Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1973–1980

TETRAHEDRON: *ASYMMETRY*

# Regio- and diastereoselective synthesis of 5-*trans*-substituted and 5,5-disubstituted 2-pyrrolidinones derived from (*S*)-malic acid

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Received 11 April 2002; accepted 19 August 2002

**Abstract**—5-*trans*-Substituted 2-pyrrolidinones **6a**, **6c** and **6d** and 5,5-disubstituted 2-pyrrolidinones **6e–k** were regio- and diastereoselectively formed through the addition of organolithium species to imides **1a**,**b** derived from malic acid, followed by addition of triethylsilane, allyltributyltin or TMSCN to the *N*-acyliminium ions formed in situ from the corresponding 5-hydroxy lactams. A short and diastereoselective synthesis of non-natural amino acid *trans*-4-hydroxy-D-proline is reported. 

## 1. Introduction

Construction of molecules with quaternary stereocenters is a subject of ongoing interest[1,2] and in the domain of nitrogenated compounds few methods are available to prepare compounds containing four different non-hydrogen substituents at the α-nitrogen position of 5- and 6-membered nitrogen heterocycles.[3–5] Recently, we reported on the formation of quaternary stereocenters through the sequential addition of organolithium reagents and allyltributyltin to the carbonyl group of $C_2$-symmetric imides derived from tartaric acid.[6]

Herein, we report the results of the addition of methyl and *n*-butyllithium, in the presence of $CeCl_3$,[7,8] and α-alkoxymethyllithium reagents[9,10] to imides **1a** and **1b** derived from malic acid and the transformation of the resulting 5-hydroxy quaternary lactams **2a–e** and **3a–e** to 5-*trans*-substituted and 5,5-disubstituted 2-pyrrolidinones (Scheme 1). Our results include a short and diastereoselective synthesis of non-natural and amino acid *trans*-4-hydroxy-D-proline from imide **1a** derived from malic acid.[11,12]

## 2. Results and discussion

Imides **1a** and **1b** were readily obtained from (*S*)-malic acid in 74 and 76% yields, respectively, after five steps.[13] In contrast to the addition of organolithium reagents to imides derived from tartaric acid which afforded the corresponding α-hydroxy lactams,[6] the addition of organolithium species to chiral imides **1a** and **1b** led to the isolation of a complex mixture of products. Fortunately, the utilization of *n*-butyllithium and methyllithium in the presence of $CeCl_3$[7,8] promoted the smooth nucleophilic addition to imides **1a** and **1b**. Surprisingly, the addition occurred mainly or exclusively at C-5 as revealed after conversion of 5-hydroxy lactams **2** and **3** to the corresponding lactams **6** and **7**, in contrast to the regiochemistry observed in the addition of Grignard reagents[14] and in the reduction of the corresponding imides derived from malic acid with metallic hydrides where C-2 addition was observed.[15] The formation of lactams **2a–c** and **3a–c** was achieved when imides **1a**,**b** were treated in THF at −78°C with pre-formed organocerium species (prepared after treating a suspension of 2.6 equiv. of anhydrous $CeCl_3$ in THF with 2.0 equiv. of methylithium or *n*-butylithium at −42°C), followed by another 2.0 equiv. of the organolithium reagent (Scheme 1). Without the addition of an extra amount of the organolithium reagent the addition of the organometallic species did not proceed. The addition of triethylsilane, allyltributyltin and trimethylsilyl cyanide to the corresponding *N*-acyliminium ions **4a–c** and **5a–c** formed in situ after treatment of the corresponding 5-hydroxy lactams with $BF_3{\cdot}OEt_2$ resulted in the isolation of 5-*trans*-alkyl substituted 2-pyrrolidinones **6a** and **6c** and 5-alkyl-5-substituted 2-pyrrolidinones **6e–h** as the major isomers (Table 1).

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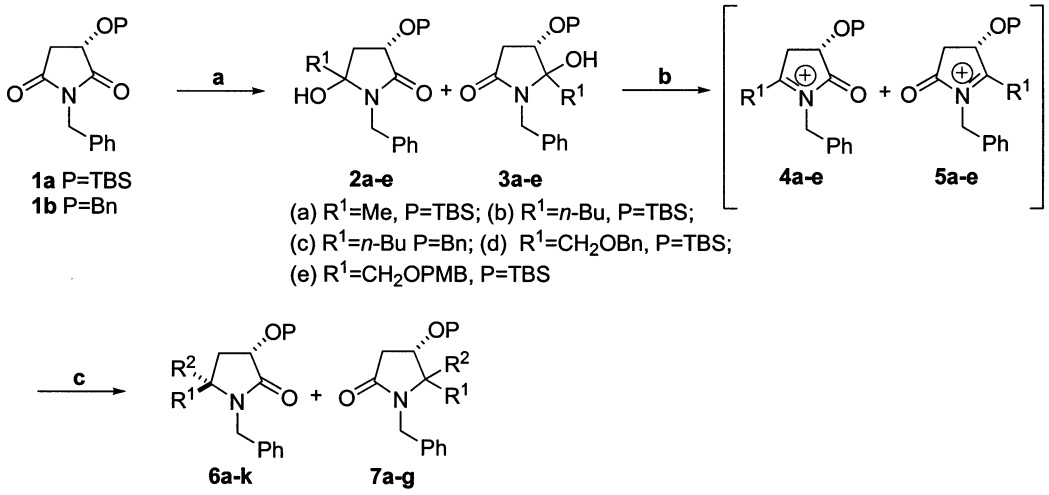
PII: S0957-4166(02)00508-6

The regiochemistry of the addition was determined after the reduction of the mixture of hydroxy lactams **2a–c** and **3a–c** with triethylsilane/$BF_3{\cdot}OEt_2$ and inspection of the corresponding homonuclear correlation spectra ($^1H$–$^1H$ COSY): a correlation between the hydrogen at the newly formed stereogenic center in the major regioisomer and the hydrogens at C-4 unambiguously established the addition at C-5 carbonyl group. The ratio of regioisomers formed was established by $^1H$ NMR and capilliary gas chromatography: a 2.7:1 regioisomeric ratio was assigned to the addition of methyllithium/$CeCl_3$ to **1a** after reduction with triethylsilane/$BF_3{\cdot}OEt_2$ of the corresponding 5-hydroxy lactam (Table 1, entries 1, 5 and 6) while the exclusive formation of **2b** and **2c** was observed as a result of the regioselective butyllithium/$CeCl_3$ addition to the carbonyl group at C-5 of imides **1a** and **1b** (Table 1, entries 2, 3, 7 and 8).

