Anodic Methoxylation of Pyrrolidinol Derivatives.* Enantioselective Synthesis of *cis*- and *trans*-(3*R*)-3-Hydroxyprolines

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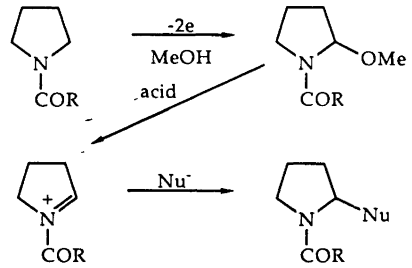
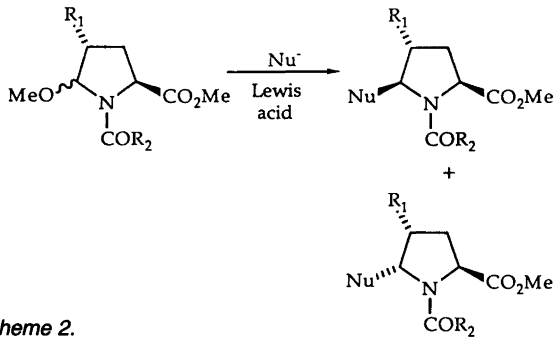
Anodic α-methoxylations of (3*R*)-1-methoxycarbonylpyrrolidin-3-ol and two *O*-protected analogs display modest regioselectivities (yield of **3** ≤ 54 %; yield of **4** ≤ 72 %). Substitution of the 2-methoxy group with a cyano group causes enhanced *cis* stereoselectivity (86 %) when a *tert*-butyldimethylsilyloxy substituent was present in the 3-position. Hydrolysis of the isomeric cyano compounds gave *cis*-3-hydroxy-L-proline and *trans*-3-hydroxy-D-proline.

The anodic α-methoxylation of amides and carbamates, also known as the Ross–Eberson–Nyberg procedure, is one of the most versatile electrochemical reactions in organic synthesis.[1] In particular, oxidation of cyclic substrates gives access to very useful synthetic intermediates, suitable for further elaboration via the corresponding *N*-acyliminium ion[2,3] according to Scheme 1.



Scheme 1.

Recently, several applications of this procedure to the synthesis of naturally occurring optically active amino acids[4–6] and alkaloids[7] have appeared in the literature, using common amino acids such as L-proline and L-lysine as starting materials. Of critical importance in such a synthetic approach is (a) the regioselectivity of the anodic methoxylation and (b) the diastereoselectivity in the subsequent amidoalkylation. The regioselectivity of the anodic methoxylation of unsymmetrically substituted amides and carbamates is often remarkably high and in fact, the reasons for the selective oxidation of the least substituted α-carbon are not entirely clear. The diastereoselectivity of the amidoalkylation reactions is usually governed by the same factors as other carbocation–nucleophile interactions, but in cyclic systems odd effects have been observed. Renaud and Seebach investigated[5] a number of reactions of the 2-acyliminium ion of *N,O*-protected 4-hydroxypyrrolidine and observed very high *cis* selectivity. Shono[8,9] and Utley[10] have both reported on the selective formation of the *cis* product when *N*-protected 2-methoxy-6-alkylpiperidines were treated with Lewis acid–nucleophile. However, our results from the 4-hydroxyproline series[11] (Scheme 2, R_1=OAc, R_2=CH_3) and Shono's work in the proline series[8] (Scheme 2, R_1=H, R_2=OCH_3) indicate that there is almost no effect due to a vicinal oxygen substituent.+ The stereoselectivity seems in the latter cases to be governed by the α′ substituent. In order to elucidate the effect of a neighbouring oxygen substituent we undertook an investigation of a substrate similar to the 4-hydroxyproline derivatives in Scheme 2 but without the directing ester group, i.e. the *N,O*-protected 3-hydroxypyrrolidine 2-iminium ion **1**.



Scheme 2.

