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Asymmetric Synthesis of 2-Alkylalkanoic Acids *via* Alkylation of Chiral Amide Anions *

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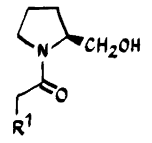
Acylation of (*S*)-proline methyl ester (*2*) gave amide ester *3* (R^1=alkyl), which on reaction with methylmagnesium iodide furnished the tertiary alcohol *4*. Alkylation of the dianion from this yielded mainly one diastereomer of the amide *5*, which on acid hydrolysis gave the chiral 2-alkylalkanoic acid *6* in 75–90 % e.e. and 55–82 % chemical yield from the hydroxyamide *4*. The latter compound could be recovered from the hydrolysate with preserved optical purity *via* acylation without isolation of the tertiary prolinol *7*. The diastereomeric mixture of amides *5'* and *5''* could be separated by column chromatography leading to the acid *6* in very high optical purity.

Chiral 2-alkylalkanoic acids are useful synthons for many compounds with branched chain structures and general methods for the preparation of these acids are therefore needed. This investigation was initiated because of our interest in the synthesis of insect pheromones using chiral 2-alkylalkanoic acids as building blocks.

Several methods for their synthesis have recently been described.[1–5] Meyers[1] found that alkylation of chiral oxazoline anions followed by hydrolysis of the products gives chiral acids. (*S*)-2-Methyldecanoic acid (≤72 % e.e.) has been prepared using this method but attempts to prepare the (*R*)-enantiomer failed.[6] Recently Sonnet[2] and Evans[3] independently described an alternative method giving high optical and chemical yields.

Alkylation of the dianion from the prolinol amide *1* (R^1=alkyl) furnishes a mixture of diastereomeric amides with one diastereomer in high excess. Acid catalysed hydrolysis then gives chiral acids of high e.e. Sonnet[2] reported the synthesis of (*S*)- and (*R*)-2-methyldecanoic acid (80 and 66 % e.e. respectively, *t*-butyllithium used as base). Employing this method we obtained the (*S*)-form in 70 % e.e. and the (*R*)-form in 80 % e.e. [lithium diisopropylamide (LDA) used as base]. It is of interest to note that α-alkylalkanoic acids of very high optical purity may also be obtained by resolution *via* crystallization with an optically active amine.[7]



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In this paper we describe an improved procedure for the preparation of chiral 2-alkylalkanoic acids which provides products of very high optical purity. The synthesis uses prolinol derivatives (*4*) with a bulky tertiary alcohol group. The chiral inducer (*7*) can be recovered and re-used. If necessary the diastereomeric mixture of the alkylation products (*5*) can be separated by liquid

* Part of this work has been published in a preliminary communication.[15]

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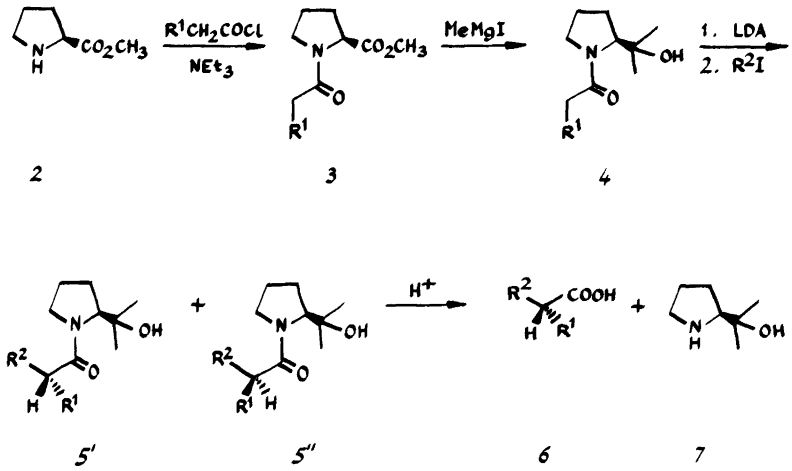


chromatography and, after hydrolysis, the desired chiral acid (*6*) is obtained in more than 99 % optical purity.

