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Asymmetric synthesis of 5-substituted pyrrolidinones via a chiral *N*-acyliminium equivalent

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Abstract—5-Substituted pyrrolidinones **5** were synthesized in good yields and with fair to good diastereoselectivities from the chiral non-racemic oxazolopyrrolidinone **4**. Various nucleophiles including cuprates, silanes and phosphites were used. The chiral induction is thought to arise from a chelated *N*-acyliminium species. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The pyrrolidine ring system is a very important structure common to many naturally occurring and medicinally important compounds.[1] It can also be used as a chiral auxiliary,[2] synthetic intermediate[3] and as a component of chiral ligands[4] in synthesis. It thus seemed pertinent to develop new asymmetric methods to construct differently substituted pyrrolidines. In this respect we have previously proposed the use of the lactam **1** and its derivatives **2** and **3** as chiral precursors for the asymmetric synthesis of various polysubstituted pyrrolidines and pyrrolidinones (Fig. 1).[6–9] Thus, 3-alkylated pyrrolidinones have been obtained with excellent diastereoselectivity by the alkylation of **1**[5] or its saturated homologue **2**.[6] Lactam **1** is also a precursor of the chiral silyloxypyrrole **3** which permits substitution at C(5) through aldol-type condensation with achiral aldehydes[7] and imines.[8] Furthermore, 1,4-addition of cuprates to these aldol adducts afforded 4,5-disubstituted pyrrolidinones with an excellent diastereoselectivity.[9]

Since the methodology using silyloxypyrrole **3** is limited to carbonyl compounds as the electrophile, we thought it might be possible to increase the range of substituents that could be introduced at C(5) by use of the oxazolopyrrolidinone **4**, easily accessible from lactam **1** (vide infra). Compound **4** has been previously described by Meyers et al.,[10] who reported the nucleophilic addition of allylsilane to this compound as the unique example of such an addition.[10b] We embarked on the study of the reaction of various nucleophiles with **4**[11] with the aim of extending the synthetic applications of lactam **1**.

Numerous examples of nucleophilic addition to chiral *N*-acyliminium species derived from pyrrolidines have been described. In most cases, the precursors used were pyroglutamic acid[12] or hydroxyproline,[13] leading to the formation of disubstituted pyrrolidines via endocyclic chiral induction. On the other hand, examples of asymmetric synthesis of mono-substituted pyrrolidines or pyrrolidinones by nucleophilic attack on a chiral *N*-acyliminium are rarer.[10,14] It must be mentioned that,

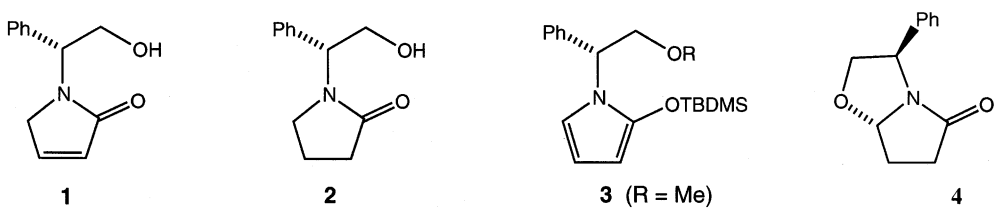

Figure 1.

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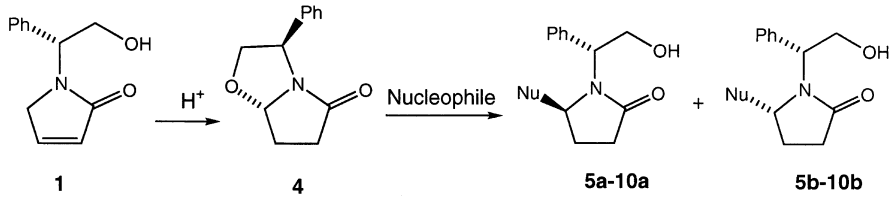
based on the examples found in the literature, the diastereoselectivity of addition can be opposite depending on the use of π or σ nucleophiles.[12c]