For the reason of future synthetic applications in the field

*Part 3 in the series: Synthetic Application of Electrochemically Produced α-Methoxy Amides. For Part 2; Thaning, M. and Wistrand, L.-G. *Helv. Chim. Acta 69* (1986) 1711.

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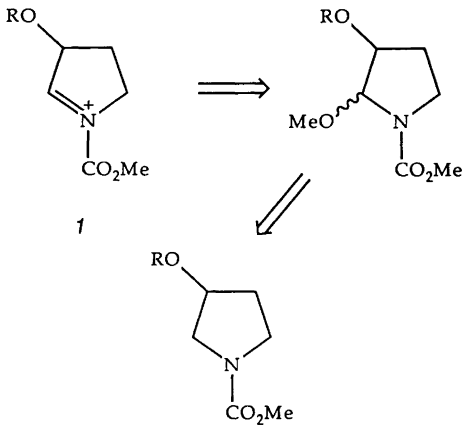
+This is in contrast with Chamberlin's work on intramolecular amidoalkylation, in which exclusive *trans*-substitution to a neighbouring acetoxy group was observed.[12]



Scheme 3.

of optically active alkaloids and amino acids, we have chosen to work with the 3*R* enantiomer of **1**. A possible precursor to the *N*-acyliminium ion **1** is the corresponding α-methoxy compound, accessible via anodic methoxylation of the *N*-protected (3*R*)-pyrrolidin-3-ol according to Scheme 3. The problem with such an electrochemical oxidation is that the regioselectivity of the reaction is unknown, and there is no precedence in the literature for regioselective substitution in a β-substituted amide.* In order to reduce problems of separation and to optimize the yield of **3** we set out to investigate the different factors determining the regiochemistry of the anodic methoxylation of **2**.

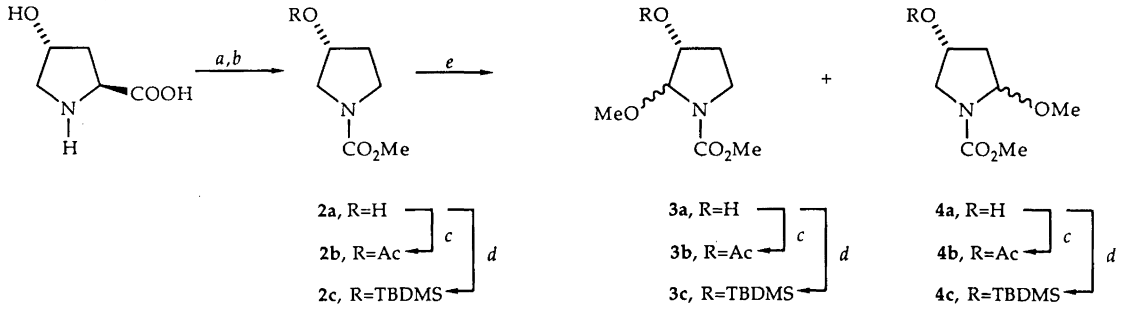
Results and discussion

Compound **2a**[14] was obtained in 95 % yield starting from *trans*-4-hydroxy-L-proline using a recently published procedure for the decarboxylation of amino acids[15] followed by acylation with methyl chloroformate (Scheme 4).

Our approach in trying to direct the anodic methoxylation towards the 2-position of **2** uses some of the mechanistic results on this reaction[10,16] in which an *N*-acyliminium ion has been postulated as an intermediate. If this intermediate could be stabilized further by, for example, a neighbouring acetoxy group, the result should be an increased rate of formation of the 2-methoxy compound.* We have also investigated the effect of different electrode materials on the regioselectivity; there are several cases where this factor has a drastic effect on the isomer distribution such as the anodic side-chain/nuclear acetoxylation of mesitylene.[17] The bulky *tert*-butyldimethylsilyl (TBDMS) group has also been used in order to detect any steric effect on the regioselectivity. In order to identify the different isomers, the two known isomeric products **4a** were prepared via anodic decarboxylation of the corresponding *N*-protected *trans*-4-hydroxy-L-proline derivative.[4] The results from the electrolysis experiments are summarized in Table 1. As can be seen, none of the variables used induced any dramatic effects; the ratio between **3** and **4** is equal to or less than 1. From a mechanistic point of view, the lack of effect is somewhat surprising, especially for the acetate case where there should be a stabilizing effect on the neighbouring cation.

