Intermolecular Stereoselective Alkenylation of Chiral *N*-Acylpyrrolidinium Ions

Mikkel Thaning[‡] and Lars-G. Wistrand[†,*]

Division of Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

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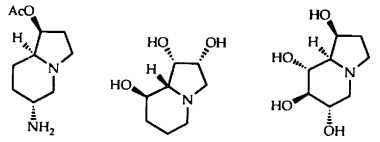
Vinylation of the three cyclic, optically active *N*-acylpyrrolidinium ions **5**, **8** and **12** with the vinylcopper reagent 2-methyl-1-propenylcopper displays a moderate-to-high *trans* selectivity with respect to the ring substituents. The absolute configuration of the vinylated products has been confirmed by ozonolysis of the double bond and subsequent degradation to the known amino acids (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid, *trans*-4-hydroxy-L-proline, and *trans*-3-hydroxy-D-proline.

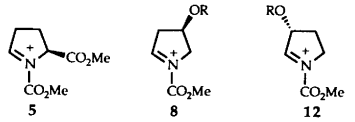
N-Acyliminium ions are useful intermediates in organic synthesis.[1] The reaction of such nitrogen-stabilized cations with various nucleophiles has been used as the key carbon–carbon bond forming step in the synthesis of many naturally occurring nitrogen-containing compounds, in particular alkaloids.[2] However, synthetic approaches to amines containing a β-hydroxy function, as exemplified by the naturally occurring substances slaframine (**1**), swainsonine (**2**) and castanospermine (**3**) require a nucleophile containing an oxygen functionality on the nucleophilic carbon if the amidoalkylation strategy is to be applied. Our interest in the synthesis of alkaloids using the amidoalkylation strategy in an intermolecular fashion prompted us to explore the possibility of using an α-functionalized nucleophile as an entry into the above alkaloids.[3] Few such nucleophiles have been used; one example has been reported by Yamamoto and coworkers[4] who used a γ-oxygenated allyltin reagent as the nucleophile to produce β-aminoalcohols.



1 **2** **3**

After some consideration we selected the vinyl group since it, if it can be introduced as the nucleophile, can easily be transformed into the desired oxygen functionality. Intermolecular amidoalkylation using olefinic nucleophiles[1] generally requires vigorous reaction conditions often incompatible with highly functionalized, chiral *N*-acyliminium ions. On the other hand, intramolecular vinylation[5] has been performed under less strenuous reaction conditions, using olefinic nucleophiles carrying cation-stabilizing groups such as a dithioacetal or a silyl group. One example involving an intermolecular vinylation was recently published by Ley and coworkers[6] who reported on the facile vinylation of α-benzenesulfonyl amides using vinylzinc reagents. Another example of a functionalized nucleophile used in an intermolecular fashion is bis(trimethylsilyl)acetylene, reported by Hacksell and coworkers.[7]

Of vital importance for the amidoalkylation to be a practical synthetic tool in the synthesis of complex molecules, is the control, or at least predictability of the stereoselective outcome of the reaction. We recently reported on the stereoselective alkylation of *N*-acyliminium ions using alkylcopper reagents.[8,9] In this report we show that vinylcopper reagents are equally efficient and selective nucleophiles. The stereoselectivity of addition of vinylcopper reagents was studied using the chiral *N*-acyliminium ions **5**, **8** and **12** as substrates. Nucleophilic addition to these



5 **8** **12**

N-acyliminium ions (R = TBDMS) has been reported to give predominantly *cis* addition using traditional π-nucleophiles such as allyltrimethylsilane[10] with varying degrees of stereoselectivity.[11–13] In contrast, nucleophilic addition to **12** (R = Ac) has been reported to give selectively *trans* addition.[3] Alkylation of **5** with alkylcopper reagents also proceeds with a high degree of *trans* selectivity.[9]

Results and discussion

2-Methyl-1-propenylcopper (**4**) was chosen as the vinylic component because of its ease of preparation from the corresponding organolithium compound and its relative

‡ Present address: Neurosearch, 26 Smedeland, DK-2600 Glostrup, Denmark.

