181. Synthetic Applications of Electrochemically Produced α-Methoxyamides

Part 2[1])

Oxidation of Hydroxyproline Derivatives

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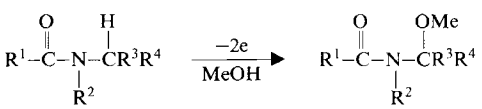
The electrochemical methoxylation of *N*-acetyl-4-hydroxyproline esters has been investigated. Both the free alcohol **3** and the corresponding 4-acetoxy derivative **4** as well as the *cis*-4-acetoxyproline **17** are methoxylated anodically preferentially at C(5), giving a mixture of stereoisomeric methoxy compounds. These mixtures can be used for further substitution as exemplified by the allylation of the methoxylated 4-acetoxy derivatives, giving substitution products preferentially *trans* to the acetoxy group although with low selectivity. The low selectivity is discussed in terms of kinetic *vs.* thermodynamic control.

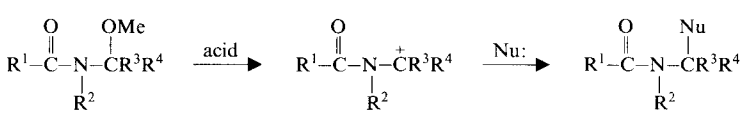
Introduction. – The electrochemical oxidation of *N*-acylamines, also known as the *Ross-Eberson-Nyberg* reaction is a unique method for the synthesis of α-methoxyamides and -carbamates from the corresponding unsubstituted compounds [2] *(Scheme 1)*.

Scheme 1



The reaction is applicable to most amides and carbamates, generally gives good yields (70–95%), and in contrast to many other electrochemical reactions, no sophisticated equipment is needed. The α-methoxylated products have been shown to be versatile synthetic intermediates, in particular with respect to their conversion to the corresponding *N*-acyliminium ion followed by nucleophilic substitution [3] *(Scheme 2)*.

Scheme 2

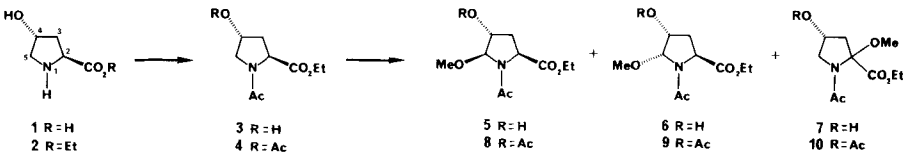


[1]) Part 1: [1].

This sequence of reactions has recently been successfully employed in the total synthesis of several N-containing natural products, such as alkaloids [1] [4] and amino acids [5]. However, only in a few cases [6], the optically active material was synthesized. In the investigation reported here, we have explored the possibility of using (2*S*, 4*R*)-4-hydroxyproline as a chiral starting material. This amino acid is an attractive chiral building block, containing two optically active centers and being easily available.

Results and Discussion. – Earlier results from anodic methoxylation of *N*-acylprolines [6b] [7] and other unsymmetrical amides [8] [9] suggest, that substitution in *N*-acyl-4-hydroxyprolines should occur at the least substituted C(5) and thus, further functionalization of this C-atom should be possible.

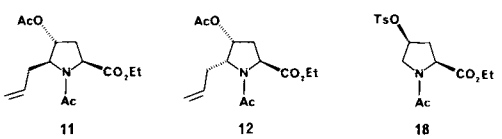
Scheme 3



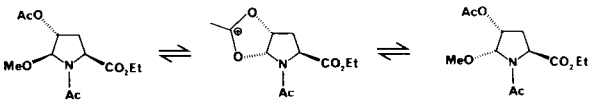
To apply the *Ross-Eberson-Nyberg* procedure, (2*S*, 4*R*)-hydroxyproline (**1**) was esterified with EtOH/HCl *(Scheme 3)*. The resulting ester **2** could be either monoacetylated exclusively on the N-atom to give **3** (65%) or diacetylated to give **4**. Anodic methoxylation of **3** gave a mixture of isomers **5–7** in a ratio of 58:26:16 (total yield of **5/6**: 60%). In a similar manner, **4** was oxidized in MeOH to the corresponding mixture of methoxylated products **8–10** in a ratio of 52:26:22 (total yield of **8/9**: 50%). The stereochemical relationship of **5–7** and **8–10** was ascertained by direct acetylation of **5**, **6**, and **7**, respectively, and comparison of spectral and chromatographic data with those for **8–10**.

