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CHIROSPECIFIC SYNTHESIS OF TRANS-2,5-DISUBSTITUTED PYRROLIDINES VIA STEREOSELECTIVE ADDITION OF ORGANOCOPPER REAGENTS TO *N*-ACYLIMINIUM IONS.

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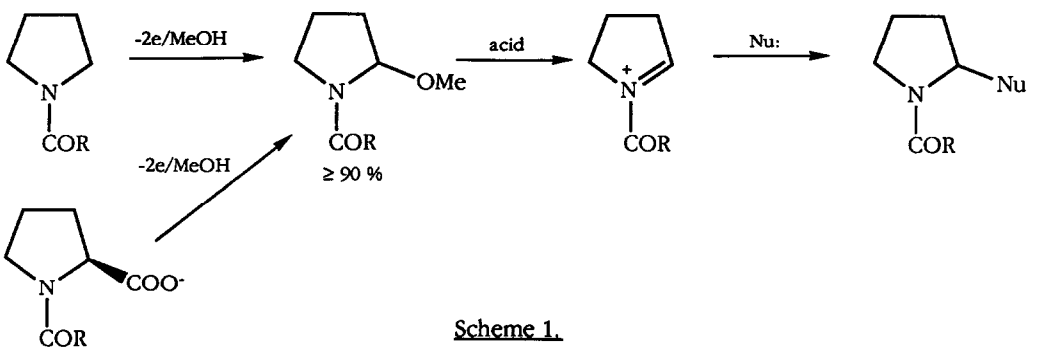
Abstract: *Reaction of the N-acyliminium ion precursor* ***1a*** *(derived from S-proline via anodic methoxylation) with RCu in the presence of* $BF_3{\cdot}Et_2O$ *gives preferentially the trans adducts* ***2*** *(trans:cis ≥96:4). Using such a procedure, a general synthetic route to (2R, 5R)-trans-2,5-dialkylpyrrolidines has been developed, as exemplified by the chirospecific syntheses of the ant feromones trans 5-butyl-2-heptylpyrrolidine (****10a****), trans-5-ethyl-2-heptylpyrrolidine (****10b****) and trans-5-heptyl-2-(5-hexenyl)pyrrolidine (****10c****).*

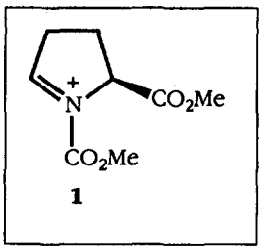
The anodic oxidation of amides and carbamates according to the Ross-Eberson-Nyberg procedure is one of the most general and efficient electrochemical reactions known.[1] In particular, oxidation of cyclic substrates gives access to α-methoxylated compounds which would require multi-step synthesis using conventional chemical reagents. An alternative method of preparation is the Kolbe-like anodic decarboxylation of *N*-acylated amino acids in basic methanol (See Scheme 1).[2] The Nyberg[3] and Shono[4] groups have shown, that such α-methoxy amides and carbamates undergo nucleophilic substitution by various π-nucleophiles (Nu:) via the corresponding *N*-acyliminium ion.[5] These possibilities are outlined in Scheme 1 using *N*-acylpyrrolidine as an example.



Scheme 1.

Recent applications of such synthetic strategies are numerous[6] and in particular, chirospecific syntheses of various alkaloids and amino acids have been highly successful.[7]

We recently reported on the facile BF_3 promoted cleavage of such cyclic, α-methoxylated amides and carbamates using organocopper reagents.[8] In a preliminary communication, we also reported on the highly diastereoselective addition of alkylcopper reagents to the optically active *N*-acyliminium ion **1** derived from proline.[9] In this report, we disclose the full details of these findings as well as applications of this synthetic strategy to the chirospecific synthesis of trans-2,5-disubstituted pyrrolidine alkaloids.



