same procedure applies for the synthesis of **6b**, **7b** and **8b**)



(a) Na, THF, TMSCl, ultrasound, under Ar. − (b) BnOH, HCl/diethyl ether, reflux. − (c) (*S*)-PEA [or (*R*)-PEA, respectively], *p*-TsOH, benzene, reflux. − (d) H_2, Raney Ni, 5 bar, 40 h, room temp. − (e) HCl/diethyl ether. − (f) 10% Pd/C, 100 mg/mmol substrate, 45°C, 24 h. − (g) 10% Pd/C, 100 mg/mmol substrate, room temp., 24 h. − (h) 10% Pd/C, 10 mg/mmol substrate, 45°C, 24 h.

a level of less than 10%. The mixture was subjected to hydrogenation without further purification. In the optimized hydrogenation procedure, the crude imine **4a**,**b** was allowed to react with ethanol-treated Raney nickel in a Parr hydrogenator at 5 bar and room temperature. The resulting crude secondary amines **5a**,**b** were obtained in 60−70% yields, based on the amount of ketone used, and were analyzed by means of ^{1}H- and ^{13}C-NMR spectroscopy. The respective ^{13}C-NMR spectra of materials obtained by following the optimized procedure showed only one set of signals for the secondary amine, indicating that only one of the four possible diastereomers was formed in a highly diastereo- and enantioselective process[3d]. Since the starting ketone **2** is racemic and the chemical yield of the secondary amine base > 50%, epimerisation must have occurred at C-2 of the unfavoured diastereomeric imines[3a][3b].

The ranges of the *cis* and *trans* ^{1}H coupling constants in the cyclobutane ring are known to overlap[11]. Therefore the relative stereochemistry of the substituents could not be undoubtedly deduced from the observed *J* values. However, this problem could be overcome by performing nuclear Overhauser experiments. Positive NO effects were observed between 1-H and 2-H, strongly indicating a *cis* arrangement of the two substituents on the cyclobutane ring. If we assume that, in analogy to our previous studies[3a][3b][3c], the catalytic hydrogenation proceeds with *like* induction at C-1, starting with (*R*)-(+)- or (*S*)-(−)-PEA will lead to the enantiomeric α*R*,1*R*,2*S*- and α*S*,1*S*,2*R*-secondary amines **5**, respectively.

In the final step, the chiral auxiliary was removed along with the benzyl protecting group by means of catalytic hydrogenolysis in the presence of 100 mg of 10% Pd/C per mmol substrate at 45°C. In this way, the desired *cis*-α-amino alcohol hydrochlorides **6a** and **6b** were obtained in 80% yields. Furthermore, it was possible to selectively deprotect the amine or the alcohol by adjusting the reaction conditions of the hydrogenolysis. Thus, by performing the reaction with 10 mg of 10% Pd/C per mmol of substrate for 24 h at 45°C, we obtained the primary amines **8a** and **8b** in yields of up to 70%, whereas when the reaction was carried out with 100 mg of 10% Pd/C per mmol of substrate for 24 h at room temperature, the secondary amines **7a** and **7b** were obtained in 50% yields.

