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N-Benzyloxymalimide for an easy access to 5-alkyl-3-pyrrolin-2-ones: asymmetric synthesis of the mixed imide substructure of the potent immunosuppressant microcolin B

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ABSTRACT

O-Benzyl-*N*-benzyloxymalimide **12** has been synthesized as a useful variant of the chiral building blocks **9**. The advantage of the malimide **12** over **9** was demonstrated by mild and high-yielding reductive N-deprotection of *N*-benzyloxylactams **18a**–**i** to give a series of (4*R*,5*S*)-5-alkyl-4-hydroxy-pyrrolidin-2-ones, which are key intermediates for the asymmetric synthesis of pyrrolidines, pyrrolizidines, and indolizidines, as well as β-hydroxy γ-amino acids. Lactam *ent*-**11a** has been applied to the synthesis of the mixed imide **25**, a key intermediate for the total synthesis of microcolin B, which also demonstrated that lactam *ent*-**11a** or **11a** can serve as a latent form of the 5-methyl-3-pyrrolin-2-one substructure of majusculamide D **4**, deoxymajusculamide D, and the jamaicamides A–C.

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1. Introduction

Protected *trans*- or *cis*-5-alkyl-4-hydroxy-pyrrolidin-2-ones **A** (Fig. 1) are versatile intermediates for the synthesis of 3-pyrrolidinol-containing alkaloids such as preussin,[1a] pyrrolizidine,[1b] and indolizidine alkaloids;[1c] naturally occurring *anti*- or *syn*-β-hydroxy γ-amino acid residues **B**/**C**,[2] as well as 5-alkyl-3-pyrrolin-2-ones[3] **D** (Fig. 1). 5-Alkyl-3-pyrrolin-2-ones **D** are found in several bioactive natural products,[4] such as the immunosuppressive agents microcolins A, B, and D (**1**–**3**, Fig. 2),[5] cytotoxins majusculamide **4** and deoxymajusculamide D,[6] jamaicamides A–C (e.g., **5**–**7**),[7] and feeding deterrent ypaoamide **8**.[8]

Microcolins A **1** and B **2** were isolated from a Venezuelan sample of the blue–green alga *Lyngbya majuscule*,[5] which exhibited very potent immunosuppressive and antiproliferative properties.[5,9,10] It has been shown that microcolins A **1** and B **2** (EC_{50} = 0.02 and 4.1 nM, respectively) are more potent inhibitors of the human two-way mixed lymphocyte response (MLR) than FK506 and cyclosporin A (EC_{50} = 20 and 23 nM, respectively), two drugs currently in clinical use in transplantation. In addition, the 3-pyrrolin-2-one moiety has been shown to be mandatory for the immunosuppressive activity.[10] Microcolins B **2** and D **3** significantly inhibited adhesion cell (IC_{50} = 0.15 and 0.9 μM, respectively), without producing a cytotoxic effect on either HL-60 or CHO-ICAM-1 cells.[11] The total syntheses of microcolins A **1**[12] and B[13] **2** as well as several synthetic analogues of microcolin A have been reported for both biological testing[9,10] and development of novel biological probes.[14] On the other hand, the jamaicamides exhibited sodium channel blocking properties at 5 μM as well as moderate cytotoxicity activities against the H-460 human lung and neuro-2a mouse neuroblastoma cell lines with LC_{50} about 15 μM.

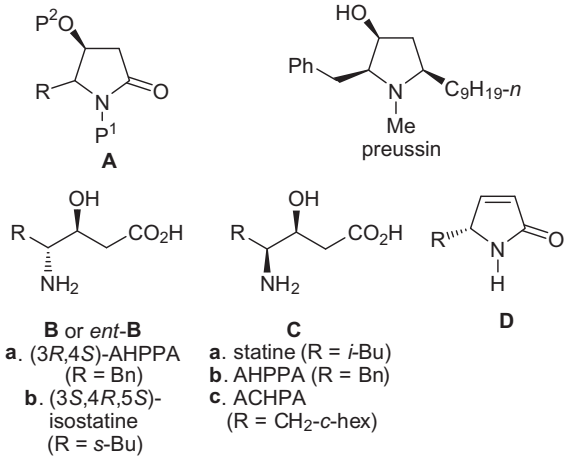

Figure 1. 5-Alkyl-4-hydroxy-pyrrolidin-2-ones **A** as versatile synthetic intermediates.

The synthesis of 5-alkyl-3-pyrrolin-2-one substructures is a key in the total synthesis of these natural products.[12,13] Although several methods have been reported for the synthesis of alkyl-3-pyrrolin-2-ones,[12,13,15,16] most of them used α-amino acids as the

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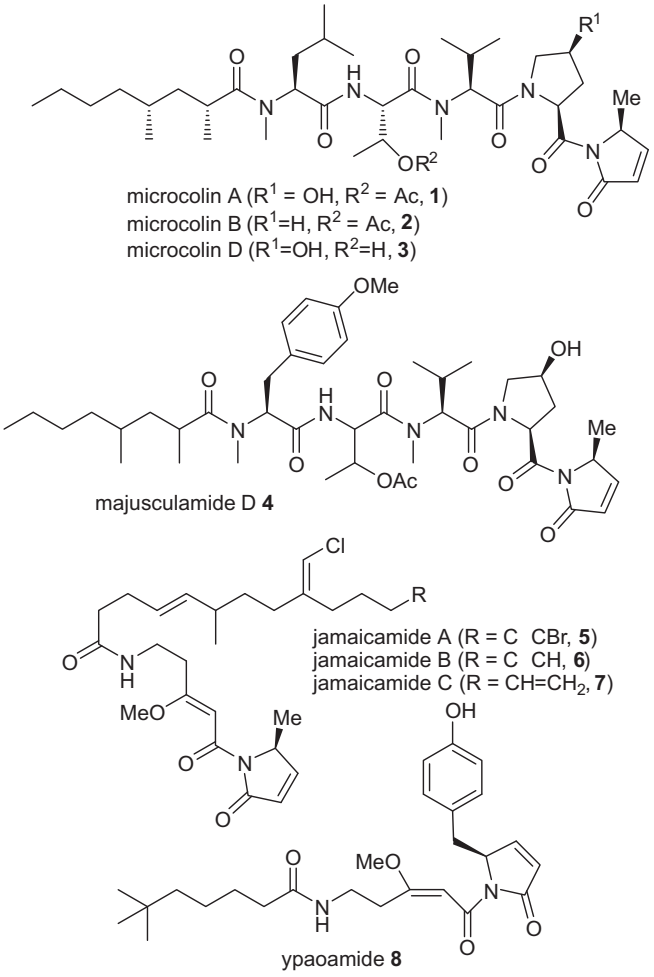


Figure 2. Some 5-alkyl-3-pyrrolin-2-one substructure-containing natural products.

starting materials,[12,13,15] which might suffer from partial racemization,[13b,15b,d] and a lack of generality. A non-amino acid-based approach would offer a greater flexibility for the synthesis of analogues bearing different C-5 substituents, which is crucial for SAR studies. In addition, methods allowing the cleavage of *N*-protecting group under racemization-free conditions to give the required 5-alkyl-3-pyrrolin-2-one substructures are even rare.[16a,b]

In recent years, we have been engaged in the development of the protected (*S*) or (*R*)-malimides **9** as versatile chiral building blocks for the asymmetric synthesis of *N*-containing bioactive natural products.[17] In this methodology, after the key *trans*- or *cis*-diastereoselective reductive alkylation reactions (Fig. 3, **9**–**10**), the smooth and efficient conversion of the 5-alkyl-4-hydroxy-pyrrolidin-2-ones **10**–**11** by *N*-deprotection turned out to be another key step in the synthesis of natural products such as melleumin A,[18a] pyrrolam A,[18b] and ypaoamide[18c] **8**. In this regard, *p*-methoxybenzyl group (PMB)[17a,18b] and allyl group[17,18a,c] were introduced as the *N*-protecting groups, which, at the stage of lactams **10**, could

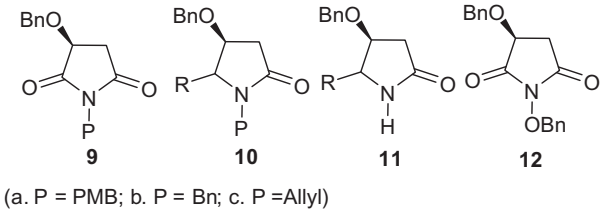


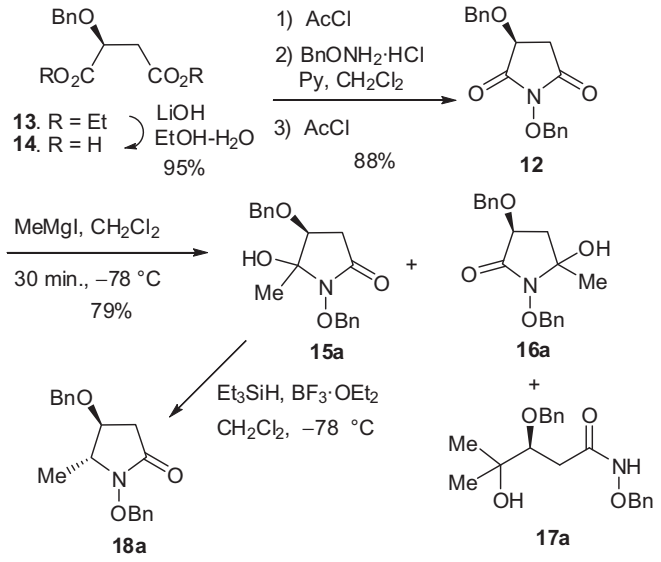
Figure 3.

be cleaved with either ceric ammonium nitrate (CAN, oxidative deprotection),[19] or $RhCl_3 \times H_2O$ (isomerization-hydrolysis).[20] In view of the importance of the protecting group strategy in the total synthesis of natural products,[21] we investigated the use of OBn as an imides/amides *N*-protecting group,[22] which has been shown to be cleavable under mild conditions with SmI_2.[23,24] Herein, we report the synthesis and regio-/diastereoselective reductive alkylation of malimide **12**, as well as the synthesis of the mixed imide **25**, a key intermediate for the total synthesis of microcolin B.