The addition of benzyloxymethyllithium[16] and *p*-methoxybenzyloxymethyllithium[17] to imides **1a** and **1b** was examined next. The reaction of **1a** with *p*-methoxybenzyloxymethyllithium proceeded smoothly and without the need for $CeCl_3$ when DMPU was employed as co-solvent affording a mixture of regioisomeric 5-hydroxy lactams **2e** and **3e** in 80% yield and as a 3:1 mixture of regioisomers, as determined after their reduction with triethylsilane/$BF_3{\cdot}OEt_2$ to the corresponding lactams **6d** and **7b** (Scheme 1). The major regioisomer **6d** (67% d.e.) was isolated after column chromatography and its stereochemistry was established after its conversion to *trans*-4-hydroxy-D-proline as discussed below. The addition of allyltributyltin and TMSCN to *N*-acyliminium ions **4d–e** and **5d–e** led to the isolation of compounds **6i–k** and **7e–g** as 3:1 mixtures of regioisomers. After separation by column chromatography, compounds **6i–k** were obtained as single diastereoisomers. Interestingly, compounds **6d**, **7b** and **6k**, **7g** were isolated as the deprotected primary alcohol due to the loss of the PMB protecting group probably by the action of Lewis acid species present in the reaction medium. The stereochemistry of the major product in each case is depicted in Table 1.




**Scheme 1.** *Reagents and conditions*: (a) $R^1Li$ ($R_1$ = alkyl, 2.0 equiv.), $CeCl_3$ (1.3 equiv.), THF, −78°C, 1 h or $POCH_2Li$ (P = PMB or Bn) (3.0 equiv.), DMPU (8.7 equiv.), THF, −78°C, 1 h; (b) $Et_3SiH$ (4.0 equiv.) or $allylSnBu_3$ (3.0 equiv.) or TMSCN (3.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), $CH_2Cl_2$, −78 to 0°C, 3 h.

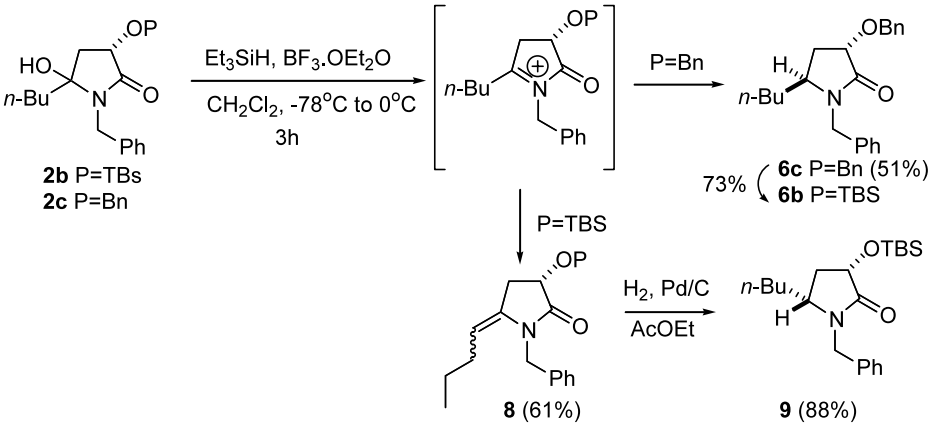
**Table 1.** Addition of triethylsilane, allyltributyltin and TMSCN to 5-hydroxylactams **2a–e**/**3a–e**

| Entry | Major regioisomer | Minor regioisomer | Ratio **6**:**7** | P | $R^1$ | $R^2$ | Yield (%)[a] | d.e. (%)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **6a** | **7a** | 2.7:1 | TBDMS | Me | H | 55 | 40 |
| 2 | **6b** | – | 100:0 | TBDMS | *n*Bu | H | –[c] | – |
| 3 | **6c** | – | 100:0 | Bn | *n*Bu | H | 51 | >95 |
| 4 | **6d** | **7b** | 3:1 | TBDMS | $CH_2OH$ | H | 63 | 67 |
| 5 | **6e** | **7c** | 2.7:1 | TBDMS | Me | Allyl | 53 | 41 |
| 6 | **6f** | **7d** | 2.7:1 | TBDMS | Me | CN | 50 | 64 |
| 7 | **6g** | – | 100:0 | Bn | *n*Bu | Allyl | 55 | 76 |
| 8 | **6h** | – | 100:0 | Bn | *n*Bu | CN | 52 | 87 |
| 9 | **6i** | **7e** | 3:1 | TBDMS | $CH_2OBn$ | Allyl | 64 | >95 |
| 10 | **6j** | **7f** | 3:1 | TBDMS | $CH_2OBn$ | CN | 55 | >95 |
| 11 | **6k** | **7g** | 3:1 | TBDMS | $CH_2OH$ | CN | 68 | >95 |

[a] Yields (**6**+**7**, two steps) are reported after purification of the crude mixture by column chromatography on silica gel.
[b] Diastereoisomeric ratio of the major regioisomer determined by $^1H$ NMR (300 MHz).
[c] Unsaturated lactam **8** isolated in 61% yield after column chromatography as a single stereoisomer (double bond configuration not determined).

We were unable to isolate the product containing the quaternary stereocenter from the addition of nucleophiles to *N*-acyliminium ion **4b** (entry 2). Unsaturated lactam **8** (61% yield) was isolated instead as a single isomer (stereochemistry not determined) as the result of elimination of the labile hydroxyl group of the tertiary hydroxy lactam, under Lewis acid conditions (Scheme 2). Surprisingly, hydrogenation of **8** afforded lactam **9** (88% yield) as a single stereoisomer. The *cis* relationship between the -OTBS group and the *n*-butyl side chain in **9** was established upon comparing its $^{1}H$ and $^{13}C$ NMR spectra with those of **6b**, prepared from **6c** after hydrogenolysis and protection of the secondary hydroxy group with TBDMSCl. NOESY experiments carried out with **6b** and **9** confirmed our assignment: irradiation at H-5 in **9** led to 0.8% increment in the H-3 signal while no increment was observed in the H-3 signal of **6b** upon irradiation of H-5.

5,5-Disubstituted 2-pyrrolidinones **6e–k** and **7c–g** were isolated in 50–68% combined yield from imides **1a** or **1b** and 41–87% diastereoisomeric excess, except for **6i–k** (entries 9–11), which were isolated as single diastereoisomers. NOE experiments (Fig. 1) carried out with the major stereoisomer **6e** and with the major and minor isomers of **6f** suggested the *cis* addition of the nucleophile (allyltributyltin and TMSCN, respectively). Additionally, the stereochemistry of the major product **6g** was unambiguously assigned after its conversion to the corresponding bicyclic derivative **10** (Scheme 3). The same stereochemical outcome was assigned to the major stereoisomers **6h–k** by inference.