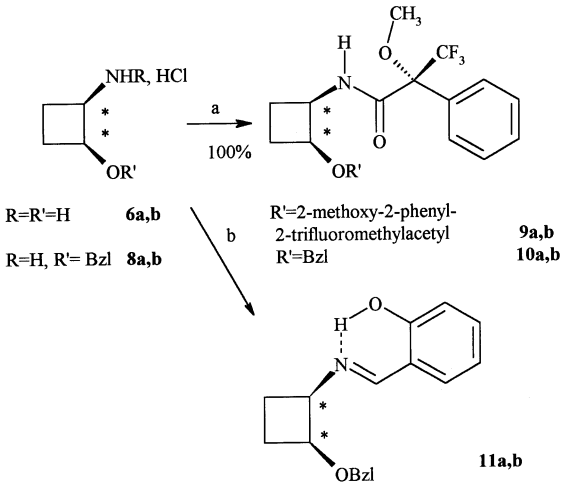
The *ee* values, summarized in Table 1, were determined by means of Mosher's derivatization[12] (Scheme 3). For this purpose, the primary amines **6a**,**b** were treated with two equivalents, and **8a**,**b** with one equivalent of (*S*)-(+)-2-methoxy-2-phenyl-2-trifluoromethylethanoyl chloride to afford the amido esters **9a**,**b** and the amides **10a**,**b** in quantitative yields. ^{19}F-NMR analysis of the diastereomeric mixtures showed *ee* values ranging from 96.9 to 99.8%. The enantiomeric excesses of **7a**,**b** were not determined, but only one set of signals in the ^{13}C-NMR spectra of **7a,b** indicate that the steric integrity is unaffected during the hydrogenolysis step. Therefore the *ee* values of **7a,b** should be of the same order as those of **6a**,**b** and **8a**,**b**, respectively. The absolute configuration was deduced from the CD spectra of the corresponding salicylidene derivatives **11a**,**b** according to the Smith rule[13]. Indeed, the CD spectrum of **11a** exhibits positive Cotton effects at 314 and 253 nm indicating the *S* configuration at C-1, whereas the opposite Cotton effects were observed for **11b**. These findings are in accordance with our previous results[3a][3b][3c] and confirm the *like* induction at C-1.

Table 1. Properties of the optically active 2-aminocyclobutanol and 2-benzyloxycyclobutanamine hydrochlorides

Compound	$[\alpha]^{25}_D$	*ee* (%)[a]	Absolute configuration[c]
6a	+4.0	96.9	1*R*,2*S*
6b	−6.8	99.0	1*S*,2*R*
7a	−64.1	n.d.[b]	1*R*,2*S*
7b	+65.2	n.d.[b]	1*S*,2*R*
8a	−20.4	97.9	1*S*,2*R*
8b	+20.9	99.8	1*R*,2*S*

[a] The *ee* values are corrected to a theoretical 100% *ee* of the chiral auxiliaries. − [b] n.d. = not determined. − [c] According to IUPAC, the carbon atom bearing the oxy substituent is labelled C-1 in **6** and **7**, while it is C-2 in **8**.

Scheme 3. Derivatizations



(a) (*S*)-(+)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride, pyridine, 12 h, room temp. − (b) sodium salicylate, MeOH, reflux.

In summary, starting from the corresponding racemic ketone, we have synthesized the hitherto unknown optically active title compounds **6a**,**b** and **7a**,**b**, along with **8a**,**b**, by means of an asymmetric reductive amination sequence in overall yields of 25, 16 and 22%, respectively. The diastereo- and enantioselective process[14] furnishes products with *de* values of almost 100% and *ee* values up to 99.8%.

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Experimental Section

General: Column chromatography was performed on Merck silica gel (70−230 mesh ASTM). The uncorrected open-capillary melting points were determined with a Mel-Temp II apparatus (Devices Laboratory, USA). Optical rotations were measured with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded in $CDCl_3$ or CD_3OD with tetramethylsilane as internal standard with a Varian Unity 300 spectrometer. CD spectra were recorded with a CD 6 Jobin Yvon Division d'Instruments spectrometer. Microanalyses were carried out at the Chemisches Laboratorium der Universität Freiburg.

1,2-Bis(trimethylsilyloxy)cyclobutene (**2**): Sodium (14 g, 0.63 mol) was refluxed with dry toluene (200 ml) in a three-necked round-bottomed flask for 0.5 h. The flask was then removed from the heating source and shaken vigorously. The mixture was cooled, the toluene was decanted, and the residue was suspended in dry THF (200 ml). The suspension was cooled to 0°C in an ultrasound bath and a solution of chlorotrimethylsilane (80 ml, 0.63 mol) and dimethyl succinate (**1**) (22 g, 0.15 mol) in THF (40 ml) was added dropwise with stirring over a period of 1.5 h under an inert atmosphere. Stirring was continued for a further 2 h, and then dry diethyl ether (200 ml) was added and the mixture was allowed to stand at 4°C overnight. The resulting precipitate was filtered off and the filtrate was concentrated in vacuo. Pure **2** (20.56 g, 0.09 mol, 60%) was obtained as a colourless oil after fractional distillation of the residue through a Vigreux column; b.p. 73°C/12 Torr (ref.[15] 80°C/10 Torr). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.09 (s, 18 H), 2.15 (s, 4 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −0.4, 25.4, 119.4.

