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A Direct and General Method for the Reductive Alkylation of Tertiary Lactams/Amides: Application to the Step Economical Synthesis of Alkaloid (−)-Morusimic Acid D

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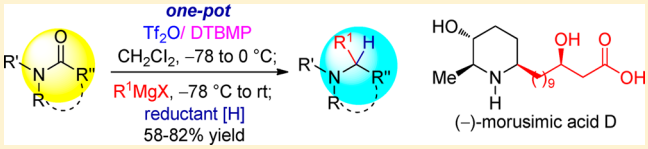
Supporting Information

ABSTRACT: Full details of the direct and general method for the reductive alkylation of tertiary lactams and amides to give tertiary *sec*-alkylamines are presented. This one-pot method consists of in situ activation of a lactam or an amide with Tf_2O/DTBMP, addition of a Grignard reagent, and reduction of the resulting iminium intermediates. Alkyl, benzyl, and aryl Grignard reagents and several reductants or reducing conditions ($LiAlH_4$, $NaBH_4$, Hantzsch ester, Bu_3SnH, $Pd(OH)_2/C$, H_2) could be used effectively. Reductive alkylations of substituted lactams demonstrated good to excellent 1,3-asymmetric induction to provide the corresponding di- or trisubstituted pyrrolidine/piperidine in 6:1 ($LiAlH_4$), 11:1 (Et_3SiH), and 20:1 (catalytic hydrogenation) *cis*/*trans* diastereoselectivity, respectively. The versatility of this methodology was demonstrated by its application in the concise stereoselective synthesis of piperidine alkaloid (−)-morusimic acid.



INTRODUCTION

sec-Alkylamines, especially α-substituted pyrrolidines, piperidines, pyrrolizidines, indolizidines, and quinolizidines, are key structural features found in many bioactive alkaloids and pharmaceutically relevant molecules.[1] Some representative pyrrolidine and piperidine alkaloids are shown in Figure 1,

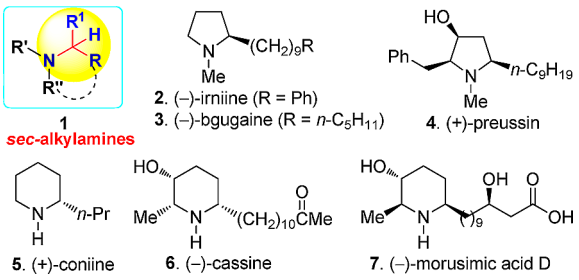
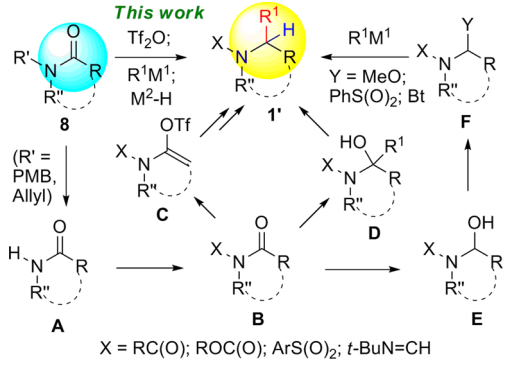


Figure 1. Selected pyrrolidine and piperidine alkaloids containing the *sec*-alkylamine motif.

which include (−)-irniine (**2**),[2] (−)-bgugaine (**3**),[3] (+)-preussin (**4**),[4] coniine (**5**),[5] (−)-cassine (**6**),[6] and (−)-morusimic acid D (**7**).[7] The broad spectrum of bioactivities exhibited by pyrrolidine and piperidine alkaloids render them attractive synthetic targets, and a number of synthetic methodologies have been developed.[8,9] Many of these converge on a common transformation of lactams (**8**, Scheme 1) to the corresponding α-substituted pyrrolidines or piperidines **1**.[8b,d−f,i] The direct reductive alkylation of **8** to **1**, although highly desirable, has been limited to some special substrates or specific nucleophiles.[10−13] Among the widely used multistep methods[14−18] were those via thioamide derivatives;[14] by *N*-deprotection−activation via *N*-carbamoylation/sulfonylation (**8** to **B** via **A**), followed by stepwise reductive alkylation on *N*-acyl/*N*-carbamoyl derivatives **B** (via **D**)[15] or *N*-α-amidoalkylation of **F**,[16] or *N*-*t*-butyl formamidines,[17] and via enol triflates **C**.[18]