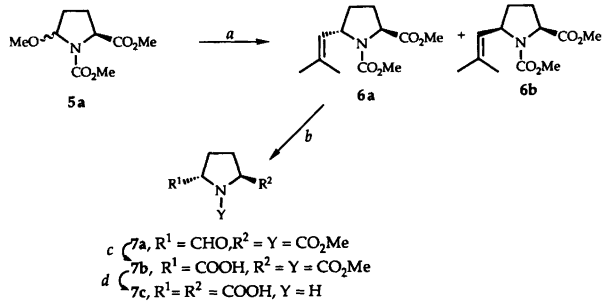
† Present address: Hafslund Nycomed Innovation AB, Ideon Malmö, S-205 12 Malmö, Sweden.

* To whom correspondence should be addressed.

Table 1. Stereoselectivity in the reaction of **5** with various nucleophiles.

Nucleophile	Lewis acid	*cis*:*trans*	Yield (%)	Ref
Allyltrimethylsilane	$TiCl_4$	72:28	74	10
Isopropenyl acetate	$BF_3 \cdot Et_2O$	70:30	85	10
Propylcopper	$BF_3 \cdot Et_2O$	3:97	75	8
4	$BF_3 \cdot Et_2O$	6:94	83	This work

stability. Treatment of **5a** with 2 equiv. each of **4** and BF_3 at −78 °C gave a 94:6 mixture of the vinyl compounds **6a** and **6b** (Table 1). After purification by column chromatography, the stereochemistry of the major product **6a** was determined by conversion into the known amino acid **7c** (Scheme 1). Thus, ozonolysis of **6a** gave the aldehyde **7a** in

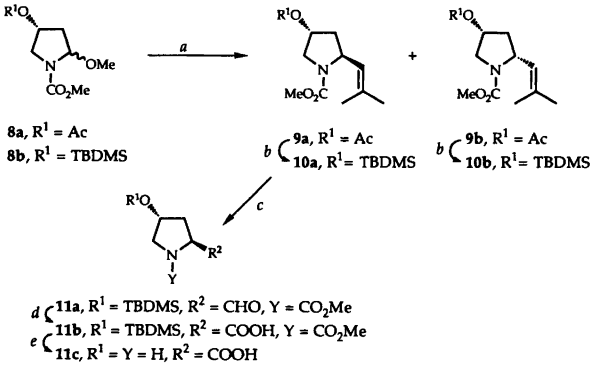


Scheme 1. *a*, **4**, $BF_3 \cdot Et_2O$; *b*, O_3, DMS; *c*, PDC, DMF; *d*, 6 M HCl.

92% yield. Sequential treatment of **7a** with pyridinium dichromate (PDC) in DMF and aqueous 6 M HCl gave *trans*-2,5-pyrrolidinedicarboxylic acid **7c** in enantiomerically pure form.

The *N*-acyliminium ion **8** undergoes highly selective *cis* addition of nucleophiles, in particular if the *O*-protective group is a silyl group (TBDMS).[12] The corresponding *O*-acetyl compound shows a somewhat lower degree of *cis* selectivity.[13] Although the origin of this high selectivity is not entirely understood, it is interesting to note that the *N*-acyliminium ion **8** shows the same 1,3 spatial relationship between the reacting center and the substituent, in this case a protected alcohol, as the *N*-acyliminium ion **5**.

In the light of the proposed mechanism for the addition of alkylcopper reagents to *N*-acyliminium ions,[9] substrate **8** provides an interesting probe into the factors governing the selectivity of nucleophilic addition to *N*-acyliminium ions. The results, shown in Table 2 reveal that the acetoxy group in **8a** gives almost no facial selectivity, whereas the OTBDMS group leads to moderate degree of *trans* selectivity. The absolute stereochemistry of the major product **10a** was deduced as before by its conversion into the naturally occurring amino acid *trans*-4-hydroxy-L-proline **11c** with the correct optical rotation (Scheme 2).



Scheme 2. *a*, **4**, $BF_3 \cdot Et_2O$; *b*, 1: K_2CO_3, MeOH; 2: TBDMSCl, imidazole; *c*, O_3, DMS; *d*, PDC, DMF; *e*, 6 M HCl.

Table 2. Stereoselectivity in the reaction of **8** with various nucleophiles.