2. Results and discussion

The bicyclic lactam **4** was synthesized by acidic treatment of the chiral lactam **1** (prepared in one step from (*R*)-(−)-phenylglycinol in 75% yield).[5] Several procedures were successfully applied (i.e. PTSA or HCl–H_2O–CH_2Cl_2), of which the best involved the treatment of lactam **1** in CH_2Cl_2 solution with Amberlyst-15 at rt for 3 h, affording **4** in quantitative yield. The diastereoselectivity of the cyclization is total and the newly formed stereogenic center has the same configuration as that previously reported by Meyers et al.[10a] (Scheme 1).



Scheme 1.

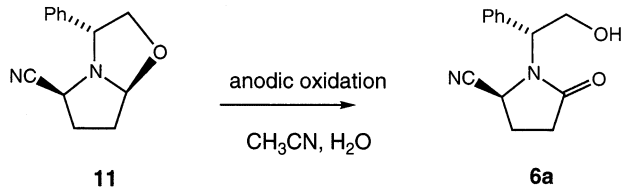
We first reproduced the reported[10b] addition of allylsilane to **4** in the presence of titanium tetrachloride in dichloromethane at room temperature. Using the same conditions, trimethylsilylcyanide and trimethylphosphite were found to add to oxazolidine **4** to give α-cyano and α-phosphono pyrrolidinones **6** and **7** with good diastereoselectivity and yield (Table 1).

Table 1. Addition of nucleophiles to **4** in CH_2Cl_2 and in the presence of 1 equiv. of $TiCl_4$

Nucleophile	Product	Yield (%)	de[a]
Allylsilane	**5**	83	74[b]
TMSCN	**6**	89	80
$P(OMe)_3$	**7**	86	62

[a] Determined by ^1H NMR analysis of the crude reaction mixture.
[b] The same experiment was reported with 92% yield and 80% de.[10b]

In each case the mixtures could be easily separated by simple flash chromatography. The relative configuration of the major isomer of these new pyrrolidinone derivatives corresponds to that depicted in Fig. 2. Lactam **5a**[10b] is a known compound. Chemical correlation was required to establish the configuration of **6a**. Indeed **6a** was found to be identical to the cyano-lactam obtained by anodic oxidation of cyano-oxazolidine **11** (Scheme 2).[15] The relative configuration of the latter was deduced from NOE experiments.



Scheme 2.

For the phosphonate **7a**, the configuration of the newly created stereogenic center was established by X-ray crystallographic analysis (Fig. 3).

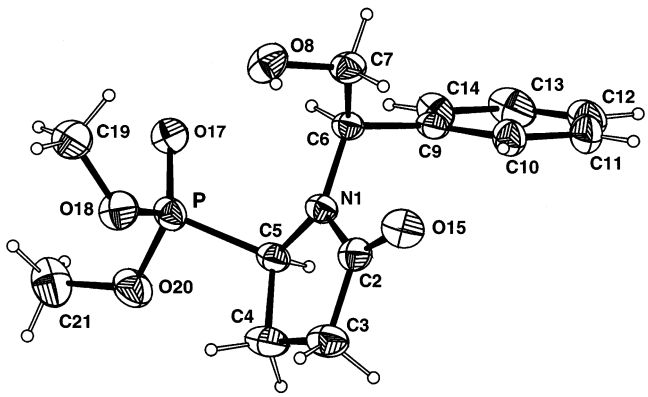


Figure 3.