In order to prepare **3**, we oxidized the alcohol **2a** at a platinum anode. After the passage of 2.34 F mol^{-1}, the starting material was consumed and a ratio of **3a** to **4a** similar to that noted in Table 1 was observed (by GC after conversion of a sample into the acetate **2b**). Two consecutive chromatographic separations gave **3a** in 43 % isolated yield.+

The amidoalkylation of **3** was performed on the *O*-TBDMS and *O*-acetyl derivatives using trimethylsilyl cyanide (TMSCN) as the nucleophile.[18] The primary reason for this choice of nucleophile was the need for an unambiguous identification of the isomeric 2-substituted products which we intended to achieve by hydrolysis to the corresponding known amino acids. Also, Seebach detected no difference in the stereoselectivity of amidoalkylation of



Scheme 4. a, Cyclohexanol, Δ; *b*, $ClCO_2Me$; *c*, Ac_2O, pyridine; *d*, TBDMSCl, imidazole; *e*, anodic oxidation, MeOH.

*There is one example of a non-selective oxidation. In spite of possible lactone formation poor regioselectivity was observed in the oxidation of a β-substituted piperidine derivative.[13]

*Similar reasoning has been used to explain the high regioselectivity in the anodic methoxylation of *N*-acyl-2-substituted piperidines.[10]

+The yield of **4a** (*cis* and *trans*) was ca. 40 %. This material could be converted into **2** (>80 % yield) by reduction with $NaBH_4$ in acetic acid[8] and thus recycled.

Table 1. Isomer distribution in the anodic methoxylation of **2** after passage of 2 F mol^{-1}.

Substrate	Anode material	3/%[a,b]	4/%[a,b]	Conversion/%[b]
2a	Pt	49.7	50.3	68.8[c]
2a	C	41.3	58.7	87.0[c]
2b	Pt	36.1	63.9	68.7
2b	C	28.0	72.0	86.8
2c	Pt	54.0	46.0	47.2[d]
2c	C	50.0	50.0	67.7[d]

[a]Given as the ratio of the sums of the respective *cis* and *trans* methoxy compounds. [b]By GC. [c]Analysed after conversion into **2b**. [d]Analysed after conversion into **2b** via **2a**.

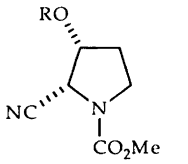
Table 2. Stereoselectivity in the nucleophilic cyanation of **3** and **4** with TMS-CN.

Substrate	Lewis acid	Temp./°C	*cis/trans*[a]	Yield/%[b]
3b	BF_3–Et_2O	RT[c]	42/58	79
3b	BF_3–Et_2O	−78	42/58	80
3b	$TiCl_4$	−78	52/48	82
3c	BF_3–Et_2O	RT[c]	66/34	74
3c	$TiCl_4$	−78	86/14	86
4b	BF_3–Et_2O	RT[c]	85/15	[d]
4b	$TiCl_4$	−78	91/9	[d]
4c	BF_3–Et_2O	RT[c]	91/9	[d]
4c	$TiCl_4$	−78	96/4	[d]

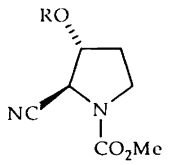
[a]**5/6** or **7/8**, respectively. [b]Isolated yield. [c]RT = room temperature. [d]Not determined.

4-substituted *N*-acyl-2-pyrrolidinium ions[5] with different nucleophiles and thus, we felt that the choice of nucleophile was not critical at this stage.