Substrate	Nucleophile	Lewis acid	*cis*:*trans*	Yield (%)[b]	Ref.
8a	Me_3SiCN	$TiCl_4$	91:9	[a]	12
8a	**4**	$BF_3 \cdot Et_2O$	45:55	[a]	This work
8b	Allyltrimethylsilane	$TiCl_4$	97:3	75	11
8b	**4**	$BF_3 \cdot Et_2O$	15:85	89	This work

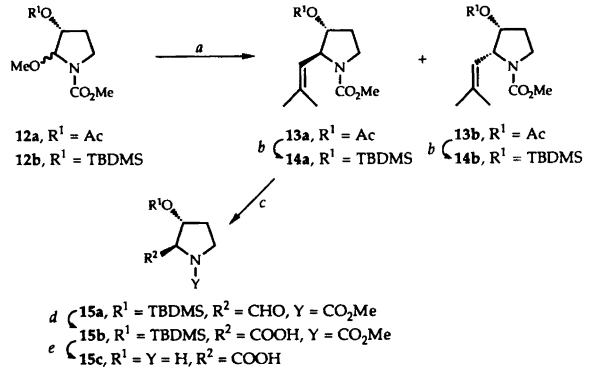
[a]Not determined. [b]Isolated yield.

Table 3. Stereoselectivity in the reaction of **12** with various nucleophiles.

Substrate	Nucleophile	Lewis acid	*cis*:*trans*	Yield (%)[a]	Ref.
12a	Allyltrimethylsilane	$BF_3 \cdot Et_2O$	21:79	64[b]	13
12a	**4**	$BF_3 \cdot Et_2O$	30:70	[b]	This work
12b	Allyltrimethylsilane	$BF_3 \cdot Et_2O$	77:23	69[a]	13
12b	**4**	$BF_3 \cdot Et_2O$	5:95	89	This work

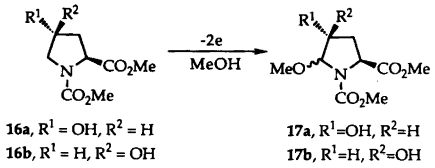
[a]Isolated yield. [b]After conversion into the free alcohol. [c]Not determined.

Preparation of compounds **12a** and **12b** by anodic methoxylation of the *N*-protected (3*R*)-pyrrolidin-3-ol has been published by us.[13] In this case, the carbon bearing the substituent is situated vicinally to the *N*-acyliminium ion. We showed,[3] as indicated in Table 3, that the stereoselectivity of the addition of a π-nucleophile to the *N*-acyliminium ion **12** can be controlled by the *O*-protective group to give *cis*:*trans* ratios varying from 77:23 to 21:79.[14] When treated with **4** and BF_3, both the *O*-acetyl (**12a**) and the *O*-TBDMS compound (**12b**) gave preferentially the *trans*-vinylated products **13a** and **14a**, respectively, although the *O*-acetyl group in compound **12a** gave a less satisfactory selectivity (Table 3). The products **14a** and **14b** were separated by column chromatography and **14a** was subjected to degradation as above to the amino acid *trans*-(3*R*)-3-hydroxyproline **15c** with the correct optical rotation (Scheme 3).



Scheme 3. a, **4**, $BF_3 \cdot Et_2O$; *b*, 1: K_2CO_3, MeOH; 2: TBDMSCl, imidazole; *c*, O_3, DMS; *d*, PDC, DMF; *e*, 6 M HCl.

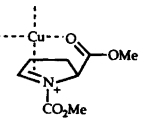
We have also investigated the vinylation of the disubstituted methoxy compound **17a** prepared by anodic oxidation of the *N*-protected amino acid **16a**.[15,16] Both the *O*-acetyl and the *O*-TBDMS derivatives of **17a** failed to react with the copper reagent **4** in the presence of BF_3 and



Scheme 4.

could be recovered almost quantitatively. Since the substituents on the *N*-acyliminium ion have been demonstrated to exert a profound effect on the selectivity of the vinylation, compound **17b** [the C(4) epimer of **17a**] would be expected to give an unambiguous *trans*-directing effect. We have previously reported on the preparation of (2*S*,4*S*)-*N*-acetyl-4-hydroxy-L-proline[15] by epimerization of (2*S*,4*R*)-*N*-acetyl-*trans*-4-hydroxy-L-proline and this method was successfully adopted to prepare **16b**. Anodic methoxylation then gave **17b** as a mixture of diastereomers. However, both the *O*-acetyl and the *O*-TBDMS derivatives of **17b** were recovered almost quantitatively after treatment with **4**–$BF_3 \cdot Et_2O$. The reason for this failure to react is at present unknown; one might speculate that formation of the *N*-acyliminium ion in these cases is, for some reason, unusually slow which would lead to decomposition of the organocopper reagent before reaction could occur.