Alkyl chains may be introduced onto acyliminium derivatives through lower order cuprates complexed with $BF_3{\cdot}OEt_2$ (Scheme 3).[12c] In our case, the best results were obtained in THF with cuprates generated from $CuBr{\cdot}Me_2S$, at rt. Simple alkyl groups (Me, Bu) were easily introduced in good yield and selectivity (Table 2) through cuprate addition in THF at −78°C followed by stirring at rt for 12 h. The phenyl group

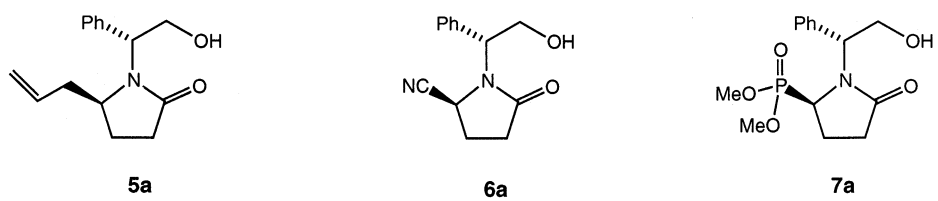
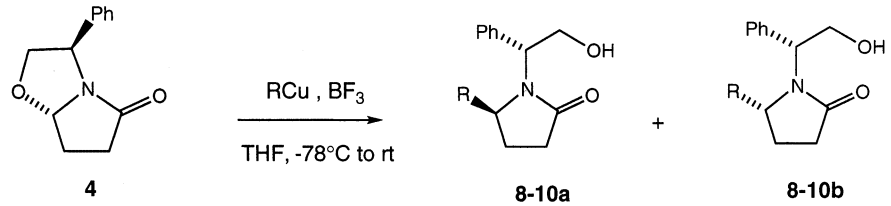


Figure 2.



Scheme 3.

Table 2. Addition of organocuprates to **4** in the presence of $BF_3{\cdot}OEt_2$

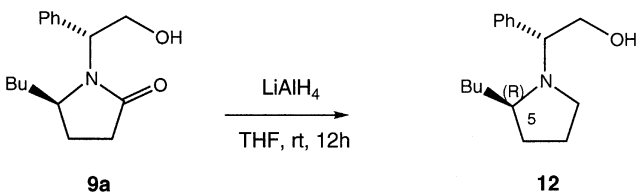
Nucleophile	Solvent	Product	Yield (%)	de[a]
MeCu	THF	**8**	85	76
*n*BuCu	THF	**9**	95	74
*n*BuCu	Et_2O	**9**	38	–
PhCu	THF	**10**	32	75

[a] Determined by ^1H NMR analysis of the crude reaction mixture.

was added with good stereoselectivity but in poor yield using this method (Table 2).

The use of higher order cuprates formed from CuCN and complexed to $BF_3{\cdot}OEt_2$ dramatically decreased the yield of the reaction and no reaction occurred when CuI was used to form the organometallic species. Furthermore, slightly lower yields and/or selectivities were observed at 0°C or if ether was used instead of THF as solvent. The variations in diastereoselectivity as a function of experimental conditions have not yet been thoroughly studied.

It was important to determine the configuration of the new stereogenic center obtained using this type of nucleophile. This was done by chemical transformation of the butyl pyrrolidinone **9a**. The comparison of spectroscopic data for pyrrolidine **12** obtained by $LiAlH_4$ reduction of pyrrolidinone **9a** (Scheme 4) with those of the known compound[16] obtained from (*R*)-(−)-phenylglycinol permitted assignment of the configuration of the newly formed stereocenter of **9a** as (5*R*).



Scheme 4.

In summary, we have shown a new reactivity of lactam **1**, which through oxazolidine **4**, permits diastereoselective substitution at C(5) of the pyrrolidin-2-one ring. It is noteworthy that both σ and π nucleophiles under different experimental conditions underwent nucleophilic approach on the same face of the pyrrolidine. The mechanism of the reaction may involve acyliminium intermediate **I** (Fig. 4) arising from **4** under Lewis acid conditions or an S_N2-like reaction through partial opening of the oxazolidine ring.[10c]

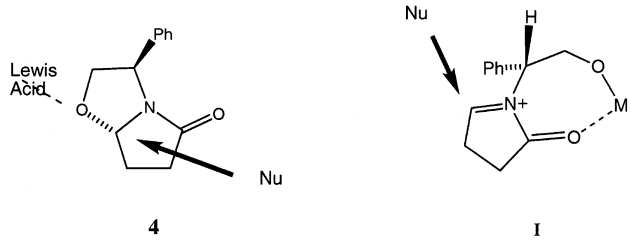


Figure 4.