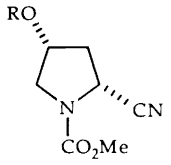
We have also repeated Seebach's cyanation of **4c** in order to be able to compare the selectivity with that in the cyanation of **3**.[+] For comparison, the corresponding acetate **4b** is also included. The results are summarized in Table 2. A few trends are noticeable. Firstly, substitution on **4b** and **4c** is more selective than on **3b** and **3c**. $TiCl_4$ appears to induce a higher degree of *cis* selectivity than BF_3–Et_2O which also is true for the TBDMS protecting group compared with the acetate. From the results in Table 2, the conclusion can be drawn that the vicinal acetate group in **3b** does not hinder attack of the nucleophile from the *cis* side, even though the neighbouring cation might be stabilized.



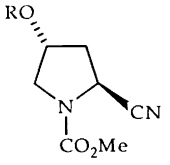
5a, R= H
5b, R= Ac
5c, R=TBDMS



6a, R= H
6b, R= Ac
6c, R=TBDMS



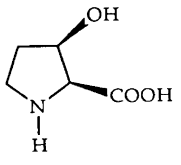
7a, R= H
7b, R= Ac
7c, R=TBDMS



8a, R= H
8b, R= Ac
8c, R=TBDMS

The structures of the substitution products **5** and **6** have been determined by 300 MHz ^1H NMR spectroscopy. In our previous work on hydroxyproline derivatives,[11] we realized that for a given pair of isomeric 4,5-disubstituted prolines, the *cis* isomer shows a J_{vic} value of 4–5 Hz, whereas in the corresponding *trans* compound, J_{vic} is 0–1 Hz. The same pattern is observed for the adducts **5** and **6** and we assigned the stereochemistry accordingly. The stereochemistry of **7** and **8** had already been established for **7c** by Seebach;[5] the structure of **8c** was determined only by MS. The structure of **7b** and **8b** was confirmed by MS and by conversion of **7c** via the alcohol into **7b**.

A final check on the stereochemistry and optical purity of the cyano compounds **5** and **6** was also performed. Thus, **5c** and **6b** were hydrolysed in 5 M aqueous hydrochloric acid to the corresponding amino acids **9** and **10** in >85 % purified yield. Both *cis*- and *trans*-3-hydroxy-L-proline are known amino acids, and both diastereomers have attracted synthetic interest.[19] The *trans* compound has been found in certain types of collagen,[20] in the peptide alkaloid amphibine[21] and in various other sources.[22] The *cis* compound is a constituent of the antibiotic telomycin.[23] The 300 MHz ^1H NMR spectra and the optical rotations of **9** ($[\alpha]_D^{25} = -101°$, c=1, H_2O) and **10** ($[\alpha]_D^{25} = +18.1°$, c=1, H_2O) prepared by our method are in agreement with published data (**9**: $[\alpha]_D^{25} = -102.7°$, c=1, H_2O; and **10**: $[\alpha]_D^{25} = +19°$, c=1, H_2O).[24] Thus, our interpretation of the ^1H NMR spectra for **5** and **6** was correct. In addition the hydrolysis of **5** and **6** constitutes the final step in the enantioselective total synthesis of the amino acids *cis*-3-hydroxy-L-proline (**9**) and *trans*-3-hydroxy-D-proline (**10**).



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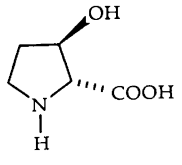

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In conclusion, we have shown, that amidoalkylation of the *N*-acyliminium ion **1** is influenced by the neighbouring R group. The nature of this influence is at presently unknown; we will continue to probe this reaction for a plausible mechanism. The possibility of controlling the stereo-

[+]In his work on the cyanation of **4c** using $Me_3SiCN/TiCl_4$, Seebach gives the stereoselectivity as being >97 % *cis*.[5]

chemistry of the amidoalkylation by means of the oxygen substituent makes **1** a versatile intermediate in the synthesis of optically active 2,3-disubstituted pyrrolidines which we will continue to explore.