The selective formation of the *trans* adduct, as has been observed in most cases in this report, is consistent with the suggested mechanism which involves an intermediate, facially biased RCu π-complex as shown in Fig. 1.[9] Such



complexes have been suggested as intermediates in the conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds.[17] Selective *trans* attack by another RCu moiety on this complex would then account for the observed selectivity.

In conclusion, we have shown that the intermolecular vinylation of the *N*-acyliminium ion **5** can be carried out using the vinylcopper reagent **4** in the presence of BF_3 with little or no loss of selectivity compared with alkylcopper reagents.[9] There is a strong possibility, that similar selectivities reported in this paper for the vinylation of the *N*-acyliminium ions **8** and **12** will be found with other organocopper reagents. Thus, it seems possible that the stereochemistry of the nucleophilic addition to the *N*-acyliminium ions **5**, **8** and **12** can be controlled from ≥85% *trans* to ≥70–80% *cis* addition by appropriate selection of the reagent and the *O*-protective group. The generality and the predictability of the reaction of organocopper reagents with chiral *N*-acyliminium ions should guarantee its preparative usefulness, e.g. in synthetic approaches to mono- and bi-cyclic alkaloids such as **1**, **2** and **3**.

Experimental

General. All chemicals used were of highest commercial quality and used without further purification with noted exceptions. Light petroleum (b.p. 60–80 °C) and ethyl acetate, used for chromatography, were distilled before use. $BF_3 \cdot Et_2O$ was distilled from CaH_2 before use. $CuBr \cdot Me_2S$ was prepared according to the method described by House.[18] 2-Methyl-1-propenyllithium (**4**) was prepared from 1-bromo-2-methyl-1-propene and lithium powder in Et_2O at −20 °C. The concentration of the alkyllithium solution (usually around 0.5 M) was determined by titration as described by Watson and Eastham.[19] Reaction mixtures were analyzed by capillary GLC using a Varian 3400 chromatograph equipped with a Varian 4270 integrator on a 25 m × 0.25 mm OV 1701 column and by TLC on commercially available silica gel/aluminum foil plates. Flash chromatography was performed on TLC grade silica gel

according to Taber.[20] ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian XL 300 instrument unless otherwise state, δ being given in ppm downfield from Me_4Si. Coupling constants, *J*, are given in Hz. Optical rotations were determined on a Perkin-Elmer 241 MC instrument. High resolution mass spectra [MS(hr)] were obtained using a Jeol SX 102 instrument, direct inlet.

General procedure for vinylation using **4**. To a suspension of $CuBr \cdot Me_2S$ (1.51 g, 7.4 mmol) in dry diethyl ether (20 ml) was added a solution of 2-methyl-1-propenyllithium (14.8 ml of a 0.50 M solution in diethyl ether) at −40 °C under an argon atmosphere. After being stirred for 30 min, the solution was cooled to −70 °C and $BF_3 \cdot Et_2O$ (0.93 ml, 7.4 mmol) was added. After 5 min, a solution of the methoxy compound (3.69 mmol) in dry ether (3.0 ml) was added. The reaction mixture was allowed to attain ambient temperature and a 1:1 mixture of a saturated solution of NH_4Cl and concentrated aqueous ammonia was added. After being stirred for 30 min, the mixture was extracted with dichloromethane (3 × 20 ml) and the organic phase was dried over $MgSO_4$. The organic phase was concentrated under reduced pressure to leave a clear oil.