2. Results and discussion

The work started with the synthesis of (*S*)-malimide **12** from (*S*)-malic acid and commercially available *O*-benzylhydroxylamine hydrochloride salt. Thus, the *O*-benzylmalic acid **14** was prepared from the known diethyl *O*-benzylmalate **13** by saponification (Scheme 1). The condensation of *O*-benzylmalic acid **13** with *O*-benzylhydroxylamine hydrochloride salt by a one-pot three-step procedure[25] led smoothly to the formation of malimide **12** in 88% overall yield.

After outlining the route to the malimide **12**, we proceeded to investigate its reductive alkylation. Treatment of *O*,*O*′-bisbenzyl-1-hydroxymalimide **12** with methyl magnesium iodide in CH_2Cl_2 at −78 °C for 30 min resulted in the formation of the desired C-2 adduct **15a** in 79% yield, along with small amounts of C-5 adduct **16a** and dimethylated side product **17a**. The C-2/C-5 regioselectivity was 95:5. The C-2 addition product **15a** is a mixture of two diastereomers in a 1.3:1 ratio as indicated by ^1H NMR analysis. It was observed that the ratio improved to 9.3:1 upon standing the mixture at 0–5 °C for seven days. Recrystallization then gave the pure major diastereomer, whose stereochemistry was determined as *trans* by NOESY experiments (Fig. 4).



Scheme 1.

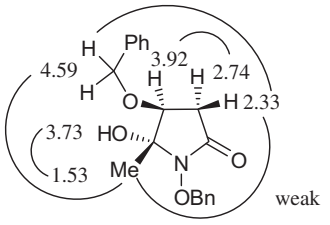
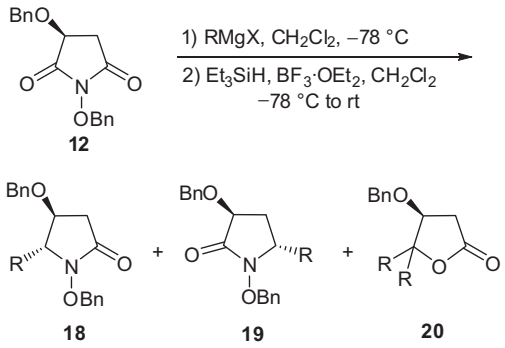


Figure 4. Observed NOESY correlations (in part) of compound *trans*-**15a**.

After securing the highly regioselective Grignard reagent addition to malimide **12**, the reductive alkylation of **12** was studied. Thus, the reaction mixture, obtained from the methyl Grignard reagent addition, was subjected to boron trifluoride etherate-mediated triethylsilane reduction[26] to give predominantly **18a**, along with small amounts of isomeric lactam **19a** and lactone **20a** (Scheme 2). The stereochemistry of compounds **18** was assigned as *trans* according to the observed vicinal coupling constants[27] ($J_{4,5}$ = 3.3 Hz for **18a**). This was further confirmed by the conversion of compound **18a** to the known compound **25**.[13] Extension of this procedure to other Grignard reagents led to corresponding products **18b–i** in similar regioselectivity (Table 1, entries 3–10).



Scheme 2.

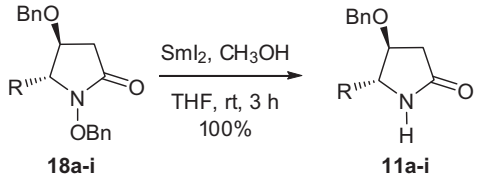
Table 1
Reductive alkylation of malimide **12** and subsequent cleavages of the *N–O* bonds

Entry	RMgX	Regioselectivity (C2/C5)[a]	*N*-Benzyloxylactams **18** (% yield from **12**)[b]	Lactams **11** (% yield from **18**)[b]
1	MeMgI	95:5	**18a** (65)	**11a** (100)
2	MeMgI	95:5	*ent*-**18a**[c] (65)	*ent*-**11a**[c] (100)
3	EtMgBr	93:7	**18b** (64)	**11b** (91)
4	*n*-PrMgBr	92:8	**18c** (65)	**11c** (96)
5	*i*-PrMgBr	91:9	**18d** (73)	**11d** (94)
6	*n*-BuMgBr	91:9	**18e** (60)	**11e** (93)
7	*i*-BuMgBr	90:10	**18f** (74)	**11f** (100)
8	n-C_7H_{15}MgBr	92:8	**18g** (59)	**11g** (91)
9	n-C_8H_{17}MgBr	91:9	**18h** (62)	**11h** (100)
10	PhMgBr	88:12	**18i** (64)	**11i** (95)

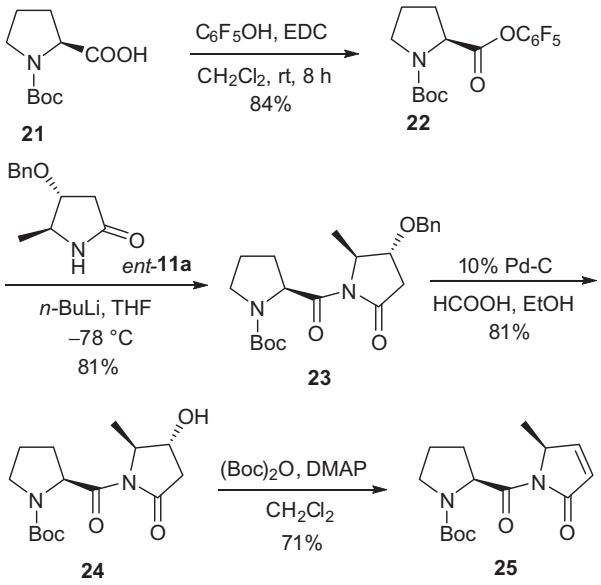
[a] Ratio determined by chromatographic separation.
[b] Isolated yield.
[c] Synthesized from (*R*)-malic acid.

As a demonstration of the suitability of compounds **18a–i** as ready precursors of the lactams **11a–i**, cleavages of the *N–O* bonds in compound **18a–i** were undertaken. Although a number of methods have been reported for the cleavage of the *N–O* bond, including the two-step procedure (*O*-debenzylation-SmI_2-mediated cleavage) reported by Keck,[23a] we elected to undertake a direct SmI_2-mediated cleavage of this *N–O* bond. To our satisfaction, in the presence of 10 mol equiv of methanol, the reaction of *N*-benzyloxylactam **18a** with 4 mol equiv of SmI_2 in THF (0.1 M, rt, 3 h) cleanly produced the desired lactam **11a** in quantitative yield (Scheme 3 and Table 1, column 4, entry 1). The SmI_2-mediated cleavage of *N–O* bond compound **18b–i** gave the corresponding 5-alkylpyrrolidin-2-one derivatives **11a–i** in 91–100% yields (Table 1, column 4, entries 3–10).