Experimental

General. All chemicals used were of highest commercial quality and were used without further purification. Petroleum ether (60–80 °C) and ethyl acetate, used for chromatography, were distilled before use. Reaction mixtures were analysed by capillary GC using a Varian 3400 gas chromatograph equipped with a Varian 4270 integrator on a 25 m × 0.25 mm OV 1701 column or, in those cases where GC was impossible (in general, all acetoxy and TBDMS derivatives gave good chromatograms while pyrrolidinol derivatives containing a free OH group decomposed on the column), by TLC on commercially available silica gel/aluminium foil plates. Flash chromatography was performed according to Taber.[25] Optical rotations: Perkin Elmer 241 MC polarimeter. ^{1}H NMR spectra were recorded on Varian XL 300 or JEOL PMX 60 instruments in $CDCl_3$ unless otherwise stated; δ in ppm downfield from $SiMe_4$ as an internal standard. MS: Finnigan 4021 mass spectrometer at 70 eV, direct inlet. MS, high resolution: VG Trio-2, direct inlet.

(3R)-1-Methoxycarbonylpyrrolidin-2-ol (**2a**). A mixture of 100 ml cyclohexanol and 1.0 ml 2-cyclohexen-1-one was placed in a dry flask fitted with a reflux condenser, under an argon atmosphere. *trans*-4-Hydroxy-L-proline (10.0 g, 76.3 mol) was added and the mixture was heated to 155 °C with vigorous stirring. After 4 h, the mixture was poured onto 250 ml 0.5 M aq. HCl. The aqueous phase was extracted with toluene (5×50 ml) and evaporated to dryness. The crude product was dissolved in a mixture of 150 ml CH_2Cl_2 and 22 ml (0.159 mol) Et_3N and then 5.9 ml (76.3 mmol) ethyl chloroformate was added dropwise with stirring. After 3 h, the reaction mixture was evaporated to dryness and the resulting semi-solid mass was triturated with ether. The organic phase was dried over $MgSO_4$, evaporated and the crude product was chromatographed, using ethyl acetate as the eluant to give 10.50 g (95 %) of **2a**. ^{1}H NMR (300 MHz): 1.80–2.05 (m, 2 H), 2.25–2.45 (m, 1 H), 3.30–3.55 [m, 2 H-C(2), 2 H-C(5)], 3.68 (s, CH_3O), 4.45 [br s, H-C(3)]. MS (high resolution): Found 145.079±0.005. Calc. 145.074. $[\alpha]_D^{25}$ = −30.3° (*c*=1.0, methanol).

(3R)-1-Benzyloxycarbonylpyrrolidin-3-ol. The previous procedure for the preparation of **2a** was checked for possible racemization by conversion into the known benzyl carbamate. Thus, the crude (3*R*)-pyrrolidin-3-ol was treated with benzylchloroformate in a manner similar to that described for the preparation of compound **2a**. $[\alpha]_D^{25}$ = −18.2° (*c*=0.5, methanol) (lit.,[26] $[\alpha]_D^{23}$ = −15.0°, *c*=0.5, methanol).

(3R)-3-Acetoxy-1-methoxycarbonylpyrrolidine (**2b**). Compound **2a** (1.0 g, 6.90 mmol) was dissolved in a mixture of 10.0 ml acetic anhydride and 1.5 ml pyridine, and the solution was heated overnight at 75 °C. The reagents were evaporated at ca. 0.5 mmHg and the resulting yellow oil was dissolved in 30 ml CH_2Cl_2, and extracted with water (15 ml) and satd. aq. $NaHCO_3$ (15 ml). The organic phase was dried over $MgSO_4$ and evaporated, and the resulting oil was chromatographed using ethyl acetate/petroleum ether (1:1) as the eluant to yield 1.1 g (85 %) of **2b**. ^{1}H NMR (300 MHz): 1.95–2.15 [m, 2 H-C(4)], 2.04 (s, CH_3CO), 3.35–3.65 [m, 2 H-C(2), 2 H-C(3)], 3.70 (s, CH_3OCO), 5.30 [m, H-C(3)]. $[\alpha]_D^{25}$ = −21.2° (*c*=1.0, methanol). MS (*m/z*, rel. %): 188 (1, *M*+1), 156 (4), 127 (56), 112 (18), 1022 (18), 82 (23), 59 (29), 43 (100).