**Scheme 2.**

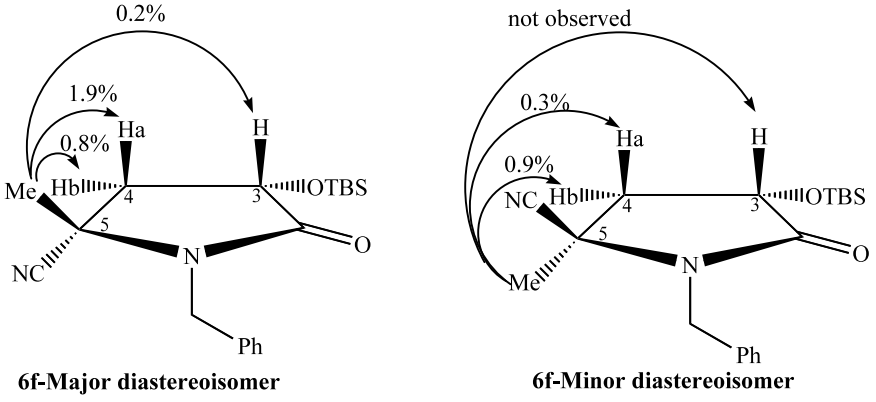
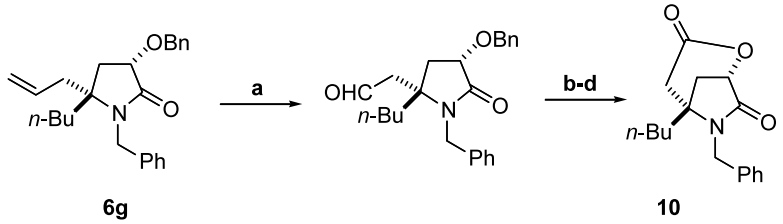



**Figure 1.** Some selected NOE correlations observed in **6f**.




**Scheme 3.** *Reagents and conditions*: (a) i. $O_3/O_2$, MeOH, −78°C, 2 h; ii. DMS, rt, 12 h; (b) $NaClO_2$, $NaH_2PO_4$, *tert*-BuOH, 2-methyl-2-butene, rt, 1 h; (c) Pd/C 10%, $H_2$ (15 bar), AcOEt, rt, 5 h; (d) *p*-TsOH, toluene, reflux, 1.5 h (25% overall yield).

The sense of regiochemistry observed in the addition of alkyllithium/$CeCl_3$ and α-alkoxymethyllithium/DMPU to imides **1a**,**b** derived from malic acid was rather surprising as it contrasts with the preferential addition to the C-2 carbonyl observed in the addition of Grignard reagents[14] and in the reduction of the corresponding imides derived from malic acid with metallic hydrides.[11,12,15] The need for $CeCl_3$ in the reactions involving methyllithium and *n*-butyllithium might be associated with the higher basicity of these organolithium reagents as compared to the corresponding benzyloxymethyl and *p*-methoxybenzyloxymethyl species. The use of organocerium reagents was pioneered by Imamoto and co-workers.[7] Their structure in solution is difficult to establish but it is recognized that they are less basic than the corresponding organolithium or Grignard reagents, adding with high 1,2-regioselectivity to α,β-unsaturated carbonyl compounds.[7,8,18] Additionally, cerium(III) species can coordinate to Lewis basic atoms and the coordination of the organocerium species to the more sterically available and more electron-rich C-5 carbonyl group accounts for the regiochemistry observed (entries 2, 3 and 7, 8, Table 1).

To rigorously establish the stereochemistry of **6d**, we carried out its conversion to the known non-natural amino acid *trans*-4-hydroxy-D-proline, a useful precursor of neuroexcitatory kainoid analogues, which is usually obtained from the expensive *cis*-4-hydroxy-D-proline via Mitsunobu reaction.[19,20] Reduction of the carbonyl group with $BH_3{\cdot}SMe_2$ led to the isolation of prolinol derivative **11** in quantitative yield (Scheme 4), which was submitted to Jones oxidation, followed by the deprotection of the silyl ether and of the *N*-benzyl groups. After chromatographic separation in Dowex cationic exchange resin, *trans*-4-hydroxy-D-proline was obtained in 52% overall yield ($[\alpha]_D$ +42.5 (*c* 1.0, 1N HCl); lit:[21] $[\alpha]_D$ −46.4 (*c* 1.0, 1N HCl) for *trans*-4-hydroxy-L-proline).

We observed that the stereochemical course of the addition of nucleophiles to 5-substituted *N*-acyliminium ions derived from (*S*)-malic acid was preferentially *cis* to the protected alkoxy group at the C3 stereogenic center. Seebach and Renaud[22] have also observed a similar stereochemical behavior in the synthesis of 2,4-*cis*-substituted pyrrolidines.[23] Allylic $A^{1,3}$-interactions involving the substituent α to the nitrogen atom and the *N*-benzyl group may determine the preferential conformation of the phenyl group in the intermediate *N*-acyl iminium ion. In such a scenario the phenyl ring would preferentially be positioned at the opposite side of the 5-membered ring with respect to the oxygenated substituent at C-3, thus directing the *cis* approach of the nucleophile.[24] Such a conformational bias is related to the relay effect invoked by some authors to explain the countersteric sense of addition observed in the alkylation of 5- and 6-membered nitrogen heterocycles bearing a stereogenic center α to the nitrogen atom.[25–28]

## 3. Conclusion

The $BF_3{\cdot}OEt_2$-promoted reduction of 5-hydroxy lactams **2a**–**e** and **3a**–**e**, prepared by the regioselective addition of alkyl lithium/$CeCl_3$ or α-alkoxy methylithium to imides **1a** and **1b**, occurred *cis* to the 3-protected alkoxy group to afford 5-*trans*-substituted 2-pyrrolidinones **6a**–**d** and **7a**–**b** with moderate to good diastereoisomeric excess (44–67%), except for **6c** where a single regio- and diastereoisomer was formed (d.e. >95%).