To demonstrate the feasibility of lactams **11a–i** to serve as a latent form of the corresponding 5-alkyl-3-pyrrolin-2-ones **D**, we undertook the synthesis of the mixed imide portion **25** of microcolin B **2**. For this purpose, L-proline was converted successively to Boc-(*S*)-proline **21** and pentafluorophenyl ester[28] **22** by butoxycarbonylation (Boc_2O, NEt_3, CH_2Cl_2, 0 °C), and EDC-mediated coupling (C_6F_5OH, EDC, CH_2Cl_2, rt, 8 h) (Scheme 4). Treatment of the lactam *ent*-**11a**, prepared from (*R*)-malic acid according to Schemes 1–3, with *n*-butyllithium in THF at −78 °C gave the imidate intermediate that was subjected to reaction with the activated ester **22** to yield the mixed imide **23** in 81% yield. The debenzylation of **23** was achieved by catalytic transfer hydrogenation (HCO_2H, 10% Pd/C, EtOH), which gave alcohol **24** in 81% yield. For the transformation of compound **24** to the final product **25**, two methods were adopted. The first approach consisted of the treatment of a CH_2Cl_2 solution of **24** with $(Boc)_2O$ (1.0 mol equiv)/DMAP (0.1 mol equiv) at 0 °C, which afforded directly the desired product **25** in 71% yield {$[\alpha]_D^{20} = -80$ (*c* 1.0, $CHCl_3$)}; lit. $[\alpha]_D^{20} = -85$ (*c* 1.1, $CHCl_3$);[13a] $[\alpha]_D^{20} = -92$ (*c* 1, $CHCl_3$) for a 5:1 diastereomeric mixture[13b]}. When the reaction was run at 30 °C, partial racemization occurred as indicated by the optical rotation of the product {$[\alpha]_D^{20} = -64$ (*c* 1.0, $CHCl_3$)}. The second method afforded a better yield. In the event, compound **24** was allowed to react with MsCl/Et_3N at −20 °C for 1 h. During the work-up procedure, elimination of the mesylate intermediate occurred spontaneously to give the desired compound **25** in 83% yield {$[\alpha]_D^{20} = -80$ (*c* 1.0, $CHCl_3$)}.



Scheme 3.



Scheme 4.

3. Conclusion

In summary, by using *O*-benzyl-*N*-benzyloxymalimide **12** as a useful variant of the building blocks **9**, the longstanding problem associated with the difficulties in the *N*-deprotection of the lactams obtained from the building blocks **9** has been resolved. *N*-benzyloxymalimide **12** not only keeps the high regio- and diastereoselectivities in the reductive alkylation reactions, but also affords the advantage of allowing a high-yielding N-deprotection of the resultant *N*-benzyloxylactams under very mild conditions. Using this method, the asymmetric synthesis of the mixed imide substruc-

ture **25** of the potent immunosuppressant microcolin B has been disclosed. This method thus detached a flexible non-amino acid-based approach to different 5-alkyl-3-pyrrolin-2-ones **D**, which are found as key substructures in several bioactive natural products.

4. Experimental section

4.1. General

Melting points were determined on a WRS-1B 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 Bruker Av 400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus liquid chromatography–mass spectrum (direct injection). HRMS spectra were recorded on a Shimadzu LC–MS-IT-TOF apparatus. Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90 °C) mixture. THF was distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

4.2. Preparation of compounds 13 and *ent*-13

4.2.1. Diethyl (*S*)-2-(benzyloxy)succinate 13

To a mixture of diethyl (*S*)-malate (2.15 g, 11.32 mmol), Ag_2O (5.25 g, 22.64 mmol), and EtOAc (37.7 mL) was added BnBr (2.0 mL, 16.98 mmol). After stirring in the dark for five days at room temperature, the mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1:20) to give compound **13** (3.01 g, yield: 95%) as a colorless oil. $[\alpha]_D^{20} = -59.9$ (*c* 1.2, $CHCl_3$);[29] IR (film) ν_{max}: 2983, 1737, 1274, 1162, 1120, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.28 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.76 (dd, *J* = 7.8, 16.0 Hz, 1H, $CH_2C{=}O$), 2.81 (dd, *J* = 5.2, 16.0 Hz, 1H, $CH_2C{=}O$), 4.136 (q, *J* = 7.1 Hz, 1H, OCH_2CH_3), 4.144 (q, *J* = 7.1 Hz, 1H, OCH_2CH_3), 4.21 (q, *J* = 7.1 Hz, 1H, OCH_2CH_3), 4.22 (q, *J* = 7.1 Hz, 1H, OCH_2CH_3). 4.39 (dd, *J* = 5.2, 7.8 Hz, 1H, CHOBn), 4.54 (d, *J* = 11.4 Hz, 1H, OCH_2Ph), 4.77 (d, *J* = 11.4 Hz, 1H, OCH_2Ph), 7.27–7.36 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 (2C), 37.9, 60.7, 61.1, 72.9, 74.6, 127.8, 127.9, 128.2, 137.2, 169.9, 171.2; MS (ESI): *m*/*z* 303 (M+Na$^+$, 100).

4.2.2. Diethyl (*R*)-2-(benzyloxy)succinate *ent*-13

$[\alpha]_D^{20} = +59.9$ (*c* 1.0, $CHCl_3$).

4.3. Preparation of compounds 14 and *ent*-14

4.3.1. (*S*)-2-(Benzyloxy)succinic acid 14

A mixture of malate derivative **13** (3.01 g, 10.75 mmol) and $LiOH{\cdot}H_2O$ (1.81 g, 43.00 mmol) in 20.3 mL of EtOH–H_2O (3:1) was stirred overnight at 0–5 °C. The solvent was removed under reduced pressure. The residue was acidified by a concentrated HCl to reach pH 2. After concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel to yield compound **14** (2.36 g, yield: 98%) as white crystals (lit.[30] mp 60–61 °C). $[\alpha]_D^{20} = -56.9$ (*c* 1.9, CH_3OH); IR (film) ν_{max}: 3411, 1598, 1415, 1092 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.22 (dd, *J* = 8.3, 16.2 Hz, 1H, CH_2COOH), 3.35 (dd, *J* = 4.5, 16.2 Hz, 1H, CH_2COOH), 4.90 (dd, *J* = 4.5, 8.3 Hz, 1H, CHOBn), 5.02 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 5.25 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 7.70–7.84 (m, 5H, Ph-*H*), 10.83 (br s, 2H, COO*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 47.8, 82.9, 85.2, 138.0, 138.2, 138.6, 148.5, 181.7, 182.7; MS (ESI): *m*/*z* 247 (M+Na$^+$, 100).

4.3.2. (*R*)-2-(Benzyloxy)succinic acid *ent*-14

White semi-solid; $[\alpha]_D^{20} = +49.6$ (*c* 1.2, CH_3OH).

4.4. Preparation of compounds 12 and *ent*-12

4.4.1. (*S*)-1,3-Dibenzyloxypyrrolidin-2,5-dione 12

A mixture of the known (*S*)-2-(benzyloxy)succinic acid **14** (1.78 g, 7.95 mmol) and AcCl (2.8 mL, 39.75 mmol) was refluxed for 2 h and then concentrated under reduced pressure. To the resulting mixture were added successively $BnONH_2{\cdot}HCl$ (1.39 g, 8.74 mmol) and CH_2Cl_2 (26.5 mL). The mixture was cooled to 0–5 °C and then pyridine (1.3 mL, 16.69 mmol) was added dropwise. The resultant mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the residue was dissolved in AcCl (2.8 mL, 39.75 mmol) and refluxed for 2 h. After concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1:5) to give compound **12** (2.17 g, yield: 88%) as white crystals. Mp 115 °C (Et_2O/EtOAc = 7:1); $[\alpha]_D^{20} = -90.2$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 1727, 1497, 1456, 1388, 1222, 1208, 1068, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.60 (dd, *J* = 3.7, 18.0 Hz, 1H, H-4), 2.91 (dd, *J* = 8.3, 18.0 Hz, 1H, H-4), 4.27 (dd, *J* = 3.7, 8.3 Hz, 1H, H-3), 4.74 (d, *J* = 11.7 Hz, 1H, $CHOCH_2Ph$), 4.95 (d, *J* = 11.7 Hz, 1H, $CHOCH_2Ph$), 5.12 (s, 2H, $NOCH_2Ph$), 7.31–7.49 (m, 10H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.2, 69.3, 72.9, 78.8, 128.2, 128.3, 128.5, 128.6, 129.5, 129.9, 133.1, 136.4, 168.6, 170.2; MS (ESI): *m*/*z* 350 (M+K$^+$, 100). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.80; H, 5.63; N, 4.71.

4.4.2. (*R*)-1,3-Dibenzyloxypyrrolidin-2,5-dione *ent*-12

Mp 114 °C; $[\alpha]_D^{20} = +90.0$ (*c* 1.2, $CHCl_3$).

4.5. Typical procedure for the reductive alkylation of *N*-benzyloxymalimide 12

To a cooled (−78 °C) solution of malimide **12** (100 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (6.4 mL) was added dropwise a solution of CH_3MgI (2 M, 0.35 mL, 0.70 mmol) in Et_2O under a nitrogen atmosphere. After stirring at −78 °C for 30 min, the reaction was quenched with saturated NH_4Cl (0.5 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Filtration through a short pad of column gave a mixture of compounds **15a**, **16a**, and **17a**, which was used as it was in the next step.

The mixture of **15a**, **16a**, and **17a** was dissolved in anhydrous CH_2Cl_2 (3.2 mL) under a nitrogen atmosphere. The solution was cooled to −78 °C, then Et_3SiH (0.51 mL, 3.21 mmol) and $BF_3{\cdot}OEt_2$ (0.12 mL, 0.96 mmol) were added. After stirring at −78 °C for 3 h, the reaction temperature was allowed to rise slowly to room temperature overnight and then the reaction was quenched by a saturated $NaHCO_3$ (0.6 mL). After extraction with CH_2Cl_2 (3 × 10 mL), the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1:3) to give compound **18a** (65 mg, yield over two steps: 65%).