3. Experimental

All starting materials were commercially available and purified following standard techniques. THF was freshly distilled from sodium benzophenone ketyl, methanol from magnesium iodine and dichloromethane from P_2O_5. Product purification was performed by flash chromatography on silica gel (Merck art. 9305). Specific rotations were measured at room temperature on a Perkin–Elmer 241 polarimeter. NMR spectra were recorded on Bruker AC-300, AC-250 or AC-200 instruments using Me_4Si as internal standard. Mass spectra were recorded on AEI MS-9 (CI; isobutane) or AEI MS-50 (EI) instruments. Elemental analyses were performed by the microanalysis laboratory at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette).

3.1. (3*R*,7a*S*)-3-Phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazol-5-one 4

The α,β-unsaturated lactam **1** (720 mg, 3.54 mmol) was dissolved in CH_2Cl_2 (20 mL) and Amberlyst-15 (1–2 g) was added. The solution was stirred at rt for 3 h. The pH was maintained below 6 during the course of the reaction by addition of Amberlyst-15. The solution was filtered and the solvent was evaporated. The oxazolopyrrolidin-2-one **4** was obtained without further purification as a white solid (720 mg, 100%) identical in all aspects (except specific rotation) with its enantiomer described by Meyers. Compound **4**: $[\alpha]_D = -179$ ($c = 1.3$, ethanol) (lit.:[10a] $[\alpha]_D = +154$ ($c = 1.29$, ethanol)). Anal. calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.11; H, 6.59; N, 7.04%.

3.2. General procedure for nucleophilic addition to the oxazolopyrrolidin-2-one 4

Method A: The bicyclic lactam **4** was dissolved in dry CH_2Cl_2 (0.10 mmol/mL) under an argon atmosphere and the solution was cooled to −78°C. The nucleophile (3 equiv.) was added to the solution via a syringe,

followed by $TiCl_4$ (1.5 equiv.). The solution was warmed to rt and, after completion of the reaction (TLC), was treated with saturated aqueous $NaHCO_3$ and then extracted twice with CH_2Cl_2. The organic layers were dried over Na_2SO_4 then the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel.

Method B: The cuprate was prepared by stirring the organolithium reagent (3 equiv.) and $CuBr{\cdot}Me_2S$ (3 equiv.) for 20 min in dry THF under an argon atmosphere at −40°C. The solution was cooled to −78°C, then 3 equiv. of $BF_3{\cdot}OEt_2$ and a solution of **4** (1 equiv.) in dry THF (0.3 mmol/mL) were added and the temperature was allowed to rise to rt. After completion of the reaction, the mixture was treated with a saturated solution of NH_4Cl and a concentrated solution of ammonia (2/1). After stirring for 15 min the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel.

3.3. (5*S*)-Allyl-1-(2-hydroxy-(1′*R*)-phenylethyl)-pyrrolidin-2-one 5a

Method A was applied to **4** (222 mg, 1.09 mmol) with allyltrimethylsilane (0.52 mL, 3.3 mmol) as nucleophile. The reaction time was 2.5 h. Flash chromatography (AcOEt–heptane: 4/1) of the crude reaction mixture afforded the major diastereomer **5a** (195 mg, 73%) as an amorphous solid and the minor diastereomer **5b** (27 mg, 10.3%).

