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A flexible non-amino acid-based formal asymmetric synthesis of naturally occurring (2*R*,3*S*)-2-aminotetradeca-5,7-dien-3-ol: observation of a remarkable protecting group effect

Bi-Yan He, Tian-Jun Wu, Xian-Yong Yu and Pei-Qiang Huang*

Department of Chemistry, Xiamen University, Xiamen, Fujian 361005, PR China

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Abstract—A flexible non-amino acid-based formal asymmetric synthesis of naturally occurring antimicrobial (2*R*,3*S*)-2-aminotetradeca-5,7-dien-3-ol is reported. The method features a flexible and highly regioselective Grignard addition to (*S*)-malimide followed by a *trans*-diastereoselective reductive deoxygenation. The scope and limitations of the highly regio and diastereoselective reductive alkylation of malimides were defined. A remarkable protecting group effect on the regio and diastereoselective reductive alkylation of malimides was observed.

1. Introduction

Both enantiomeric forms of *anti*-2-amino-3-hydroxypentyl and *anti*-2-amino-3-hydroxypent-5-enyl are homochiral residues found in many bioactive natural products of marine origin. Examples include antimicrobial (2*R*,3*S*)-2-aminotetradeca-5,7-dien-3-ol **1** (Fig. 1),[1] cytotoxic and antimicrobial (2*R*,3*S*)-crucigasterin 277 **2**,[2] cytotoxic (2*R*,3*S*)-amaminol B **3**,[3] antifungal (2*S*,3*R*)-halaminol A **4**,[4] antiparasitic and antimicrobial (2*S*,3*R*)-xestoaminol A **5**,[5] and cytotoxic (2*S*,3*R*)-obscuraminol A **6**.[6]

(2*R*,3*S*)-2-Aminotetradeca-5,7-dien-3-ol **1** and its (2*R*,3*R*)-epimer were isolated from Papua New Guinea sponge *Xestospongia* sp., which possess inhibitory activity towards the growth of *Candida albicans*.[1] The relative stereochemistries of the 2-amino-3-hydroxy moieties of these amino alcohols were deduced by the analysis of ^{1}H NMR spectra of the corresponding oxazolidinone derivatives. The initially proposed (2*S*) absolute configuration based on the degradation to L-alanine and HPLC analysis of the derivatives,[1] has subsequently been corrected to (2*R*) by comparing the specific rotations of natural products with those of

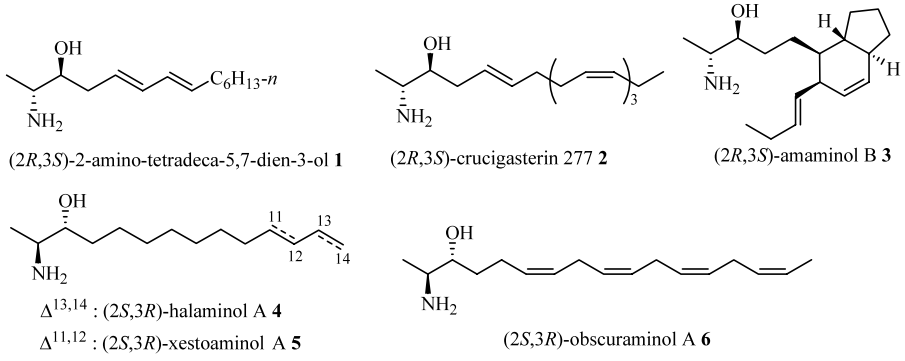

Figure 1.

* Corresponding author. E-mail: pqhuang@xmu.edu.cn

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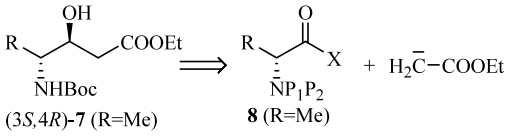
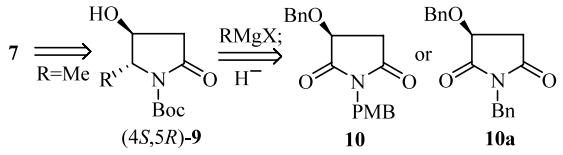
synthetic enantiomers.[7] To date, only one asymmetric synthesis of (2*R*,3*S*)-**1** has been reported which used *N*-Boc-(3*S*,4*R*)-*anti*-4-amino-3-hydroxypentanoate **7** as the key building block.[7,8] The latter was derived from unnatural (*R*)-alanine via a Reformatsky type reaction in modest 1:2 stereoselectivity (Scheme 1). Recently, (3*S*,4*R*)-**7** was prepared starting from (*S*)-pyroglutamic acid.[9]



Scheme 1.

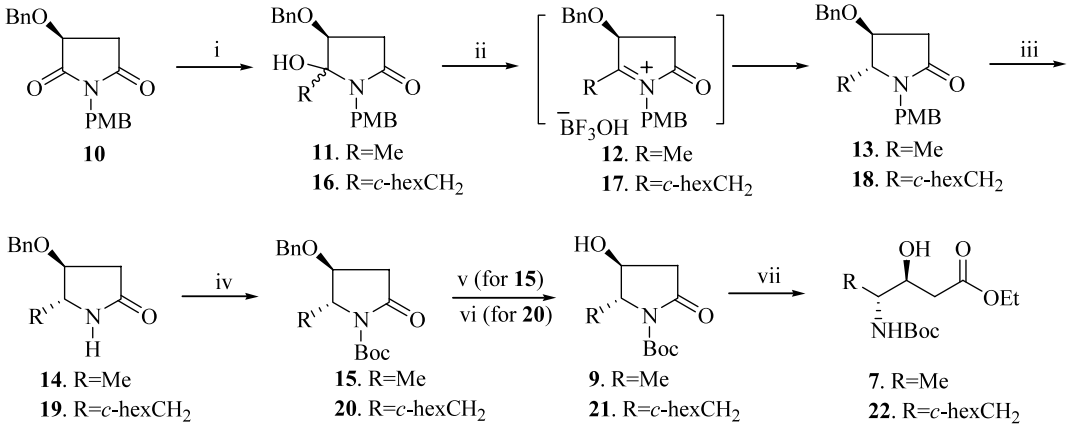
Although the synthesis of *anti*-γ-amino-β-hydroxy acids, via the elongation of α-amino acids or α-amino aldehydes by a C_2 synthon, is a straightforward approach (Scheme 1),[2,7,8,10] it can often suffer from drawbacks such as low stereoselectivity,[2,7,10] difficulties in separating isomers, the necessity to use expensive, unnatural D-alanine as a chiral pool source, a lack of flexibility, since the methyl group presents in (3*S*,4*R*)-**7** comes from the side chain of the starting α-amino acid, and more importantly, partial racemization has been observed in such an approach.[11] Consequently, the development of flexible non-amino acid-based approaches to *anti*-γ-amino-β-hydroxy carboxylic acids is highly desirable. In continuation of our efforts to use cheap and easily available (*S*)-malic acid in the asymmetric synthesis of nitrogen-containing bioactive compounds,[12] we now report a flexible asymmetric synthesis of (3*S*,4*R*)-**7** (Scheme 2). The scope and limitation of the key reductive alkylation of the protected malimides **10** and **10a** is discussed. This approach not only allows the synthesis of *anti*-γ-amino-β-hydroxy carboxylic acid esters, but also provides an easy and flexible access to (4*S*,5*R*)-5-alkyl-4-hydroxy-2-pyrrolidinones[13] (e.g. **9**), which are useful building blocks for pharmaceutically interesting compounds.[14]