4.5.1. (4*S*,5*R*)-1,4-Dibenzyloxy-5-methylpyrrolidin-2-one 18a

Compound **18a**: colorless oil. Yield over two steps: 65%. $[\alpha]_D^{20} = +89.7$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3034, 2963, 2930, 2872, 1715, 1453, 1379, 1101, 1064 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ: 1.17 (d, J = 6.5 Hz, 3H, CH_3), 2.38 (dd, J = 3.7, 17.3 Hz, 1H, H-3), 2.64 (dd, J = 7.3, 17.3 Hz, 1H, H-3), 3.53 (dq, J = 3.3, 6.5 Hz, 1H, H-5), 3.69 (ddd, J = 3.3, 3.7, 7.3 Hz, 1H, H-4), 4.40 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.45 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.96 (d, J = 10.7 Hz, 1H, $NOCH_2Ph$), 5.00 (d, J = 10.7 Hz, 1H, $NOCH_2Ph$), 7.28–7.44 (m, 10H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.4, 34.4, 59.5, 70.7, 75.3, 76.5, 127.3, 127.7, 128.2 (2C), 128.5, 129.3, 134.8, 137.0, 167.8; MS (ESI): m/z 334 (M+Na$^+$, 100). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.90; H, 6.65; N, 4.90.

4.5.2. (4*R*,5*S*)-1,4-Dibenzyloxy-5-methylpyrrolidin-2-one *ent*-18a

$[\alpha]_D^{20} = -95.5$ (c 1.2, $CHCl_3$).

4.5.3. (4*S*,5*R*)-1,4-Dibenzyloxy-5-ethylpyrrolidin-2-one 18b

Compound **18b**: colorless oil. Yield over two steps: 64%. $[\alpha]_D^{20} = +86.8$ (c 1.2, $CHCl_3$); IR (film) ν_{max}: 3029, 2963, 2930, 1714, 1458, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (t, J = 7.5 Hz, 3H, CH_3), 1.43 (qdd, J = 7.5, 8.0, 15.1 Hz, 1H, CH_2CH_3), 1.74 (dqd, J = 3.8, 7.5, 15.1 Hz, 1H, CH_2CH_3), 2.40 (dd, J = 2.5, 17.4 Hz, 1H, H-3), 2.61 (dd, J = 7.2, 17.4 Hz, 1H, H-3), 3.39 (ddd, J = 2.3, 3.8, 8.0 Hz, 1H, H-5), 3.77 (ddd, J = 2.3, 2.5, 7.2 Hz, 1H, H-4), 4.38 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.42 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.98 (d, J = 11.0 Hz, 1H, $NOCH_2Ph$), 5.00 (d, J = 11.0 Hz, 1H, $NOCH_2Ph$), 7.28–7.45 (m, 10H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.0, 23.3, 34.9, 64.8, 70.6, 73.1, 77.0, 127.5, 127.9, 128.4 (2C), 128.7, 129.5, 135.0, 137.2, 167.8; MS (ESI): m/z 348 (M+Na$^+$, 100). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.62; H, 6.83; N, 3.92.

4.5.4. (4*S*,5*R*)-1,4-Dibenzyloxy-5-propylpyrrolidin-2-one 18c

Compound **18c**: colorless oil. Yield over two steps: 65%. $[\alpha]_D^{20} = +88.7$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 2956, 2933, 1713, 1453, 1069 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.2 Hz, 3H, CH_3), 1.18–1.37 (m, 3H, $C_2H_4CH_3$), 1.63–1.71 (m, 1H, CH_2CHN), 2.38 (dd, J = 2.4, 17.4 Hz, 1H, H-3), 2.60 (dd, J = 7.2, 17.4 Hz, 1H, H-3), 3.42 (ddd, J = 2.2, 4.0, 7.8 Hz, 1H, H-5), 3.75 (ddd, J = 2.2, 2.4, 7.2 Hz, 1H, H-4), 4.37 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.41 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.97 (d, J = 11.0 Hz, 1H, $NOCH_2Ph$), 4.99 (d, J = 11.0 Hz, 1H, $NOCH_2Ph$), 7.25–7.45 (m, 10H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 18.1, 32.7, 34.8, 63.6, 70.6, 73.7, 77.0, 127.5, 127.8, 128.4 (2C), 128.7, 129.5, 135.1, 137.3, 167.7 ppm. MS (ESI): m/z 340 (M+H$^+$, 100). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.33; H, 7.39; N, 4.15.

4.5.5. (4*S*,5*R*)-1,4-Dibenzyloxy-5-isopropylpyrrolidin-2-one 18d

Compound **18d**: colorless oil. Yield over two steps: 73%. $[\alpha]_D^{20} = +69.5$ (c 1.3, $CHCl_3$); IR (film) ν_{max}: 2969, 2928, 1707, 1449, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.78 (d, J = 6.9 Hz, 3H, $CHCH_3$), 0.91 (d, J = 6.9 Hz, 3H, $CHCH_3$), 2.10 (dq, J = 3.8, 6.9 Hz, 1H, $CHCH_3$), 2.40 (dd, J = 2.0, 17.6 Hz, 1H, H-3), 2.55 (dd, J = 7.3, 17.6 Hz, 1H, H-3), 3.39 (dd, J = 1.6, 3.8 Hz, 1H, H-5), 3.80 (ddd, J = 1.6, 2.0, 7.3 Hz, 1H, H-4), 4.37 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.41 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.97 (d, J = 10.6 Hz, 1H, $NOCH_2Ph$), 5.02 (d, J = 10.6 Hz, 1H, $NOCH_2Ph$), 7.25–7.45 (m, 10H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.7, 18.0, 27.9, 35.5, 68.8, 70.3, 70.4, 76.6, 127.5, 127.9, 128.2, 128.4, 128.7, 129.5, 135.1, 137.3, 167.8; MS (ESI): m/z 362 (M+Na$^+$, 100). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13; Found: C, 74.35; H, 7.37; N, 4.52.

4.5.6. (4*S*,5*R*)-1,4-Dibenzyloxy-5-butylpyrrolidin-2-one 18e

Compound **18e**: colorless oil. Yield over two steps: 60%. $[\alpha]_D^{20} = +84.9$ (c 1.0, $CHCl_3$); IR (film) ν_{max}: 2956, 2930, 2866, 1713, 1450, 1089, 1069 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.0 Hz, 3H, CH_3), 1.14–1.38 (m, 5H, $C_3H_6CH_3$), 1.66–1.74 (m, 1H, CH_2CHN), 2.39 (dd, J = 2.5, 17.4 Hz, 1H, H-3), 2.61 (dd, J = 7.2, 17.4 Hz, 1H, H-3), 3.41 (ddd, J = 2.3, 3.8, 8.2 Hz, 1H, H-5), 3.76 (ddd, J = 2.3, 2.5, 7.2 Hz, 1H, H-4), 4.38 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.42 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.98 (d, J = 11.1 Hz, 1H, $NOCH_2Ph$), 5.00 (d, J = 11.1 Hz, 1H, $NOCH_2Ph$), 7.28–7.45 (m, 10H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 22.5, 26.9, 30.2, 34.9, 63.9, 70.6, 73.7, 77.1, 127.6, 127.9, 128.5 (2C), 128.8, 129.6, 135.2, 137.4, 167.8 ppm. MS (ESI): m/z 376 (M+Na$^+$, 100). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.50; H, 7.85; N, 4.10.

4.5.7. (4*S*,5*R*)-1,4-Dibenzyloxy-5-isobutylpyrrolidin-2-one 18f

Compound **18f**: colorless oil. Yield over two steps: 74%. $[\alpha]_D^{20} = +90.7$ (c 1.1, $CHCl_3$); IR (film) ν_{max}: 2959, 1711, 1590, 1449, 1383, 1366, 1093, 1068, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (d, J = 6.2 Hz, 3H, CH_3), 0.87 (d, J = 6.2 Hz, 3H, CH_3), 1.09–1.17 (m, 1H, $CHCH_3$), 1.55–1.65 (m, 2H, CH_2CHN), 2.39 (dd, J = 2.1, 17.4 Hz, 1H, H-3), 2.61 (dd, J = 6.9, 17.4 Hz, 1H, H-3), 3.43 (ddd, J = 1.9, 4.0, 9.2 Hz, 1H, H-5), 3.72 (ddd, J = 1.9, 2.1, 6.9 Hz, 1H, H-4), 4.36 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.40 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.97 (d, J = 10.9 Hz, 1H, $NOCH_2Ph$), 5.00 (d, J = 10.9 Hz, 1H, $NOCH_2Ph$), 7.27–7.45 (m, 10H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 23.2, 24.5, 34.5, 39.7, 62.3, 70.6, 74.3, 77.2, 127.5, 127.9, 128.4, 128.5, 128.8, 129.7, 135.2, 137.3, 167.7; MS (ESI): m/z 376 (M+Na$^+$, 100). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.37; H, 8.05; N, 3.86.