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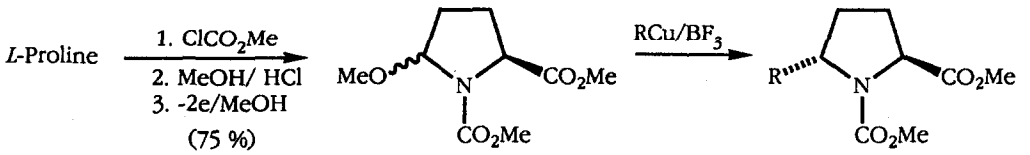
The precursor to **1**, **1a**, was prepared from natural *S*-proline via *N*-protection, esterification and anodic methoxylation following the procedure published by Shono[10] in ca. 75 % overall yield. The simplicity of the procedure makes **1a** available in 100 g quantities. Shono has shown, that reaction of **1a** with π-nucleophiles such as isopropenylacetate and allyltrimethyl silane in the presence of $TiCl_4$ preferably gives the cis-substituted product (cis:trans ~7:3).[11] However, reaction of **1a** with BuCu in the presence of $BF_3{\cdot}Et_2O$ gave the trans compound **2b** with a high degree of stereoselectivity (trans:cis = 96:4). In order to optimize the stereoselectivity, a series of experiments were run varying the copper reagent and the stoichiometry. From these results, which are summarized in Table 1, it can be concluded, that the highest selectivity is obtained when using 2 equivalents each of BuCu and $BF_3{\cdot}Et_2O$. Other organocopper reagents are less efficient. Moreover,



1a

2a, R=n-Pr
2b, R=n-Bu
2c, R=n-Hept

using the $CuBr{\cdot}Me_2S$ complex as the source of Cu(I) produces a higher selectivity than with CuI. Using the same conditions, the corresponding trans-5-propyl (**2a**) and 5-heptyl (**2c**) compounds were prepared with similar high stereoselectivities. Thus, addition of RCu to **1** gives a reversed and increased stereoselectivity compared to that observed for π-nucleophiles.

The absolute stereochemistry at C-5 of **2a-c** was determined by removal of the carboxylic acid moiety using the method described by Shono[11] according to Scheme 2. Hydrolysis of the esters **2** followed by anodic decarboxylation in basic methanol gave the α-methoxy carbamates **3a-c** in 60-70

% isolated yield. Reduction with $NaBH_4$ in acetic acid then gave the corresponding monosubstituted pyrrolidine carbamates **4a-c**. Hydrolysis of **4a** and **4c** provided the 2-substituted pyrrolidines **5** which had a 2*R* stereochemistry as determined by optical rotation measurements.[12]

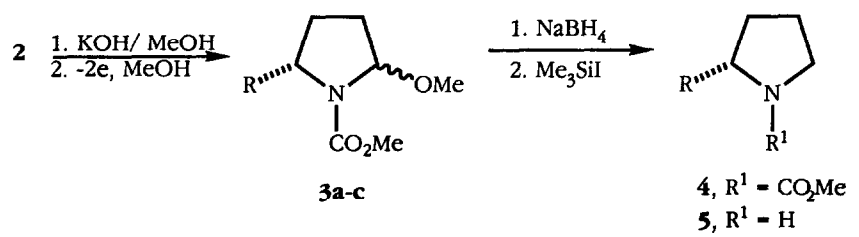
A possible explanation of the reversed stereoselectivity observed for additions of RCu to **1** is the formation of a complex between **1** and a copper species. Such a complex, with copper binding to the ester and carbamate groups as shown in Figure 1, would hinder attack from the *Si* face and account for the observed stereoselectivity. We have tested this hypothesis by reacting $BuCu/BF_3$ with the *N*-acyliminium ion precursor **3c**. Using the procedure outlined above, a mixture of cis and trans butylated products (cis:trans 1:3) was formed from which the trans disubstituted pyrrolidine **9a** could be isolated in 57 % yield. This decrease in selectivity supports the proposed formation of a complex between the *N*-acyliminium ion and some copper species, since **3c** lacks the necessary carbonyl group for the formation of a face-selective copper complex.

Table 1. Isomer distribution in the reaction of **1a** with organocopper reagents in the presence of $BF_3{\cdot}Et_2O$.

Reagent[a] (Eq)	BF_3 (Eq)	trans:cis	Yield (%)[b]
BuCu (2)	-	-	0
BuCu (1)	1	91:9	85[c]
BuCu (1)	2	92:8	93[c]
BuCu (2)	1	80:20	74[c]
BuCu (2)	2	96:4	84
BuCu (2)[d]	2	91:9	67
Bu_2CuLi (2)	2	60:40	40[c]
BuCuCNLi (2)[e]	2	55:45	15[c]
PrCu (2)	2	97:3	75
HeptCu (2)	2	97:3	73

[a] Prepared from RLi and $CuBr{\cdot}Me_2S$. [b] Isolated yields. [c] Yields determined by GLC analysis. [d] Prepared from CuI and BuLi. [e] Prepared from CuCN and BuLi.