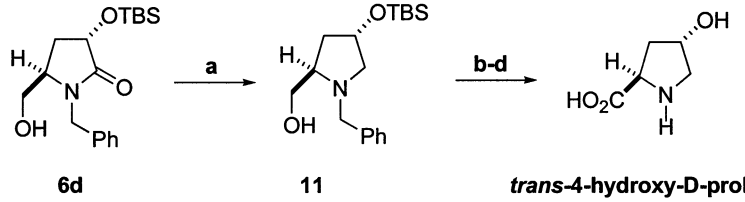
In a similar way, 5,5-disubstituted 2-pyrrolidinones **6e**–**k**, **7c**–**g** were prepared in 50–68% yields after two steps and 41–>95% diastereoisomeric excess employing allyltributyltin and TMSCN as carbon nucleophiles. The relative stereochemistry of the major pyrrolidinones was assigned by $^1H$ NMR spectroscopy (NOE studies) and through the conversion of compound **6g** to the bicyclic derivative **10** and **6d** to *trans*-4-hydroxy-D-proline, which was prepared in six steps and 33% overall yield from the (*S*)-malic acid imide **1a**.

In summary, we have disclosed the unusual stereochemical outcome of the addition of methyl and *n*-butylithium/$CeCl_3$, benzyloxymethyllithium and *p*-methoxybenzyloxymethyllithium to cyclic imides derived from (*S*)-malic acid, which provides a stereoselective access to 3,5-disubstituted- and 3,5,5-trisubstituted pyrrolidine derivatives.

## 4. Experimental

### 4.1. General

All solvents and reagents were purchased from commercial suppliers and used as received, unless otherwise indicated. Imides **1a** and **1b** were synthesized from (*S*)-(−)-malic acid, as indicated in Ref. 12, in 74 and




**6d** **11** ***trans*-4-hydroxy-D-proline**

**Scheme 4.** *Reagents and conditions*: (a) $BH_3{\cdot}SMe_2$, THF, rt, 3 h, quant.; (b) Jones' reagent 2.6 M (2.0 equiv.), 0°C to rt, 1 h; (c) 40% HF/MeCN (1:9), 1 h; (d) $H_2$, $Pd(OH)_2/C$, MeOH, 1 h; Dowex 5W 8×200 (52%, four steps).

76% overall yield, respectively. Commercial solutions of *n*BuLi (2.5 M in hexane) and MeLi (1.0 M in ether) were employed. Tetrahydrofuran (THF) and toluene were distilled from Na-benzophenone ketyl. Dichloromethane and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) were distilled from calcium hydride. Cerium trichloride heptahydrate was dried under reduced pressure (2 mm/Hg) at 120°C for 5 h immediately before use. All reactions were performed under a positive argon pressure. The normal processing of organic extracts consisted of drying over $MgSO_4$, filtration and concentration in a rotary evaporator. $^1H$ and $^{13}C$ NMR data were recorded in $CDCl_3$ (except where indicated otherwise) on Varian Gemini 300, Bruker AC 300P (7.05 T) or Varian Inova (11.7 T). Chemical shifts are reported in ppm ($\delta$ relative to $(CH_3)_4Si$ for $^1H$ and $CDCl_3$ for $^{13}C$ NMR. Coupling constants $J$ are reported in Hz. IR spectra were obtained on Nicolet Impact 410 FT (film and KBr). High resolution mass spectra (HRMS) were measured on a VG Autospec-Micromass spectrometer. Chromatographic separations were performed using 70–230 or 230–400 mesh (E. Merck) silica gel. Thin-layer chromatography was carried out on Macherey–Nagel precoated silica plates (0.25 mm layer thickness). GC analyses were performed with a HP-5890 chromatograph with a HP-5 (30 m×0.53 mm×1.3 μm) column. Optical rotation measures were measured with a Polamat A polarimeter.

### 4.2. Synthesis of 5-*trans*-substituted and 5,5-disubstituted 2-pyrrolidinones

**4.2.1. General procedure for the addition of alkyllithium to imides 1a and 1b in the presence of $CeCl_3$: synthesis of α-hydroxylactams 2a–c and 3a–c**. Anhydrous $CeCl_3$ (1.3 mmol) was cooled to room temperature under an argon atmosphere, THF (2.0 mL) was added and the mixture was maintained under sonication for 30 min to obtain a homogeneous suspension which was cooled to −42°C. A solution of the alkyllithium reagent (1.0 mmol) was added and the color of the suspension immediately changed to pale yellow. The mixture was vigorously stirred for 40 min and cooled to −78°C. A solution of imide **1a** or **1b** (0.50 mmol) in THF (1.0 mL) was added dropwise followed by addition of the alkyllithium (1.0 mmol). After complete consumption of the imide (TLC monitoring), the reaction was quenched with $NH_4Cl$ (1.0 mL) and the mixture was allowed to stir 10 min at rt, when it was diluted with $CHCl_3$ (10 mL), and washed with brine (5.0 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resultant oil was employed in the next step without further purification.

**4.2.2. General procedure for the addition of α-alkoxymethyllithium to imides 1a and 1b: synthesis of α-hydroxylactams 2d–e**. To a solution of *p*-methoxybenzyloxymethyllithium or benzyloxymethyllithium[16] (2.7 mmol) at −78°C, under an argon atmosphere, was added a solution of imide **1a** or **1b** (0.9 mmol) in THF (2.0 mL) and DMPU (7.8 mmol). The mixture was stirred at −78°C for 1 h. After complete consumption of the imide, the reaction was quenched with $NH_4Cl$ (1.0 mL) and the mixture was allowed to stir for 10 min at room temperature, when it was diluted with $CHCl_3$ (10 mL), and washed with brine (5.0 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Purification of the resultant oil by column chromatography on silica gel 230–400 mesh (27% EtOAc/hexane, v/v) afforded the α-hydroxylactams **2d–e** and **3d–e** as colorless crystals (0.70 mmol) in 78% yield, as a mixture of regio- and diastereoisomers.

**4.2.3. $BF_3{\cdot}OEt_2$-mediated reduction of α-hydroxy lactams 2a–e with $Et_3SiH$**. To a solution of hydroxylactams **2a–e**/**3a–e** (0.35 mmol) in $CH_2Cl_2$ (3.5 mL), under an argon atmosphere at −78°C, was added $Et_3SiH$ (0.20 mL, 1.4 mmol) followed by dropwise addition of $BF_3{\cdot}OEt_2$ (80 μL, 0.70 mmol). Stirring was continued for 15 min at −78°C, followed by 3 h at 0°C. The reaction was quenched with $H_2O$ (1.0 mL) and extracted with $CH_2Cl_2$ (2×5.0 mL). The organic phase was washed with brine (5.0 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (25–50% EtOAc/hexane, v/v) afforded pyrrolidinones **6a–d** and **7a–b** (Table 1).