Scheme 1. Transformation of Amides/Lactams into the Corresponding *sec*-Alkylamines



Our continuing interest in bioactive alkaloids[8e,19] has led us to focus our attention on the development of step-economical synthetic methods.[19−22] One of the methods developed involves the first general one-pot transformation of tertiary lactams and amides into the corresponding *tert*-alkylamines by

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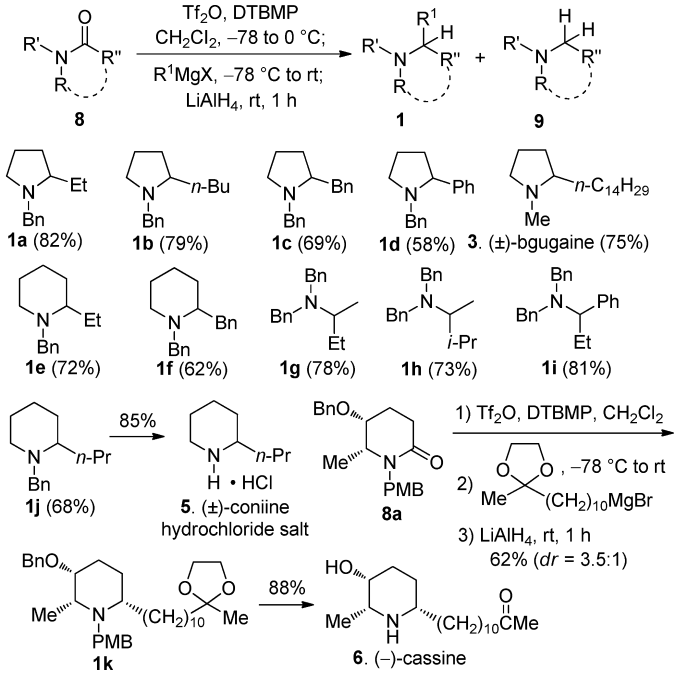
Scheme 2. One-Pot Reductive Alkylation of Lactams/Amides and Its Application to the Syntheses of Alkaloids (±)-Bgugaine, (±)-Coniine, and (−)-Cassine



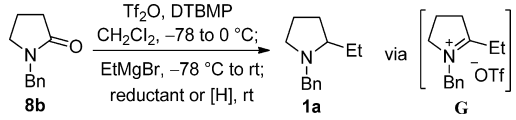
bis-reductive alkylation with organometallic reagents.[20a] Our recent interest was expanded to the development of a direct and general reductive alkylation method for the one-pot transformation of tertiary amides/lactams into tertiary *sec*-alkylamines, and the preliminary results have been communicated.[21] We now report the full account of this study, which includes optimizing reaction conditions to achieve a highly diastereoselective one-pot reductive alkylation of lactams and applying the methodology to the improved synthesis of (−)-morusimic acid D (**7**).

RESULTS AND DISCUSSION

In our preliminary communication,[21] reductive alkylation of both lactams and amides was achieved by successive treatment of lactams/amides **8** with Tf_2O/DTBMP[23] (−78 to 0 °C), RMgX, and $LiAlH_4$ (or $NaBH_4$). The corresponding *sec*-alkylamines **1a**−**1j** were obtained in yields ranging from 58% to 82%, along with 7−26% of the side products **9** (Scheme 2). The synthetic utility of this one-pot transformation was demonstrated by the concise syntheses of alkaloids (±)-bgugaine, (±)-coniine, and (−)-cassine.