The formation of **7** and **10** is not consistent with the generally accepted mechanism for anodic methoxylation involving *N*-acyliminium-ion intermediates [9]. Earlier investigations on oxidation of cyclic, unsymmetrical amides and carbamates such as proline esters and 2-methylpiperidine derivates show that substitution occurs in the least substituted exclusively. In our case, we have at the moment no explanation for this lack of selectivity; the COOEt group should destabilize an adjacent cation intermediate, and it is hard to see how the OH group can cause a change in selectivity. One clue is the fact, that only one of the two possible stereoisomers of **7** and **10** was isolated in both cases.

The mixture of α-methoxy compounds **5/6** was then subjected to amidoalkylation conditions [10] using $BF_3 \cdot Et_2O$ as the *Lewis* acid and allyl(trimethyl)silane as the nucleophile. However, only unchanged starting material was recovered after 24 h at ambient temperature. When the corresponding 4-acetoxy isomers **8/9** were treated similarly, the two isomeric allyl compounds **11** and **12** were isolated in a ratio of 82:18 (yield of **11/12**: 71%). When the reaction was followed by GC, two different reactions were observed, the



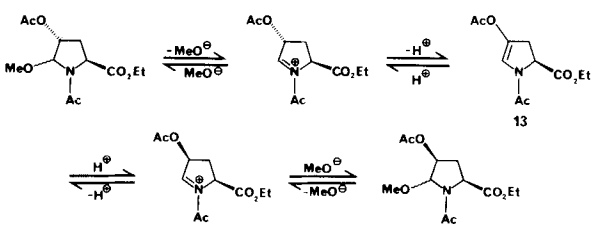
Scheme 4



faster isomerization of **9** into **8** and the substitution reaction leading to **11** and **12**. We also observed the same ratio **11/12** independent of the ratio of **8/9**, which was expected in view of the probable common intermediate cation. The complete conversion of **9** into **8** was also observed on treatment of pure **9** with $BF_3 \cdot Et_2O$ in CH_2Cl_2. A possible explanation for these observations is the intermediacy of a bridged ion (see *Scheme 4*); a reversible loss of the MeO ion should produce the thermodynamically most stable isomer **8**, whereas the irreversible nature of the allylation reaction gives rise to a kinetically controlled product mixture. This implies that the electrochemical reaction is also kinetically controlled, at least with regard to the stereochemical outcome. Substitution exclusively *trans* to a β-acetate group has been observed earlier for other acyliminium ions, which has been attributed to a bridging, neighbouring group effect [11].

The general uncertainty in the magnitude of vicinal coupling constants in five-membered rings makes structural assignments based solely on ^{1}H-NMR spectra somewhat ambiguous. We could not, at this point, exclude a reaction involving a reversible elimination of a proton from the intermediate acyliminium ion to give the corresponding enamide **13** *(Scheme 5)*. This racemization at C(4) could then give rise to allyl com-

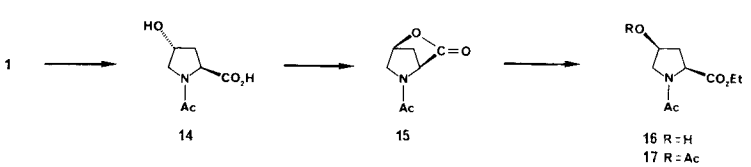
Scheme 5



pounds of the (2*S*,4*S*)-configuration. To solve this problem, we also investigated the use of (2*S*,4*S*)-4-hydroxyproline as a chiral starting material. This amino acid occurs only rarely in nature, and we chose to prepare a derivative, suitable for anodic oxidation, by inversion at C(4) of (2*S*,4*R*)-4-hydroxyproline.

N-Acetylation of **1** proceeded smoothly and gave **14** in 67% yield *(Scheme 6)*. Intramolecular lactonization [12] according to the *Mitsunobu* procedure [13] gave the bicyclic product **15** (90%). This was followed by an acid-catalyzed ethanolysis using the strongly acidic resin *Amberlyst 15* as catalyst to give **16** with (4*S*)-configuration which

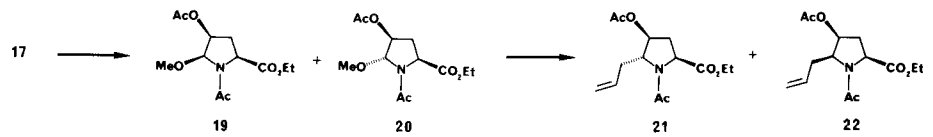
Scheme 6



was converted to the 4-acetoxy derivative **17** (76% from **15**). The stereochemistry of the ring-opening reaction was ascertained by conversion to a known (2*S*,4*S*)-4-hydroxyproline derivative; thus, **15** was opened in MeOH using the same procedure as described above. Tosylation of the crude alcohol gave the known methyl ester **18** [14]. Physical data for **18** were in agreement with those reported in the literature and thus, the acid-catalyzed ring-opening of lactone **15** proceeds with retention of configuration at C(4).