**4.2.3.1. (3*S*,5*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-benzyl-5-methyl-2-pyrrolidinone, 6a**. Colorless oil; 55% yield as a 2.7:1 mixture of regioisomers **6a** (40% d.e.) and **7a** (d.e. not determined). Data for the major isomer **6a**: $^1H$ NMR (300 MHz): $\delta$ 0.20 (s, 3H); 0.22 (s, 3H); 0.95 (s, 9H); 1.15 (d, $J$=6.2, 3H); 1.90 (ddd, $J$=4.4, 7.0 and 13.0, 1H); 2.06 (ddd, $J$=5.5, 7.0 and 13.0, 1H); 3.59 (m, 1H); 3.98 (d, $J$=15.0, 1H); 4.43 (t, $J$=7.0, 1H); 4.99 (d, $J$=15.0, 1H); 7.29 (m, 5H). $^{13}C$ NMR (75.5 MHz): $\delta$ −5.1, −4.5, 18.3, 19.3, 25.7, 37.7, 43.9, 49.6, 70.4, 127.4, 127.9, 128.6, 136.3, 173.4. IR (film, $cm^{-1}$): 3072, 3030, 2968, 2920, 1668, 1442. HRMS $C_{18}H_{29}NO_2Si$ ($M^+$, calcd): 319.19676 ($M^+$, found): 319.19656.

**4.2.3.2. (3*S*,5*S*)-3-Benzyloxy-1-benzyl-5-*n*-butyl-2-pyrrolidinone, 6c**. Colorless oil, 51% yield (single regioisomer and d.e. >95%). $^1H$ NMR (300 MHz): $\delta$ 0.85 (t, $J$=7.0, 3H); 1.19 (m, 4H); 1.64 (m, 2H); 1.98 (ddd, $J$=4.4; 7.7 and 13.2, 1H); 2.08 (ddd, $J$=5.6; 7.7 and 13.2, 1H); 3.48 (m, 1H); 3.95 (d, $J$=15.0, 1H); 4.21 (t, $J$=7.7, 1H); 4.77 (d, $J$=12.0, 1H); 5.02 (d, $J$=15.0, 1H); 5.04 (d, $J$=12.0, 1H); 7.31 (m, 10H). $^{13}C$ NMR (75.5 MHz): $\delta$ 13.9, 22.5, 26.6, 32.3, 32.6, 44.0, 54.2, 72.0, 75.3, 127.5, 127.7, 127.9, 128.1, 128.4, 128.7, 136.1, 138.0, 172.9. IR (film, $cm^{-1}$): 3077, 3030, 2940, 2864, 1695. HRMS $C_{22}H_{27}NO_2$ ($M^+$–$C_7H_7$, calcd): 246.14940 ($M^+$–$C_7H_7$, found): 246.15358.

**4.2.3.3. (3*S*,5*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-benzyl-5-hydroxymethyl-2-pyrrolidinone, 6d**. Colorless oil, 63% yield as a 3:1 mixture of regioisomers **6d** (67% d.e.)and **7b** (d.e. not determined). Major isomer **6d** was isolated by column chromatography on silica gel (40% EtOAc/hexane, v/v). $^1H$ NMR (300 MHz, $C_6D_6$): $\delta$ 0.41 (s, 3H); 0.52 (s, 3H); 1.17 (s, 9H); 1.85 (m, 1H); 2.29 (m, 1H); 3.12 (m, 3H); 3.65 (dd, $J$=2.2 and 12.1,

1H); 4.03 (d, $J=15.0$, 1H); 4.88 (t, $J=7.7$, 1H); 5.20 (d, $J=15.0$, 1H); 7.19 (m, 5H). $^{13}$C NMR (125.7 MHz): $\delta$ −5.1, −4.5, 18.3, 25.8, 33.2, 44.8, 55.9, 61.7, 70.5, 127.7; 128.0; 128.8; 136.3; 174.8. IR (film, cm$^{-1}$): 3408 (broad), 3030, 2960, 2929, 2856, 1693. HRMS $C_{18}H_{29}NO_3Si$ ($M^+-C_4H_9$, calcd): 278.12125 (found, $M^+-C_4H_9$): 278.12122. $[\alpha]_D$ −143.6 (*c* 3.6, EtOAc).

**4.2.4. General procedure for the synthesis of 5,5-disubstituted pyrrolidinones 6e–k and 7c–g**. To a solution of α-hydroxylactam **2a**–**e** and **3a**–**e** (0.50 mmol) in $CH_2Cl_2$ (5.0 mL), under an argon atmosphere at −78°C, was added allyltributyltin (0.46 mL, 1.5 mmol) or TMSCN (0.20 mL, 1.5 mmol) followed by $BF_3{\cdot}OEt_2$ (0.13 mL, 1.0 mmol) dropwise. Stirring was continued for 15 min at −78°C, followed by 3 h at 0°C. The reaction was quenched with a 10% aq. KF solution (2.0 mL) and allowed to stir for 1 h at room temperature. The mixture was diluted with $CH_2Cl_2$ (10 mL) and washed with brine (5.0 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (30–50% EtOAc/hexane, v/v) afforded 5,5-disubstituted pyrrolidinones **6e**–**k** and **7c**–**g** (Table 1).

**4.2.4.1. (3*S*,5*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-benzyl-5-allyl-5-methyl-2-pyrrolidinone, 6e**. Colorless oil, 53% yield as a 2.7:1 mixture of regioisomers **6e** (41% d.e.) and **7c** (d.e. not determined). Major isomer **6e** was isolated by column chromatography on silica gel (30% EtOAc/hexane, v/v). $^1$H NMR (500 MHz): $\delta$ 0.18 (s, 3H); 0.22 (s, 3H); 0.95 (s, 9H); 1.01 (s, 3H); 1.97 (dd, $J=7.8$ and 12.9, 1H); 2.01 (dd, $J=6.8$ and 12.9, 1H); 2.29 (m, 2H); 4.37 (d, $J=15.4$, 1H); 4.42 (dd, $J=6.8$ and 7.8, 1H); 4.52 (d, $J=15.4$, 1H); 5.07 (ddd, $J=1.5$; 2.0 and 17.2, 1H); 5.10 (ddd, $J=1.5$; 2.0 and 10.1, 1H); 5.66 (m, 1H); 7.30 (m, 5H). $^{13}$C NMR (75.5 MHz): $\delta$ −5.1, −4.4, 18.3, 25.4, 25.8, 41.6, 43.1, 44.9, 60.7, 70.1, 119.2, 127.1, 127.9, 128.4, 132.7, 138.5, 173.7. IR (film, cm$^{-1}$): 3076, 3028, 2930, 2854, 1699. HRMS $C_{21}H_{33}NO_2Si$ ($M^+-C_4H_9$, calcd): 302.15763 ($M^+-C_4H_9$, found): 302.15765. $[\alpha]_D$ −25.9 (*c* 1.5, $CHCl_3$).