The substance **9a** could be converted into the corresponding free amine **10a** which has been isolated from the thief ant *Solenopsis Fugax* and identified as a repellent of other species of ants.



3a-c

4, $R^1 = CO_2Me$
5, $R^1 = H$

Scheme 2.

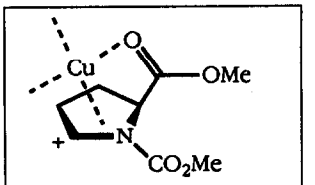
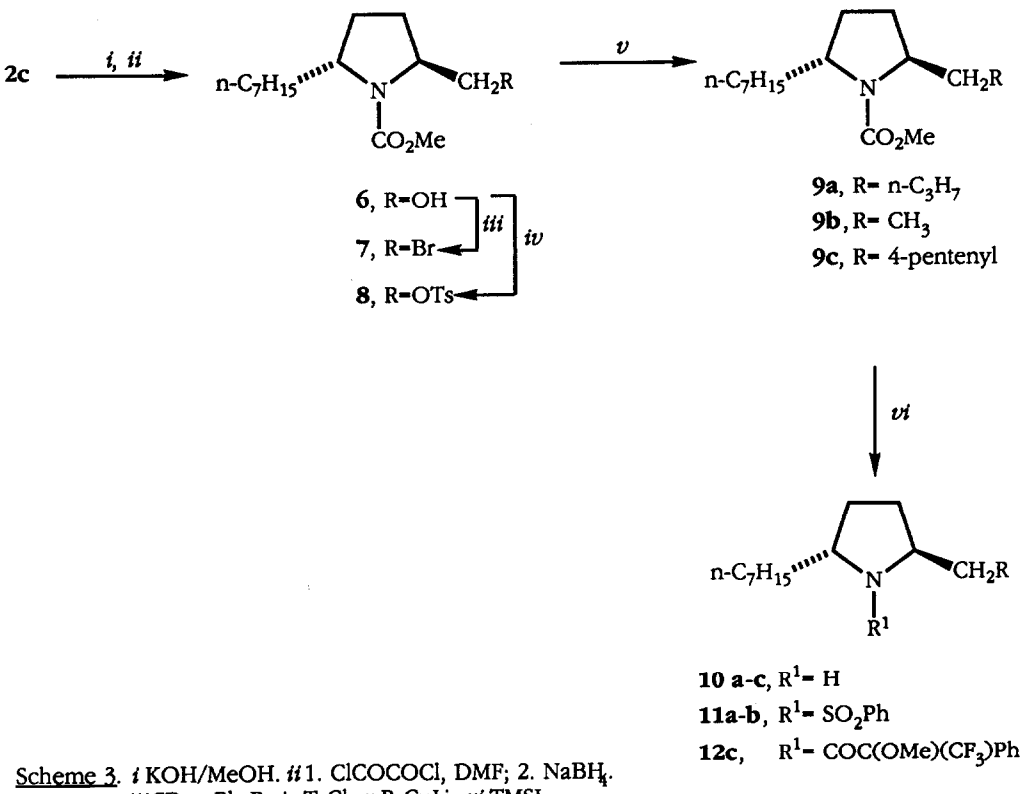


Figure 1.

The chirospecific synthesis of the (2*S*, 5*S*) enantiomer has been reported by Rapoport[13] and by Husson.[14] Various other trans-2,5-disubstituted pyrrolidines have been isolated from several species of ants, in particular of the *Solenopsis* and *Monomorium* families.[15] Due to the small amounts isolated, identification is often based only on mass spectrometry and comparison with a synthetic (racemic) sample. The absolute configuration is, in most cases, not known. The chirospecific synthesis of such compounds is therefore of particular interest. However, the method described above for the preparation of **10a** is not optimal, since the chirality in the 2-position in **2c** is first destroyed on conversion into **3c** and then only partially recreated. We have developed a general synthetic method for the (2*R*, 5*R*) series of compounds from **2c** using a more straightforward approach which is outlined in Scheme 3. Thus, **2c** was hydrolyzed and reduced[16] to the alcohol **6** in 70 % yield. Conversion to the bromide[17] **7** followed by coupling with lithium dialkylcuprates[18,19] gave low yields of alkylated products. In addition, 10-20 % of the corresponding cis compound was usually formed. Similar results were observed using higher order