The 4-acetoxy derivative **17** was oxidized in MeOH at a Pt anode to give the two isomeric methoxy compounds **19** and **20** (ratio **19/20**: 3:2) in 50% yield *(Scheme 7)*. In this case, we could not detect a product where substitution had occurred in the α position to the ester group (analogous to **7** and **10**); however, the amount of by-products as judged by GC was larger than in the oxidation of **4** (*ca.* 10–15%) and a small amount of this product could possibly have eluded detection.

Scheme 7



Finally, the mixture **19/20** was treated with allyl(trimethyl)silane in the presence of $BF_3 \cdot Et_2O$ to give the allyl compounds **21** and **22** in a ratio of 54:46 (70% yield). The same behaviour as for the methoxy compounds **8** and **9** was observed in this reaction, *i.e.* a relatively fast conversion of **19** into **20** followed by a slower substitution reaction giving the allyl compounds **21** and **22**. These allyl compounds were clearly different from **11** and **12** as judged by GC and thus, the possibility of racemization at C(4) in the allylation or in the anodic methoxylation can be excluded.

In conclusion, we have shown that it is possible to functionalize C(5) of 4-hydroxyproline derivatives without causing racemization at C(4) using the anodic methoxylation technique. Further formation of a C–C bond at C(5) is also possible, albeit with low stereoselectivity.

Configurational Relationships Based on ^{1}H-NMR Measurements. Vicinal coupling constants are generally a good indication of the stereochemical relation of these protons in cyclic systems. In five-membered rings, however, no correlation between the magnitude of *J* and the configurational relationship between these protons exist [15]. We have observed, that the vicinal coupling constants between H–C(4) and H–C(5) actually correlates well with

Table. *^{1}H-NMR Double-Irradiation Experiments* ($CDCl_3$)

Compd.	Signal irradiated (δ)	Signal perturbed[a])
10	3.89 (*d*, J = 4.4)	5.21 (*dd*, $J(4,3\alpha)$ = 6.6, $J(4,3\beta)$ = 3.2)
	3.68 (*ddd*, J = 11.5, 2.2, 1.0)	5.30 (*ddd*, $J(4,5\alpha)$ = 6.1, $J(4,3\alpha)$ = 6.2, $J(4,3\beta)$ = 2.0)
		2.35 (*d*, $J(3\alpha,3\beta)$ = 15.0)
11	2.34 (*m*, CH_2CH)	3.90 (*s*, H_α–C(5))
	2.13 (*m*, CH_2CH)	4.36 (*s*, H_α–C(5))
12	2.28 (*m*, CH_2CH)	5.38 (*d*, $J(4\beta,5\beta)$ = 11.5)
	2.41 (*m*, CH_2CH)	5.28 (*d*, $J(4\beta,5\beta)$ = 11.5)

[a]) α and β refer to the H-atoms below and above the plane of the ring, respectively.

the spatial arrangement of these protons for any given pair of isomers where the substituent on C(5) is inverted. For the pairs of compounds **5** and **6**, **8** and **9**, **11** and **12**, **19** and **20**, one isomer shows a J_{vic} of *ca.* 4–5 Hz, whereas the other isomer does not show any vicinal coupling (a small J_{trans} of *ca.* 1 Hz was observed for **20**). The hindered rotation of the *N*-acyl group complicates the spectra further. Quite often, different coupling constants are observed in the different rotamers. Hence, the elucidation of these spectra becomes difficult, and in a few cases we have had to use the decoupling technique to simplify these spectra. The results are given in the *Table*.