*(5S)-1-Methoxycarbonyl-5-(2-methyl-1-propenyl)-*L*-proline methyl ester* (**6a**). Vinylation of **5a** according to the general procedure followed by purification by column chromatography (ethyl acetate–light petroleum 1:2) gave pure **6a** (55 %) and a mixture of **6a** and **6b** (28 %). ^{1}H NMR (300 MHz): 5.1 (t, *J* 7.8, 1 H), 4.76 (t, *J* 9.0, 0.5 H), 4.69 (t, *J* 9.0, 0.5 H), 4.41 (d, *J* 8.4, 0.5 H), 4.36 (d, *J* 8.4, 0.5 H), 3.73, 3.72, 3.66, 3.63 (4 s, 1:1:1:1, 6 H) 2.07–2.39 (m, 2 H), 1.93–2.07 (m, 1 H) 1.56–1.80 (m, 7 H). $[\alpha]_D^{25} = -7.2°$ (*c* 1.0, MeOH). MS (hr): 241.1321. Calc. for $C_{12}H_{19}NO_4$: 241.1314.

*(5S)-1-Methoxycarbonyl-5-formyl-*L*-proline methyl ester* (**7a**). A solution of **6a** (465 mg, 1.93 mmol) in methanol (10 ml) was cooled to −70 °C and treated with a stream of oxygen–ozone until the blue color persisted. The mixture was purged with a stream of argon until colorless and Me_2S (1.0 ml) was added. The mixture was stirred overnight and allowed to attain ambient temperature. After evaporation, the reaction mixture was purified by column chromatography (ethyl acetate–light petroleum 2:1) to give **7a** (380 mg, 92 % yield), ^{1}H NMR (300 MHz): 9.64, 9.64, 9.58, 9.58 (4 s, 1:1:1:1, 1 H), 4.51–4.58 (m, 1 H), 4.40–4.50 (m, 1 H), 3.76, 3.74, 3.71 (3 s, 1:1:2, 6 H), 1.96–2.30 (m, 4 H). $[\alpha]_D^{25} = -95.7°$ (*c* 1.0, MeOH). MS (hr): 186.0764. Calc. for $C_9H_{13}NO_5 - CHO$: 186.0766.

(2S,5S)-Pyrrolidine-2,5-dicarboxylic acid (**7c**). Compound **7a** (284 mg, 1.32 mmol) dissolved in dry dimethylformamide (DMF) was added to a solution of pyridinium dichromate (1.74 g, 4.62 mmol) in dry DMF (5.0 ml) and the mixture was stirred overnight. After addition of water (50 ml), the mixture was acidified with hydrochloric acid and extracted with with diethyl ether (4×20 ml). The ethereal phase was concentrated under reduced pressure to leave crude **7b** (220 mg). A sample of crude **7b** was heated to reflux in 6 M HCl for 6 h and, after evaporation, purified on an ion-exchange column (Dowex 50×8, 200–400 mesh) using 1.3 M NH_3 as the eluant to give **7c**. Spectral data (^{1}H NMR and optical rotation) were in agreement with the reported literature data.[21]

*(2S,4R)-4-*tert*-Butyl(dimethyl)silyloxy-1-methoxycarbonyl-2-(2-methyl-1-propenyl)-pyrrolidine* (**10a**). Vinylation of **8b** (289 mg, 1.0 mmol) according to the general procedure followed by purification by column chromatography (ethyl acetate–light petroleum 1:5) gave **10a** (209 mg) and a mixture of **10a** and **10b** (70 mg) in a total yield of 89 % yield. ^{1}H NMR (300 MHz): 4.94–5.04 (br d, 1 H), 4.52–4.72 (m, 1 H), 4.32–4.40 (m, 1 H), 3.66 (s, 3 H), 3.28–3.53 (m, 2 H), 1.94–2.05 (m, 1 H), 1.63–1.77 (m, 7 H), 0.87 (s, 9 H), 0.06, 0.06 (2 s, 6 H). $[\alpha]_D^{25} = +24.5°$ (*c* 1.0, MeOH). MS (hr): 256.1355. Calc. for $C_{16}H_{31}NO_3Si - C_4H_9$: 256.1369.