Scheme 3. *i* KOH/MeOH. *ii* 1. ClCOCOCl, DMF; 2. $NaBH_4$. *iii* CBr_4, Ph_3P. *iv* TsCl. *v* R_2CuLi. *vi* TMSI.

cyanocuprates.[20] However, the tosylate **8** reacted with Pr_2CuLi very cleanly to give **9a** in 70 % yield with no evidence of epimerization. The spectral data of this material was identical in all respects to those of the compound obtained by butylation of **3c**. Conversion to the free amine **10a** was then carried out with Me_3SiI. The enantiomeric purity of **10a** was verified by conversion into the phenylsulfonamide **11a** and comparison of the optical rotation with the reported literature values (see Table 2). Similarly, the 5-ethyl-2-heptyl carbamate **9b** was prepared by reaction of **8** with Me_2CuLi. The enantiomeric purity of the free amine **10b**[21] was also ascertained by conversion into the known phenylsulfonyl derivative **11b**.[14] Trans-5-ethyl-2-heptylpyrrolidine has been isolated from the venom of the fire ant *Solenopsis Punctaticeps*.[22,23]

Table 2. Optical rotations[a] of 2,5-disubstituted pyrrolidines **9-11**.

Compound	$[\alpha]_D^{25}$	Lit. value
9a	-77.8	
9b	-49.6	
9c	-74.7	
10a	-62	+60.1,[b] +7.5[c]
10b	-4.4	+4[c]
10c	-3.2	
11a	-62.0	+59.7,[b] +58[c]
11b	-61.4	+62[c]
11d	-74.5	

[a] For solvents and concentrations, see the experimental part. [b] According to ref. 13. [c] According to ref 14.

Finally, we have prepared (2*R*, 5*R*)-5-heptyl-2-(5-hexenyl)pyrrolidine **10c** using an analogous procedure. **10c**, also known as Monomorine IV, has been isolated from the pharaoh ant *Monomorium pharaonis*[24] as well as other *Monomorium* species,[25] but has, to our knowledge, never been prepared in an enantiomerically pure form. Alkylation of **8** with lithium dipentenylcuprate proceeded smoothly to give **9c** in 66 % yield. Deacylation with TMSI gave the free amine **10c** which was converted into its Mosher amide[26] **12c** in order to determine its enantiomeric purity. ^1H, ^{13}C and ^{19}F NMR spectra all showed the presence of only one diastereomer, and thus, **10c** is of high enantiomeric purity.[27]

In conclusion, we have developed a general synthesis of trans-2-heptyl-5-alkylpyrrolidines in an enantiomerically pure form , using the common, late stage intermediate **8**. In principle, the method is applicable to most of the naturally occurring trans-2,5-dialkylpyrrolidines. We are currently investigating the mechanism of the addition as well as its application to the synthesis of other, more complex target molecules.

Acknowledgements: Financial support from the Swedish Natural Science Research Council and the Swedish Board for Technical Development is gratefully acknowledged.

EXPERIMENTAL SECTION:

All chemicals used were of the highest commercial purity and were used without further purification. Petroleum ether (60-80°C) and ethyl acetate, used for chromatography, were distilled before use. $BF_3{\cdot}Et_2O$ was distilled before use and stored under an atmosphere of argon. $CuBr{\cdot}Me_2S$ was prepared

according to the method described by House.[28] MeLi in diethyl ether and BuLi in hexane were commercially available, other alkyllithium reagents were prepared from the corresponding alkyl bromide and lithium powder in Et_2O at -10 °C. Concentrations of alkyllithium solutions were determined by titration as described by Watson and Eastham.[29] Reaction mixtures were analyzed by capillary GLC using a Varian 3400 chromatograph equipped with a Varian 4270 integrator on a 25 m x 0.25 mm OV 1701 column and by TLC on commercially available silica gel-aluminium foil plates. Flash chromatography was performed on TLC grade silica gel according to Taber.[30] NMR spectra were recorded in $CDCl_3$ on a Varian XL 300 machine; δ in ppm downfield from TMS as an internal standard. Optical rotations were determined on a Perkin-Elmer 241 MC instrument. High resolution mass spectra (HRMS) were obtained using a JEOL JMS SX-102 instrument, direct inlet.