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Experimental Part

General. All chemicals used were of highest commercial quality and were used without further purification except petroleum ether (60–80°) and AcOEt, used for chromatography, which was distilled before use. Reaction mixtures were analyzed 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 4-acetoxy derivatives gave good chromatograms while proline derivatives containing a free OH group gave very broad peaks), by TLC on commercially available silica gel/aluminum foil plates. In all chromatographic separations, flash chromatography on TLC-grade silica gel was used [16]. We found this method superior to conventional flash chromatography [17]. Optical rotations: *Perkin Elmer 241 MC* polarimeter. ^{1}H-NMR spectra: *Varian XL 300*; $CDCl_3$ as solvent; δ in ppm downfield from TMS as an internal standard. MS: *Finnigan 4021* mass spectrometer at 70 eV, direct inlet. Elemental analysis was carried out by *Mikro Kemi AB*, Uppsala, Sweden.

(2S,4R)-4-Hydroxyproline Ethyl Ester (**2**) was prepared according to [18]. The crude product was used without further purification.

(2S,4R)-1-Acetyl-4-hydroxyproline Ethyl Ester (**3**). Compound **2** (5.0 g, 31.5 mmol) was dissolved in AcOH (50 ml). Ac_2O (2.97 ml, 31.5 mmol) was added and the mixture was stirred overnight at 65°. After completed reaction (TLC; *ca.* 20 h), the solvents were evaporated and the residue taken up in 2M aq. Na_2CO_3. This soln. was extracted with CH_2Cl_2 (3 × 50 ml). After drying ($MgSO_4$), the combined org. extracts were evaporated and the residual oil was purified by column chromatography (AcOEt/MeOH 10:1) to yield **3** (4.1 g, 65%) as a slightly yellow oil. $[\alpha]_D^{25} = -86.1$ ($CHCl_3$, $c = 1.0$). ^{1}H-NMR: 4.45–4.60 (*m*, H–C(2), H–C(4)); 4.15–4.26 (*m*, CH_3CH_2); 3.82 (*dt*, $J_d = 12.4$, $J_t = 2.1$, 0.3 H, H_α–C(5)); 3.78 (*dd*, $J = 10.8$, 4.5, 0.7 H, H_β–C(5)); 3.54 (*dd*, $J = 12.8$, 4.6, 0.3 H, H_β–C(5)); 3.51 (*ddd*, $J = 10.6$, 2.1, 1.4, 0.7 H, H_α–C(5)); 2.80 (br. *s*, OH); 2.45, 2.30 (2 *dddd*, 3:7, $J = 13.0$, 8.5, 3.5, 2.0, H–C(3)); 2.04–2.25 (*m*, H–C(3)); 2.08, 2.00 (2 *s*, 3:7, AcN); 1.29, 1.28 (2 *t*, 3:7, $J = 7.0$, CH_3CH_2). Anal. calc. for $C_9H_{15}NO_4$ (201.22): C 53.7, H 7.5; found: C 53.1, H 7.7.

(2S,4R)-4-Acetoxy-1-acetylproline Ethyl Ester (**4**). Compound **2** (5.0 g, 31.5 mmol) in AcOH (50 ml) and Ac_2O (30 ml) and stirred at 70° overnight. After completed reaction (TLC; *ca.* 24 h), the solvents were evaporated and the residue dissolved in CH_2Cl_2 (50 ml). After washing with a sat. aq. $NaHCO_3$ soln. and extracting the aq. washings with CH_2Cl_2 (3 × 25 ml), the combined org. extracts were dried ($MgSO_4$) and evaporated. Column chromatography (AcOEt) of the resulting yellow oil gave **4** (6.45 g, 84%) as a colourless oil. $[\alpha]_D^{25} = 49.0$ ($CHCl_3$, $c = 1.0$). ^{1}H-NMR: 5.32 (*tt*, $J = 2.7$, 2.0, H–C(4)); 4.52 (*t*, $J = 8.1$, H–C(2)); 4.17–4.23 (*m*, CH_3CH_2); 3.90, 3.66 (2 *dd*, 2:1, $J = 11.5$, 5.0, H–C(5)); 3.92, 3.60 (2 *dt*, 1:2, $J_d = 11.5$, $J_t = 1.7$, H–C(5)); 2.32–2.53 (*m*, H–C(3)); 2.22, 2.17 (2 *dd*, 2:1, $J = 8.3$, 5.5, H–C(3)); 2.07, 2.04 (2 *s*, 2:1, AcN); 2.06, 1.99 (2 *s*, 2:1, AcO); 1.30, 1.29 (2 *t*, 2:1, $J = 7.0$, CH_3CH_2). Anal. calc. for $C_{11}H_{17}NO_5$ (243.26): C 54.3, H 7.0; found: C 53.9, H 7.2.