Major diastereoisomer **5a**: $[\alpha]_D = +26$ ($c = 1.1$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.3 (5H, m), 5.64 (1H, tdd, 7.2, 11.2, 16.0 Hz), 5.07 (2H, 2d, 10.9, 17.0 Hz), 4.87 (1H, dd, 6.3, 7.3 Hz), 4.64 (1H, dd, 4.0, 8.0 Hz), 4.26 (1H, ddd, 7.1, 8.0, 11.0 Hz), 4.01 (1H, ddd, 4.0, 6.0, 11.0 Hz), 3.55 (1H, ddd, 3.7, 7.7, 11.6 Hz), 2.52 (1H, td, 8.9, 17.3 Hz), 2.37 (1H, ddd, 5.0, 9.6, 17.1 Hz), 1.95–2.25 (3H, m), 1.8 (1H, ddd, 4.7, 9.2, 17.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 176.7, 137.5, 132.5, 128.4, 127.5, 127.1, 118.5, 63.1, 60.8, 58.0, 37.0, 30.7, 23.4; MS (IC; isobutane): $m/z = 246$ (MH^+), 204 (MH^+–CH_2=$CHCH_2$), 126 (MH^+–PhCH=CHOH). Anal. calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.16; H, 7.89; N, 5.61%.

Minor diastereomer **5b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.3 (5H, m), 5.55 (1H, tdd, 7.0, 10.3, 17.0 Hz), 5.0 (2H, 2d, 10.3, 17.0 Hz), 4.76 (1H, dd, 4.4, 7.8 Hz), 4.25 (1H, m), 4.08 (1H, m), 3.9 (1H, m), 3.58 (1H, ddd, 3.7, 8.1, 12.1 Hz), 2.57 (1H, ddd, 8.3, 9.3, 17.2 Hz), 2.42 (1H, ddd, 5.2, 9.7, 17.1 Hz), 2.25 (1H, m), 1.95–2.17 (2H, m), 1.8 (1H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 177.3, 137.7, 133.0, 128.7, 127.9, 118.7, 64.6, 61.9, 60.9, 39.2, 30.8, 24.0.

3.4. 1-(2-Hydroxy-(1′*R*)-phenylethyl)-5-oxo-pyrrolidin-(2*S*)-carbonitrile 6a

Method A was applied to **4** (198 mg, 0.975 mmol) with trimethylsilylcyanide (0.39 mL; 2.92 mmol) as nucleophile. The reaction time was 2.5 h. Flash chromatography (AcOEt–heptane: 9/1) of the crude reaction mixture afforded the major diastereomer **6a** (179 mg, 80%) as a white amorphous solid and the minor diastereomer **6b** (20 mg, 9%).

Major diastereomer **6a**: $[\alpha]_D = -46$ ($c = 2.4$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.35 (5H, m), 4.86 (1H, dd, 3.9, 8.1 Hz), 4.34 (1H, dd, 3.9, 8.0 Hz), 4.24 (1H, dd, 8.1, 12.4 Hz), 4.05 (1H, dd, 4.0, 12.4 Hz), 3.8 (1H, sl), 2.73 (1H, td, 9.2, 16.9 Hz), 2.54 (1H, ddd, 4.7, 8.6, 17.0 Hz), 2.38 (2H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 175.4, 135.6, 128.9, 128.6, 127.6, 117.5, 62.2, 60.5, 47.8, 30.0, 24.5; MS (IC; isobutane): $m/z = 231$ (MH^+), 204 (MH^+–HCN), 111 (MH^+–PhCH=CHOH). Anal. calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.82; H, 6.32; N, 11.99%.

Minor diastereomer **6b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.4 (5H, m), 5.35 (1H, dd, 4.1, 8.2 Hz), 4.40 (1H, m), 4.25 (1H, m), 4.15 (1H, dd, 3.8, 8.2 Hz), 2.8 (1H, td, 9.0, 16.9 Hz), 2.60 (1H, ddd, 4.6, 8.6, 17.0 Hz), 2.35 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 175.0, 135.1, 129.4, 128.9, 128.1, 118.1, 61.8, 58.5, 46.6, 29.7, 25.1.