Scheme 2.

2. Results and discussion

As shown in Scheme 3, the synthesis started with the known (*S*)-malimide **10**, derived from (*S*)-malic acid as described previously.[12d] Reaction of an excess of methyl magnesium iodide to malimide **10** at −78°C occurred regioselectively at the C-2 position, leading to **11** as a diastereomeric mixture in a ratio of 18:82 (combined yield, 82%). The undesired regioisomer (as a diastereomeric mixture) was also isolated in a yield of 5%. The high regioselectivity (94:6) of the Grignard reaction to the more hindered carbonyl, α to the C-3 benzyloxy group, can be attributed to both the oxygen inductive effect and the complex induced proximity effects (CIPE).[15] The stereochemistry of the isomeric **11** was not assigned. The diastereomeric mixture **11** was then subjected to Lewis acid mediated ionic hydrogenation.[16] Thus, in the presence of 2.0 equivalents of boron trifluoride etherate, hydroxy lactam **11** was reduced with an excess of triethylsilane (CH_2Cl_2, −78°C ~ rt) to yield *trans*-(+)-**13** as the only isolable diastereomer in 89% yield and indicating a diastereoselectivity higher than 95%. The fact that starting from an 18:82 diastereomeric mixture **11**, we obtained only one diastereomer **13**, might implicate that the transformation of **11** to **13** proceeded via the intermediacy of *N*-acyliminium[17] **12**. The stereochemistry of compound **13** was assigned to *trans* according to the observed vicinal coupling constant[12a–e,18] ($J_{4,5}$ = 2.5 Hz), which was further confirmed by converting **13** to the known (3*S*,4*R*)-**7**. The observed high regioselectivity in the Grignard addition to **10** and the high diastereoselectiv-



Scheme 3. *Reagents and conditions*: (i) MeMgI, THF, −78°C, 82%; *c*-hexCH$_2$MgBr, THF, rt, 73%; ii) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C–rt, 89% for **13**; 78% for **18**; iii) CAN, MeCN–H_2O (3:1), 23°C, 70% for **14**; 67% for **19**; iv) $(Boc)_2O$, DMAP, NEt_3, CH_2Cl_2, rt, 81% for **15**; 92% for **20**; v) H_2, 1 atm, 10% Pd/C, 95% EtOH, rt, 89% for **9**; vi) Pd–C, HCOOH, MeOH, rt, 91% for **21**; vii) KCN, EtOH, THF, rt, 97% for **7**; 95% for **22**.

ity in the ionic hydrogenation of **11** are in agreement with our previous results.[12]

Oxidative *N*-deprotection of **13** using ceric ammonium nitrate[19] in a mixed MeCN–H_2O (3:1, v/v) solvent system provided (+)-**14** {white crystals, mp 55–57°C. $[\alpha]_D^{20}=+60.5$ (*c* 1.0, $CHCl_3$)} in 70% yield. Lactam **14** was then converted to activated lactam (−)-**15** {81% yield. white crystals, mp 93–94°C. $[\alpha]_D^{20}=-21.1$ (*c* 1.1, $CHCl_3$)} by treatment with di-*tert*-butyl dicarbonate in the usual way. Catalytic hydrogenolysis (10% Pd/C, H_2, 1 atm) of (−)-**15** afforded (−)-**9** {89% yield. white crystals, mp 142–143°C. $[\alpha]_D^{20}=-48.4$ (*c* 0.7, MeOH)}. Potassium cyanide promoted[20] lactam ring opening[9,13] by ethanolysis of **9** in a mixed EtOH–THF (1:1, v/v) solvent system at room temperature led smoothly to the formation of the desired *N*-Boc-(3*S*,4*R*)-*anti*-4-amino-3-hydroxypentanoic acid ethyl ester **7** as white crystals {97% yield. mp 67–68°C. $[\alpha]_D^{20}=+10.0$ (*c* 0.6, MeOH); Lit.[9] mp 69–71°C. $[\alpha]_D^{20}=+10$ (*c* 0.58, MeOH)}. Since (3*S*,4*R*)-**7** has been converted into (2*R*,3*S*)-2-aminotetradeca-5,7-dien-3-ol **1**,[7] the present work constitutes a new formal asymmetric synthesis of the natural enantiomer of this antimicrobial amino alcohol.

In order to demonstrate the flexibility of the method, the synthesis of an analogue of **7** was considered. Both *syn*- and *anti*-γ-amino-β-hydroxy carboxylic acids have been found in many biologically active peptides and antibiotics; among them, (3*S*,4*S*)-statine (Fig. 2), (3*S*,4*S*)-3-amino-2-hydroxy-5-phenylpentanoic acid (AHPPA) which are important peptide mimetics.[21] The substitution of the *i*-butyl group (in statine) or the benzyl group (in AHPPA) by a cyclohexylmethyl group has resulted in the development of (3*S*,4*S*)-3-amino-5-cyclohexyl-2-hydroxypentanoic acid (ACHPA) as an unnatural peptide mimetic with improved bioactivity compared with statine and AHPPA. Based on these considerations, protected (3*S*,4*R*)-ACHPA was chosen as our target.