(3R)-1-Methoxycarbonyl-3-(tert-butyldimethylsilyloxy)pyrrolidine (**2c**). Compound **2a** (500 mg, 3.45 mmol) and imidazole (352 mg, 5.17 mmol) were dissolved in 4.0 ml dry DMF in a dry flask under an argon atmosphere. *tert*-Butyldimethylsilyl chloride (780 mg, 5.17 mmol) was added and the mixture was stirred at room temperature for three days. CH_2Cl_2 (40 ml) was added and the organic phase was extracted with 1 M aq. HCl (25 ml) and satd. aq. NaCl (3×25 ml), and then dried over $MgSO_4$. The resulting oil was chromatographed using petroleum ether/diethyl ether (1:1) as the eluant giving 849 mg (95 %) of **2c**. ^{1}H NMR (300 MHz): 0.06 [s, $(CH_3)_2Si$], 0.80 (s, t-Bu), 1.75–2.00 [m, 2 H-C(4)], 3.15–3.35 [m, H-C(2)], 3.35–3.55 [m, H-C(2), 2 H-C(5)], 3.70 (s, CH_3OCO), 4.4 [br s, H-C(3)]. $[\alpha]_D^{25}$ = −25.0° (*c*=1.0, methanol). MS (*m/z*, rel. %): 260 (0.5, *M*+1), 244 (1), 228 (1), 212 (1), 202 (28), 174 (10), 101 (5), 89 (100), 73 (21), 59 (26).

General procedure for anodic oxidation. A 50 ml water-cooled cell was charged with 30 ml methanol, **2** (1.0 mmol) and Bu_4NBF_4 (100 mg, 0.3 mmol). A Pt-foil (5 cm^2) or a graphite rod (5 cm^2) was used as the anode and a Pt wire as the cathode. A charge of 2 F mol^{-1} was passed at a current of 50 mA through the stirred solution, the solvent was evaporated and the residue was triturated with ether to leave the supporting electrolyte. The crude product from oxidation of **2b** was analysed by GC. The product mixtures from the oxidation of **2a** and **2c** had to be transformed into the corresponding acetates (*O*-acetylation was carried out as described for the preparation of compound **2b**, desilylation was performed according to Brussani *et al.*[27] using a non-aqueous work-up) before GC analysis.

(3R-)-2-Methoxy-1-methoxycarbonylpyrrolidin-3-ol (**3a**). A 500 ml water-cooled cell was charged with 9.77 g (67.4 mmol) **2a**, 400 ml methanol and 6.6 g (20.0 mmol) Bu_4NBF_4. The stirred solution was oxidized at a Pt foil anode (4×12 cm) using a constant current of 10 mA cm^{-2}. The reaction was followed by TLC and interrupted after 2.34 F mol^{-1}. The solvent was evaporated and the residue was treated with ether (4×100 ml) leaving the crystalline

supporting electrolyte. The combined organic phases were evaporated and the desired 2-methoxy compounds were isolated via two subsequent chromatographic separations using (a) CH_2Cl_2/EtOH 9:1 and (b) ether/EtOH 20:1 as eluants yielding 5.07 g (43 %) of **3a** as a mixture of *cis* and *trans* isomers. ^{1}H NMR (60 MHz): 1.6–2.3 (m, 2 H), 2.8–3.6 (m, 3 H), 3.5 (br s, CH_3O), 3.7 (s, CH_3OCO), 3.8–4.3 (m, 1 H), 4.8–5.1 (m, 1 H).