3.5. [1-(2-Hydroxy-(1′*R*)-phenylethyl)-5-oxo-pyrrolidin-(2*R*)-yl]-phosphonic acid dimethyl ester 7a

Method A was applied to **4** (1.03 g, 5.07 mmol) with trimethylphosphite (1.79 mL, 5.21 mmol) as nucleophile. The reaction time was 2 h. Flash chromatography (CH_2Cl_2–MeOH: 97/3) of the crude reaction mixture afforded the major diastereomer **7a** as an amorphous solid (1.11 g, 70%) and the minor diastereomer **7b** (253 mg, 16%).

Major diastereomer **7a**: $[\alpha]_D = -40$ ($c = 1$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.3 (5H, m), 4.85 (1H, dd, 3.3, 7.9 Hz), 4.57 (1H, dd, 6.6, 7.8 Hz), 4.32 (1H, ddd, 7.7, 8.0, 12.5 Hz), 4.00 (1H, ddd, 3.4, 6.2, 12.4 Hz), 3.83+3.79 (2×3H, 2d, 10.5 Hz), 2.75 (1H, td, 10.5, 17.4 Hz), 2.45 (1H, m), 2.3 (2H, m); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (ppm) = 177.0, 137.2, 128.9, 128.1, 127.3, 64.9, 64.1, 56.0 (d, 160 Hz), 53.8+52.9 (2d, 8 Hz), 31.3, 21.4; MS (IC; isobutane): $m/z = 314$ (MH^+), 282 (MH^+–CH_2OH), 203 (MH^+–$PO(OMe)_2$), 194 (MH^+–PhCH=CHOH). Anal. calcd for $C_{14}H_{20}NO_5P$: C, 53.67; H, 6.43; N, 4.47. Found: C, 53.44; H, 6.33; N, 4.41%.

Crystallographic data: Colorless crystal of 0.30×0.30×0.35 mm. $C_{14}H_{20}NO_5P$, $M_w = 313.28$. Monoclinic system, space group $P2_1$, $Z = 2$, $a = 6.374(4)$, $b = 8.026(6)$, $c = 15.115(8)$ Å, $\beta = 95.05$ (2)°, $V = 770.2$ Å^3, $d_c = 1.351$ g cm^{-3}, $F(000) = 332$, λ (Mo Kα) = 0.71073 Å, $\mu = 0.20$ mm^{-1}; 10585 data measured ($-5 \le h \le 5$, $-9 \le k \le 9$, $-17 \le l \le 17$) with a Nonius Kappa-CCD area-detector diffractometer, of which 1912 reflections were unique and 1766 observed having $I \ge 2\sigma(I)$.

The structure was solved with *SHELXS86*[17] and refined with *SHELXL93*.[17] H atoms riding. Refinement

converged to $R_1(F)=0.0376$ for the 1766 observed reflections and $wR_2(F^2)=0.0949$ for all the 1912 data, goodness-of-fit $S=1.067$. Residual electron density between −0.25 and 0.15 e Å^{-3}. In the crystal, the molecules are linked in chains along the *a* axis direction through hydrogen bonds established between the hydroxyl groups O(8)-H and the oxygen atoms O(17) (distances O(8)···O(17) = 2.744, HO(8)···O(17) = 1.83 Å, angle O–H–O = 167.7°). Full crystallographic results have been deposited as supplementary material (CIF file) at the Cambridge Crystallographic Data Centre, UK.

Minor diastereomer **7b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.35 (5H, m), 5.25 (1H, dd, 4.6, 9.0 Hz), 4.38 (1H, dd, 9.1, 11.9 Hz), 4.20 (1H, dd, 4.6, 11.9 Hz), 3.78 (1H, dd, 10.5, 15.7 Hz), 3.64+3.72 (2×3H, 2d, 10.6 Hz), 2.65 (1H, ddd, 1.4, 11.7, 16.7 Hz), 2.0–2.4 (3H, m); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (ppm) = 178.2, 136.5, 128.6, 128.1, 127.9, 62.5, 60.4, 54.3 (d, 162 Hz), 53.8+ 52.8 (2d, 8 Hz), 30.4, 22.6.