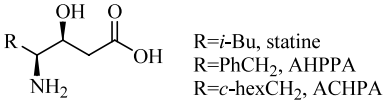
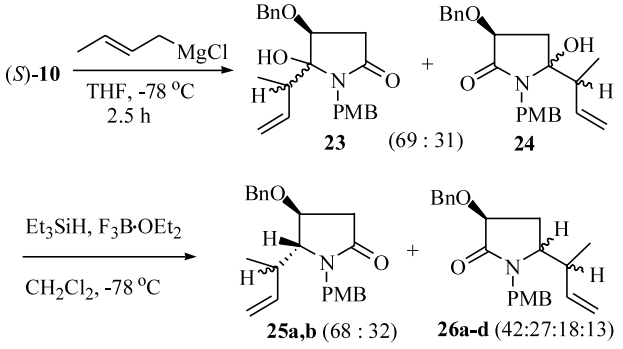


Figure 2.

Thus, using cyclohexylmethyl magnesium bromide as the nucleophile in the reductive alkylation of malimide (*S*)-**10**, and following the same reaction sequence described for (3*S*,4*R*)-**7**, the synthesis of *N*-Boc-(3*S*,4*R*)-*anti*-4-amino-5-cyclohexyl-3-hydroxypentanoate **22** was achieved as depicted in Scheme 3. In addition, since several other Grignard reagents have successfully been used in the reductive alkylation of the malimides **10** and **10a**, which showed high regio and diastereoselectivity,[12] the present approach to *anti*-γ-amino-β-hydroxy carboxylic acid esters is flexible.

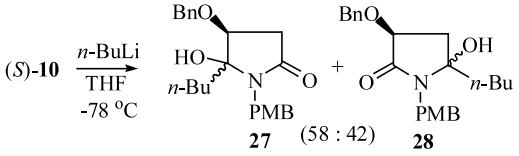
At this stage, it was important to define the scope and limitation of the highly regio and diastereoselective reductive alkylation of malimides. Indeed, since our first demonstration on the use of (*S*)-*N*,*O*-dibenzyl malimide **10a** as a valuable intermediate in the asymmetric synthesis of nitrogen containing bioactive compounds,[12a,b] this compound is becoming a suitable molecule for testing new synthetic methodologies.[22] Cha et al showed that the addition of titanium reagent [(EtMgBr/ClTi(O-*i*-Pr)$_3$] to **10a** led to a 2:1 C-2/C-5 regioselectivity,[22a] while Pilli et al. demonstrated that the addition of a cerium reagent (RMgX/$CeCl_3$) to **10a**, gave modest to exclusive C-5 regioselectivities.[22b]

In the reductive alkylation of malimides **10** and **10a**, we observed that the addition of Grignard reagents derived from alkyl halides, arylmethyl halides and phenyl bromide proceeded with high C-2 regioselectivity and the subsequent reductive deoxygenation, was also highly diastereoselective.[12] However, we observed that the addition of crotyl magnesium chloride to **10** resulted in 70:30 C-2/C-5 regioselectivity (deduced from the followed step, Scheme 4). Treatment of the mixture of the addition products **23**/**24** with $Et_3SiH/BF_3{\cdot}OEt_2$ produced, after chromatographic separation, two fractions in a 69:31 ratio, corresponding to C-2 and C-5 addition products **25a**,**b** and **26a**,**b**. The C-2 adducts **25a**,**b** contained only two diastereomers, which showed that the reductive deoxygenation was still highly *trans*-diastereoselective. The C-5 adduct **26a**,**b** was an inseparable mixture of four diastereomers in the ratio of 42:27:18:13 (deduced from ^{1}H NMR spectra of the mixture), which implicated a poor diastereoselectivity during the reductive deoxygenation at C-5.

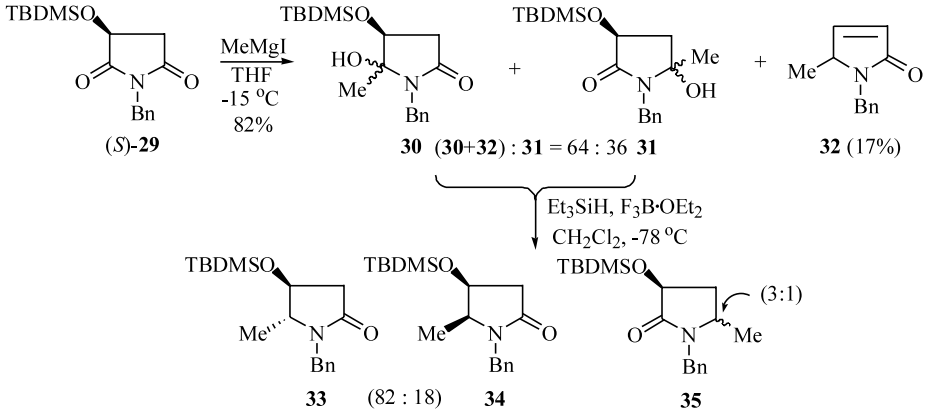


Scheme 4.

On the other hand, the use of *n*-butyllithium instead of a Grignard reagent gave similar poor C-2 regioselectivity (C-2/C-5 = 58:42, Scheme 5). These results suggest that when comparing with the Grignard reagents derived from alkyl halides, the addition of more reactive organometallics, such as crotyl magnesium chloride and *n*-butyllithium is less regioselective.



Scheme 5.



Scheme 6.

More surprisingly, the addition of methyl magnesium iodide to the *O*-*tert*-butyldimethylsilyl protected malimide[22b] (*S*)-**29** proceeded with poor C-2 regioselectivity (C-2/C-5 = 64:36, deduced from the subsequent step and taking into account **32** as a C-2 addition product, Scheme 6). These results are also different to those observed for *O*,*O*-di-(*tert*-butyldimethylsilyl)-tartarimide, a C_2-symmetric imide derived from tartaric acid, where the reductive alkylation is highly diastereoselective (*trans*:*cis* $\geq$95:5).[16c,d]

The low regioselectivity observed in the addition of both crotyl magnesium chloride and *n*-butyllithium to malimide **10a** can be understood in terms of the higher reactivity associated with these two nucleophiles, which can add to either the C-2 or C-5 carbonyl before the pre-coordination with the oxygen atom at the C-3 position, while the protecting group effect on the regio and diastereoselective reductive alkylation of malimides **10**/**10a**[12a,b] (regioselectivity: C-2/C-5 = 95:5) versus **29** (regioselectivity: C-2/C-5 = 64:36) is due to the steric hindrance of the *O*-*tert*-butyldimethylsilyl group present in **29**, which counteracts, or at some extends, the complex induced proximity effects (CIPE).