General Procedure for Anodic Methoxylation of Amides. In a 50-ml water-cooled cell, the amide (0.4M) was dissolved in MeOH containing Bu_4NBF_4 (0.05M). The stirred soln. was oxidized at a Pt foil anode and cathode (1 × 1 cm) using a constant current of 10 mA/cm^2. The reaction was followed by TLC or GC. After completed reaction, the solvent was evaporated and the residue treated with Et_2O (3 × 75 ml) leaving the crystalline supporting electrolyte. The combined extracts were evaporated and the resulting oil purified by column chromatography.

Anodic Methoxylation of **3**. The electrolysis of **3** (6.70 mmol) on a 3 × 5-cm Pt anode was followed by TLC and interrupted after a passage of 4 F/mol. The crude product was chromatographed with AcOEt. Two different fractions were collected, the first consisting of 0.93 g (60%) of the *1-acetyl-4-hydroxy-5-methoxyproline ethyl esters* (**5/6**) and the second consisting of 181 mg (12%) of pure *1-acetyl-4-hydroxy-2-methoxyproline ethyl ester* (**7**). The mixture **5/6** was then separated *via* a second column chromatography (CH_2Cl_2/MeOH 40:3) giving 407 mg of **5** and 183 mg of **6** as white solids. M.p. 62–67° for **5** and 72–77° for **6**. ^{1}H-NMR of **5**: 5.44, 4.90 (2*s*, 1:2, H–C(5)); 4.65,

4.57 (2*t*, 2:1, J = 9.0, H–C(2)); 4.30–4.35 (*m*, 0.6 H, H–C(4)); 4.15-4.25 (*m*, 2.4 H, H–C(4), CH_3CH_2); 3.44, 3.41 (2*s*, 2:1, CH_3O); 2.23–2.50 (*m*, 2H–C(3), OH); 2.22, 2.05 (2*s*, 2:1 AcN); 1.30, 1.27 (2*t*, 1:2, J = 7.0, CH_3CH_2). ^{1}H-NMR of **6**: 5.30 (*d*, J = 4.9, 0.3 H, H–C(5)); 4.96 (*d*, J = 4.5, 0.7 H, H–C(5)); 4.10–4.50 (*m*, H–C(2), H–C(4), CH_3CH_2); 3.65, 3.55 (2*s*, 3:7, CH_3O); 2.00–2.50 (*m*, 2H–C(3), OH); 2.20, 2.05 (2*s*, 7:3, AcN); 1.28, 1.25 (2*t*, 3:7, J = 7.0, CH_3CH_2). ^{1}H-NMR of **7**: 4.40–4.50 (*m*, H–C(4)); 4.15–4.40 (*m*, CH_3CH_2); 3.86 (*dd*, J = 10.7, 4.4, H_B–C(5)); 3.74 (*d*, J = 10.9, H_α–C(5)); 3.52, 3.36 (2*s*, 13:2, CH_3O); 2.43, 2.38 (2*dd*, 2:13, J = 14.0, 5.0, H_β–C(3)); 2.30 (*dt*, J_d = 14.0, J_t = 1.5, 0.9 H, H_α–C(3)); 2.22–2.30 (*m*, 0.1 H, H_β–C(3)); 2.14, 2.10 (2*s*, 2:13, AcN); 1.36, 1.29 (2*t*, 2:13, J = 7.0, CH_3CH_2).