3.6. 1-(2-Hydroxy-(1′*R*)-phenylethyl)-(5*R*)-methyl-pyrrolidin-2-one 8a

Method B was applied to **4** (215 mg, 1.06 mmol) with methylcuprate (from 3.18 mL of 1 M MeLi in THF and 654 mg of CuBr·Me_2S). The reaction time was 12 h. After purification (CH_2Cl_2–MeOH: 97/3), the major diastereomer **8a** was obtained pure as an oil (174 mg, 75% yield) and the minor diastereomer **8b** (22.5 mg, 9.7%) was also isolated.

Major diastereomer **8a**: $[\alpha]_D = +86$ ($c = 1.4$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.3 (5H, m), 4.9 (1H, dd, 6.5, 7.4 Hz), 4.57 (1H, dd, 3.7, 7.7 Hz), 4.23 (1H, ddd, 7.3, 7.7, 11.9 Hz), 4.01 (1H, ddd, 4.0, 6.0, 12.0 Hz), 3.55 (1H, qd, 6.2, 12.6 Hz), 2.48 (2H, m), 2.16 (1H, m), 1.62 (1H, m), 1.12 (3H, d, 6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 176.4, 137.5, 128.4, 127.5, 127.1, 63.4, 60.8, 54.5, 30.6, 26.7, 19.5; MS (IC; isobutane): $m/z = 220$ (MH^+), 202 (MH^+-H_2O), 100 (MH^+–PhCH=CHOH). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.01; H, 8.02; N, 5.87%.

Minor diastereomer **8b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 7.3 (5H, m), 4.77 (1H, dd, 4.5, 7.1 Hz), 4.12 (3H, m), 3.64 (1H, qd, 6.4, 12.8 Hz), 2.55 (1H, dd, 7.6, 9.2 Hz), 2.48 (1H, dd, 6.3, 9.2 Hz), 2.20 (1H, m), 1.62 (1H, m), 1.07 (3H, d, 6.3 Hz); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (ppm) = 176.9, 137.9, 128.6, 127.8, 127.3, 64.4, 61.4, 56.9, 30.8, 27.6, 21.7.

3.7. (5*R*)-Butyl-1-(2-hydroxy-(1′*R*)-phenylethyl)-pyrrolidin-2-one 9a

Method B was applied to **4** (1.10 g, 5.42 mmol) with butylcuprate (from 10.2 mL of 1.6 M BuLi in hexanes and 654 mg of CuBr·Me_2S). The reaction time was 12 h. After purification (CH_2Cl_2–MeOH: 97.5/2.5), the major diastereomer **9a** was obtained pure as an amorphous solid (1.188 g, 84%); the minor diastereomer **9b** (172 mg, 12%) was also obtained.

Major diastereomer **9a**: $[\alpha]_D = +32$ ($c = 2$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.3 (5H, m), 4.75 (1H, sl), 4.5 (1H, dd, 3.5, 7.9 Hz), 4.25 (1H, dd, 7.9, 12.2 Hz), 3.98 (1H, dd, 3.6, 12.2 Hz), 3.4 (1H, m), 2.54 (1H, td, 8.5, 17.1 Hz), 2.43 (1H, ddd, 5.6, 9.6, 17.1 Hz), 2.09 (1H, m), 1.75 (1H, m), 1.6 (1H, m), 1.1–1.4 (5H, m), 0.9 (3H, t, 6.6 Hz); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (ppm) = 176.9, 137.6, 128.7, 128.5, 66.0, 61.7, 59.2, 32.2, 31.2, 26.6, 24.1, 22.2, 13.9; MS (IC; isobutane): $m/z = 262$ (MH^+), 142 (MH^+–PhCH=CHOH). Anal. calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.21; H, 8.87; N, 5.11%.