The synthetic procedure is as follows. (*S*)-Proline methyl ester (*2*) was first converted to *3* followed by treatment with methylmagnesium iodide to yield *4*. Treatment of *4* with LDA in tetrahydrofuran (THF) furnished the corresponding dianions, which were alkylated with the appropriate alkyl halide (−100−0 °C). The crude product consisted of a diastereomeric mixture of *5'* and *5''* in a ratio between 88/12 and 95/5. These mixtures could be separated by column chromatography to give the pure diastereomers, which upon hydrolysis gave the 2-alkylalkanoic acids (*6*) in very high e.e. (96−>99 %). Alternatively we found that treatment of (*R*)-2-methyldecanoic acid of 72 % e.e. with (*S*)-(−)-1-phenylethylamine in acetone yielded a salt. This salt was recrystallized once from acetone to yield a product from which acid *6d* of 96 % e.e. was liberated. The experimental results are summarized in Tables 1 and 2 (the latter *cf.* Experimental).

The 5'/5'' compositions were determined by capillary gas chromatography and by ^{1}H NMR. The spectra of the 5'/5'' mixtures displayed two doublets between δ 1.1 and 1.2 ppm, due to the protons of the α-methyl groups. Determination of the 5'/5'' ratios was done either by directly comparing the integrals of these doublets or by comparing the integrals from the singlets obtained by irradiation of the α-proton. Calculations based on the ratio between the integral of one of these singlets and the integral obtained from the signal representing one of the methyls in the tertiary alcohol group then gave the 5'/5'' ratios. NMR spectra of the amides of type *5* do not contain any signals indicating the presence of a second detectable rotamer. Either rotation around the CO−N bond is too fast or only one rotamer is present (presumably the one with the possibility for hydrogen bonding). The NMR and GLC methods gave very similar results and correlated well with the results from measuring the optical rotations of the acids *6* obtained by hydrolysis of the crude alkylation mixture before separation of the diastereomers. The amide *4a* (R^1=CH_3) was found to be optically pure by ^{1}H NMR in the presence of tris[3-(2.2.2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium, [Eu(TFC)$_3$]. It showed only one triplet due to the methyl protons of the propionyl group whereas a racemic sample showed two separate triplets under identical conditions.

The prolinol amides *1* (or alkylated *1*) readily undergo hydrolysis (1 M HCl, 100 °C, 2 h) proceeding *via* amide to ester rearrangement.[3] Since tertiary alcohols are less readily acylated than primary alcohols, it is not surprising that the amide tertiary alcohols *5* required prolonged heating for successful hydrolysis (1.5 M HCl in H_2O−dioxane 1:1, 90−95 °C, 42 h).

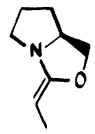
The chiral inducer (*7*) is in principle recoverable. However, since compounds of this type are highly water soluble, it was simpler to recover it as the less hydrophilic amidols of type *4*. Thus, after removal of the chiral acids by extraction

Table 1. Experimental yields.

Exp	R^1	R^2	*5* Chemical Yield %	*5'/5"* ratio GC[b]	NMR	*5→6* Chemical Yield %	$[\alpha]_D^{20}$ neat	Acid *6*[a] config.	% e.e.
a	CH_3	C_2H_5	86	92/8 98/2[e]	92/8	74	−15.8[c] −18.2[e]	*R* *R*	84[d] 96[d,e,f]
b	CH_3	n-C_4H_9	77	95/5	95/5	84	−16.3	*R*	87
c	n-C_4H_9	CH_3	96	88/12 >99/1[e]	89/11	86	+14.0 +18.6[e,g]	*S* *S*	75 >99[e]
d	CH_3	n-C_8H_{17}	75	93/7 >99/1[e]	94/6	77	−14.0	*R*	90
e	n-C_8H_17	CH_3	82	88/12 >99/1[e]	88/12	75	+12.1	*S*	78
f	CH_3	$C_6H_5CH_2$	87		94/6 98/2[e]	79	−22.1 −24.6[e,h]	*R* *R*	87 97[e]
g	$C_6H_5CH_2$	CH_3	72		94/6 >99/1[e]	76	+25.2[e]	*S*	>99[e]