(4R)-4-Acetoxy-1-methoxycarbonyl-2-(2-methylpropenyl)-pyrrolidine (**9**). Vinylation of **8a** (215 mg, 0.99 mmol) according to the general procedure gave crude **9** as a 45:55 isomeric mixture. In order to identify the products, **9** was transformed into **10** by treatment with K_2CO_3 (276 mg, 2.0 mmol) in methanol (10 ml). After completion of the reaction as determined by TLC, the mixture was evaporated and the residue filtered through a silica pad using ethyl acetate as the eluant. The filtrate was evaporated and the residue treated with TBDMSCl (226 mg, 1.5 mmol) and imidazole (136 mg, 2.0 mmol) in dry DMF (5.0 ml). After overnight stirring, CH_2Cl_2 (25 ml) was added and the mixture was washed with 1 M aq. HCl (20 ml) and satd. aq. NaCl (3×20 ml). The organic phase was dried over $MgSO_4$ and the products were analyzed by capillary GLC and compared with authentic **10** obtained from **8b**.

*(2S,4R)-4-*tert*-Butyl(dimethyl)silyloxy-2-formyl-1-methoxycarbonylpyrrolidine* (**11a**). Ozonolysis of **10a** (209 mg, 0.67 mmol) was carried out as above. The crude product was purified by column chromatography using ethyl acetate–light petroleum (2:3) as the eluant to give **11a** (171 mg, 89 % yield). ^{1}H NMR (300 MHz): 9.46, 9.47, 9.57, 9.58 (4 s, 1:1:1:1, 1 H), 4.24–4.40 (m, 2 H), 3.70, 3.74 (2 s, 1:1, 3 H), 3.58–3.36 (m, 2 H), 1.90–2.13 (m, 2 H), 0.87 (s, 9 H), 0.07 (s, 6 H). MS (hr): 258.1525. Calc. for $C_{13}H_{25}NO_4Si - CHO$: 258.1525.

trans-*4-Hydroxy-*L*-proline* (**11c**). The procedure described for the transformation of **7a** into **7b** was used starting from **11a** (160 mg, 0.56 mmol) to give crude **11b** (152 mg, 89 % yield). A sample of crude **11b** was heated to reflux in 6 M HCl for 6 h. After evaporation the solid residue was purified on an ion-exchange column (Dowex 50×8, 200–400 mesh) using 1.3 M NH_3 as the eluant to give **11c** which, after recrystallization from ethanol–water, was obtained as

white needles. Spectral data (^{1}H NMR and optical rotation) were in agreement with the reported literature data.[22]

*(2S,3R)-3-*tert*-Butyl(dimethyl)silyloxy-1-methoxycarbonyl-2-(2-methyl-1-propenyl)pyrrolidine* **14a**. Vinylation of **12b** (500 mg, 1.73 mmol) with **4** according to the general procedure gave crude **14a** which was purified by column chromatography using ethyl acetate–light petroleum (7:1) as the eluant. Yield: 424 mg, 78 %. ^{1}H NMR (300 MHz): 4.85, 4.81 (2 s, 1:1, 1 H), 4.19–4.42 (m, 1 H), 3.96 (br s, 1 H), 3.67 (s, 3 H), 3.40–3.62 (m, 2 H), 1.90–2.05 (m, 1 H), 1.69–1.82 (m, 7 H), 0.87 (s, 9 H), 0.06, 0.05 (2 s, 1:1, 6 H). MS (hr): 313.2065. Calc. for $C_{16}H_{31}NO_3Si$: 313.2073. $[\alpha]_D^{25} = -70.6°$ (*c* 1.0, MeOH).

(3R)-3-Acetoxy-1-methoxycarbonyl-2-(2-methyl-1-propenyl)-pyrrolidine (**13**). Vinylation of **12a** (217 mg, 1.0 mmol) according to the general procedure gave crude **13** as a mixture of isomers in the ratio 29:71 (260 mg). In order to identify the products, the crude product was transformed into its TBDMS derivative using the procedure described above. Comparison by GLC with an authentic sample of **14** identified the major isomer as being *trans*.