5-Methoxy-1-methoxycarbonyl-*L*-proline methyl ester (1a): *L*-proline was *N*-acylated with $ClCO_2Me$ in basic aqueous solution using the procedure reported by Seebach.[31] The crude acid was then esterified in a saturated solution of gaseous HCl in methanol. Distillation using a kugelrohr apparatus (bath temperature: 90 °C at 0.1 mmHg) gave the starting material for anodic methoxylation which was carried out as follows: A 500 ml water-cooled cell was charged with 93.5 g substrate (0.5 mol), 500 ml methanol and 8.2 g (0.05 M) Bu_4NBF_4. Two identical graphite plates (20x5 cm) were placed in the solution at a distance of 5 mm. A constant current of 500mA was passed through the stirred solution. The electrolysis was terminated when 95 % of the starting material had been converted into product as determined by GLC analysis (after passage of 2.2 F/mol). The solvent was evaporated and the residue was treated with ether several times in order to remove the supporting electrolyte. Filtration and evaporation followed by distillation gave **1a** as a 1:1 mixture of diastereomers. Yield: 97.7 g (90 %); b. p. 95-97 °C (0.5 mmHg).

General procedure for the reaction of 1a with RCu·BF_3: To a suspension of CuBr·Me_2S (1.03 g, 5 mmol) in dry diethyl ether (25 ml) was added a solution of alkyllithium (5 mmol) at -40 °C under an argon atmosphere. After stirring for 30 minutes, the solution was cooled to -78 °C and BF_3·Et_2O (0.52 ml, 5 mmol) was added. After 5 minutes, a solution of **1a** (0.54 g, 2.5 mmol) in dry ether (5 ml) was added. The reaction mixture was allowed to attain room temperature whereby a mixture of concentrated aqueous ammonia and a saturated solution of NH_4Cl (1:1) was added. After stirring for another 30 minutes, 3 extractions with dichloromethane gave the crude product.

(5*R*)-1-Methoxycarbonyl-5-propyl-*L*-proline methyl ester (2a). Purification by column chromatography (ethyl acetate:petroleum ether 3:7) gave **2a** as a colorless oil. ^1H NMR: 4.30 (1H, dd, *J* 13.2, 9.0 Hz, 2-H), 3.9-4.1 (1H, m, 5-H), 3.64, 3.71, 3.72, 3.73 (6H, 4s, CO_2Me), 1.55-2.30 (4H, m), 1.20-1.36 (4H, m), 0.90 (3H, t, *J* 7.5 Hz, CH_2CH_3). $[\alpha]_D^{25}$= -84.7° (c 1.0, MeOH). HRMS: 229.1307, calc. for $C_{11}H_{19}NO_4$: 229.1314.

(5*R*)-5-Butyl-1-methoxycarbonyl-*L*-proline methyl ester (2b). Purification by column chromatography (ethyl acetate:petroleum ether 3:7) gave **2b** as a colorless oil. ^1H NMR: 4.30 (1H, dd, *J* 12.8, 8.2 Hz, 2-H), 3.9-4.05 (1H, m, 5-H), 3.63, 3.69, 3.70, 3.71 (6H, 4s, CO_2Me), 1.65-2.28 (4H, m), 1.19-1.40 (6H, m), 0.90 (3H, t, *J* 7.3 Hz, CH_2CH_3). $[\alpha]_D^{25}$= -84.4° (c 1.0, MeOH). HRMS: 243.1471, calc. for $C_{12}H_{21}NO_4$: 243.1471.

(5*R*)-5-Heptyl-1-methoxycarbonyl-*L*-proline methyl ester (2c). Purification by column chromatography (ethyl acetate:petroleum ether 3:7) gave **2c** as a colorless oil. ^1H NMR: 4.30 (1H, dd, *J* 13.0, 8.1 Hz ,2-H), 3.90-4.06 (1H, m, 5-H), 3.69, 3.71, 3.72, 3.73 (6H, 4s, CO_2Me), 1.62-2.30 (4H, m), 1.19-1.38 (12H, m), 0.85-0.92 (3H, m, CH_2CH_3). $[\alpha]_D^{25}$= -80.2° (c 1.0, MeOH). HRMS: 285.1936, calc. for $C_{15}H_{27}NO_4$: 285.1940.