[a] Calculated values for e.e. are based on the highest literature rotations available unless otherwise noted. Maximum rotations from the literature: (*R*)-2-methylbutanoic acid, −19.8° (neat)[8]; (*S*)-2-methylhexanoic acid, +18.7° (neat)[9]; (*S*)-2-methyldecanoic acid, +15.5° (neat)[6]; (*S*)-2-methyl-3-phenylpropanoic acid, +25.4° (neat).[10] [b] Gas chromatography was run prior to work up of the reaction mixture. Conditions for *5b* (R^1=CH_3, R^2=n−C_4H_9): column SP 1000, 25m, i.d. 0.35 mm, carrier gas N_2, 0.38 kg/cm^2, 80−160°C, 2°C/min, ret, time for *5b'* 79.0 min, for *5b"* 77.6 min. [c] (c 1.275, CH_3OH). [d] In previously published work on the synthesis of chiral α-alkylated acids[1,3] the reference rotation value used for enantiomerically pure (*R*)-2-methylbutanoic acid has varied. We use $[\alpha]_D^{25}$=−18.9° for 100 % optically pure *5a*. This value was established by Korver and van Gorkom[11] and is also inferable from the result of a ^{1}H NMR determination of the optical purity of (*R*)-2-methylbutanol obtained after reduction of chromatographically purified *5a* (*cf.* footnote f). [e] The *5'/5"* diastereomers were separated by silica gel chromatography prior to hydrolysis. [f] Confirmed by LAH-reduction of this acid followed by reaction with (+)−MTPA−Cl (methoxy-trifluoromethyl-phenylacetic acid chloride) to give the corresponding pair of diastereomeric MTPA-esters[12] of 2-methylbutanol. The ratio between these diastereomers was determined to be 98/2 by ^{1}H NMR (200 MHz) which corresponds to an alcohol of 96 % e.e. and consequently[13] to (*R*)-2-methyl-butanoic acid of the same optical purity. [g] (c 0.985, CH_3OH). [h] (c 1.175, CH_3OH).

from the hydrolysis mixture, this was neutralised, concentrated and acylated (acyl chloride/triethylamine). The amidol *4a* ($R^1=CH_3$) was obtained optically pure in 67 % yield and was used for a second reaction cycle.



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The rigid bicyclic ethylidene oxazolidine *8* would be a suitable intermediate for chiral alkylations. Related asymmetric syntheses in which the nucleophilic properties of the ethylidene oxazolidine are used should also be possible. Various reaction conditions were investigated to accomplish the synthesis of *8* from prolinol by reacting it with the orthoester of propionic acid. However, we were not able to obtain the desired product. We are continuing our studies and are investigating the use of related bicyclic prolinol derivatives for asymmetric synthesis.

EXPERIMENTAL

Infrared spectra were measured as liquid films on a Perkin-Elmer 257 spectrophotometer. NMR-spectra were recorded in deuteriochloroform using a Varian EM 360 (60 MHz) or a Bruker WP 200 (200 MHz) spectrometer. Gas chromatographic analyses were performed on a Pye Unicam Series 204 instrument utilizing a FID detector. Columns employed were 25 m capillary columns coated with SP 1000 or Carbowax 20M. Optical rotations were determined on a Perkin-Elmer 141 Polarimeter. Merck Kieselgel 60, 230–400 mesh, was used for flash column chromatography with light petroleum (40–60 °C) –ethyl acetate systems for elution. All boiling points are uncorrected and are given as air bath temperatures in a Büchi GKR-50 oven. Elemental analyses were performed by Centrala Analyslaboratoriet, Uppsala, Sweden.

General procedure for preparation of chiral α-alkylated acids. (*S*)-Proline methyl ester [b.p. 60 °C/8 mmHg, IR (film): 3320, 1735, 1210 cm^{-1}, freshly distilled immediately prior to use, since the free methyl ester amine is easily dimerized to a diketopiperazine on standing, *cf.* Ref. 14] and triethylamine (1.9 molar eq.) were stirred in tetrahydrofuran (THF, 0.5 ml/mmol of ester). The acyl chloride (1.2 mol.eq. in 0.5 ml THF/mmol of ester) was then added (5 min., 0 °C). Stirring was continued (1 h), the reaction mixture was diluted with ether and the precipitate was filtered off. Concentration *in vacuo*, purification by flash column chromatography, drying over $MgSO_4$ and bulb to bulb distillation then gave the amide *3* in 82–95 % yield.