3. Conclusion

In summary, starting from the cheap and easily available (*S*)-malic acid, we have developed a flexible non-amino acid-based approach to (3*S*,4*R*)-*anti*-γ-amino-β-hydroxy carboxylic acid esters in high regio and stereoselective manner. The scope and limitations of the key highly regio and diastereoselective reductive alkylation of malimides were also defined. A protecting group effect on the regio and diastereoselective reductive alkylation of malimides was also observed.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-500 micro melting point apparatus. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian unity +500 spectrometer or a Varian unity +300 spectrometer with tetramethylsilane as the internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography–mass spectrum (ESI direct injection). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. THF and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane was distilled over P_2O_5. Silica gel (Zhifu, 300–400 mesh) was used for column chromatography, eluated (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90°C) mixtures.

4.2. (4*S*,5*R*)-4-Benzyloxy-1-(4-methoxybenzyl)-5-methyl-2-pyrrolidinone, (+)-13

To a stirred solution of (*S*)-*O*-benzyl-1-(*p*-methoxybenzyl)malimide[12d] (834 mg, 2.57 mmol) in THF (25 mL) at −78°C was added, dropwise, a 2.0 M solution of methyl magnesium iodide in diethyl ether (2.0 mol L^{-1}, 4.5 mL, 8.98 mmol) under an atmosphere of N_2. The mixture was stirred at −78°C for 6 h and then quenched by adding a saturated aqueous solution of NH_4Cl. The mixture was extracted with CH_2Cl_2 (4 ×10 mL). The combined organic phases were washed with brine and dried with anhydrous $MgSO_4$. After flash chromatography purification (eluent: EtOAc/PE = 1:2; then 2:1), two diastereomers **11a** (132 mg), **11b** (585 mg) and a C-5 regioisomer (47 mg, white crystalline, mp 90–92°C) were obtained. **11a**: less polar isomer, white crystals, mp 104–106°C. $[\alpha]_D^{20}$ = +5.5 (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3441, 3126, 2925, 1647, 1614, 1513, 1146 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ: 1.34 (s, 3H, CH_3), 2.45 (dd, *J* = 4.2, 16.9 Hz, 1H, H-3), 2.69 (dd, *J* = 6.5, 16.9 Hz, 1H, H-3), 3.81 (s, 3H, OCH_3), 3.99 (s, 1H, OH, D_2O exchangeable), 4.00 (dd, *J* = 4.2, 6.5 Hz, 1H, H-4), 4.31 (d, *J* = 15.4 Hz, 1H, $PhCH_2N$), 4.48 (d, *J* = 15.4 Hz, 1H, $PhCH_2N$), 4.67 (d, *J* = 11.6 Hz, 1H, $PhCH_2O$), 4.71 (d, *J* = 11.6 Hz, 1H, $PhCH_2O$). MS (ESI, *m*/*z*): 364

(M+Na$^+$, 21), 342 (M+H$^+$, 90), 324 (100). HRMS calcd for [$C_{20}H_{23}NO_4$ +H]$^+$: 342.1700. Found: 342.1698. **11b**: more polar isomer, white crystals, mp 116–117°C. $[\alpha]_D^{20}=+46.5$ (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3164, 2931, 1656, 1612, 1512, 1242, 1145 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ: 1.38 (s, 3H, CH_3), 2.40 (dd, $J=4.7$, 16.7 Hz, 1H, H-3), 2.75 (dd, $J=6.7$, 16.7 Hz, 1H, H-3), 3.81 (s, 3H, OCH_3), 3.97 (s, 1H, OH, D_2O exchangeable), 3.98 (dd, $J=4.7$, 6.7 Hz, 1H, H-4), 4.28 (d, $J=15.5$ Hz, 1H, $PhCH_2N$), 4.50 (d, $J=15.5$ Hz, 1H, $PhCH_2N$), 4.63 (d, $J=11.8$ Hz, 1H, $PhCH_2O$), 4.68 (d, $J=11.8$ Hz, 1H, $PhCH_2O$). MS (ESI, *m*/*z*): 364 (M+Na$^+$, 23), 342 (M+H$^+$, 47), 324 (100). HRMS calcd for [$C_{20}H_{23}NO_4$ +H]$^+$: 342.1700. Found: 342.1700.

The diastereomeric mixture **11a**,**b** (585 mg, 1.72 mmol) was dissolved in dry dichloromethane (17 mL), and cooled to −78°C. Et_3SiH (3.1 mL, 19.7 mmol) and $BF_3{\cdot}OEt_2$ (0.42 mL, 3.4 mmol) were successively added. The resulting mixture was stirred at −78°C for 6 h, and then allowed to rise to room temperature. After being stirred at room temperature for 6 h, the mixture was quenched by adding a saturated solution of $NaHCO_3$ (5 mL) at 0°C. The mixture was extracted with CH_2Cl_2 (4×10 mL). The combined organic phases were washed with brine, and dried with anhydrous $MgSO_4$. After flash chromatography purification (eluent: EtOAc/PE = 1:1; then, 2:1), pyrrolidinone **13** (497 mg, 89%) was obtained as a colorless oil. $[\alpha]_D^{20}=+91.2$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3031, 2966, 2929, 1680, 1612, 1513, 1414, 1246, 1068 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.13 (d, $J=6.6$ Hz, 3H, CH_3), 2.51 (dd, $J=3.1$, 17.3 Hz, 1H, H-3), 2.75 (dd, $J=6.6$, 17.3 Hz, 1H, H-3), 3.53 (dq, $J=2.5$, 6.6 Hz, 1H, H-5), 3.76 (m, 1H, H-4), 3.78 (s, 3H, OCH_3), 3.91 (d, $J=15.0$ Hz, 1H, $PhCH_2N$), 4.42 (d, $J=11.7$ Hz, 1H, $PhCH_2O$), 4.48 (d, $J=11.7$ Hz, 1H, $PhCH_2O$), 4.96 (d, $J=15.0$ Hz, 1H, $PhCH_2N$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.29, 37.12, 43.11, 55.24, 58.52, 70.86, 78.16, 114.02, 127.58, 127.84, 128.32, 128.46, 129.14, 137.54, 158.94, 172.16 ppm. MS (ESI, *m*/*z*): 326 (M+H$^+$, 100), 218 (20). HRMS calcd for [$C_{20}H_{23}NO_3$ +H]$^+$: 326.1751. Found: 326.1746.