*(2R,3R)-3-*tert*-Butyl(dimethyl)silyloxy-2-formyl-1-methoxycarbonylpyrrolidine* (**15a**). Ozonolysis of **14a** (370 mg, 1.18 mmol) was carried out as above. The crude product was purified by column chromatography using ethyl acetate–light petroleum ether (2:3) as the eluant to give **15a** (262 mg, 77 %). ^{1}H NMR (300 MHz): 9.50, 9.51, 9.59, 9.60 (4 s, 1:1:1:1, 1 H), 4.43 (br s, 1 H), 4.04, 4.20 (2 br s, 1:1, 1 H), 3.55–3.75 (m, 5 H), 1.82–1.92 (m, 2 H), 0.88 (s, 9 H), 0.10, 0.09 (2 s, 1:1, 6 H). MS (hr): 258.1520. Calc. for $C_{13}H_{25}NO_4Si - CHO$: 258.1525. $[\alpha]_D^{25} = +7.6°$ (*c* 1.0, MeOH).

trans-*3-Hydroxy-*D*-proline* (**15c**). The procedure described for the transformation of **7a** into **7b** was used starting from **15a** (100 mg, 0.35 mmol) to give crude **15b** (95 mg). A sample of crude **15b** was heated to reflux in 6 M HCl for 6 h and evaporated to leave a solid residue. Purification of this on an ion-exchange column (Dowex 50×8, 200–400 mesh) using 1.3 M NH_3 as the eluant gave **15c** which, after recrystallization from ethanol–water, was obtained as white needles. Spectral data (^{1}H NMR and optical rotation) were in agreement with the reported literature data.[23]

(2S,4R)-4-Hydroxy-1-methoxycarbonylproline methyl ester (**16a**). To a solution of *trans*-4-hydroxy-L-proline (13.1 g, 0.10 mol) in 2 M aq. NaOH (50 ml) were added simultaneously methyl chloroformate (7.75 ml, 0.10 mol) and 4 M aqueous KOH (25 ml). After being stirred for 1 h the neutral mixture was reduced to 20 ml under reduced pressure and acidified with hydrochloric acid. After evaporation to dryness, the residue was triturated with ethyl acetate and the organic phase was dried with $MgSO_4$ and evaporated to give crude 4-hydroxy-1-methoxycarbonyl-L-proline (17.8 g, 94 % yield) as a glass. The crude carboxylic acid (5.00 g, 26.44 mmol) was dissolved in methanol (150 ml) and gaseous hydrogen chloride was bubbled through the cooled solution. The saturated mixture was stirred overnight at ambient temperature and evaporated and the crude product was purified by column chromatography with ethyl acetate as the eluant to give **16a** as soft white crystals (4.83 g, 90 % yield). M.p. 49–50 °C. ^{1}H NMR (300 MHz): 4.40–4.55 (m, 2 H), 3.47–3.77 (m, 8 H), 2.21–2.40 (m, 2 H), 2.04–2.13 (m, 1 H). MS (hr): 203.0794. Calc. for $C_8H_{13}NO_5$: 203.0794. $[\alpha]_D^{25} = -95.5°$ (*c* 1.0, MeOH).

(2S,4R)-4-Hydroxy-5-methoxy-1-methoxycarbonylproline methyl ester (**17a**). In a 200 ml water-cooled cell was placed **16a** (3.30 g, 16.24 mmol), methanol (150 ml) and Bu_4NBF_4 (1.5 g, 4.55 mmol). The stirred solution was electrolyzed using a Pt foil anode (12×4 cm) and a Pt wire cathode at a constant current of 500 mA. The electrolysis was interrupted after passage of 2.4 F mol^{-1} and the solution was evaporated leaving an oil which was triturated with diethyl ether. The ether phase was evaporated and **16b** was isolated as a diastereomeric mixture (2.40 g, 63 % yield) after purification by column chromatography using ethyl acetate–light petroleum (4:1) as the eluant. ^{1}H NMR (300 MHz): 4.20–5.20 (m, 3 H), 3.30–3.90 (m, 9 H), 2.15–2.46 (m, 3 H).

(2S,4S)-4-Hydroxy-5-methoxy-1-methoxycarbonylproline methyl ester (**17b**). This compound was prepared by anodic methoxylation of **16b** and isolated as a diastereomeric mixture after column chromatography, using ethyl acetate–light petroleum (3:1) as the eluant in 59 % yield. ^{1}H NMR (300 MHz): 4.06–5.13 (3 H, m), 3.67 (3 H, 2 s), 3.34 (3 H, 2 s), 3.33–3.61 (3 H, m), 2.08–2.42 (3 H, m).

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