The amide *3* in ether (0.9 ml/mmol amide) was added rapidly to a vigorously stirred solution of the Grignard reagent prepared from Mg (2.2 mol.eq.) and methyl iodide (2.4 mol.eq.) in ether (0.7 ml/mmol amide) at 0 °C under N_2. The reaction mixture was refluxed for 4 h followed by stirring overnight at ambient temperature. Dilution with aqueous HCl, followed by 3–4 ether extractions of the aqueous phase, drying of the combined etheral solutions over $MgSO_4$, concentration and purification by flash column chromatography afforded, after bulb to bulb distillation, the amide *4* in 82–86 % yield. (When small amounts of starting material remained, they were removed by overnight treatment with a solution of potassium hydroxide in methanol).

Freshly distilled amide *4* dissolved in THF (0.75 ml/mmol amide), was injected into a solution of LDA (2.25 mol.eq.) in THF (0.5 ml/mmol amide) at 0 °C under nitrogen and kept at 0 °C for 2 h. The enolate solution thus formed was cooled to −100 °C. (Except in the experiment with $R^1=CH_3$, $R^2=C_2H_5$, which was stirred at 0 °C, *cf.* the results of Ref. 4). The alkyl iodide (2.5 mol.eq.) in THF (0.75 ml/mmol amide) was added and stirring was continued for 2 h, maintaining the low temperature. In the low temperature reactions the temperature was then allowed to rise to −50 °C before quenching with ammonium chloride (aq. sat. soln.). After several extractions with ether, followed by washing with brine and finally drying over $MgSO_4$, a crude mixture of diastereomeric amides *5′* and *5″* was obtained. Column chromatography followed by bulb to bulb distillation gave the pure mixture of *5′* and *5″* in 72–96 % yield. The predominant diastereomer *5′* in most cases was isolated in a second more carefully controlled flash chromatography (*cf.* below).

Hydrolysis of amides *5′* and *5″* was carried out in a solution of equal volumes of 3 M HCl (aq) and dioxane (15 ml/mmol amide), which was stirred at 90–95 °C for 42 h. After cooling followed by 4–5 extractions with ether, washing of the combined etheral extracts with sodium carbonate (aq. sat. soln.), acidification of this water extract with HCl and extraction with ether, the ether phases were combined and dried over $MgSO_4$. Concentration *in vacuo* and distillation

Table 2.

Cpd.	R^1	Yield %	B.p. °C/0.1 mmHg	$[\alpha]_D^t$ °	*t*	(c MeOH)	NMR (60 MHz)	IR cm^{-1}	Anal.
3a	CH_3	95	110–115	−103.8	23	1.317	δ 1.1(3H,t), 2.0(4H,m), 2.25(2H,q), 3.3–3.8(2H,m), 3.7(3H,s), 4.07(1H,t)	2500, 1730, 1640	
3c	n-C_4H_9	91	125–140	−85.9	23	1.776	δ 0.86(3H,t), 1.05–2.4(12H,m), 3.5(2H,m), 3.75(3H,s), 4.45 (1H,t)	1740, 1650	
3e	n-C_8H_{17}	91	155–165	−72.8	23	1.400	δ 0.9(3H,t), 1.3(20H, broad s), 3.25–3.6(2H,m), 3.7(3H,s), 4.53(1H,t)	3500, 1735, 1640	
3g	$CH_2C_6H_5$	82	180–190	−76.8	19	1.800	–	–	
4a	CH_3	82	115–118	−94.3	22	1.700	δ 1.04–1.22(9H,m), 1.4–2.1(4H,m) 2.35(2H,q), 3.1–3.8(2H,m), 4.1(1H,t) 6.39(1H,s)	3300(m), 1630(s)	C,H
4c	n-C_4H_9	86	150–155	−66.5	24	1.000	δ 0.95(3H,t), 1.1(3H,s), 1.25(3H,s) 1.3–2.1(10H,m), 2.3(2H,q), 3.1–3.9 (2H,m), 4.1(1H,t), 6.45(1H,s)	3300(m), 1620(s)	C,H
4e	n-C_8H_{17}	84	170–180	−55.7	20	1.800	δ 0.85(3H,t), 1.05(3H,s), 1.15(3H,s) 1.28(16H, broad s), 1.5–2.5(4H,m), 3.05–3.7(2H,m), 4.1(1H,t), 6.42(1H,s)	3300(m), 1620(s)	C,H
4g	$CH_2C_6H_5$	83	180–185	−61.7	19	1.520	δ 1.0(3H,s), 1.16(3H,s), 1.3–2.2(4H,m) 2.4–3.2 (4H,m), 3.2–3.6(2H,m), 4.1 (1H,t), 6.32(1H,s), 7.20(5H,m)	3300(m), 3020–3080(m) 1620(s)	C,H

furnished chiral α-alkylated acid *6* in 74–86 % yield, 75–99 % enantiomeric excess (e.e.).