General procedure for the removal of the ester group in 2: Compound **2** (2.5 mmol) was dissolved in 3.5 ml methanol. After cooling to 0°C, a solution of KOH (0.83 g) in water (3.5 ml) was added. The mixture was then stirred at ambient temperature for 5 hours. Partial evaporation followed by acidification with conc. HCl and extraction with CH_2Cl_2 gave the free acid in 95-100 % yield. The acid was then dissolved in methanol (25 ml) containing 0.1 equivalent of NaOMe in a water-cooled cell containing a Pt wire anode (1 mm diameter) and a Pt foil cathode. 2.0 F/mol was passed through the solution at a constant current of 150 mA. Evaporation of the solvent followed by chromatography (ethyl acetate:petroleum ether 3:7) gave **3a-c** as mixtures of diastereomeric methoxy compounds in 75-85 % yield. Reduction was then carried out by adding 25 equivalents of $NaBH_4$ in small portions to a solution of **3** in glacial acetic acid. After stirring for 8 hours, aqueous work-up followed by column chromatography gave **4a-c** in 75-90 % yield. ^{1}H NMR spectra for **4b** and **4c** were identical to those for the corresponding racemic compounds.[8]

(2*R*)-1-Methoxycarbonyl-2-propylpyrrolidine (4a). Purification by column chromatography (ethyl acetate:petroleum ether 1:3) gave **4a** as a colorless oil. ^{1}H NMR: 3.70-3.87 (1H, m, H-2), 3.67 (3H, s, CO_2Me), 3.26-3.48 (2H, m, H-5), 1.61-1.96 (4H, m), 1.21-1.38 (4H, m), 0.92 (3H, t, *J* 7.2 Hz, CH_2CH_3). $[\alpha]_D^{25}$= -69.4° (c 1.0, MeOH). HRMS: 171.1263, calc. for $C_9H_{17}NO_2$: 171.1259.

(2*R*)-2-Butyl-1-Methoxycarbonylpyrrolidine (4b). Purification by column chromatography (ethyl acetate:petroleum ether 1:3) gave **4b** as a colorless oil. $[\alpha]_D^{25}$= -67.0° (c 1.0, MeOH).

(2*R*)-2-Heptyl-1-Methoxycarbonylpyrrolidine (4c). Purification by column chromatography (ethyl acetate:petroleum ether 1:3) gave **2a** as a colorless oil. $[\alpha]_D^{25}$= -52.0° (c 1.0, $CHCl_3$).

(2*R*)-2-Butylpyrrolidine (5b). Compound **4b** was treated with Me_3SiI[32] in $CHCl_3$ at 50 °C for 5 hours. After quenching with methanol and sodium methoxide, aqueous work-up gave the free amine. $[\alpha]_D^{25}$= -15.0° (c 1.1, $CHCl_3$). Lit. value for the 2*S* enantiomer: +12° (c 1.1, $CHCl_3$).[12]

(2*R*)-2-Heptylpyrrolidine (5c) was obtained analogous to **5b**. $[\alpha]_D^{25}$= -18.0° (c 1.1, $CHCl_3$). Lit. value for the 2*S* enantiomer: +14° (c 1.1, $CHCl_3$).[12]

(2*S*,5*R*)-5-Heptyl-2-hydroxymethyl-1-methoxycarbonylpyrrolidine (6). Compound **2c** was hydrolyzed to the corresponding acid following the procedure given above in 95 % yield. ^{1}H NMR: 4.35 (1H, dd, *J* 16.5, 9.0 Hz, 2-H), 3.79-4.09 (2H, m), 3.64, 3.71 (3H, 2s, CO_2Me), 1.94-2.33 (2H, m), 1.60-1.88 (2H, m), 1.12-1.35 (12H, m), 0.81-0.91 (3H, m, CH_2CH_3). $[\alpha]_D^{25}$= -66.1° (c 1.0, MeOH). Reduction was then carried out using *N,N*-dimethylchloromethyleniminium chloride and $NaBH_4$.[33] Column chromatography (ethyl acetate:petroleum ether 1:1) gave pure **6** as a colorless oil in 72 % yield. ^{1}H NMR: 3.96-4.13 (1H, m), 3.69 (3H, s, CO_2Me), 3.45-3.86 (3H, m), 1.53-2.12 (4H, m), 1.18-1.37 (12H, m), 0.83-0.92 (3H, m, CH_2CH_3). $[\alpha]_D^{25}$= -72.3° (c 1.0, MeOH). HRMS: 257.1976, calc. for $C_{14}H_{27}NO_3$: 257.1991.