2-Benzyloxycyclobutanone (**3**): A mixture of benzyl alcohol (10 g, 0.09 mol) and HCl-saturated diethyl ether (30 ml) was cooled to 0°C and **2** (18 g, 0.078 mol) was added dropwise with stirring. After completion of the addition, the mixture was heated to 80°C for 4 h, concentrated in vacuo, and the residue was distilled under reduced pressure to give **3** (9.69 g, 0.055 mol, 61%) as a colourless oil; b.p. 93°C/0.5 Torr (ref.[16] 90°C/0.4 Torr). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.93 (dddd, *J* = 7.8, 7.4, 10.2, 21.3 Hz, 1 H, 3-H), 2.29 (dddd, *J* = 5.37, 8.06, 9.77, 21.0 Hz, 1 H, 3-H), 2.72 (m, 2 H, 4-H), 4.61 (d, J_{AB} = 11.7 Hz, 1 H, $PhCH_2$), 4.73 (d, J_{AB} = 11.7 Hz, 1 H, $PhCH_2$), 4.75 (m, 1 H, 2-H), 7.25 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.5 (C-3), 39.1 (C-4), 71.9 (C-2), 86.9 (C benzyl), 127.9 (C-4′), 127.9 (C-3′), 128.3 (C-2′), 137.1 (C-1′), 206.5 (C-1).

2-Benzyloxy-N-(1-phenylethyl)cyclobutanimine (**4a**,**b**): The ketone **3** (8.81 g, 0.05 mol) was taken up in benzene (100 ml) and (*R*)-(+)- or (*S*)-(−)-PEA (6.06 g, 0.05 mol) was added, along with a catalytic amount of *p*-toluenesulfonic acid. The solution was refluxed for 2 h under an inert atmosphere in an apparatus fitted with a Dean-Stark head. The reaction was monitored by IR and NMR spectroscopy. After completion, the benzene was evaporated

in vacuo and the crude residue was used for the subsequent reaction without further purification.

(1S,2R)- and (1R,2S)-2-Benzyloxy-N-(1-phenylethyl)cyclobutanamine Hydrochlorides (**5a**,**b**): The crude imine **4** (14.0 g, 0.05 mol) was taken up in absolute ethanol (50 ml) and 2.0 g of ethanol-treated Raney nickel was added. Hydrogenation was carried out at 5 bar and room temperature for 40 h in a Parr hydrogenator. The catalyst was then removed by filtration through Celite and the filtrate was concentrated. The residue was purified by means of flash chromatography, with elution by cyclohexane/ethyl acetate, 7.5:2.5. The crude amine was obtained in 60−70% yield and was precipitated as its hydrochloride in HCl-saturated diethyl ether. Recrystallization from ethyl acetate afforded **5** (5.08 g, 16 mmol, 32%) as white crystals. − **5a**: M.p. 145°C. − $[\alpha]^{25}_D$ = +115.6. − $C_{19}H_{24}ClNO$ (317.8): calcd. C 71.8, H 7.61, N 4.39; found C 71.7, H 7.57, N 4.41. − **5b**: M.p. 145°C. − $[\alpha]^{25}_D$ = −114.6. − $C_{19}H_{24}ClNO$ (317.8): calcd. C 71.8, H 7.61, N 4.39; found C 71.7, H 7.68, N 4.44. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.94 (d, J = 6.8 Hz, 3 H, CH_3), 1.97 (m, 1 H, 3-H), 2.12 (m, 1 H, 4-H), 2.58 (m, 1 H, 3-H), 2.77 (m, 1 H, 4-H), 3.38 (m, 1 H, 1-H), 4.40 (d, J_{AB} = 12 Hz, 1 H, $PhCH_2$), 4.06 (m, 1 H, 2-H), 4.81 (d, J_{AB} = 12 Hz, 1 H, $PhCH_2$), 7.2−7.6 (m, 10 H, ArH), 10.0 (br. s, 1 H, NH_2^+), 10.5 (br. s, 1 H, NH_2^+). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.8 (CH_3), 21.7 (C-4), 24.6 (C-3), 52.3 (C-1), 58.4 (C-α), 69.7 (Ph*C*H_2), 72.1 (C-1), 127.7 (ArC), 128.1 (ArC), 128.2 (ArC), 128.4 (ArC), 128.8 (ArC), 129.0 (ArC), 136.7 (ArC), 137.4 (ArC).