To explore the generality of reducing agents needed for this method, we set out to screen other milder reductants or reducing conditions. The reductive ethylation of *N*-benzyl-2-pyrrolidinone **8b** was selected as the model reaction for this purpose. Successive treatment of 2-pyrrolidinone **8b** (1.0 equiv) and DTBMP (1.2 equiv) with 1.0 mol equiv each of Tf_2O (−78 to 0 °C) and ethylmagnesium bromide (−78 °C to rt) gave the presumed intermediate **G**, which was trapped with different reductants to give pyrrolidine **1a** (Table 1). $LiAlH_4$ was found to give the best yield of pyrrolidine **1a** (82%, entry 1). Other reductants, such as $NaBH_4$, Hantzsch ester (HEH), and Bu_3SnH, also gave pyrrolidine **1a** in ≥70% yield (entries 2−4). Notably, catalytic hydrogenation [20% $Pd(OH)_2/C$, H_2, rt, 2 h] also furnished the desired product in 68% yield (entry 5). These results are promising because of their potentials for chemo- and stereoselective reduction. However, silane reductants gave poor results even with a prolonged reaction time (8 h) (entries 6−8).

Table 1. Results of the One-Pot Reductive Alkylation of 2-Pyrrolidinone 8b



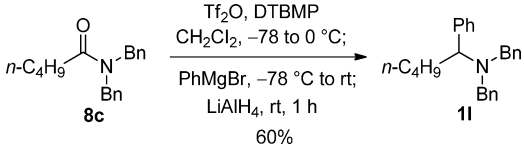
entry	reductant or [H]	yield (%)[a]
1	$LiAlH_4$ (3.0 equiv), 1 h	82
2	$NaBH_4$ (3.0 equiv), 1 h	71
3	Hantzsch ester (3.0 equiv), 1 h	70
4	Bu_3SnH (3.0 equiv), 1 h	75
5	20% $Pd(OH)_2/C$, H_2, 2 h	68
6	Et_3SiH (10.0 equiv), 8 h	15
7	$(EtO)_3SiH$ (10.0 equiv), 8 h	19
8	Ph_3SiH (10.0 equiv), 8 h	0

[a]Isolated yield.

Perhaps not surprisingly, we were able to apply this one-pot reductive alkylation method to the case of amides as well (Scheme 3). Thus, successive treatment of amide **8c** with Tf_2O/DTBMP, phenylmagnesium bromide, and $LiAlH_4$ gave the desired amine **1l** in 60% yield.

With the optimized reaction conditions defined, we next studied the stereoselectivity of the reductive alkylation. Thus,

Scheme 3. One-Pot Reductive Arylation of Amides 8c



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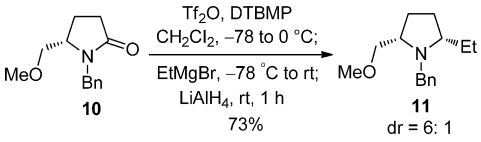
(*S*)-pyroglutaminol derivative **10**[24] was subjected to the reductive ethylation conditions (Scheme 4), which produced

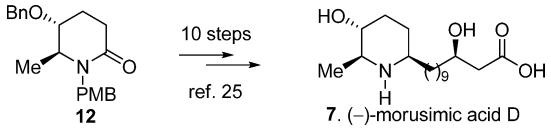
Scheme 4. 1,3-Asymmetric Induction in the One-Pot Reductive Ethylation of Lactam 10



the desired pyrrolidine **11** and its diastereomer with a dr = 6:1 (determined by ^{1}H NMR analysis of the crude reaction mixture) in a combined yield of 73%. NOESY experiments (cf. the Supporting Information) established a 2,5-*cis*-stereochemistry for the major diastereomer **11**. This demonstrated that reductive alkylation proceeds with a good 1,3-asymmetric induction, with the hydride approaching the iminium intermediate (cf. **G** in Table 1) from the opposite face of the existing substituent on the pyrrolidine ring.

To demonstrate the power of this direct reductive alkylation method, the synthesis of (−)-morusimic acid D (**7**)[7] was envisaged. Although this alkaloid has been synthesized from our laboratory, the previous approach is lengthy, 10 steps required for the transformation of lactam **12** to (−)-morusimic acid D (**7**) (Scheme 5).[25] A combination of the present direct reductive alkylation method with Noyori catalytic asymmetric hydrogenation[26] allowed shortening the synthetic routes by five steps.