(2*S*,5*R*)-2-Bromomethyl-5-heptyl-1-methoxycarbonylpyrrolidine (7). Bromination of **6** was carried out with CBr_4 in the presence of Ph_3P according to the procedure described by Hooz and Gilani.[34] Compound **7** was isolated after column chromatography (ethyl acetate:petroleum ether 1:5) as a colorless oil in 100 % yield. ^{1}H NMR: 3.99-4.12 (1H, m), 3.70, 3.71 (3H, 2s, 1:1, CO_2Me), 3.70-3.84 (1.5 H, m), 3.60 (0.5H, dd, *J* 9.5, 2.5 Hz), 3.30 (0.5 H, t, *J* 9.3 Hz), 3.09 (0.5H, t, *J* 9.8 Hz), 1.58-2.10 (4H, m), 1.13-1.34 (12H, m), 0.83-0.92 (3H, m, CH_2CH_3). $[\alpha]_D^{25}$= -39.3° (c 1.0, MeOH). HRMS: 221.9961, calc. for $C_7H_{11}BrNO_2$ (M-C_7H_{15}): 221.9953.

Tosylate 8. Tosylation of **6** was carried out according to Kabalka *et al.*[35] Pure **6** was isolated after column chromatography (ethyl acetate:petroleum ether 3:7) in 97 % yield. ^{1}H NMR: 7.80 (2H, d, *J* 8.3 Hz), 7.29 (2H, t, *J* 8.0 Hz), 3.60-4.19 (4H, m), 3.61, 3.54 (3H, 2s, 1:1, CO_2CH_3), 2.46, 2.44 (3H, 2s), 1.51-2.08 (4H, m), 1.17-1.36 (12H, m), 0.82-0.98 (3H, m, CH_2CH_3). $[\alpha]_D^{25}$= -55.7° (c 1.0, MeOH). HRMS: 412.2162, calc. for $C_{21}H_{34}NO_5S$: 412.2158.

General procedure for the coupling of 8 with lithium dialkylcuprates. To a solution of the proper lithium dialkylcuprate (2 equivalents, prepared from CuBr·Me_2S and alkyllithium in ether at -40 °C) was added a solution of **8** in dry ether at -70 °C under an atmosphere of argon. The mixture was stirred for several hours at -20 °C and interrupted when the starting material had been consumed as determined by TLC. Work-up was identical to that described for the preparation of **2**.

(2*R*,5*R*)-5-Butyl-2-heptyl-1-methoxycarbonylpyrrolidine (9a). Purification by column chromatography (ethyl acetate:petroleum ether 1:9) gave **9a** as a colorless oil in 76% yield. ^{1}H NMR has been reported earlier.[9] $[\alpha]_D^{25}$= -77.8° (c 1.0, MeOH). HRMS: 283.2513, calc. for $C_{17}H_{33}NO_2$: 283.2511.

(2*R*,5*R*)-5-Ethyl-2-heptyl-1-methoxycarbonylpyrrolidine (9b). Purification by column chromatography (ethyl acetate: petroleum ether 1:9) gave **9b** as a colorless oil in 70% yield. ^{1}H NMR: 3.67 (3H, s, CO_2Me), 3.58-3.75 (2H, m), 1.79-1.98 (2H, m), 1.57-1.72 (2H, m), 1.12-1.33 (14H, m), 0.79-0.92 (6H, m). $[\alpha]_D^{25}$= -49.6° (c 1.0, MeOH). HRMS: 255.2207, calc. for $C_{15}H_{29}NO_2$: 255.2198.

(2*R*,5*R*)-5-Heptyl-2-(5-hexenyl)-1-methoxycarbonylpyrrolidine (9c). Purification by column chromatography (benzene:dichloromethane 9:1) gave **9c** as a colorless oil in 66% yield. ^{1}H NMR: 5.71-5.88 (1H, m, vinylic CH), 4.87-5.04 (2H, m, vinylic CH_2), 3.70-3.81 (2H, m), 3.69 (3H, s, CO_2Me), 2.00-2.10 (2H, m, allylic CH_2), 1.78-1.97 (2H, m), 1.55-1.71 (2H, m), 1.16-1.47 (16H, m), 0.82-0.93 (3H, m, CH_2CH_3). $[\alpha]_D^{25}$= -74.7° (c 1.0, MeOH). HRMS: 309.2663, calc. for $C_{19}H_{35}NO_2$: 309.2668.