4.3. (4*S*,5*R*)-4-Benzyloxy-5-methyl-2-pyrrolidinone, (+)-14

To a solution of compound **13** (549 mg, 1.69 mmol) dissolved in a mixed solvent system (MeCN–H_2O, 3:1 v/v, 28 mL) was added, at 0°C, ceric ammonium nitrate (3.70 g, 6.76 mmol). After being stirred at 23°C for 25 min, H_2O (8 mL) was added. The resulting mixture was extracted with ethyl acetate (3×10 mL). The combined extracts were successively washed with a saturated aqueous solution of sodium bicarbonate (2×10 mL) and brine, dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (EtOAc/PE = 2:1; then 4:1; 6:1) afforded **14** (243 mg, 70% yield) as white crystals. Mp 55–57°C. $[\alpha]_D^{20}=+60.5$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3234, 2924, 1699, 1096, 1071, 741, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23 (d, $J=6.6$ Hz, 3H, CH_3), 2.41 (dd, $J=4.6$, 17.2 Hz, 1H, H-3), 2.65 (dd, $J=7.0$, 17.2 Hz, 1H, H-3), 3.74 (m, 1H), 3.84 (m, 1H), 4.50 (d, $J=11.8$ Hz, 1H, $PhCH_2O$), 4.56 (d, $J=11.8$ Hz, 1H, $PhCH_2O$), 5.87 (s br, 1H, NHCO). MS (ESI, *m*/*z*): 433 (2M+Na$^+$, 12), 411 (2M+H$^+$, 11), 228 (M+Na$^+$, 31), 206 (M+H$^+$, 100). HRMS calcd for [$C_{12}H_{15}NO_2$ +H]$^+$: 206.1176. Found: 206.1172.

4.4. (4*S*,5*R*)-4-Benzyloxy-1-(*tert*-butyloxycarbonyl)-5-methyl-2-pyrrolidinone, (−)-15

To an ice-bath cooled mixture of **14** (103 mg, 0.50 mmol) and a catalytic amount of DMAP in dry THF (25 mL) was added successively di-*tert*-butyl dicarbonate (0.23 mL, 1.0 mmol) and triethylamine (0.07 mL, 0.5 mmol). The mixture was allowed to stir at room temperature for 14 h and then quenched with water (2 mL). The resulting mixture was extracted with dichloromethane (3×2 mL). The combined extracts were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (EtOAc/PE = 1:2) afforded **15** (124 mg, 81% yield) as a colorless oil which crystallized on standing at low temperature. Mp 93–94°C. $[\alpha]_D^{20}=-21.1$ (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 2977, 1742, 1711, 1367, 1308, 1216, 1153, 1099 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (d, $J=6.8$ Hz, 3H, CH_3), 1.53 (s, 9H, *t*-Bu), 2.61 (d, $J=18.1$ Hz, 1H, H-3), 2.78 (dd, $J=5.7$, 18.1 Hz, 1H, H-3), 3.74 (d, $J=5.7$ Hz, 1H, H-4), 4.28 (q, $J=6.8$ Hz, 1H, H-5), 4.51 (d, $J=11.9$ Hz, 1H, $PhCH_2O$), 4.55 (d, $J=11.9$ Hz, 1H, $PhCH_2O$). MS (ESI, *m*/*z*): 328 (M+Na$^+$, 85), 250 (100). HRMS calcd for [$2C_{17}H_{23}NO_4$ +Na]$^+$: 633.3146. Found: 633.3137. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.89; H, 7.54; N, 4.59. Found: C, 66.90; H, 7.65; N, 4.43.

4.5. (4*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-4-hydroxy-5-methyl-2-pyrrolidinone, (−)-9

To a mixture of **15** (56 mg, 0.18 mmol) and 10% Pd–C (28 mg) was added ethanol (1.8 mL). The mixture was stirred at room temperature and under an atmosphere of H_2 for 7 days. The mixture was filtered over Celite. Flash chromatography purification on silica gel (eluent: EtOAc: PE = 2:1) provided **9** as white crystals (35 mg, 89%). Mp 142–143°C. $[\alpha]_D^{20}=-48.4$ (*c* 0.7, MeOH); $[\alpha]_D^{20}=-36.4$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3483, 2976, 2937, 1765, 1368, 1345, 1288, 1158 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (d, $J=6.6$ Hz, 3H, CH_3), 1.53 (s, 9H, *t*-Bu), 2.44 (d, $J=17.9$ Hz, 1H, H-3), 2.82 (dd, $J=5.1$, 17.9 Hz, 1H, H-3), 2.94 (s, 1H, OH, D_2O exchangeable), 4.06 (m, 1H, H-4), 4.13 (q, $J=6.6$ Hz, 1H, H-5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.8, 28.0, 40.8, 63.3, 69.5, 83.0, 149.9, 172.7 ppm. MS (ESI, *m*/*z*): 238 (M+Na$^+$, 73), 160 (100). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.81, H, 7.91, N, 6.51. Found: C, 56.10, H, 7.93, N, 6.49.

4.6. (3*S*,4*R*)-4-[(*tert*-Butyloxycarbonyl)amino]-3-hydroxypentanoic acid ethyl ester, (+)-7

To a solution of pyrrolidinone **9** (26 mg, 0.12 mmol) in a mixed solvent system (EtOH–THF, 1:1, v/v, 0.6 mL), was added KCN (2 mg, 0.024 mmol). The mixture was

allowed to stir at room temperature for 36 h and then concentrated in vacuo. Flash chromatography (EtOAc/PE, 3:7) afforded **7** (35 mg, 97% yield) as white crystals. Mp 67–68°C (Lit.[9] mp 69–71°C). $[\alpha]_D^{20}=+10.0$ (*c* 0.6, MeOH) {Lit.[9] $[\alpha]_D^{20}=+10$ (*c* 0.58, MeOH)}. IR (film) ν_{max}: 3426, 3355, 1731, 1685, 1526, 1168 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.14 (d, $J=6.8$ Hz, 3H, H-5), 1.26 (t, $J=7.1$ Hz, 3H, CH_2CH_3), 1.44 (s, 9H, *t*-Bu), 2.46 (m, 2H, H-2), 3.40 (s, 1H, OH, D_2O exchangeable), 3.69 (m, 1H, H-4), 4.04 (m, 1H, H-3), 4.18 (q, $J=7.1$ Hz, 2H, OCH_2), 4.81 (s br, 1H, NHBoc). MS (ESI, *m*/*z*): 284 ($M+Na^+$, 7), 262 ($M+H^+$, 8), 233 (17), 232 (100). HRMS calcd for $[C_{12}H_{23}NO_5+H]^+$: 262.1649. Found: 262.1645. Anal. Calcd for $C_{12}H_{23}NO_5$: C, 55.17; H, 8.81; N, 5.36. Found: C, 55.46; H, 8.97; N, 5.61.