4.5.8. (4*S*,5*R*)-1,4-Dibenzyloxy-5-heptylpyrrolidin-2-one 18g

Compound **18g**: colorless oil. Yield over two steps: 59%. $[\alpha]_D^{20} = +62.7$ (c 0.6, $CHCl_3$); IR (film) ν_{max}: 2926, 2855, 1715, 1453, 1101, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.9 Hz, 3H, CH_3), 1.16–1.36 (m, 11H, $C_6H_{12}CH_3$), 1.66–1.72 (m, 1H, CH_2CHN), 2.39 (dd, J = 2.5, 17.4 Hz, 1H, H-3), 2.61 (dd, J = 7.2, 17.4 Hz, 1H, H-3), 3.40 (ddd, J = 2.2, 3.8, 8.2 Hz, 1H, H-5), 3.75 (ddd, J = 2.2, 2.5, 7.2 Hz, 1H, H-4), 4.37 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.41 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.97 (d, J = 11.2 Hz, 1H, $NOCH_2Ph$), 5.00 (d, J = 11.2 Hz, 1H, $NOCH_2Ph$), 7.27–7.45 (m, 10H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 24.8, 29.1, 29.4, 30.5, 31.7, 34.8, 63.8, 70.6, 73.6, 77.1, 127.6, 127.9, 128.5 (2C), 128.8, 129.6, 135.2, 137.3, 167.8; MS (ESI): m/z 418 (M+Na$^+$, 100). Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.60; H, 8.65; N, 3.70.

4.5.9. (4*S*,5*R*)-1,4-Dibenzyloxy-5-octylpyrrolidin-2-one 18h

Compound **18h**: colorless oil. Yield over two steps: 62%. $[\alpha]_D^{20} = +64.3$ (c 1.1, $CHCl_3$); IR (film) ν_{max}: 2924, 2853, 1713, 1454, 1089, 1069 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, J = 6.9 Hz, 3H, CH_3), 1.16–1.36 (m, 13H, $C_7H_{14}CH_3$), 1.66–1.72 (m, 1H, CH_2CHN), 2.38 (dd, J = 2.6, 17.4 Hz, 1H, H-3), 2.61 (dd, J = 7.2, 17.4 Hz, 1H, H-3), 3.41 (ddd, J = 2.3, 3.9, 8.2 Hz, 1H, H-5), 3.75 (ddd, J = 2.3, 2.6, 7.2 Hz, 1H, H-4), 4.37 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.42 (d, J = 11.8 Hz, 1H, $CHOCH_2Ph$), 4.97 (d, J = 11.1 Hz, 1H, $NOCH_2Ph$), 5.00 (d, J = 11.1 Hz, 1H, $NOCH_2Ph$), 7.25–7.45 (m, 10H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 24.7, 29.1, 29.3, 29.4, 30.5, 31.7, 34.8, 63.8, 70.6, 73.6, 77.0, 127.5, 127.9, 128.4 (2C), 128.7, 129.5, 135.2, 137.3, 167.8 ppm; MS (ESI): m/z: 410 (M+H$^+$, 100). Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.25; H, 8.61; N, 3.42. Found: C, 76.30; H, 8.62; N, 3.40.

4.5.10. (4*S*,5*R*)-1,4-Dibenzyloxy-5-phenylpyrrolidin-2-one 18i

Compound **18i**: white crystals. Yield over two steps: 64%. Mp 105–106 °C (Et_2O/EtOAc = 8:1); $[\alpha]_D^{20} = +53.3$ (c 1.1, $CHCl_3$); IR (film) ν_{max}: 3025, 2921, 1714, 1449, 1075 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ: 2.50 (dd, J = 3.1, 17.4 Hz, 1H, H-3), 2.79 (dd, J = 7.1, 17.4 Hz, 1H, H-3), 3.96 (ddd, J = 2.7, 3.1, 7.1 Hz, 1H, H-4), 4.41 (d, J = 11.6 Hz, 1H, CHOCH_2Ph), 4.47 (d, J = 11.6 Hz, 1H, CHOCH_2Ph), 4.49 (d, J = 2.7 Hz, 1H, H-5), 4.84 (d, J = 10.7 Hz, 1H, NOCH_2Ph), 5.05 (d, J = 10.7 Hz, 1H, NOCH_2Ph), 7.17–7.41 (m, 15H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.7, 68.6, 71.2, 76.9, 77.3, 126.7, 127.5, 127.9, 128.3, 128.4 (2C), 128.7, 128.9, 129.5, 134.9, 137.1, 137.1, 168.7; MS (ESI): m/z 396 (M+Na$^+$, 100). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.45; H, 5.84; N, 3.78.

4.6. Typical procedure for the SmI_2-mediate *N–O* bond cleavage of nitrone 18

Preparation of 0.1 M SmI_2 solution in THF:[31] To 501 mg (3.34 mol) of samarium powder were added successively 20 mL of anhydrous THF and I_2 (746 mg, 2.94 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred for 3 h at 60 °C, during which time the color of the solution changed from yellow to blue–green.

To a solution of *N*-benzyloxylactam **18a** (110 mg, 0.35 mmol) in anhydrous THF (7.1 mL) were added successively CH_3OH (0.14 mL, 3.5 mmol) and a solution of SmI_2 (0.1 M, 14.0 mL, 1.40 mmol) in THF under a nitrogen atmosphere. After stirring at room temperature for 3 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (3 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with an aqueous solution of $Na_2S_2O_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 2:1) to give lactam **11a** (72 mg, yield: 100%) as white crystals.

4.6.1. (4*S*,5*R*)-4-Benzyloxy-5-methylpyrrolidin-2-one 11a

Mp 55–57 °C (EtOAc/PE = 1:3) (lit.[32] mp 55–57 °C); $[\alpha]_D^{20}$ = +58.2 (*c* 1.1, $CHCl_3$) {lit.[32] $[\alpha]_D^{20}$ = +60.5 (*c* 1.0, $CHCl_3$)}; IR (film) ν_{max}: 3241, 1694, 1449, 1379, 1088, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, J = 6.5 Hz, 3H, CH_3), 2.40 (dd, J = 4.5, 17.2 Hz, 1H, H-3), 2.65 (dd, J = 7.0, 17.2 Hz, 1H, H-3), 3.73 (dq, J = 3.5, 6.5 Hz, 1H, H-5), 3.83 (ddd, J = 3.5, 4.5, 7.0 Hz, 1H, H-4), 4.55 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.49 (d, J = 11.8 Hz, 1H, CH_2Ph), 6.54 (br s, 1H, N*H*), 7.27–7.37 (m, 5H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.4, 37.5, 56.5, 71.4, 80.4, 127.8, 127.9, 128.5, 137.3, 176.5; MS (ESI): m/z 228 (M+Na$^+$, 100).

4.6.2. (4*R*,5*S*)-4-Benzyloxy-5-methylpyrrolidin-2-one *ent*-11a

Mp 57–59 °C; $[\alpha]_D^{20}$ = −59.4 (*c* 1.2, $CHCl_3$).

4.6.3. (4*S*,5*R*)-4-Benzyloxy-5-ethylpyrrolidin-2-one 11b

Colorless oil. Yield: 91%. $[\alpha]_D^{20}$ = +44.9 (*c* 1.5, $CHCl_3$); IR (film) ν_{max}: 3224, 2963, 2930, 2876, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, J = 7.4 Hz, 3H, CH_3), 1.43–1.51 (m, 1H, CHCH$_3$), 1.52–1.61 (m, 1H, CH_2CHN), 2.41 (dd, J = 3.6, 17.4 Hz, 1H, H-3), 2.62 (dd, J = 6.9, 17.4 Hz, 1H, H-3), 3.54–3.58 (m, 1H, H-5), 3.83 (ddd, J = 3.4, 3.6, 6.9 Hz, 1H, H-4), 4.49 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.54 (d, J = 11.8 Hz, 1H, CH_2Ph), 7.13 (br s, 1H, N*H*), 7.27–7.37 (m, 5H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.0, 27.5, 37.1, 62.1, 71.0, 78.6, 127.6, 127.8, 128.4, 137.5, 175.6 ppm; MS (ESI): m/z 242 (M+Na$^+$, 100). HRESIMS calcd for $[C_{13}H_{17}NO_2+Na]^+$: 242.1157. Found: 242.1146.