(1R,2S)- and (1S,2R)-2-Aminocyclobutanol Hydrochlorides (**6a**,**b**): 10% Pd/C (250 mg) was suspended in ethanol (50 ml) and prehydrogenated at 5 bar and 45°C for 15 min. The amine hydrochloride **5** (800 mg, 2.5 mmol) in ethanol (75 ml) was then added and hydrogenolysis was allowed to proceed for 24 h. The catalyst was then removed by filtration through Celite, the filtrate was concentrated, and the residue was recrystallized from ethyl acetate to yield **6** (247 mg, 2.0 mmol, 80%) as white crystals. − **6a**: M.p. 115−117°C. − $[\alpha]^{25}_D$ = +4.0. − $C_4H_{10}ClNO$ (123.6): calcd. C 38.9, H 8.16, N 11.33; found C 38.7, H 7.97, N 11.26. − **6b**: M.p. 116−118°C. − $[\alpha]^{25}_D$ = −6.8. − $C_4H_{10}ClNO$ (123.6): calcd. C 38.9, H 8.16, N 11.33; found C 38.3, H 8.04, N 11.05. − ^{1}H NMR (CD_3OD, 300 MHz): δ = 2.05 (m, 1 H, 4-H), 2.10 (m, 1 H, 3-H), 2.20 (m, 1 H, 4-H), 2.30 (m, 1 H, 3-H), 3.78 (m, 1 H, 1-H), 4.45 (m, 1 H, 2-H). − ^{13}C NMR (CD_3OD, 75 MHz): δ = 22.0 (C-4), 29.0 (C-3), 51.6 (C-1), 66.5 (C-2).

(1R,2S)- and (1S,2R)-2-[(1-Phenylethyl)amino]cyclobutanol Hydrochlorides (**7a**,**b**): 10% Pd/C (250 mg) was suspended in ethanol (50 ml) and prehydrogenated at 5 bar and room temperature for 15 min. The amine hydrochloride **5** (800 mg, 2.5 mmol) in ethanol (75 ml) was then added and hydrogenolysis was allowed to proceed for 24 h. The catalyst was then removed by filtration through Celite, and the filtrate was concentrated. Recrystallization of the residue from ethyl acetate afforded **7** (284 mg, 1.25 mmol, 50%) as white crystals. − **7a**: M.p. 121−123°C. − $[\alpha]^{25}_D$ = −64.1. − $C_{12}H_{18}ClNO$ (227.7): calcd. C 63.3, H 7.97, N 6.15; found C 63.2, H 7.85, N 6.15. − **7b**: M.p. 122°C. − $[\alpha]^{25}_D$ = +65.2. − $C_{12}H_{18}ClNO$ (227.7) : calcd. C 63.3, H 7.97, N 6.15; found C 63.2, H 8.02, N 6.13. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.90 (d, J = 7.0 Hz, 3 H, CH_3), 1.95 (m, 1 H, 4-H), 2.25 (m, 2 H, 3-H), 2.52 (m, 1 H, 4-H), 3.45 (m, 1 H, 1-H), 4.45 [m, 2 H, C*H*(Ph)CH_3, 2-H], 7.18 (m, 3 H, ArH), 7.62 (m, 2 H, ArH), 9.38 (br. s, 1 H, NH_2^+), 9.78 (br. s, 1 H, NH_2^+). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.5 (CH_3), 22.0 (C-4), 27.8 (C-3), 54.2 (C-1), 58.8 [*C*H(Ph)CH_3], 68.0 (C-2), 128.1 (ArC), 129.3 (ArC), 129.4 (ArC), 136.1 (ArC).