(2*R*,5*R*)-5-Butyl-2-heptylpyrrolidine (10a). Deacylation of **9a** using Me_3SiI was carried out as described for the preparation of **5b**. Yield: 88 %. ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[14] $[\alpha]_D^{25}$= -62° (c 1.5, MeOH). Reported lit. values for the (2*S*,5*S*) enantiomer: +60.1° (c 1.5, MeOH)[13] and +7.5° (c 2.5, MeOH)[14].

(2*R*,5*R*)-5-Ethyl-2-heptylpyrrolidine (10b). Prepared from **9b** using the same procedure as for **5b**. Yield: 100%. ^{1}H and ^{13}C NMR were in complete agreement with reported data.[14] $[\alpha]_D^{25}$= -4.4° (c 2.0, $CHCl_3$). Reported lit. value for the (2*S*,5*S*) enantiomer: +4° (c 2.0, $CHCl_3$).[14]

(2*R*,5*R*)-5-Heptyl-2-(5-hexenyl)pyrrolidine (10c). Prepared from **9c** using the same procedure as for the preparation of **5b**. Yield: 100 %. ^{1}H NMR: 5.79 (1H, ddt, *J* 16.9, 10.3 Hz; J_t 6.6 Hz, vinylic CH), 4.99 (1H, ddd, *J* 16.9, 3.5, 1.5 Hz, $CHCH_2$), 4.93 (1H, dddd, *J* 10.3, 2.1, 1.1, 1.1 Hz, $CHCH_2$), 4.51 (1H, br s, NH), 3.36-3.52 (2H, m), 1.93-2.13 (4H, m), 1.69-1.86 (2H, m), 1.19-1.62 (18H, m), 0.79 (3H, t, *J* 7.1 Hz, CH_3). ^{13}C NMR: 138.6, 114.6, 59.2, 59.1, 34.8, 34.6, 33.6, 31.8, 31.3, 29.5, 29.2, 28.7, 27.0, 26.4, 22.6, 14.1. $[\alpha]_D^{25}$= -3.2° (c 1.0, MeOH). HRMS: 251.2605, calc. for $C_{17}H_{33}N$: 251.2613.

(2*R*,5*R*)-5-Butyl-2-heptyl-1-phenylsulfonylpyrrolidine (11a). Compound **11a** was prepared from **10a** and phenylsulfonyl chloride according to reference 13. ^{1}H and ^{13}C NMR were in complete agreement with reported data.[13,14] $[\alpha]_D^{25}$= -62.0° (c 1.1, CH_2Cl_2). Reported lit. values for the (2*S*,5*S*)

enantiomer: +59.7° (c 1.8, CH_2Cl_2)[13] and +58° (c 1.1, CH_2Cl_2).[14]

(2*R*,5*R*)-5-Ethyl-2-heptyl-1-phenylsulfonylpyrrolidine (11b). Prepared from **10b** analogously to compound **11a**. ^1H and ^{13}C NMR were in complete agreement with reported data.[14] $[\alpha]_D^{25}$= -61.4° (c 0.87, $CHCl_3$). Reported lit. value for the (2*S*,5*S*) enantiomer: +62° (c 0.87, $CHCl_3$).[14]

Mosher amide 12c. Acylation of **10c** with (-) MTPA chloride was carried out according to Husson *et al.*[14] Yield: 50%. ^1H NMR: 7.62-7.71 (2H, m), 7.32-7.49 (3H, m), 5.58-5.88 (1H, m), 4.85-5.04 (2H, m), 4.02-4.18 (2H, m), 3.70 (3H, d), 1.53-2.18 (6H, m), 0.60-1.50 (18H, m), 0.86 (3H, m). ^{13}C NMR: 139.4, 129.2, 128.1, 127.1, 114.4, 114.2, 59.5, 59.3, 58.3, 58.2, 54.7, 33.8, 33.5, 32.4, 32.1, 31.7, 30.9, 29.4, 29.2, 29.1, 28.6, 28.4, 27.3, 27.0, 26.6, 26.4, 25.1, 22.6, 14.1, 14.0. ^{19}F NMR: 8.88 (s). $[\alpha]_D^{25}$= -74.5° (c 1.0, $CHCl_3$). MS: 468 (1), 384 (20), 368 (9), 278 (100), 189 (48).

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