Anodic Methoxylation of **4**. The electrolysis of **4** (20 mmol) was interrupted after a passage of 6F/mol and the crude product was chromatographed using AcOEt/petroleum ether 3:1 (*v*/*v*). The two isomeric *4-acetoxy-1-acetyl-5-methoxyproline ethyl esters* (**8** and **9**) were isolated as a mixture (2.73 g, 50%; ratio 66:34 by GLC), together with *4-acetoxy-1-acetyl-2-methoxyproline ethyl ester* (**10**; 0.76 g, 14%). The isomers **8** and **9** were prepared in a pure state *via* acetylation of **5** and **6**, respectively, using the procedure for preparation of **4**. ^{1}H-NMR of **8**: 5.50, 4.92 (2*s*, 3:7, H–C(5)); 5.16 (br. *d*, J = 3.5, 0.7 H, H–C(4)); 5.06 (*dd*, J = 3.9, 2.4, 0.3 H, H–C(4)); 4.58, 4.52 (2*dd*, 7:3, $J \approx 9, 9$, H–C(2)); 4.16–4.30 (*m*, CH_3CH_2); 3.49, 3.42 (2*s*, 7:3, CH_3O); 2.25–2.55 (*m*, 2 H–C(3)); 2.20, 2.08 (2*s*, 7:3, AcN); 2.07, 2.04 (2*s*, 7:3, AcO); 1.30, 1.28 (2*t*, 3:7, J = 7.1, CH_3CH_2). ^{1}H-NMR of **9**: 5.57 (*d*, J = 5.0, 0.2 H, H–C(5)); 5.25 (*d*, J = 4.5, 0.8 H, H–C(5)); 5.17, 4.95 (2*ddd*, 6:1, J = 11.7, 7.3, 4.4, H–C(4)); 4.48 (*dd*, J = 10.0, 1.0, 0.8 H, H–C(2)); 4.42 (*d*, J = 10.0, 0.2 H, H–C(2)); 4.24, 4.18 (2*q*, 6:1, J = 7.3, CH_3CH_2); 3.54, 3.44 (2*s*, 1:6, CH_3O); 2,58, 2.40 (2*ddd*, 1:6, J = 12.7, 11.2, 10.0, H_α–C(3)); 2.35, 2.25 (2*ddd*, 1:6, J = 12.5, 7.0, 1.5, H_β–C(3)); 2.18, 2.12 (2*s*, 6:1, AcN); 2.14, 1.95 (2*s*, 6:1, AcO); 1.30, 1.27 (2*t*, 1:6, J = 7.6, CH_3CH_2). ^{1}H-NMR of **10**: 5.30 (*dddd*, J = 6.2, 6.1, 2.2, 2.0, 0.7 H, H–C(4)); 5.21 (*dddd*, J = 6.6, 4.4, 4.4, 3.2, 0.3 H, H–C(4)); 4.18–4.32 (*m*, CH_3CH_2); 4.05 (*dd*, J = 11.7, 6.1, 0.7 H, H_α–C(5)); 3.89 (*d*, J = 4.4, 0.6 H, H_α–C(5), H_β–C(5)); 3.68 (*ddd*, J = 11.5, 2.2, 1.0, 0.7 H, H_β–C(5)); 3.42, 3.39 (2*s*, 7:3, CH_3O); 2.65, 2.51 (2*dd*, 3:7, J = 15.0, 6.6, H_α–C(3)); 2.49 (*dd*, J = 15.0, 3.4, 0.3 H, H_β–C(3)); 2.35 (br. *d*, J = 15.0, 0.7 H, H_β–C(3)); 2.09, 2.01(2*s*, 7:3, AcN); 2.08, 2.06 (2*s*, 7:3, AcO); 1.30, 1.28 (2*t*, 3:7, J = 7.5, CH_3CH_2).

(2S,4R)-4-Acetoxy-1-acetyl-5-allylproline Ethyl Ester (**11/12**). The mixture **8/9** (0.59 g, 2.16 mmol) produced from **4** was dissolved in CH_2Cl_2 (8 ml) in a dry flask under N_2. Allyl(trimethyl)silane (0.69 ml, 8.4 mmol) and $BF_3 \cdot Et_2O$ (0.54 ml, 4.30 mmol) were added, and the mixture was stirred at r.t. The reaction was checked by GC (**11/12** 82:18 by GLC), and, when completed (*ca.* 24 h), quenched with a sat. aq. soln. of $NaHCO_3$. The org. phase was separated and the aq. phase washed with CH_2Cl_2 (3 × 25 ml). After drying and evaporation, the combined org. extracts were purified by column chromatography (AcOEt/petroleum ether 6:1): **11** and **12** as colourless oils (380 mg (62%) and 54 mg (9%), resp.).