The results of various experiments following this procedure are summarized in Tables 1 (*cf.* above) and 2 (*cf.* below).

Chromatographic separation of diastereomeric amides 5′ and 5″. A typical separation is described: Amide *5a* [1.07 g, GLC purity 92 %, (*R,S*)/(*S,S*) diastereomer ratio=92/8] was chromatographed on a silica gel column (*h*=26 cm, i.d.=33 mm). The (*R,S*) diastereomer eluted first, appearing after elution of approx. 7 l of a 10/90 ethyl acetate/petroleum ether mixture. Fractions containing pure (*R,S*) diastereomer were collected, then as the (*S,S*)-diastereomer appeared, elution was continued with a 20/80 ethyl acetate/light petroleum mixture and fractions with gradually decreasing (*R,S*)/(*S,S*) ratio were collected until no amide remained on the column. Evaporation gave 0.38 g essentially pure *5a′*, 97 % d.e. (GLC) and a 0.42 g fraction of *5a′* and *5″* in a ratio of 87/13.

Recovery of the chiral inducer 7. The chiral inducer *7* was recovered as the amide *4a* from the hydrolysis mixture in the following experiment: Amide *4e* (350 mg, 1.24 mmol) was dissolved in 3 M HCl (aq) and dioxane (1/1, 40 ml) and stirred at 90 °C for 40 h. Ether extraction of the hydrolysis mixture removed the acid and left an acidic aqueous layer which was neutralized to pH 3–4 with NaOH and concentrated to give an oil which was treated with an excess triethylamine (1.5 ml) and propionylchloride (600 mg) and stirred at ice-bath temperature for 1 h. Dilution with ether, filtration, drying over $MgSO_4$, concentration, flash chromatography and final bulb to bulb distillation afforded *4a* (153 mg, 0.83 mmol) in 67 % yield without loss of optical purity [$[\alpha]_D^{18}$ −93.4° (c. 2.987, CH_3OH)].

5a, [S-(R,S*)]-α,α-Dimethyl-1-(2-methyl-1-oxobutyl)-2-pyrrolidinemethanol, (R^1=CH_3, R^2=C_2H_5).* Alkylation of amide *4a* (800 mg, 4.32 mmol) with ethyl iodide furnished amide *5a* (793 mg, 86 %), b.p. 145–150 °C/0.1 mmHg, $[\alpha]_D^{22}$ −101.4° (c 1.705, CH_3OH).

NMR (200 MHz): δ 0.90 [3H,t,−C(H_2)CH_3], 1.04 [3H,s,>C(OH)CH_3], 1.17 [3H,d,−C(H)CH_3], 1.19 [3H,s,>C(OH)CH_3], 1.34–2.18 (6H,m,C−CH_2−C), 2.58 [1H,m,−C(CH_3)*H*], 3.36 [1H,m,C−C(H)*H*−N], 3.78 [1H,m,C−C(H)*H*−N], 4.17 [1H,t,N−C(C)*H*−C(H_2)], 6.55 (1H,s,O*H*). Comparing the integral of the doublet at δ 1.17 to the integral of a minor doublet at δ 1.11 (corresponding signal from the (*S,S*)-isomer) gave 83 % d.e. for this amide. GLC gave 83 % d.e. Amide *5a* was also chromatographically purified to yield *5a′* in 97 % d.e. (GLC).

5b, [S-(R,S*)]-α,α-Dimethyl-1-(2-methyl-1-oxohexyl)-2-pyrrolidinemethanol, (R^1=CH_3, R^2=n-C_4H_9).* Alkylation of amide *4a* (185 mg, 1.00 mmol) with n-butyl iodide furnished amide *5b* (181 mg, 77 %), b.p. 145–155 °C/0.1 mmHg $[\alpha]_D^{19}$ −78.9° (c 1.900, CH_3OH).