Scheme 5. Previous Approach to (−)-Morusimic Acid D

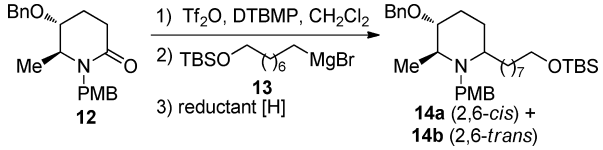


The synthesis of (−)-morusimic acid D (**7**) commenced with the reductive alkylation of piperidin-2-one **12**.[25] Successive treatment of **12** with Tf_2O/DTBMP, Grignard reagent **13**, and $LiAlH_4$, or $NaBH_4$ or Bu_3SnH, gave piperidine **14a** in disappointing diastereoselectivities (Table 2, entries 1−3). The use of milder reductant Et_3SiH led to an improved ratio of 11:1 but in only 32% yield (entry 4). To our delight, under the catalytic hydrogenation conditions [20% $Pd(OH)_2/C$, H_2, rt, 2 h], the desired piperidine **14a** was obtained in 60% yield with a diastereoselectivity of 20:1 (entry 5). The 2,6-*cis* stereochemistry of compound **14a** was confirmed by NOESY experiments.

A plausible rationale for the stereochemical outcomes in Table 2 is depicted in Scheme 6. After Tf_2O-activated Grignard reagent addition, an iminium ion intermediate is generated, which may exist as conformer **M1** or **M2**. Because of the stereoelectronic effects, the down-face attack of a hydride on conformer **M1** will lead to the formation of the chair conformer **M3**, which is favored over the up-face attack, leading to an unfavorable twisted boat conformer. For the same reason, up-face attack of a hydride on conformer **M2** is favored over the down-face attack. The relative stability of the transition states leading to **M3** and **M4** depends on the competing $A^{1,2}$-interaction (between the Me and PMB groups) in conformer **M1** and $A^{1,3}$-interaction (between Me and the approaching hydride) in conformer **M2**. For reactive hydride donors $LiAlH_4$, $NaBH_4$, and Bu_3SnH, the $A^{1,3}$-interaction between a neat hydride (a small nucleophile) and the methyl group is less important compared to the $A^{1,2}$-interaction in conformer **M1**, resulting in the formation of 2,6-*trans*-diastereomer **14b** as the major diastereomer. In contrast, for the less-polarized reductant Et_3SiH, a severe $A^{1,3}$-interaction exists between Me and the incoming Et_3SiH in conformer **M2**. This favors the predominant down-face hydride attack on conformer **M1**, resulting in diastereomer **14a**. Under the $Pd(OH)_2/C$-catalyzed conditions, the adsorbed H_2 on the $Pd(OH)_2/C$ surface becomes even more hindered, and attacks exclusively on conformer **M1**. This results in the formation of 2,6-*cis*-diastereomer **14a** in excellent diastereoselectivity.

To pursuing the synthesis of (−)-morusimic acid D, silyl ether **14a** was treated with the Br_2/PPh_3 complex,[27] which gave the bromide **15** in 82% yield (Scheme 7). Reacting **15** with the dianion generated in situ from benzyl 3-oxobutanoate produced **16** in 73% yield. The Noyori catalytic asymmetric hydrogenation[26] of the HCl salt of **16** produced *β*-hydroxy ester **17** as the sole diastereomer in 73% yield. The stereochemistry of the newly formed chiral center was confirmed by its conversion into (−)-morusimic acid D. $Pd(OH)_2/C$-catalyzed hydrogenolysis of **17** under H_2 (6 atm) at rt for 24 h afforded (−)-morusimic acid D (**7**) {$[\alpha]_D^{20} = -13.9$ (*c* 0.25, MeOH); lit.[7] $[\alpha]_D^{20} = -14.6$ (*c* 0.25, MeOH)} in 85% yield. The ^{1}H and ^{13}C NMR spectral data of our synthetic product are in good agreement with those reported.[7]