4.6.4. (4*S*,5*R*)-4-Benzyloxy-5-propylpyrrolidin-2-one 11c

Colorless oil. Yield: 96%. $[\alpha]_D^{20}$ = +45.5 (*c* 2.1, $CHCl_3$); IR (film) ν_{max}: 3220, 2955, 2930, 2872, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.1 Hz, 3H, CH_3), 1.31–1.55 (m, 4H, $C_2H_4CH_3$), 2.41 (dd, J = 3.6, 17.4 Hz, 1H, H-3), 2.63(dd, J = 6.9, 17.4 Hz, 1H, H-3), 3.60–3.64 (m, 1H, H-5), 3.83 (ddd, J = 3.4, 3.6, 6.9 Hz, 1H, H-4), 4.49 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.55 (d, J = 11.8 Hz, 1H, CH_2Ph), 6.86 (br s, 1H, N*H*), 7.27–7.37 (m, 5H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 19.1, 36.9, 37.0, 60.5, 71.1, 79.1, 127.6, 127.9, 128.5, 137.5, 175.5 ppm; MS (ESI): m/z 256 (M+Na$^+$, 100). HRESIMS calcd for $[C_{14}H_{19}NO_2+Na]^+$: 256.1313. Found: 256.1301.

4.6.5. (4*S*,5*R*)-4-Benzyloxy-5-isopropylpyrrolidin-2-one 11d

Colorless oil. Yield: 94%. $[\alpha]_D^{20}$ = +42.6 (*c* 2.0, $CHCl_3$); IR (film) ν_{max}: 3216, 2963, 2934, 2876, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (d, J = 5.4 Hz, 3H, CH_3), 0.93 (d, J = 5.4 Hz, 3H, CH_3), 1.63–1.75 (m, 1H, CHCH$_3$), 2.41 (dd, J = 3.4, 17.5 Hz, 1H, H-3), 2.61 (dd, J = 6.9, 17.5 Hz, 1H, H-3), 3.42–3.44 (m, 1H, H-5), 3.96 (ddd, J = 3.4, 3.4, 6.9 Hz, 1H, H-4), 4.48 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.54 (d, J = 11.8 Hz, 1H, CH_2Ph), 7.13 (br s, 1H, N*H*), 7.27–7.37 (m, 5H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.1, 18.6, 31.7, 37.4, 66.7, 70.8, 76.8, 127.7, 127.8, 128.4, 137.5, 175.9 ppm; MS (ESI): m/z 256 (M+Na$^+$, 100). HRESIMS calcd for $[C_{14}H_{19}NO_2+Na]^+$: 256.1313. Found: 256.1302.

4.6.6. (4*S*,5*R*)-4-Benzyloxy-5-butylpyrrolidin-2-one 11e

Colorless oil. Yield: 93%. $[\alpha]_D^{20}$ = +44.8 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 3216, 2959, 2930, 2859, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J = 6.9 Hz, 3H, CH_3), 1.28–1.37 (m, 4H, $C_2H_4CH_3$), 1.38–1.56 (m, 2H, CH_2CHN), 2.40 (dd, J = 3.6, 17.4 Hz, 1H, H-3), 2.62 (dd, J = 6.9, 17.4 Hz, 1H, H-3), 3.58–3.62 (m, 1H, H-5), 3.87 (ddd, J = 3.4, 3.6, 6.9 Hz, 1H, H-4), 4.48 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.54 (d, J = 11.8 Hz, 1H, CH_2Ph), 7.13 (br s, 1H, N*H*), 7.26–7.37 (m, 5H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 22.4, 27.8, 34.3, 37.0, 60.7, 71.0, 78.9, 127.6, 127.8, 128.4, 137.5, 175.6 ppm; MS (ESI): m/z 270 (M+Na$^+$, 100). HRESIMS calcd for $[C_{15}H_{21}NO_2+Na]^+$: 270.1470. Found: 270.1463.

4.6.7. (4*S*,5*R*)-4-Benzyloxy-5-isobutylpyrrolidin-2-one 11f

Colorless oil. Yield: 100%. $[\alpha]_D^{20}$ = +47.8 (*c* 0.9, $CHCl_3$); IR (film) ν_{max}: 3212, 2955, 2930, 2864, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (d, J = 6.6 Hz, 3H, CH_3), 0.95 (d, J = 6.6 Hz, 3H, CH_3), 1.32–1.36 (m, 1H, CHCH$_3$), 1.37–1.42 (m, 1H, CH_2CHN), 1.59–1.69 (m, 1H, CH_2CHN), 2.40 (dd, J = 3.7, 17.3 Hz, 1H, H-3), 2.62 (dd, J = 6.8, 17.3 Hz, 1H, H-3), 3.68 (m, 1H, H-5), 3.86 (ddd, J = 3.4, 3.7, 6.8 Hz, 1H, H-4), 4.48 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.56 (d, J = 11.8 Hz, 1H, CH_2Ph), 6.39 (br s, 1H, N*H*), 7.28–7.38 (m, 5H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 23.1, 25.1, 36.8, 44.0, 58.8, 71.2, 79.6, 127.7, 127.9, 128.5, 137.5, 175.2 ppm; MS (ESI): m/z 270 (M+Na$^+$, 100). HRESIMS calcd for $[C_{15}H_{21}NO_2+Na]^+$: 270.1470. Found: 270.1461.

4.6.8. (4*S*,5*R*)-4-Benzyloxy-5-heptylpyrrolidin-2-one 11g

Colorless oil. Yield: 91%. $[\alpha]_D^{20}$ = +39.3 (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 3216, 2926, 2851, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.9 Hz, 3H, CH_3), 1.21–1.36 (m, 10H, $C_5H_{10}CH_3$), 1.39–1.55 (m, 2H, CH_2CHN), 2.40 (dd, J = 3.6, 17.4 Hz, 1H, H-3), 2.62 (dd, J = 6.9, 17.4 Hz, 1H, H-3), 3.58–3.62 (m, 1H, H-5), 3.88 (ddd, J = 3.4, 3.6, 6.9 Hz, 1H, H-4), 4.48 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.55 (d, J = 11.8 Hz, 1H, CH_2Ph), 6.50 (br s, 1H, N*H*), 7.27–7.37 (m, 5H, Ph-*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 25.7, 29.0, 29.3, 31.7, 34.7, 36.9, 60.7, 71.1, 79.0, 127.7, 127.9, 128.5, 137.5, 175.3 ppm; MS (ESI): m/z 312 (M+Na$^+$, 100). HRESIMS calcd for $[C_{18}H_{27}NO_2+Na]^+$: 312.1939. Found: 312.1930.

4.6.9. (4*S*,5*R*)-4-Benzyloxy-5-octylpyrrolidin-2-one 11h

Colorless oil. Yield: 100%. $[\alpha]_D^{20}$ = +38.3 (*c* 1.3, $CHCl_3$); IR (film) ν_{max}: 3212, 2955, 2930, 2851, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.8 Hz, 3H, CH_3), 1.26–1.34 (m, 12H, $C_6H_{12}CH_3$), 1.38–1.54 (m, 2H, CH_2CHN), 2.40 (dd, J = 3.6, 17.4 Hz, 1H, H-3), 2.62 (dd, J = 6.9, 17.4 Hz, 1H, H-3), 3.58–3.62 (m, 1H, H-5), 3.83 (ddd, J = 3.4, 3.6, 6.9 Hz, 1H, H-4), 4.48 (d, J = 11.8 Hz, 1H,

CH_2Ph), 4.55 (d, J = 11.8 Hz, 1H, CH_2Ph), 6.74 (br s, 1H, NH), 7.28–7.37 (m, 5H, Ph-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 25.7, 29.1, 29.3, 29.4, 31.8, 34.7, 37.0, 60.7, 71.1, 79.0, 127.7, 127.9, 128.4, 137.5, 175.4 ppm; MS (ESI): m/z 326 (M+Na$^+$, 100). HRESIMS calcd for $[C_{19}H_{29}NO_2+H]^+$: 304.2277. Found: 304.2262.

4.6.10. (4*S*,5*R*)-4-Benzyloxy-5-phenylpyrrolidin-2-one 11i

Colorless oil. Yield: 95%.white crystals. Mp 109.7–110.4 °C (EtOAc/PE = 1:2); $[\alpha]_D^{20} = +46.4$ (c 2.2, $CHCl_3$); IR (film) ν_{max}: 3220, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (dd, J = 4.4, 17.2 Hz, 1H, H-3), 2.69 (dd, J = 7.0, 17.2 Hz, 1H, H-3), 4.51 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.54 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.72 (d, J = 3.4 Hz, 1H, H-5), 6.72 (br s, 1H, NH), 7.25–7.38 (m, 10H, Ph-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.8, 64.4, 71.5, 82.0, 125.8, 127.6, 127.9, 128.1, 128.4, 128.9, 137.3, 140.0, 175.6 ppm; MS (ESI): m/z 290 (M+Na$^+$, 100). HRESIMS calcd for $[C_{17}H_{17}NO_2+Na]^+$: 290.1157. Found: 290.1154.