(1S,2R)- and (1R,2S)-2-Benzyloxycyclobutanamine Hydrochlorides (**8a**,**b**): 10% Pd/C (25 mg) was suspended in ethanol (50 ml) and prehydrogenated at 5 bar and 45°C for 15 min. The amine hydrochloride **5** (800 mg, 2.5 mmol) in ethanol (75 ml) was then added and hydrogenolysis was allowed to proceed for 24 h. The catalyst was then removed by filtration through Celite, and the filtrate was concentrated. Recrystallization of the residue from ethyl acetate afforded **8** (375 mg, 1.75 mmol, 70%) as white crystals. − **8a**: M.p. 153°C. − $[\alpha]^{25}_D$ = −20.4. − $C_{11}H_{16}ClNO$ (197.7): calcd. C 61.8, H 7.55, N 6.55; found C 61.7, H 7.42, N 6.55. − **8b**: M.p. 155°C. − $[\alpha]^{25}_D$ = +20.9. − $C_{11}H_{16}ClNO$ (197.7): calcd. C 61.8, H 7.55, N 6.55; found C 61.5, H 7.53, N 6.53. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.00 (m, 1 H, 4-H), 2.08 (m, 1 H, 4-H), 2.12 (m, 1 H, 3-H), 2.48 (m, 1 H, 3-H), 3.84 (m, 1 H, 1-H), 4.11 (q, J = 6.6 Hz, 1 H, 2-H), 4.49 (d, J = 12.2 Hz, 1 H, $PhCH_2$), 4.69 (d, J = 12.2 Hz, 1 H, $PhCH_2$), 7.25 (m, 3 H, ArH), 7.39 (m, 2 H, ArH), 8.6 (br. s, 3 H, NH_3^+). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.5 (C-4), 26.5 (C-3), 49.9 (C-1), 70.7 (Ph*C*H_2), 71.2 (C-2), 127.6 (ArC), 127.8 (ArC), 128.3 (ArC), 137.5 (ArC).

General Procedure for Conversion to the Mosher Amides **9a**,**b** (*and* **10a**,**b**): The primary amine hydrochlorides **6a**,**b** (or **8a**,**b**) (0.15 mmol) were taken up in $CHCl_3$ (1 ml), pyridine (2 ml) was added, followed by (*S*)-(+)-2-methoxy-2-phenyl-2-trifluoromethylethanoyl chloride (0.30 mmol) (0.15 mmol for **8a**,**b**). Stirring was maintained for 18 h. The solvent was then removed in vacuo, the residue was taken up in H_2O (3 ml) and extracted with diethyl ether (3 × 5 ml). The combined organic extracts were washed with 1 N HCl (5 ml), a saturated solution of Na_2CO_3 (5 ml) and H_2O, dried, and concentrated in vacuo. The crude residue was analyzed by ^{19}F-NMR spectroscopy.

General Procedure for the Conversion to the Salicylidene Derivatives **11a**,**b**: The primary amine hydrochlorides **8a**,**b** (0.3 mmol) were taken up in MeOH (2 ml), and sodium 2-formylphenolate (0.3 mmol) was added. The mixture was refluxed for 15 min and then allowed to stand at room temperature overnight. The solvent was removed in vacuo and the residue was submitted to CD spectroscopy.

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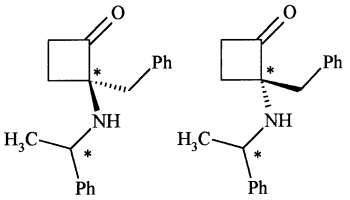
[10] When the imine condensation was attempted by refluxing for 6 h in xylene, the desired imine was not obtained. Instead, we isolated two diastereomeric amino ketones (Figure 2), separable by flash chromatography, the structures of which were established by means of ^{13}C- and ^{1}H-NMR spectroscopy.
We assume that these structures are the result of a non-stereoselective 1,2-rearrangement, probably via an enamine intermediate, which is currently being investigated.

Figure 2. The rearranged α-amino ketones



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