Table 2. Influence of the Reductants on the Reductive Alkylation of Piperidin-2-one 12



entry	reductant [H]	product (% yield)[a]	dr (**14a**/**14b**)[b]
1	$LiAlH_4$ (3.0 equiv), 0 °C, 1 h	75	1:1.4
2	$NaBH_4$ (3.0 equiv), 0 °C, 1 h	71	1:1.5
3	Bu_3SnH (3.0 equiv), 0 °C, 1 h	67	1:2
4	Et_3SiH (10.0 equiv), rt, 24 h	32	11:1
5	20% $Pd(OH)_2/C$, H_2, rt, 2 h	60	20:1

[a]Isolated yield. [b]Determined by ^{1}H NMR.

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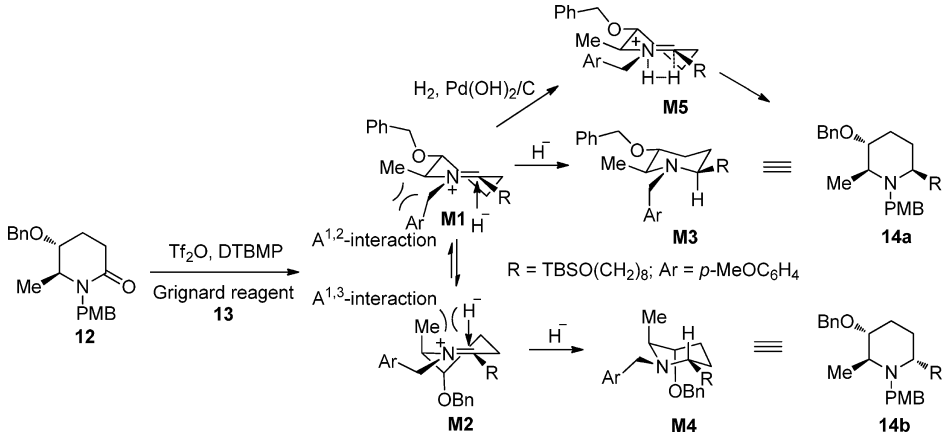
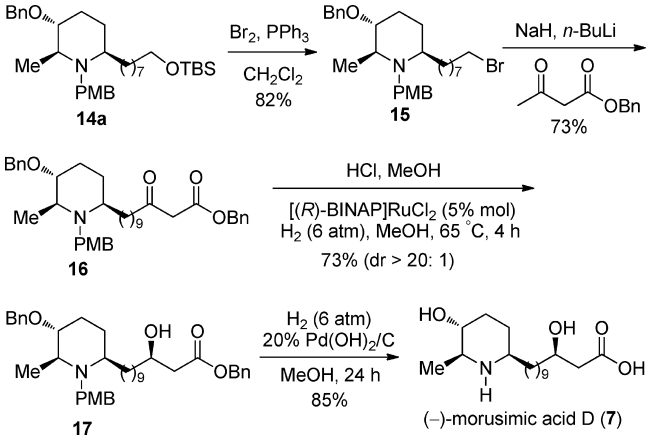
Scheme 6. Plausible Stereochemical Courses of the Reductive Alkylation Reaction of Lactam 12



Scheme 7. Improved Stereoselective Synthesis of (−)-Morusimic Acid D



CONCLUSION

In summary, we have developed a general method for the direct reductive alkylation of lactams/amides to give *sec*-alkylamines. A number of Grignard reagents and several reductants or reducing conditions can be used for this one-pot reductive alkylation reaction, which displayed good to excellent 1,3-asymmetric induction in cyclic systems. By combining this method with Noyori catalytic asymmetric hydrogenation, we achieved a highly efficient five-step stereoselective synthesis of (−)-morusimic acid D from lactam **12**. The use of Et_3SiH as a mild and highly diastereoselective reductant, and that of catalytic hydrogenation conditions, found a basis for expanding this method to a catalytic enantioselective methodology.