Minor diastereomer **9b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.45 (5H, m), 4.87 (1H, m), 4.38 (1H, m), 4.22 (2H, m), 3.63 (1H, m), 2.68 (1H, ddd, 7.6, 9.4, 17.1 Hz), 2.56 (1H, ddd, 5.8, 9.7, 17.0 Hz), 2.27 (1H, m), 1.86 (1H, m), 1.65 (1H, m), 1.05–1.45 (5H, m), 0.9 (3H, t, 6.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 176.8, 137.8, 128.4, 127.7, 127.5, 63.4, 61.4, 61.2, 34.2, 30.9, 26.6, 24.1, 22.3, 13.8.

3.8. 1-(2-Hydroxy-(1′*R*)-phenylethyl)-(5*R*)-phenyl-pyrrolidin-2-one 10a

Method B was applied to **4** (223 mg, 1.1 mmol) with phenylcuprate (from 1.65 mL of 2 M PhLi and 678 mg of CuBr·Me_2S). The reaction time was 12 h. After purification (AcOEt–heptane: 4/1), the major diastereomer **10a** (87 mg, 28%) was obtained pure as a yellow oil. The minor diastereomer **10b** (11 mg, 3.7%) was also isolated.

Major diastereomer **10a**: $[\alpha]_D = +11$ ($c = 0.7$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.05–7.4 (10H, m), 4.87 (1H, dd, 6.1, 7.9 Hz), 4.4 (1H, dd, 5.5, 8.1 Hz), 4.18 (1H, ddd, 7.8, 8.1, 11.9 Hz), 4.07 (1H, dd, 1.9, 9.2 Hz), 3.93 (1H, ddd, 5.2, 6.3, 12.0 Hz), 2.68 (1H, dd, 7.1, 9.5 Hz), 2.59 (1H, dd, 6.4, 9.4 Hz), 2.42 (1H, m), 1.97 (1H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 177.4, 140.6, 137.3, 129.1, 128.2, 128.1, 127.8, 127.4, 126.6, 64.2, 63.9, 62.9, 31.3, 28.8; MS (IC; isobutane): $m/z = 282$ (MH^+), 162 (MH^+–PhCH=CHOH). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.25; H, 7.11; N, 4.62%.

Minor diastereomer **10b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.05–7.4 (10H, m), 5.10 (1H, m), 4.4 (1H, dd, 5.4, 14.0 Hz), 3.82 (1H, m), 3.75 (1H, m), 2.8 (1H, m), 2.55 (1H, m), 2.40 (1H, m), 1.90 (1H, m); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (ppm) = 175.7, 142.5, 135.7, 128.7, 128.5, 127.9, 127.5, 126.8, 126.6, 63.2, 60.0, 30.1, 29.2.

3.9. ((2*S*)-Butyl-pyrrolidin-1-yl)-(1′*R*)-phenyl-ethan-2-ol 12

The lactam **9a** (288 mg, 1.10 mmol) was dissolved in dry THF (5 mL) under an argon atmosphere; $LiAlH_4$ (125 mg; 3.31 mmol) was slowly added to the solution

which was stirred at rt for 18 h. The mixture was cooled to 0°C then aqueous HCl (1N, 10 mL) was added dropwise and the solution was stirred for a further 30 min. After extraction with CH_2Cl_2, the organic layer was washed with aqueous NaOH (1N) and further washed with brine and then concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2–MeOH: 95/5). The pyrrolidine **12** was obtained as a colorless oil in 80% yield. Analytical data are identical with those reported in the literature,[16] indicating the same relative stereochemistry and thus the same absolute configuration, since both products were prepared from (*R*)-(−)-phenylglycinol. Nevertheless, a difference was observed in the specific rotation: $[\alpha]_D = -129$ ($c = 2.5$, CH_2Cl_2) (lit.[15] $[\alpha]_D = -123.3$ ($c = 2$, CH_2Cl_2)). Anal. calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 76.75; H, 10.19; N, 5.46%.

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