(3R)-3-Acetoxy-2-methoxy-1-methoxycarbonylpyrrolidine (**3b**). The procedure described for compound **2b** was used starting from **3a**. The resulting oil was chromatographed using ethyl acetate/petroleum ether (2:1) as the eluant to yield **3b** (90 %). ^{1}H NMR (60 MHz): 1.70–2.50 [m, 2 H-C(4)], 2.00 (s, CH_3CO), 3.30–3.70 [m, 2 H-C(5)], 3.40 (s, CH_3O), 3.70 (s, CH_3OCO), 4.90–5.20 [m, H-C(2), H-C(3)].

*(3R)-*tert*-Butyldimethylsilyloxy-2-methoxy-1-methoxycarbonylpyrrolidine* (**3c**). The procedure described for compound **2c** was used starting from **3a**. The resulting oil was chromatographed with petroleum ether/ethyl acetate (6:1) to give **3c** (80 %) as a colourless oil. ^{1}H NMR (60 MHz): 0.1 [s, $(CH_3)_2Si$], 0.9 (2 s, t-Bu), 1.3–2.1 [m, 2 H-C(4)], 3.2–3.6 [M, 2 H-C(5), CH_3O], 3.7 (s, CH_3OCO), 4.1–4.2 (m, 1 H), 4.7–5.1 (m, 1 H).

General procedure for nucleophilic cyanation. A dry flask was charged with starting material (0.25 M) in CH_2Cl_2 and trimethylsilyl cyanide (1.5 equiv.) under an argon atmosphere. The Lewis acid (BF_3–Et_2O, 2.0 equiv. or $TiCl_4$, 1.1 equiv.; 2 M in CH_2Cl_2) was slowly added at the temperature given in Table 2 and the reaction was followed by TLC/GC and quenched by being poured into a stirred slurry of $Na_2CO_3 \cdot 10\ H_2O$ in CH_2Cl_2. After 15 min, $MgSO_4$ was added and the mixture was stirred for 30 min. The filtered organic phase was evaporated to leave the crude product.

(3R)-3-Acetoxy-2-cyano-1-methoxycarbonylpyrrolidine (**5b**, **6b**). The general procedure for nucleophilic cyanation was followed starting from **3b**. The crude product was chromatographed using ethyl acetate/petroleum ether (1:1) as the eluant to give 130 mg of the faster *trans* isomer (**6b**) and 80 mg of the slower *cis* isomer (**5b**) in a total yield of 79 %. **6b** ^{1}H NMR (300 MHz): 2.08 (s, CH_3CO), 2.11–2.24 [m, H-C(4)], 2.28–2.48 [m, H-C(4)], 3.45–3.75 [m, 2 H-C(5)], 3.78 (s, CH_3OCO), 4.50, 4.60 [s, H-C(2)], 5.4 [d, J 4.5 Hz, H-C(3)]. $[\alpha]_D^{25} = +42.0°$ (c=1.0, methanol). MS (high resolution): Found: 212.083±0.005. Calc. 212.080.

5b ^{1}H NMR (300 MHz, recorded at 50 °C): 2.15–2.40 [m, 2 H-C(4)], 2.17 (s, CH_3CO), 3.42–3.70 [m, 2 H-C(5)], 3.78 (s, CH_3OCO), 4.92 [d, J 6.6 Hz, H-C(2)], 5.24 [dt, J_d 8.2, J_t 6.6 Hz, H-C(3)]. $[\alpha]_D^{25} = -34.0°$ (c=1.0, methanol). MS (high resolution): Found: 212.075±0.005. Calc. 212.080.