11: $[\alpha]_D^{25}$ = 22.9° ($CHCl_3$, c = 1.0). ^{1}H-NMR: 5.78–5.96 (*m*, CH_2=C*H*CH_2); 5.06–5.26 (*m*, H–C(4), CH_2=CHCH_2); 4.55 (*dd*, J = 10.0, 8.3, 0.7 H, H–C(2)); 4.48 (*t*, J = 8.5, 0.3 H, H–C(2)); 4.36 (*dd*, J = 10.2, 4.8, 0.2 H, H–C(5)); 4.15–4.28 (*m*, CH_3CH_2); 3.90 (*dd*, J = 9.5, 5.6, 0.7 H, H–C(5)); 2.15–2.70 (*m*, 2 H–C(3), CH_2=CHCH_2); 2.12, 2.00 (2*s*, 3:1, AcN); 2.05, 2.03 (2*s*, 3:1, AcO); 1.30, 1.27 (2*t*, 1:3, J = 7.6, CH_3CH_2). MS: 242 (8), 200 (48), 108 (20), 43 (100). Anal. calc. for $C_{14}H_{21}NO_5$ (283.32): C 59.4, H 7.5; found: C 58.9, H 7.7.

12: $[\alpha]_D^{25}$ = 19.6° ($CHCl_3$, c = 1.0). ^{1}H-NMR: 5.68–5.82 (*m*, CH_2=C*H*CH_2); 5.38, 5.28 (2*dt*, 4:1, J_t = 7.2, J_d = 11.5, H–C(4)); 4.98–5.16 (*m*, CH_2=CHCH_2); 4.54 (*dt*, J_t = 7.6, J_d = 3.2, 0.2 H, H–C(5)); 4.32–4.42 (*m*, 1.8 H, H–C(5), H–C(2)); 4.12–4.25 (*m*, CH_3CH_2); 2.12–2.65 (*m*, H–C(3), CH_2=CHCH_2); 2.13, 1.99 (2*s*, 2:9, AcN); 2.06, 2.05 (2*s*, 9:2, AcO); 1.30, 1.26 (2*t*, 2:9, J = 6.9, CH_3CH_2). MS: 242 (5), 200 (38), 108 (20), 43 (100). Anal. calc. for $C_{14}H_{21}NO_5$ (283.32): C 59.4, H 7.5; found: C 58.9, H 7.5.

(2S,4R)-1-Acetyl-4-hydroxyproline (**14**) was prepared according to [19] in 67% yield. M.p. 132–135° ([19]: 135°).

Lactonization of **14** was performed according to [13], yield 90% of *5-acetyl-2-oxa-5-azabicyclo[2.2.1]heptan-3-one* (**15**). M.p. 96–99° ([12]: 95.5–98°). $[\alpha]_D^{25}$ = 65.0° ($CHCl_3$, c = 1.9; [12]: 67.3° ($CHCl_3$, c = 1.9)). ^{1}H-NMR: 5.16–5.21 (*m*, H–C(4)); 5.09, 4.47 (2*ddd*, 1:2, J = 1.2, 1.1, 1.0, H–C(4)); 3.70 (*dd*, J = 10.0, 1.2, 0.3 H, H_α–C(5)); 3.61–3.64 (*m*, 1.3 H, H_α–C(5), H_β–C(5)); 3.55 (br. *d*, J = 10.0, 0.3 H, H_β–C(5)); 2.34, 2.28 (2*dddd*, 2:1, J = 11.0, 2.6, 1.3, 1.3, H_β–C(3)); 2.20, 2.07 (2*s*, 2:1, AcN); 2.14, 1.98 (2*dd*, 2:1, J = 11.0, 1.7, H_α–C(3)).

(2S,4S)-4-Acetoxy-1-acetylproline Ethyl Ester (**17**). Coumpound **15** (2.0 g, 12.9 mmol) was dissolved in abs. EtOH (26 ml) and *Amberlyst 15* (540 mg) was added. The mixture was stirred for 16 h, filtered, and evaporated. The crude alcohol **16**, a yellowish oil, was acetylated by heating to 75° in Ac_2O (15 ml) and pyridine (1.3 ml) for 20 h. After evaporation of the solvents, the residue was purified by column chromatography (AcOEt/MeOH 18:1) to give **17** (2.40 g, 76% from **15**) as a colourless oil. $[\alpha]_D^{25}$ = − 105.1° ($CHCl_3$, c = 1.0). ^{1}H-NMR: 5.29 (*ddd*, J = 8.3, 5.2, 2.4, H–C(4)); 4.70 (*dd*, J = 9.0, 3.0, 0.7 H, H–C(2)); 4.46 (*dd*, J = 9.0, 2.0, 0.3 H, H–C(2)); 4.14–4.30 (*m*, CH_3CH_2); 3.87 (*dd*, J = 12.0, 5.8, 0.7 H, H_α–C(5)); 3.83 (*dd*, J = 12.0, 5.2, 0.3 H, H_α–C(5)): 3.64–3.70 (*m*,

H_β–C(5)); 2.26–2.60 (*m*, 2 H–C(3)); 2.10, 2.05 (2*s*, 5:2, AcN); 2.03, 1.98 (2*s*, 5:2, AcO); 1.31, 1.28 (2*t*, 2:5, J = 7.0, CH_3CH_2). Anal. calc. for $C_{11}H_{17}NO_5$ (243.26): C 54.3, H 7.0; found: C 53.8, H 7.0.