**4.2.4.2. (3*S*,5*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-benzyl-5-cyano-5-methyl-2-pyrrolidinone, 6f**. Colorless solid, 50% yield as a 2.7:1 mixture of regioisomers **6f** (64% d.e.) and **7d** (d.e. not determined). Major isomer **6f** was isolated by column chromatography on silica gel (40% EtOAc/hexane, v/v). Mp 70–71°C. $^1$H NMR (500 MHz): $\delta$ 0.11 (s, 3H); 0.15 (s, 3H); 0.85 (s, 9H); 1.43 (s, 3H); 1.92 (dd, $J=8.3$ and 12.9, 1H); 2.74 (dd, $J=7.8$ and 12.9, 1H); 4.30 (d, $J=15.4$, 1H); 4.43 (dd, $J=7.8$ and 8.3, 1H); 4.67 (d, $J=15.4$, 1H); 7.24 (m, 5H). $^{13}$C NMR (75.5 MHz): $\delta$ −5.5, −5.3, 18.2, 25.6, 26.1, 43.0, 44.7, 54.3, 69.1, 119.6, 127.9, 128.1, 128.7, 136.3, 173.3. IR (film, cm$^{-1}$): 3032, 2929, 2856, 2233, 1716. HRMS $C_{19}H_{28}N_2O_2Si$ ($M^+-C_4H_9$, calcd): 287.12158 ($M^+-C_4H_9$, found): 287.12152. $[\alpha]_D$ −51.1 (*c* 1.8, $CH_2Cl_2$).

**4.2.4.3. (3*S*,5*R*)-3-Benzyloxy-1-benzyl-5-allyl-5-*n*-butyl-2-pyrrolidinone, 6g**. Colorless oil, 55% yield, single regioisomer (76% d.e.). Data for the major isomer **6g**: $^1$H NMR (300 MHz): $\delta$ 0.90 (t, $J=7.1$, 3H); 1.11 (m, 4H); 1.49 (m, 1H); 1.78 (m, 1H); 2.56 (dd, $J=7.3$ and 14.2, 1H); 2.73 (m, 2H); 2.90 (dd, $J=7.8$ and 16.8, 1H); 4.18 (t, $J=7.3$, 1H); 4.37 (d, $J=15.4$, 1H); 4.64 (d, $J=11.7$, 1H); 4.82 (d, $J=11.7$, 1H); 4.85 (d, $J=15.4$, 1H); 5.19 (dd, $J=1.5$ and 17.1, 1H); 5.22 (d, $J=10.2$, 1H); 6.00 (m, 1H); 7.40 (m, 10H). $^{13}$C NMR (75.5 MHz): $\delta$ 13.8, 22.9, 25.6, 36.9, 38.2, 38.3, 43.5, 69.7, 71.5, 77.0, 119.0, 127.1, 127.5, 127.8, 128.0, 128.3, 128.4, 133.7, 137.6, 138.4; 173.2. IR (film, cm$^{-1}$): 3064, 3030, 2954, 2870, 1693. HRMS $C_{25}H_{31}NO_2$ ($M^+$+1, calcd): 378.24330 ($M^+$+1, found): 378.24335.

**4.2.4.4. (3*S*,5*S*)-3-Benzyloxy-1-benzyl-5-cyano-5-*n*-butyl-2-pyrrolidinone, 6h**. Colorless oil, 52% yield as a single regioisomer (87% d.e.). Data for the major isomer **6h**: $^1$H NMR (300 MHz): $\delta$ 0.81 (t, $J=7.0$, 3H); 1.12–1.69 (m, 5H); 1.92 (m, 1H); 2.06 (dd, $J=8.4$ and 13.5, 1H); 2.75 (dd, $J=8.1$ and 13.5, 1H); 4.35 (dd, $J=8.1$ and 8.4, 1H); 4.38 (d, $J=15.4$, 1H); 4.79 (d, $J=15.4$, 1H); 4.83 (d, $J=11.7$, 1H); 5.11 (d, $J=11.7$, 1H); 7.40 (m, 10H). $^{13}$C NMR (75.5 MHz): $\delta$ 13.5, 22.1, 25.5, 37.9, 37.9, 44.9, 58.9, 72.7, 73.3, 119.1, 127.9, 127.9, 128.0, 128.1, 128.5, 128.7, 136.2, 137.1, 173.1. IR (film, cm$^{-1}$): 3062, 3030, 2956, 2931, 2871, 1716. HRMS $C_{23}H_{26}N_2O_2$ ($M^+-C_7H_7$, calcd): 271.14465 ($M^+-C_7H_7$, found): 271.14462.

**4.2.4.5. (3*S*,5*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-benzyl-5-allyl-5-benzyloxymethyl-2-pyrrolidinone, 6i**. Colorless oil, 64% yield as a 3:1 mixture of regioisomers **6i** (>95% d.e.) and **7e** (d.e. not determined). Data for **6i**: $^1$H NMR (300 MHz): $\delta$ 0.07 (s, 3H); 0.10 (s, 3H); 0.85 (s, 9H); 1.25 (m, 2H) 2.25 (m, 2H); 2.95 (d, $J=9.5$, 1H); 3.09 (d, $J=9.5$, 1H); 3.92 (d, $J=11.7$, 1H); 4.03 (d, $J=11.7$, 1H); 4.12 (d, $J=15.4$, 1H); 4.57 (t, $J=8.1$, 1H); 4.69 (d, $J=15.4$, 1H); 5.06 (m, 2H); 5.56 (m, 1H); 7.19 (m, 10H). $^{13}$C NMR (75.5 MHz): $\delta$ −5.2, −4.6, 17.4, 25.8, 27.7, 38.9, 43.2, 63.2, 70.0, 72.7, 73.6, 119.7, 127.2, 127.6, 128.0, 128.1, 128.3, 128.4, 131.8, 137.9, 138.5, 175.1. IR (film, cm$^{-1}$): 3064, 3030, 2954, 2930, 2856, 1699, 1651. HRMS $C_{28}H_{39}NO_3Si$ ($M^+-C_4H_9$, calcd): 408.19950; (found, $M^+-C_4H_9$): 408.19944.