NMR (200 MHz): δ 0.89 [3H,t,−C(H_2)CH_3], 1.04 [3H,s,>C(OH)CH_3], 1.05–1.20 [6H,s,d,>C(OH)CH_3,>C(H)CH_3], 1.23–2.20 (10H,m,C−CH_2−C), 2.64 [1H,m,>C(CH_3)*H*], 3.34 [1H,m,C−C(H)*H*−N], 3.75 [1H,m,C−C(H)*H*−N], 4.16 [1H,t,N−C(C)*H*−C(H_2)], 6.54 (1H,s,O*H*). Irradiation at δ 2.64 gave a minor singlet at δ 1.11. This signal represents the methyl α to the carbonyl in the (*S,S*)-isomer. Comparison between integrals of the δ 1.11 signal and the δ 1.04 signal gave 89 % d.e. GLC gave 90 % d.e.

5d, [S-(R,S*)]-α,α-Dimethyl-1-(2-methyl-1-oxodecyl)-2-pyrrolidinemethanol, (R^1=CH_3, R^2=n-C_8H_{17}).* Alkylation of amide *4a* (180 mg, 0.97 mmol) with n-octyl iodide furnished amide *5d* (218 mg, 75 %) b.p. 170–180 °C/0.1 mmHg, $[\alpha]_D^{19}$ −70.2° (c 1.100, CH_3OH).

NMR (200 MHz): δ 0.88 [3H,t,−C(H_2)CH_3], 1.04 [3H,s,>C(OH)CH_3], 1.08–1.22 [6H,s,d,>C(OH)CH_3,−C(H)CH_3], 1.26 (12H, broad s, C−CH_2−C), 1.32–2.12 (6H,m,C−CH_2−C), 2.63 [1H,m,>C(CH_3)*H*], 3.36 [1H,m,C−C(H)*H*−N], 3.76 [1H,m,C−C(H)*H*−N], 4.16 [1H,t,N−C(C)*H*−C(H_2)], 6.54 (1H,s,O*H*). D.e.: 87 % (NMR with decoupl. *cf. 5b)* and 86 % (GLC). Amide *5d* was also chromatographically purified to yield *5d′* in >99 % d.e. (GLC), $[\alpha]_D^{22}$ −79.3° (c 1.155, CH_3OH).

5f, [S-(R,S*)]-α,α-Dimethyl-1-(2-benzyl-1-oxopropyl)-2-pyrrolidinemethanol, (R^1=CH_3, R^2=$CH_2C_6H_5$).* Alkylation of amide *4a* (155 mg, 0.84 mmol) with benzyl bromide furnished amide *5f* (200 mg, 87 %), b.p. 170–175 °C/0.1 mmHg, $[\alpha]_D^{19}$ −133.4° (c 1.730, CH_3OH).

NMR (200 MHz): δ 1.00 [3H,s,>C(OH)CH_3], 1.16 [3H,s,>C(OH)CH_3], 1,24 [3H,d,>C(H)CH_3], 1.38–2.00 (4H,m,C−CH_2−C), 2.67 [1H,dd,C−C(H)*H*−C_6H_5], 2.84–3.37 [4H,m,N−CH_2−C,C−C(H)*H*−C_6H_5+−(CH_3)*H*], 4.03 [1H,t,N−C(C)*H*−C(H_2)], 6.58 (1H,s,O*H*), 7.23 (5H,m,C_6H_5). D.e.: 88 % (NMR with decoupl. *cf. 5b)*. Amide *5f* was also chromatographically purified to yield *5f′* in 97 % d.e. (NMR).

5c, [S-(R,R*)]-α,α-Dimethyl-1-(2-methyl-1-oxohexyl)-2-pyrrolidinemethanol (R^1=n-C_4H_9, R^2=CH_3).* Alkylation of amide *4c* (340 mg, 1.50 mmol) with methyl iodide furnished amide *5c* (350 mg, 96 %), b.p. 145–155 °C/0.1 mmHg $[\alpha]_D^{22}$ −40.4° (c 1.423, CH_3OH).