The ring-opening of **15** was also carried out in MeOH and the resulting crude alcohol was tosylated to give the known *(2S,4S)-1-acetyl-4-(*p*-toluenesulfonyloxy)proline methyl ester* (**18**). $[\alpha]_D^{25} = -32.8°$ (MeOH, c = 1.6; [14]: −33.6° (MeOH, c = 1.6)). M.p. 142–145° ([14]: 142–143°).

Anodic Methoxylation of **17** (20 mmol) was carried out according to the general procedure. After passage of 4 F/mol, the electrolysis was interrupted and worked up as usual. Chromatography with AcOEt gave **19/20** (60:40; 2.73 g, 50%). This mixture was used for further reactions. For anal. purposes, **19** and **20** were separated by chromatography using CH_2Cl_2/CH_3CN 3:1. ^{1}H-NMR of **19**: 5.69, 5.27 (2*d*, 3:7, J = 4.4, H–C(5)); 4.84 (*ddd*, J = 10.8, 8.0, 4.6, 0.7 H, H–C(4)); 4.77 (*ddd*, J = 11.0, 7.9, 4.3, 0.3 H, H–C(4)); 4.46, 4.35 (2*dd*, 7:3, $J \simeq 8.5$, 8.5, H–C(2)); 4.15–4.30 (*m*, CH_3CH_2); 3.50, 3.45 (2*s*, 7:3, CH_3O); 2.82 (*ddd*, J = 12.4, 9.0, 7.9, 0.3 H, H_β–C(3)); 2.64 (*ddd*, J = 12.0, 8.5, 7.7, 0.7 H, H_β–C(3)); 2.35, 2.21 (2*ddd*, 3:7, J = 12.5, 10.6, 8.6, H_α–C(3)); 2.25, 2.12 (2*s*, 7:3, AcO); 2.14, 2.02 (2*s*, 7:3, AcN); 1.30, 1.27 (2*t*, 3:7, J = 7.1, CH_3CH_2).^{1}H-NMR of **20**: 5.25 (*d*, J = 1.5, 0.2 H, H–C(5)); 5.11 (*d*, J = 4,6, 0.8 H, H–C(2)); 4.98 (*d*, J = 4.4, 0.2 H, H–C(2)); 4.89 (*d*, J = 0.7, 0.8 H, H–C(5)); 4.70 (*dd*, J = 10.0, 1.0, 0.8 H, H–C(4)); 4.50 (*dd*, J = 9.6, 0.9, 0.2 H, H–C(4)); 4.12–4.30 (*m*, CH_3CH_2); 3.54, 3.48 (2*s*, 1:6, CH_3O); 2.73 (*ddd*, J = 12.5, 8.6, 3.8, 0.2 H, H_α–C(3)); 2.58 (*ddd*, J = 14.7, 10.2, 4.7, 0.8 H, H_α–C(3)); 2.0–2.14 (*m*, H_β–C(3)); 2.23, 2.18 (2*s*, 1:6, AcO); 2.04, 1.98 (2*s*, 1:6, AcN); 1.30, 1.27 (2*t*, 1:6, J = 7.1, CH_3CH_2).

(2S,4S)-4-Acetoxy-1-acetyl-5-allylproline Ethyl Ester (**21** and **22**). A mixture **19/20** was allylated using the same procedure as for **8/9**. After stirring for 24 h, **19/20** was consumed and **21/22** (ratio 54:46 by GC) was isolated by column chromatography (CH_3CN/Et_2O 1:5) in 70% yield. The isomers could not be separated by chromatography, identification was based solely on GC and GC/MS and comparison with **11** and **12**. MS (**21**): 242 (7), 200 (44), 108 (33), 43 (100), **22**: 242 (8), 200 (48), 108 (25), 43 (100). Anal. calc. for $C_{14}H_{21}NO_5$ (283.32): C 59.4, H 7.5; found (**21/22**): C 59.4, H 7.6.

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