4.7. (4*S*,5*R*)-4-Benzyloxy-1-(4-methoxybenzyl)-5-cyclohexylmethyl-2-pyrrolidinone, (+)-18

Following the same procedure described for (+)-**13**, namely the treatment of the malimide (*S*)-**10** (2.397 g, 7.38 mmol) with cyclohexylmethyl magnesium bromide (1 mol/L, 22.1 mL, 22.1 mmol) at −10°C for 1.5 h then slowly warm up to 10°C (yield 73%), followed by the reaction of the resulting regio and diastereomeric mixture (2.272 g, 5.37 mmol) with $Et_3SiH/BF_3{\cdot}OEt_2$ (−78°C, 6 h; then rt, 11 h). **18** (1.437 g, yield 78%) was obtained as a colorless oil. $[\alpha]_D=+33.5$ (*c* 2.1, $CHCl_3$). IR (film) ν_{max}: 2900, 2830, 1688, 1610, 1510, 1445, 1243, 1063, 1028 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.78 (dm, $J=11.00$ Hz, 1H, *c*-hexCH_2), 0.91 (dm, $J=11.00$ Hz, 1H, *c*-hexCH_2), 1.14, 1.45, 1.54, 1.65, 1.73 (5×m, 11H, *c*-hex), 2.52 (d, $J=17.5$ Hz, 1H, H-3), 2.73 (dd, $J=6.0$, 17.5 Hz, 1H, H-3), 3.48 (dm, $J=8.0$ Hz, 1H, H-5), 3.80 (s and m superposed, 4H, OCH_3, H-4), 3.84 (d, $J=15.0$ Hz, 1H, NCH_2Ar), 4.37 (d, $J=12.0$ Hz, 1H, $PhCH_2O$), 4.45 (d, $J=12.0$ Hz, 1H, $PhCH_2O$), 5.02 (d, $J=15.0$ Hz, 1H, NCH_2Ar), 6.84, 7.18–7.32 (2m, 9H, H_{aro}) ppm. MS (EI, *m*/*z*): 407 (M^+, 34), 310 (6), 162 (19), 121 (100), 91 (33). HRMS calcd for $C_{26}H_{33}NO_3$: 407. 2460. Found: 407.2461.

4.8. (4*S*,5*R*)-4-Benzyloxy-5-cyclohexylmethyl-2-pyrrolidinone, (+)-19

Cleavage of the *N*-protecting group in (+)-**18** by CAN was performed as described for (+)-**13**, which afforded **19** (yield, 67%) as a white solid. Mp 96–98°C. $[\alpha]_D=+50.0$ (*c* 1.0, $CHCl_3$). IR (KBr) ν_{max}: 3180, 2900, 2820, 1680, 1645, 1445, 1280, 1260, 1062, 970, 730 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.91 (m, 2H, *c*-hexCH_2), 1.20–1.80 (m, 6H, $3CH_2$), 1.70 (m, 5H, *c*-hex), 2.41 (dd, $J=3.8$, 17.4 Hz, 1H, H-3), 2.63 (dd, $J=6.8$, 17.4 Hz, 1H, H-3), 3.72 (ddd, $J=2.9$, 5.4, 8.3 Hz, 1H, H-5), 3.86 (ddd, $J=2.9$, 3.8, 6.8 Hz, 1H, H-4), 6.27 (s, br, 1H, NH), 7.32 (m, 5H, H*aro*) ppm. MS (EI, *m*/*z*): 287 (M^+, 21), 270 (67), 196 (100), 91 (96). HRFABMS calcd for $[C_{18}H_{25}NO_2+H]^+$: 288.1958. Found: 288.1959. Anal. Calcd for $C_{18}H_{25}NO_2{\cdot}0.5H_2O$: C, 72.92; H, 8.86; N, 4.73. Found: C, 72.56; H, 8.57; N, 5.10.

4.9. (4*S*,5*R*)-4-Benzyloxy-1-(*tert*-butyloxycarbonyl)-5-cyclohexylmethyl-2-pyrrolidinone, (−)-20

N-Boc re-protection of (+)-**19** was performed as described for (+)-**14**, which afforded **20** (yield, 92%) as a colorless oil. $[\alpha]_D=-34.8$ (*c* 0.87, $CHCl_3$). IR (film) ν_{max}: 2900, 2830, 1780, 1747, 1710, 1450, 1365, 1307, 1148, 1065 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.90, 1.20, 1.40–1.90 (3m, 11H, *c*-hex), 1.52 (s, 9H, Bu-*t*), 2.58 (d, $J=17.9$ Hz, 1H, H-3), 2.75 (dd, $J=5.3$, 17.9 Hz, 1H, H-3), 3.78 (d, $J=5.3$ Hz, 1H, H-4), 4.23 (dd, $J=3.1$, 10.6 Hz, H-5), 4.48 (d, $J=12.2$ Hz, 1H, Bn), 4.58 (d, $J=12.2$ Hz, 1H, Bn), 7.30 (m, 5H, Ph) ppm. MS (EI, *m*/*z*): 331 (15), 287 (17), 270 (19), 225 (100), 196 (30), 91 (79). HRFABMS calcd for $[C_{23}H_{33}NO_4+H]^+$: 388.2482. Found: 388.2484.