*(3R)-(*tert*-Butyldimethylsilyloxy)-2-cyano-1-methoxycarbonyl-3-pyrrolidine* (**5c**,**6c**). The general procedure for nucleophilic cyanation was followed starting from **3c**. The crude product was chromatographed using ethyl acetate/petroleum ether (1:4) as the eluant to give 480 mg of the faster *trans* isomer **6c** and 847 mg of the slower *cis* isomer **5c** (total yield 74 %). **5c** ^{1}H NMR (300 MHz): 0.13 [2 s, $(CH_3)_2Si$], 0.94 (s, t-Bu), 2.00–2.17 [m, 2 H-C(4)], 3.35–3.50 [m, H-C(5)], 3.52–3.67 [m, H-C(5)], 3.76 (2 s, 1:1, CH_3OCO), 4.38–4.48 [m, H-C(3)], 4.55, 4.63 [2 d, 1:1, J 6.2 Hz, H-C(2)]. $[\alpha]_D^{25} = -45.0°$ (c=1.0, methanol). MS (high resolution): Found: (M^++1) 285.160±0.005. Calc. 285.163.

6c ^{1}H NMR (300 MHz): 0.11 [2 s, $(CH_3)_2Si$], 0.90 (s, t-Bu) 1.90–2.00 [m, H-C(4)], 2.10–2.29 [m, H-C(4)], 3.52–3.66 [m, 2 H-C(5)], 3.80 (2 s, 1:1, CH_3OCO), 4.22, 4.33 [2 br s, 1:1, H-C(2)], 4.55–4.63 [m, H-C(3)]. $[\alpha]_D^{25} = +26.7°$ (c=1.0, methanol). MS (high resolution): Found: (M^++1) 285.150±0.005. Calc. 285.163.

cis-*3-Hydroxy-*L*-proline* (**9**). Compound **5c** (250 mg, 0.88 mmol) was refluxed in 25 ml 6 M HCl for 17 h, and then evaporated to dryness. The residue was dissolved in 1.0 ml water and purified on an ion-exchange column (3.5 g, 1×4 cm, Dowex 50×8, 200–400 mmesh, activated with 2.5 M HCl and washed with water) using 1.3 M NH_3 as the eluant to give 100 mg (87 %) of **9** as off-white crystals after evaporation. For analytical purposes the product was recrystallized from ethanol/water. M.p. 220–230 °C (decomp.) (lit.,[21] 220–230 °C with decomp.). ^{1}H NMR (D_2O, 300 MHz): 2.09 [dddd, J 14.1, 7.3, 3.1, 1.5 Hz, H-C(4)], 2.19 [dddd, J 14.1, 10.8, 9.0, 4.1 Hz, H-C(4)], 3.44 [ddd, J 11.7, 9.0, 3.1 Hz, H-C(5)], 3.54 [ddd, J 11.7, 10.8, 7.3 Hz, H-C(5)], 4.10 [d, J 4.1 Hz, H-C(2)], 4.68 [dt, J_t 4.1, J_d 1.5 Hz, H-C(3)]. $[\alpha]_D^{25} = -101.0°$ [c=1.0, H_2O) (lit.,[24] $[\alpha]_D^{25} = -102.7°$ (c=1.0, H_2O)].

trans-*3-Hydroxy-*D*-proline* (**10**). The procedure described for the *cis* compounds was used starting from **6b**. The product, isolated after ion-exchange chromatography (95 % yield), was recrystallized from ethanol/water to yield compound **10** as fine white needles. M.p. 220–230 °C (decomp.) (lit.,[21] 220–230 °C with decomp.). ^{1}H NMR (D_2O, 300 MHz): 1.97–2.04 [m, 2 H-C(4)], 3.40–3.61 [m, 2 H-C(5)], 4.03–4.04 [m, H-C(2)], 4.63–4.65 [m, H-C(3)]. $[\alpha]_D^{25} = +18.1°$ (c=1.0, H_2O), (lit.,[24] $[\alpha]_D^{25} = +19.0°$, c=1.0, H_2O).

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