4.7. 1-*tert*-Butyl 2-perfluorophenyl (*S*)-pyrrolidine-1,2-dicarboxylate 22

Acid **21** (215 mg, 1.0 mmol), pentafluorophenol (202 mg, 1.1 mmol), and *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride salt (EDC·HCl) (576 mg, 3.0 mmol) were dissolved in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at room temperature for 8 h. The reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/PE = 1:2) to give compound **22** (320 mg, yield: 84%) as a colorless oil. $[\alpha]_D^{20} = -58$ (c 1.2, $CHCl_3$); IR (film) ν_{max}: 2976, 1793, 1711, 1520, 1388 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of two rotamers (m/M) in a ratio of 1:2.6, δ: 1.45 (s, m+M, 9H, *t*-Bu), 1.88–2.12 (m, m+M, 2H, H-4), 2.10–2.26 (m, m+M, 1H, H-3a), 2.31–2.50 (m, m+M, 1H, H-3b), 3.40–3.65 (m, m+M, 2H, H-5), 4.60 (dd, J = 8.9, 3.7 Hz, m+M, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.4, 24.4, 28.0, 28.2, 30.0, 31.2, 46.3, 46.5, 58.6 (2C), 80.3, 80.8, 124.9, 136.6, 138.3, 139.1, 139.7, 139.9, 140.0, 142.3, 153.5, 154.2, 169.0, 169.2; MS (ESI): m/z 404 (M+Na$^+$, 100). Anal. Calcd for $C_{16}H_{16}F_5NO_4$: C, 50.40; H, 4.23; N, 3.67. Found: C, 50.44; H, 4.23; N, 3.68.

4.8. (4*R*,5*S*,1′*S*)-4-Benzyloxy-1-(*N*-butyloxycarbonylprolyl)-5-methylpyrrolidin-2-one 23

To a solution of (4*R*,5*S*)-4-(benzyloxy)-5-methylpyrrolidin-2-one *ent*-**11a** (100 mg, 0.47 mmol) in THF (1.6 mL) was added dropwise *n*-BuLi (1.6 M in hexane) (0.29 mL, 0.47 mmol) at −78 °C. The mixture was stirred for 15 min. To the resulting mixture was added a THF solution (1.0 mL) of ester **22** (200 mg, 0.52 mmol). After stirring for 1.5 h at −78 °C, the reaction temperature was allowed to rise to −5 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl (2.0 mL). The resulting mixture was extracted with EtOAc (3 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1:5) to give compound **23** (158 mg, yield: 81%) as a pale yellow oil. $[\alpha]_D^{20} = -49$ (c 0.9, $CHCl_3$); IR (film) ν_{max}: 2976, 1734, 1696, 1672, 1404, 1365, 1232 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of two rotamers (m/M) in a ratio of 1:1.4, δ: 1.28 (d, J = 6.7 Hz, M+m, 3H, CH_3), 1.42 (s, m+M, 9H, *t*-Bu), 1.80–1.98 (m, m+M, 2H, H-4), 1.90–1.98 (m, m+M, 1H, H-3a), 2.25–2.42 (m, m+M, 1H, H-3b), 2.57–2.70 (m, m+M, 1H, H-3′a), 2.85–2.96 (m, m+M, 1H, H-3′b), 3.40–3.65 (m, m+M, 2H, H-5), 3.77–3.82 (m, m+M, 1H, H-4′), 4.48–4.60 (m, m+M, 2H, ArCH_2), 4.55–4.65 (m, m+M, 1H, H-5′), 5.30 (dd, J = 8.8, 2.5 Hz, m+M, 1H, H-2), 7.26–7.39 (m, m+M, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.1, 17.5, 22.8, 23.8, 28.2, 28.3, 29.6, 30.5, 38.6, 38.7, 46.6, 46.9, 58.8, 58.9, 60.2 (2C), 70.5 (2C), 76.2, 76.6, 79.3, 79.4, 127.5, 127.6, 127.9, 128.0, 128.4, 128.5, 137.0, 137.1, 153.7, 154.2, 172.9, 173.0, 173.6, 173.7; MS (ESI): m/z 425 (M+Na$^+$, 100). HRESIMS calcd for $[C_{22}H_{30}N_2O_5+H]^+$: 403.2232. Found: 403.2236.

4.9. (4*R*,5*S*,1′*S*)-1-(*N*-Butyloxycarbonylprolyl)-4-hydroxyl-5-methylpyrrolidin-2-one 24

To 10% Pd/C (710 mg) was added a solution of compound **23** (790 mg, 1.96 mmol) in anhydrous EtOH (32 mL) and formic acid (4 mL). The mixture was stirred for 5 h at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The oily residue was purified by flash column chromatography on silica gel (EtOAc/PE = 2:1) to give compound **24** (489 mg, yield: 81%) as a white solid. Mp 140–141 °C (EtOAc/PE); $[\alpha]_D^{20} = -40.0$ (c 1.3, $CHCl_3$); IR (film) ν_{max}: 3424, 2976, 1740, 1696, 1675, 1400, 1240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of two rotamers (m/M) in a ratio of 1:1.5, δ: 1.26 (d, J = 6.7 Hz, M+m, 3H, CH_3), 1.40 (s, m+M, 9H, *t*-Bu), 1.78–1.95 (m, m+M, 2H, H-4), 1.90–1.95 (m, m+M, 1H, H-3a), 2.21–2.40 (m, m+M, 1H, H-3b), 2.40–2.52 (m, m+M, 1H, H-3′a), 2.85–2.96 (m, m+M, 1H, H-3′b), 3.15 (br s, 1H, OH), 3.33–3.60 (m, m+M, 2H, H-5), 4.06–4.13 (m, m+M, 1H, H-4′), 4.25–4.35 (m, m+M, 1H, H-5′), 5.28 (dd, J = 8.8, 2.5 Hz, m+M, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.7, 17.1, 22.9, 23.8, 28.3, 28.4, 29.7, 30.6, 41.1, 41.2, 46.7, 47.0, 60.3 (2C), 62.3, 62.4, 69.5, 69.8, 79.6 (2C), 153.9, 154.4, 173.3 (2C), 173.8, 173.9; MS (ESI): m/z 335 (M+Na$^+$, 100). HRESIMS calcd for $[C_{15}H_{24}N_2O_5+H]^+$: 313.1763. Found: 313.1761.

4.10. (5*S*,1′*S*)-1-(*N*-*tert*-Butyloxycarbonylprolyl)-5-methylpyrrol-2(5*H*)-one 25

To a solution of compound **24** (46 mg, 0.15 mmol) and DMAP (1.5 mg, 0.01 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added $(Boc)_2O$ (0.04 mL, 0.16 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 10 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (2.0 mL). The resulting mixture was extracted with CH_2Cl_2 (2 mL × 3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1:2) to give compound **25** (31 mg, yield: 71%) as a colorless oil. $[\alpha]_D^{20} = -80$ (c 1.0, $CHCl_3$) {lit. $[\alpha]_D^{20} = -85$ (c 1.1, $CHCl_3$);[13a] $[\alpha]_D^{20} = -92$ (c 1, $CHCl_3$) for a 5:1 diastereomeric mixture[13b]}; IR (film) ν_{max}: 2976, 1730, 1699, 1688, 1400, 1240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of two rotamers (m/M) in a ratio of 1:2, δ: 1.40 (s, m+M, 9H, *t*-Bu), 1.45 (d, J = 6.7 Hz, M+m, 3H, CH_3), 1.81–2.00 (m, m+M, 2H, H-4), 1.90–2.00 (m, m+M, 1H, H-3a), 2.30–2.47 (m, m+M, 1H, H-3b), 3.40–3.70 (m, m+M, 2H, H-5), 4.70–4.80 (m, m+M, 1H, H-5′), 5.35 (dd, J = 9.5, 3.0 Hz, m+M, 1H, H-2), 6.07 (dd, J = 6.0, 1.5 Hz, M+m, 1H, H-3′), 7.24 (dd, J = 6.0, 2.0 Hz, M+m, 1H, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.0, 17.8, 22.8, 23.9, 28.3, 28.4, 29.5, 30.5, 46.8, 47.1, 58.0 (2C), 59.7 (2C), 79.4 (2C), 125.4, 125.5, 153.6, 153.7, 153.8, 154.2, 169.8 (2C), 173.0, 173.2; MS (ESI): m/z 317 (M+Na$^+$, 100).