NMR (200 MHz): δ 0.89 [3H, t,−C(H_2)CH_3], 1.05 [3H,s,>C(OH)CH_3], 1.11 [3H,d,>C(H)CH_3], 1.19 [3H,s, >C(OH)CH_3], 1.21–

2.20 (10H,m,C−CH_2−C), 2.63 [1H,m,>C(CH_3)H], 3.37 [1H,m,C−C(H)H−N], 3.75 [1H,m,C−C(H)H−N], 4.15 [1H,t,N−C(C)H−C(H_2)], 6.50 (1H,s,OH). The diastereomeric excess was 78 %, determined by calculating the relative areas of the integrals for the δ 1.11 doublet representing the major (*S,S*)-isomer and a minor doublet at δ 1.16 representing the (*R,S*)-isomer. GLC gave 76 % d.e. Amide *5c* was also chromatographically purified to yield *5c'* in >99 % d.e. (GLC).

5e, [S-(R,R*)]-α,α-Dimethyl-1-(2-methyl-1-oxodecyl)-2-pyrrolidinemethanol* (R^1=*n*-C_8H_{17}, R^2=CH_3). Alkylation of amide *4e* (560 mg, 1.98 mmol) with methyl iodide furnished amide *5e* (489 mg, 82 %), b.p. 180−185 °C/0.1 mmHg, $[\alpha]_D^{23}$ −35.8° (c 1.104, CH_3OH).

NMR (200 MHz): δ 0.88 [3H,t,−C(H_2)CH_3], 1.05 [3H,s,>C(OH)CH_3], 1.11 [3H,d, >C(H)CH_3], 1.18 [3H,s,−C(OH)CH_3], 1.26 (12H, broad s, C−CH_2−C), 1.60−2.12 (6H,m,C−CH_2−C), 2.60 [1H,m,>C(CH_3)H], 3.38 [1H,m,C−C(H)H−N], 3.73 [1H,m,C−C(H)H−N], 4.15 [1H,t,N−C(C)H−C(H_2)], 6.50 (1H,s,OH). D.e.: 76 % (NMR with decoupl. *cf. 5b*) and 76 % (GLC). Amide *5e* was also chromatographically purified to yield *5e'* in >99 % d.e. (GLC), $[\alpha]_D^{22}$ −35.2° (c 0.685, CH_3OH).

5g, [S-(R,R*)]-α,α-Dimethyl-1-(2-benzyl-1-oxopropyl)-2-pyrrolidinemethanol* (R^1=$CH_2C_6H_5$, R^2=CH_3). Alkylation of amide *4g* (261 mg, 1.00 mmol) with methyl iodide furnished amide *5g* (199 mg, 72 %), b.p. 185−190 °C/0.1 mmHg, $[\alpha]_D^{19}$ +31.0° (c 1.376, CH_3OH).

NMR (200 MHz): δ 0.72 [3H,s,>C(OH)CH_3], 1.13 [3H,s,>C(OH)CH_3], 1.18 [3H,d, >C(H)CH_3], 1.53−2.07 (4H,m,C−CH_2−C), 2.70 [1H,dd,C−C(H)H−C_6H_5], 2.92−3.16 [3H,m,N−C(H)H−C+−C(CH_3)H,C−C(H)H−C_6H_5], 3.67 [1H,m,N−C(H)H−C], 4.11 [1H,t,N−C(C)H−C(H_2)], 6.36 (1H,s,OH), 7.25 (5H,m,C_6H_5). D.e.: 88 % (NMR with decoupl. *cf. 5b*). Amide *5g* was also chromatographically purified to yield *5g'* in >99 % d.e. (NMR), $[\alpha]_D^{19}$ +30.8° (c 1.145, CH_3OH).

Purification of (R)-2-methyldecanoic acid via crystallization. (*R*)-2-Methyldecanoic acid (1.74 g, 72 % e.e.) was stirred in acetone (10 ml). (*S*)-(−)-1-Phenylethylamine (1.16 g) was added dropwise and the solution was left at −20 °C for two days. The crystals were collected and recrystallized from acetone (6 ml) to give the salt (1.43 g). This was decomposed by 2 M HCl and the resulting mixture was extracted twice with pentane. The combined pentane extracts were dried and concentrated to give an oil which was distilled to give (*R*)-2-methyldecanoic acid (0.87 g, 50 %), $[\alpha]_D^{20}$ −14.82° (neat) corresponding to 96 % e.e.

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