**4.2.4.6. (3*S*,5*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-benzyl-5-cyano-5-benzyloxymethyl-2-pyrrolidinone, 6j**. Colorless oil, 55% yield as a 3:1 mixture of regioisomers **6j** (>95% d.e.) and **7f** (d.e. not determined). Data for **6j**: $^1$H NMR (300 MHz): $\delta$ 0.20 (s, 3H); 0.23 (s, 3H); 0.94 (s, 9H); 2.21 (dd, $J=7.7$ and 13.2, 1H); 2.72 (dd, $J=7.7$ and 13.2, 1H); 3.43 (s, 2H); 4.29 (d, $J=12.1$, 1H); 4.32 (d, $J=12.1$, 1H); 4.40 (d, $J=15.4$, 1H); 4.52 (t, $J=7.7$, 1H); 4.81 (d, $J=15.4$, 1H); 7.29 (m, 10H). $^{13}$C NMR (75.5 MHz): $\delta$ −5.2, −4.5, 18.2, 25.7, 38.2, 45.5, 58.5, 68.8, 72.1, 73.5, 118.1, 127.8, 127.9, 128.1, 128.5, 128.5, 128.5, 136.4, 136.4, 173.6. IR (film, cm$^{-1}$): 3061, 3031, 2952, 2927, 2856, 1724. HRMS $C_{26}H_{34}N_2O_3Si$ ($M^+-C_4H_9$, calcd): 393.16345; found ($M^+-C_4H_9$): 393.16344.

**4.2.4.7. (3*S*,5*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-benzyl-5-cyano-5-hydroxymethyl-2-pyrrolidinone, 6k**. Colorless oil, 68% yield as a 3:1 mixture of regioisomers **6k** (>95% d.e.) and **7g** (d.e. not determined). Data for **6k**: $^1$H NMR (300 MHz): $\delta$ 0.20 (s, 3H); 0.23 (s, 3H); 0.94

(s, 9H); 1.71 (t, $J=7.0$, 1H); 2.31 (dd, $J=7.7$ and 13.5, 1H); 2.67 (dd, $J=7.7$ and 13.5, 1H); 3.56 (dd, $J=7.0$ and 12.1, 1H); 3.70 (dd, $J=5.9$ and 12.1, 1H); 4.20 (d, $J=15.4$, 1H); 4.52 (t, $J=7.7$, 1H); 4.99 (d, $J=15.4$, 1H); 7.35 (m, 5H). $^{13}$C NMR (75.5 MHz): $\delta$ −5.2, −4.5, 18.2, 25.7, 37.0, 45.3, 60.1, 64.3, 68.7, 117.8, 128.0, 128.4, 129.2, 136.4, 173.8. IR (film, cm$^{-1}$): 3419 (broad); 2954, 2931, 2856, 1714. HRMS $C_{19}H_{28}N_2O_3Si$ ($M^+$–$C_4H_9$, calcd): 303.11649 (found, $M^+$–$C_4H_9$): 303.11641.

**4.2.4.8. (*S*)-5-Butyliden-3-[-(*tert*-butyldimethylsilyl)-oxy]-1-benzyl-2-pyrrolidinone, 8**. Colorless oil, 61% yield. $^1$H NMR (300 MHz): $\delta$ 0.12 (s, 3H), 0.13 (s, 3H), 0.73 (t, $J=7.3$, 3H), 0.87 (s, 9H), 1.22 (dd, $J=7.3$ and 14.6, 2H), 1.84 (dd, $J=7.3$ and 14.6, 2H), 2.41 (ddt, $J=1.2$, 5.9 and 16.1, 1H), 2.94 (dd, $J=8.8$ and 16.1, 1H), 4.43 (dd, $J=5.9$ and 8.8, 1H), 4.54 (d, $J=15.4$, 1H), 4.56 (m, 1H), 4.61 (d, $J=15.4$, 1H), 7.13–7.24 (m, 5H). $^{13}$C NMR (75.5 MHz): $\delta$ −5.1, −4.8, 13.5, 18.3, 23.2, 25.8, 28.8, 32.8, 43.7, 69.3, 103.0, 115.0, 127.2, 128.5, 136.1, 174.1. IR (film, cm$^{-1}$): 2960, 2929, 2856, 1714, 1682. HRMS $C_{21}H_{33}NO_2Si$ ($M^+$–$C_4H_9$, calcd): 302.15763 (found, $M^+$–$C_4H_9$): 302.15759.

### 4.3. Synthesis of (3*S*,5*R*)-3-[*tert*-butyldimethylsilyl)-oxy]-1-benzyl-5-*n*-butyl-2-pyrrolidinone, 9

To a solution of **8** (0.050 g, 0.10 mmol) in ethyl acetate (2.0 mL) was added 10% Pd/C (10 mg) and the mixture was stirred under hydrogen (1 atm) for 3 h at rt. The mixture was filtered over a pad of Celite, the solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford **9** (0.040 g, 0.088 mmol) in 88% yield. Colorless oil. $^1$H NMR (300 MHz): $\delta$ 0.17 (s, 3H), 0.20 (s, 3H), 0.86 (t, $J=7.1$, 3H), 0.93 (s, 9H), 1.24 (m, 4H), 1.59 (m, 1H), 1.78 (m, 2H), 2.48 (m, 1H), 3.25 (m, 1H), 4.00 (d, $J=14.9$, 1H), 4.31 (t, $J=8.0$, 1H), 4.97 (d, $J=14.9$, 1H), 7.30 (m, 5H). $^{13}$C NMR (75.5 MHz): $\delta$ −5.1, −4.5, 13.9, 18.3, 22.6, 25.8, 26.5, 32.8, 35.2, 44.1, 53.3, 70.8, 127.4, 128.0, 128.6, 136.7, 173.8. IR (film, cm$^{-1}$): 3030, 2966, 2929, 2856, 1705, 1252. HRMS $C_{21}H_{35}NO_2Si$ ($M^+$–$C_4H_9$, calcd): 304.17328 (found, $M^+$–$C_4H_9$): 304.17303.