4.10. (4*S*,5*R*)-1-(*tert*-Butyloxycarbonyl)-4-hydroxy-5-cyclohexylmethyl-2-pyrrolidinone, (−)-21

To a suspension of 10% Pd–C (260 mg) in formic acid (0.52 mL) and methanol (4.68 mL) was added dropwise a solution of **20** (260 mg, 0.672 mmol) in 10% HCO_2H–MeOH (5.2 mL) at room temperature. After being stirred at rt for 2 h, the reaction mixture was filtered through Celite and the residue washed with CH_2Cl_2. The filtrate was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. Flash chromatography purification (EtOAc/PE = 1:1) of the residue afforded **21** (181 mg, yield, 91%) as a white solid. Mp 113–114°C. $[\alpha]_D^{20}=-48.4$ (*c* 1.1, $CHCl_3$). IR (KBr) ν_{max}: 3391, 2924, 2851, 1774, 1718, 1452, 1367, 1295, 1155, 1045, 1023, 835, 779, 605 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.92–1.42 (m, 8H), 1.54 (s, 9H, Bu-*t*), 1.64–1.77 (m, 4H), 1.88 (m, 1H), 2.07 (s, 1H, OH, D_2O exchangeable), 2.42 (d, $J=18.0$ Hz, 1H, H-3), 2.88 (dd, $J=5.3$, 18.0 Hz, 1H, H-3), 4.10 (ddd, $J\approx2.0$, 3.2, 11.3 Hz, 1H, H-5), 4.16 (dd, $J\approx2.0$, 5.3 Hz, 1H, CHOH) ppm. MS (ESI, *m*/*z*): 320 ($M+Na^+$, 100), 274 (10), 242 (23), 218 (6). HRMS calcd for $[C_{16}H_{27}NO_4+NH_4]^+$: 315.2278. Found: 315.2278.

4.11. (3*S*,4*R*)-4-[(*tert*-Butyloxycarbonyl)amino]-5-cyclohexyl-3-hydroxypentanoic acid ethyl ester, (+)-22

Ring opening ethanolysis of (−)-**21** was performed as described for (−)-**9**, which afforded known **22** (yield, 95%) as a white solid. Mp 80–81°C (Lit.[23] mp 81–83°C). $[\alpha]_D^{20}=+21.5$ (*c* 1, MeOH) {Lit.[23] for (3*R*,4*S*)-**22**, $[\alpha]_D=-16.7$ (*c* 1.6, MeOH)}. IR (KBr) ν_{max}: 3380, 2959, 2926, 2855, 1728, 1514, 1465, 1275, 1171, 1124, 1073, 1040, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.82 (m, 1H), 1.00 (m, 1H), 1.20–1.40 (m, 9H, containing 3H, t, at δ 1.27, $J=7.14$ Hz), 1.45 (s, 9H, Bu-*t*), 1.62–1.72 (m, 4H), 1.85 (m, 1H), 2.46 (m, 2H, CH_2CO), 3.38 (s, 1H, OH), 3.70 (m, 1H, CHN), 3.98 (m, 1H, CHOH), 4.17 (q, $J=7.14$ Hz, 2H, CH_2Me), 4.53 (br, 1H, NH) ppm. MS (ESI, *m*/*z*): 366 ($M+Na^+$, 100), 274 (10), 218 (7). HRMS calcd for $[C_{18}H_{33}NO_5+H]^+$: 344.2431. Found: 344.2432.

4.12. (4*S*,5*R*)-4-Benzyloxy-1-(4-methoxybenzyl)-5-(1-methylprop-2-enyl)-2-pyrrolidinone, 25 and (3*S*,5*RS*)-3-benzyloxy-1-(1-methoxybenzyl)-5-(1-methylprop-2-enyl)-2-pyrrolidinone, 26

Following the same procedure described for (+)-**13**, namely the treatment of the malimide (*S*)-**10** (219 mg, 0.674 mmol) with freshly prepared crotyl magnesium chloride at −78°C for 2.5 h, followed by the reaction of the resulting regio and diastereomeric mixture with $Et_3SiH/BF_3{\cdot}OEt_2$ (−78°C, 8 h; then rt, 32 h), **25** (159 mg, yield 65%) and **26** (72 mg, yield 29%) were obtained both as a colorless oil. Regioisomer **25** is a mixture of two diastereomers **25a** and **25b** (ratio, 68:32): IR (film) ν_{max}: 2962, 2931, 1690, 1513, 1454, 1247, 1176, 1090, 1030, 739, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.84 (d, $J=7.0$ Hz, 0.96H, CH_3C-1′, **25a**), 1.02 (d, $J=7.0$ Hz, 2.04H, CH_3C-1′, **25b**), 2.71–2.44 (m, 3H, 2H-3 and H-1′, **25a**,**b**), 3.45 (dd, $J=1.1$, 3.5 Hz, 0.68 H, H-5, **25a**), 3.53 (dd, $J=1.1$, 4.0 Hz, 0.32 H, H-5, **25b**), 3.79 (s, 3H, OCH_3, **25a**,**b**), 3.86 (pseudo dt, overlapped, $J=1.1$, 6.5 Hz, H-4, 1H, **25a**,**b**), 3.91 (d, $J=15.0$ Hz, NCH_2-Ph, **25b**), 3.92 (d, $J=15.0$ Hz, overlapped with δ 3.91, NCH_2-Ph, 1H, **25a**), 4.31, 4.36 and 4.43, 4.47 (each d, overlapped, $J=11.4$, 11.71, 11.4, 11.7 Hz, 2H, OCH_2-Ph, **25a**,**b**), 5.18–4.90 (m, 3H, 2 H-3′ and NCH_2), 5.58 (ddd, $J=6.6$, 10.5, 17.1 Hz, 1H, H-2′, **25a**), 5.72 (ddd, $J=6.2$, 10.8, 17.0 Hz, 1H, H-2′, **25b**), 6.84 (d, $J=8.6$ Hz, 2H, PMB, **25a**,**b**), 7.40–7.10 (m, 7H, Ph and PMB, **25a**,**b**) ppm. MS (ESI, m/z): 388 ($M+Na^+$, 33), 366 ($M+H^+$, 100), 274 (27). Regioisomer **26** is a mixture of four diastereomers (ratio, **26a**:**26b**:**26c**:**26d** = 27:13:18:42): IR (film) ν_{max}: 2961, 2932, 1693, 1513, 1454, 1304, 1247, 1176, 1109, 1031, 737, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.79 (d, $J=7.0$ Hz, 0.81H, CH_3C-1′, isomer **26a**), 0.81 (d, $J=6.6$ Hz, 0.39H, CH_3C-1′, isomer **26b**), 0.89 (d, $J=7.0$ Hz, 0.54H, CH_3C-1′, isomer **26c**), 0.94 (d, $J=7.0$ Hz, 1.26H, CH_3C-1′, isomer **26d**), 1.86 (m, 1H, H-4, 4 isomers), 2.05 (m, 1H, H-4, 4 isomers), 2.80–2.50 (m, 1H, H-1′, 4 isomers), 3.60–3.41 (m, 1H, H-5, 4 isomers), 3.78 (m, 3H, OCH_3, 4 isomers), 3.86 (m, 1H, NCH_2, 4 isomers), 4.15 (m, 1H, H-3, 4 isomers), 4.76 (m, 1H, OCH_2-Ph, 4 isomers), 5.04 (m, 4H, 2 H-8, NCH_2 and OCH_2-Ph, 4 isomers), 5.59 (m, 1H, H-7), 6.80 (m, 2H, PMB, 4 isomers), 7.40–7.10 (m, 7H, Ph and PMB, 4 isomers) ppm. MS (ESI, m/z): 388 ($M+Na^+$, 19), 366 ($M+H^+$, 100), 274 (15).