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References

1. (a) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660–4663; (b) Reddy, P. V.; Veyron, A.; Koos, P.; Bayle, A.; Greene, A. E.; Delair, P. *Org. Biomol. Chem.* **2008**, *6*, 1170–1172; (c) Ceccon, J.; Danoun, G.; Greene, A. E.; Poisson, J.-F. *Org. Biomol. Chem.* **2009**, *7*, 2029–2031.
2. For selected synthesis of *syn*-β-hydroxy γ-amino acids via lactam intermediates, see: (a) Galeotti, N.; Poncet, J.; Chiche, L.; Jouin, P. *J. Org. Chem.* **1993**, *58*, 5370–5376; (b) Bhziger, M.; McGarrity, J. F.; Meul, T. *J. Org. Chem.* **1993**, *58*, 4010–4012; (c) Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210–5211; for selected synthesis of *anti*-β-hydroxy γ-amino acids via lactam intermediates, see: (d) Luo, J.-M.; Dai, C.-F.; Lin, S.-Y.; Huang, P.-Q. *Chem. Asian J.* **2009**, *4*, 328–335. and references cited therein.
3. Schmidt, U.; Riedl, B.; Haas, G.; Griesser, H.; Vetter, A.; Weinbrenner, S. *Synthesis* **1993**, 216–220.
4. For reviews, see: (a) Nagle, D. G.; Camacho, F. T.; Paul, V. J. *Mar. Biol.* **1998**, *132*, 267–273; (b) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347–9377; (c) Tan, L. T. *Phytochemistry* **2007**, *68*, 954–968; (d) Rastogi, R. P.; Sinha, R. P. *Biotech. Adv.* **2009**, *27*, 521–539.
5. Koehn, F. E.; Longley, R.; Reed, J. K. *J. Nat. Prod.* **1992**, *55*, 613–619.
6. Moore, R. E.; Entezeroth, M. *Phytochemistry* **1988**, *27*, 3101–3103.
7. Edwards, D. J.; Marquez, B. L.; Nogle, L. M.; McPhail, K.; Goeger, D. E.; Roberts, M. A.; Gerwick, W. H. *Chem. Biol.* **2004**, *11*, 817–833.
8. Nagle, D. G.; Paul, V. J.; Roberts, M. A. *Tetrahedron Lett.* **1996**, *37*, 6263–6266.
9. (a) Zhang, L.-H.; Langley, R. E.; Koehn, F. E. *Life Sci.* **1997**, *60*, 751–762; (b) Zhang, L.-H.; Langley, R. E.; Koehn, F. E. *Life Sci.* **1999**, *64*, 1013–1028.
10. Koehn, F. E.; McConnell, O. J.; Longley, R. E.; Sennett, S. S.; Reed, J. K. J. *J. Med. Chem.* **1994**, *37*, 3181–3186.
11. Takamatsu, S.; Nagle, D. G.; Gerwick, W. H. *Planta Med.* **2004**, *70*, 127–131.
12. Decicco, C. P.; Grover, P. *J. Org. Chem.* **1996**, *61*, 3534–3541.
13. For the total synthesis of microcolin B, see: (a) Andrus, M. B.; Li, W.-K.; Keyes, R. E. *J. Org. Chem.* **1997**, *62*, 5542–5549; For synthetic studies on microcolin B, see: (b) Mattern, R. H.; Gunasekera, S.; McConnell, O. *Tetrahedron* **1996**, *52*, 425–434.
14. Mandal, A. K.; Hines, J.; Kuramochi, K.; Crews, C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4043–4047.
15. (a) For amino acid-based approaches to 5-alkyl-3-pyrrolin-2-ones, see: Ref. 3.; (b) Mattern, R. H. *Tetrahedron Lett.* **1996**, *37*, 291–294; (c) Cuiper, A. D.; Brzostowska, M.; Gawronski, J. K.; Smeets, W. J. J.; Spek, A. L.; Hiemstra, H.; Kellogg, R. M.; Feringa, B. L. *J. Org. Chem.* **1999**, *64*, 2567–2570; (d) Courcambeck, J.; Bihel, F.; Michelis, C. D.; Quelever, G.; Kraus, J. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1421–1430; (e) Bower, J. F.; Chakthong, S.; Svenda, J.; Williams, A. J.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2006**, *4*, 1868–1877.
16. For non-amino acid-based synthetic approaches to 5-alkyl-3-pyrrolin-2-one derivatives, see: (a) de Koning, H.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N. *Eur. J. Org. Chem.* **1998**, 1729–1737; (b) Spiess, S.; Berthold, C.; Weihofen, R.; Helmchen, G. *Org. Biomol. Chem.* **2007**, *5*, 2357–2360; For plausible methods, see: (c) Arai, Y.; Fujii, A.; Ohno, T.; Koizumi, T. *Chem. Pharm. Bull.* **1992**, *40*, 1670–1672; (d) Rassu, G.; Casiraghi, G.; Spanu, P.; Pinna, L.; Fava, G. G.; Ferrari, M. B.; Pelosi, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1035–1048; (e) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1759–1769; (f) Baussanne, I.; Royer, J. *Tetrahedron Lett.* **1998**, *39*, 845–848; (g) Sanyal, A.; Yuan, Q.; Snyder, J. K. *Tetrahedron Lett.* **2005**, *46*, 2475–2478; (h) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428–3431.
17. (a) Huang, P.-Q. *Synlett* **2006**, 1133–1149; (b) Huang, P.-Q.; Wang, S.-L.; Ye, J.-L.; Ruan, Y.-P.; Huang, Y.-Q.; Zheng, H.; Gao, J.-X. *Tetrahedron* **1998**, *54*, 12547–12560; For related work from other groups, see: (c) Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1973–1980; (d) Kim, S.-H.; Park, Y.; Choo, H.; Cha, J. K. *Tetrahedron Lett.* **2002**, *43*, 6657–6660.
18. (a) Luo, J.-M.; Dai, C.-F.; Lin, S.-Y.; Huang, P.-Q. *Chem. Asian J.* **2009**, *4*, 328–335; (b) Huang, P.-Q.; Chen, Q.-F.; Chen, C.-L.; Zhang, H.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 3827–3832; (c) Chen, J.; Huang, P.-Q.; Queneau, Y. *J. Org. Chem.* **2009**, *74*, 7457–7463.
19. (a) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413–1420; (b) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001–1002.
20. (a) Koch, T.; Hesse, M. *Synthesis* **1992**, 931–932; (b) Kanno, O.; Miyauchi, M.; Kawamoto, I. *Heterocycles* **2000**, *53*, 173–181; (c) Kitov, P. I.; Bundle, D. R. *Org. Lett.* **2001**, *3*, 2835–2838; (d) Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, *72*, 6298–6300.
21. (a) Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056–2083; (b) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 2004.
22. (a) Narita, M.; Teramoto, T.; Okawara, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1084–1089; (b) Teramoto, T.; Deguchi, M.; Kurosaki, T.; Okawara, M. *Tetrahedron Lett.* **1981**, *22*, 1109–1112; (c) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928–4933; (d) Shibuya, M.; Jinbo, Y.; Kubota, S. *Chem. Pharm. Bull.* **1984**, *32*, 1303–1312; (e) Davies, S. G.; Dixon, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2635–2643; (f) Adams, D. J.; Blake, A. J.; Cooke, P. A.; Gill, C. D.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4603–4615; (g) Pohlmann, J.; Lampe, T.; Shimada, M.; Nell, P. G.; Pernerstorfer, J.; Svenstrup, N.; Brunner, N. A.; Schiffer, G.; Freiberg, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1189–1192; (h) Miyata, O.; Takahashi, S.; Tamura, A.; Ueda, M.; Naito, T. *Tetrahedron* **2008**, *64*, 1270–1284.
23. (a) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755–11772; (b) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron Lett.* **2004**, *45*, 8375–8377; (c) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459–1462; (d) Burchak, O. N.; Philouze, C.; Chavant, P. Y.; Py, S. *Org. Lett.* **2008**, *10*, 3021–3023; (e) Wu, S.-F.; Zheng, X.; Ruan, Y.-P.; Huang, P.-Q. *Org. Biomol. Chem.* **2008**, *7*, 2967–2975.
24. For other methods to cleave an *N*–*O* bond by Raney nickel: (a) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647–4648; by In metal: (b) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773–1776; by Li/di-*tert*-butylbiphenyl or Birch condition: (c) Yus, M.; Radivoy, G.; Alonso, F. *Synthesis* **2001**, 914–918; (d) Taillier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2145–2147; by a metal-free method: (e) Cutulic, S. P. Y.; Murphy, J. A.; Farwaha, H.; Zhou, S.-Z.; Chrystal, E. *Synlett* **2008**, 2132–2136.
25. Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653–3656.
26. (a) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859; (b) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662; (c) Yoda, H.; Kitayama, H.; Yamade, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451–1453.
27. (a) Koot, W. J.; Ginkel, R. V.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401–404; (b) Ohta, T.; Shiokawa, S.; Sakamoto, R.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 7329–7332; (c) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949–4952.
28. (a) Andrus, M. B.; Li, W.; Keyes, R. F. *Tetrahedron Lett.* **1998**, *39*, 5465–5468; (b) Hosseini, M.; Kringrlum, H.; Murray, A.; Tonder, J. E. *Org. Lett.* **2006**, *8*, 2103–2106.
29. For racemic compound see: Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *J. Org. Chem.* **1968**, *33*, 544–547.
30. Kudo, J.; Azumai, T.; Mizuno, M. Japan Patent: 2004059491, 2004.
31. (a) Zheng, X.; Feng, C.-G.; Ye, J.-L.; Huang, P.-Q. *Org. Lett.* **2005**, *7*, 553–556; (b) Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501–502.
32. He, B.-Y.; Wu, T.-J.; Yu, X.-Y.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2003**, *14*, 2101–2108.