### 4.4. Synthesis of (1*S*,5*S*)-5-*n*-butyl-6-benzyl-2-oxa-6-azabicyclo-[3.2.1]octan-3,7-dione, 10

A solution of **6g** (58 mg, 0.10 mmol, 76% d.e.) in MeOH (3.0 mL) was treated with $O_3/O_2$ stream at −78°C for 2 h. After argon purging, methyl sulfide (0.2 mL) was added to the colorless solution, stirred overnight and evaporated to give an oil. The crude mixture was diluted with *tert*-BuOH (0.40 mL) and 0.1 mL (0.10 mmol) of 2-methyl-2-butene was added at 0°C. A solution containing $NaClO_2$ (35 mg, 0.40 mmol) and $NaH_2PO_4$ (0.10 g, 0.80 mmol) in water (0.30 mL) was added dropwise. The mixture was vigorously stirred for 1 h at room temperature. After the total consumption of the reagent, $NaHSO_3$ (30 mg) was added and the stirring was continued for 30 min. Chloroform was added (3.0 mL) and the aqueous phase was extracted three times with $CHCl_3$ (2.0 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude oil was dissolved in 2.0 mL of EtOAc, 25 mg of 10% Pd/C was added and a hydrogen atmosphere (15 bar) was admitted into the system, maintaining the mixture under magnetic stirring at room temperature for 5 h. The crude mixture was filtered on Celite™ and the solvent was evaporated under reduced pressure. The crude oil was dissolved in toluene (2.0 mL), transferred to a sealed flask and 5.0 mg of *p*-toluenesulphonic acid was added. The flask was heated to 110°C for 1.5 h. The mixture was cooled to rt and the solvent was removed under reduced pressure. Purification of the crude oil by column chromatography on silica gel (50% EtOAc/hexane, v/v) afforded bicyclic compound **10** as a colorless oil (11 mg) in 25% overall yield. $^1$H NMR (500 MHz): $\delta$ 0.75 (t, $J=7.0$, 3H); 0.98 (m, 4H); 1.57 (m, 1H); 1.77 (m, 1H); 2.33 (d, $J=18.3$, 1H); 2.55 (d, $J=18.3$, 1H); 2.73 (dd, $J=2.5$ and 4.8, 2H); 4.19 (d, $J=15.4$, 1H); 4.61 (d, $J=15.4$, 1H); 4.71 (dd, $J=2.5$ and 4.8, 1H); 7.23 (m, 5H). $^{13}$C NMR (125.5 MHz): $\delta$ 13.7, 22.5, 25.7, 35.7, 36.9, 38.5, 43.5, 70.1, 80.1, 127.8, 128.0, 128.8, 136.9, 171.8, 173.3. IR (film, cm$^{-1}$): 2956, 2929, 2872, 1788, 1699. HRMS $C_{17}H_{21}NO_3$ ($M^+$, calcd): 287.15214 (found, $M^+$): 287.15266. $[\alpha]_D$ +33.3 (*c* 0.2, $CHCl_3$).

### 4.5. Synthesis of *trans*-4-hydroxy-D-proline

To a solution of **6d** (35 mg, 0.10 mmol) in THF (1 mL) under an argon atmosphere at 0°C, was added dropwise a solution of $BH_3{\cdot}SMe_2$ complex (10 M, 0.1 mL, 1.0 mmol). The mixture was stirred at rt for 3 h, MeOH (0.50 mL) was added and the mixture was stirred for 10 min. The solvent was removed under reduced pressure and then treatment with methanol was repeated twice. Purification of the crude oil by column chromatography on silica gel (8% EtOAc/hexane, v/v) afforded (2*R*,4*S*) - 4 - [(*tert* - butyldimethylsilyl)oxy] - 2 - hydroxymethyl-1-benzyl-pyrrolidine, **11** as a colorless oil (33 mg, 98%). $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ −0.02 (s, 3H); −0.01 (s, 3H); 0.91 (s, 9H); 1.58 (m, 1H) 2.20 (s, br, 1H); 2.60 (m, 1H); 2.87 (dd, $J=5.6$ and 11.0, 1H); 3.27 (m, 1H); 3.42 (dd, $J=6.1$ and 11.0, 1H); 3.84 (dd, $J=2.9$ and 12.7, 1H); 3.97 (dd, $J=6.1$ and 12.7, 1H); 4.13 (s, 2H); 4.61 (m, 1H); 7.23 (m, 5H). $^{13}$C NMR (125.7 MHz): $\delta$ −5.3, −5.2, 17.7, 25.5, 35.4, 60.4, 65.3, 65.7, 67.8, 68.6, 127.7, 128.6, 133.0, 131.3. IR (film, cm$^{-1}$): 3501 (broad), 2952, 2924, 2859, 1471. HRMS $C_{18}H_{31}NO_2Si$ ($M^+$–$C_4H_9$, calcd): 321.21241 (found, $M^+$–$C_4H_9$): 321.21240.

To a solution of **11** (50 mg, 0.20 mmol) in acetone (2.0 mL) at 0°C was added a solution of Jones reagent dropwise (2.6 M, 0.20 mL, 0.40 mmol). The mixture was vigorously stirred at rt for 1 h and then $^i$PrOH (0.5 mL) was added. Stirring was continued for 30 min, the organic phase was separated and the aqueous phase was extracted with dichloromethane (3×2.0 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was dissolved in MeCN (1.0 mL) and five drops of a

40% aqueous HF solution were added dropwise. The mixture was stirred for 2 h at rt and the solvent was removed under reduced pressure. The crude residue was dissolved in MeOH (1.0 mL), 10% $Pd(OH)_2/C$ (5 mg) was added, a hydrogen atmosphere (2 bar) was admitted into the system and the mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the amino acid was purified in Dowex 50W×8 resin (200–400 mesh) employing a mixture of $H_2O$/MeOH/$NH_4OH$ (1:1:1, v/v/v) as eluent.

*trans-4-Hydroxy-D-proline* (11 mg, 52% overall yield, four steps) as a white solid (mp >250°C, decomp.). $^1$H NMR ($D_2O$, 300 MHz): $\delta$ 2.15 (ddd, $J$=4.4, 10.2 and 14.6, 1H); 2.43 (ddt, $J$=1.8, 8.0 and 14.6, 1H); 3.35 (d, br, $J$=12.8, 1H); 3.47 (dd, $J$=3.7 and 12.8, 1H); 4.34 (dd, $J$=8.0 and 10.2, 1H); 4.67 (m, 1H). $^{13}$C NMR (125.5 MHz): $\delta$ 37.1, 52.6, 59.5, 69.7, 173.9. IR (film, $cm^{-1}$): 3224 (broad); 2808, 1732, 1402. $[\alpha]_D$ +42.5 (*c* 1.00, 1N HCl); (lit.:[21] $[\alpha]_D$ −46.4, *c* 1.0; 1N HCl, *trans*-4-hydroxy-L-proline).

## Acknowledgements

The authors thank FINEP for financial support and FAPESP and CNPq for fellowships.

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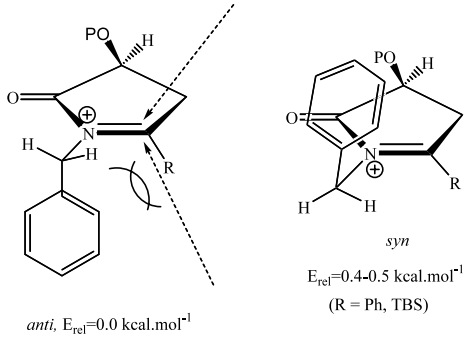


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