4.13. (*S*)-1-Benzyl-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-2,5-dione, (−)-29

A mixture of (*S*)-1-benzylmalimide[12a,b] (270 mg, 1.32 mmol), TBDMSCl (250 mg, 1.67 mmol), imidazole (234 mg, 3.44 mmol) and DMF (1 mL) was stirred at 40°C for 24 h and quenched with glacial H_2O (1 mL). The resulting mixture was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel to provide compound **29** (302 mg, 94% based on the recovered staring material, 63 mg, 12%) as a white solid. Mp 75.5–77.0°C. $[\alpha]_D^{20}=$ −41.2 (*c* 1.2, $CHCl_3$). IR (film) ν_{max}: 2956, 2929, 2857, 1712, 1398, 1345, 1257, 1164, 1147, 1106, 949, 836, 781 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.16 (s, 3H, CH_3), 0.17 (s, 3H, CH_3), 0.95 (s, 9H, 3×CH_3), 2.60 (dd, $J=18.0$, 4.4 Hz, 1H, H-4), 3.00 (dd, $J=18.0$, 8.1 Hz, 1H, H-4), 4.56 (dd, $J=8.1$, 4.4 Hz, 1H, H-3), 4.60 (d, $J=14.1$ Hz, 1H, $PhCH_2$), 4.68 (d, $J=14.1$ Hz, 1H, $PhCH_2$), 7.20–7.40 (m, 5H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 176.99, 174.55, 136.22, 129.48, 128.75, 68.73, 68.53, 43.02, 39.53, 26.28, 18.91, −3.96, −4.59 ppm. MS (ESI, m/z): 342 ($M+Na^+$, 100), 337 (39), 320 ($M+H^+$, 71), 304 (50), 274 (29). Anal. Calcd for $C_{17}H_{25}NO_3Si{\cdot}0.25H_2O$: C, 63.04; H, 7.94; N, 4.32. Found: C, 63.39; H, 8.01; N, 4.46.

4.14. (4*S*,5*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-benzyl-2-pyrrolidinone, (+)-33 and (3*S*,5*RS*)-4-(*tert*-butyldimethylsilyloxy)-1-benzyl-2-pyrrolidinone, 35

Following the procedure described for (+)-**13**, namely the treatment of the malimide (*S*)-**29** (450 mg, 1.41 mmol) with methyl magnesium iodide at −15°C for 1 h, followed by the reaction of the resulting regio and diastereomeric mixture (**30** 178 mg and **31** 135 mg) with $Et_3SiH/BF_3{\cdot}OEt_2$ (−78°C, 4 h; then warm up), **33**/**34** (136 mg, yield 65%, **33**/**34** = 82:28) and **35** (114 mg, as a 3:1 diastereomeric mixture, yield 29%) were obtained. A sample of pure **33** was obtained after further column chromatography purification on silica gel. Regioisomer **33**: colorless oil. $[\alpha]_D^{20}=+58.1$ (*c* 1.2, $CHCl_3$). IR (film) ν_{max}: 2955, 2929, 2856, 1697, 1411, 1252, 1112, 1069, 927, 831, 777 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: −0.01 (s, 3H, CH_3), 0.04 (s, 3H, CH_3), 0.85 (s, 9H, 3×CH_3), 1.11 (d, $J=6.6$ Hz, 3H, CH_3), 2.35 (dd, $J=3.3$, 16.9 Hz, 1H, H-3), 2.71 (dd, $J=6.1$, 16.9 Hz, 1H, H-3), 3.32 (dq, $J=2.6$, 6.6 Hz, 1H, H-5), 3.92 (d, $J=15.5$ Hz, 1H, $PhCH_2$), 3.97 (m, 1H, H-4), 5.06 (d, $J=15.5$ Hz, 1H, $PhCH_2$), 7.20–7.40 (m, 5H, Ph) ppm. MS (ESI, m/z): 321 (M^++H, 100), 278 (7), 254 (6), 92 ($PhCH_2^+$, 3). Regioisomer **35** (as a 3:1 diastereomeric mixture): colorless oil. IR (film) ν_{max}: 2950, 2929, 2856, 1704, 1420, 1361, 1253, 1144, 1080, 984, 837, 779, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): major diastereomer δ: 0.18 (s, 3H, CH_3), 0.20 (s, 3H, CH_3), 0.93 (s, 9H, 3×CH_3), 1.12 (d, $J=8.4$ Hz, 3H, CH_3), 1.88 (m, 1H, H-4), 2.04 (m, 1H, H-4), 3.57 (m, 1H, H-5), 3.97 (d, $J=15.0$ Hz, 1H, $PhCH_2$), 4.41 (t, $J=6.4$ Hz, 1H, H-3), 4.97 (d, $J=15.0$ Hz, 1H, $PhCH_2$), 7.20–7.40 (m, 5H, Ph) ppm; minor diastereomer δ: 0.17 (s, 3H, CH_3), 0.20 (s, 3H, CH_3), 0.94 (s, 9H, 3×CH_3), 1.21 (d, $J=6.4$ Hz, 3H, CH_3), 1.56 (m, 1H, H-4), 2.43 (m, 1H, H-4), 3.37 (m, 1H, H-5), 4.04 (d, $J=14.9$ Hz, 1H, $PhCH_2$), 4.37 (t, $J=7.8$ Hz, 1H, H-3), 4.96 (d, $J=14.9$ Hz, 1H, $PhCH_2$), 7.20–7.40 (m, 5H, Ph) ppm. MS (ESI, m/z): 321 (M^++H, 100), 305 (20).

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