EXPERIMENTAL SECTION

Unless otherwise stated, reactions were performed in oven-dried glassware under a nitrogen atmosphere. Dichloromethane was distilled over calcium hydride under a nitrogen atmosphere. THF was distilled over sodium benzophenone ketyl under a nitrogen atmosphere. Silica gel (300−400 mesh) was used for flash column chromatography, eluting with ethyl acetate (EtOAc)/*n*-hexane. Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Mass spectra were obtained using electrospray ionization and an FT-ICR analyzer (ESI-MS) for high-resolution mass spectra (HRMS). Tf_2O was distilled over phosphorus pentoxide and was stored for use within a week. All the Grignard reagents were titrated before use.[28] All other commercially available compounds were used as received.

1-Benzyl-2-ethylpyrrolidine (1a). Tf_2O (101 μL, 0.60 mmol) was added dropwise to a cooled (−78 °C) solution of lactam **8b** (88 mg, 0.50 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 123 mg, 0.60 mmol) in CH_2Cl_2 (5 mL). The resultant mixture was allowed to warm to 0 °C over 1 h. After being cooled to −78 °C, a solution of ethylmagnesium bromide (0.44 M, 1.14 mL, 0.50 mmol) in Et_2O was added dropwise. The mixture was allowed to warm slowly to rt and stirred for 1 h. $LiAlH_4$ (57 mg, 1.50 mmol) was then added in one portion at 0 °C. After being stirred for 1 h, the reaction was quenched by careful addition of a 20% NaOH solution. The mixture was filtered, and the solid was washed with CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/20) to afford pyrrolidine **1a** (106 mg, yield: 82%) as a colorless oil. IR (KBr) 3062, 3028, 2961, 2926, 2854, 1495, 1455, 1380, 1029, 747, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.93 (dd, J = 7.5, 7.5 Hz, 3H), 1.35 (ddq, J = 13.3, 9.0, 7.5 Hz, 1H), 1.45−1.56 (m, 1H), 1.58−1.84 (m, 2H), 1.78 (dqd, J = 13.3, 7.5, 2.9 Hz, 1H), 1.87−1.98 (m, 1H), 2.12 (dd, J = 16.8, 9.2 Hz, 1H), 2.29 (ddd, J = 16.8, 8.2, 3.3 Hz, 1H), 2.92 (ddd, J = 9.0, 7.8, 2.9 Hz, 1H), 3.18 (d, J = 12.9 Hz, 1H), 4.04 (d, J = 12.9 Hz, 1H), 7.21−7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.4, 21.8, 26.5, 29.8, 54.2, 58.5, 65.8, 126.8, 128.1 (2C), 129.0 (2C), 139.5 ppm; MS (ESI) m/z 190 (M + H^+, 100%); Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.57; H, 10.17; N, 7.37.

***N,N*-Dibenzyl-1-phenylpentan-1-amine (1l).** Following the procedure described for the synthesis of compound **1a**, the reductive alkylation of amide **8c** (281 mg, 1.00 mmol) with phenylmagnesium bromide and $LiAlH_4$ gave, after flash chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/100), amine **1l** (343 mg, yield: 60%) as a colorless oil. IR (KBr) 3061, 3026, 2954, 2929, 2858, 1493, 1453, 1028, 744, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.85 (t, J = 7.2 Hz, 3H), 1.18−1.43 (m, 2H), 1.72−1.84 (m, 1H), 1.98−2.09 (m, 1H), 3.15 (d, J = 13.8 Hz, 2H), 3.66 (dd, J = 7.4, 7.4 Hz, 1H), 3.81 (d, J = 13.8 Hz, 2H), 7.18−7.41 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.0, 22.7, 29.1, 30.2, 30.9, 53.7 (2C), 61.8, 126.7 (2C), 126.9, 127.9 (2C), 128.2 (4C), 128.7 (4C), 129.0 (2C), 139.3, 140.5 (2C) ppm; MS (ESI) m/z 344 (M + H^+, 100%); HRESIMS calcd for $[C_{25}H_{30}N]^+$ (M + H^+) 344.2373, found 344.2376.

(2*S*,5*S*)-1-Benzyl-2-ethyl-5-(methoxymethyl)pyrrolidine (11). Following the procedure described for the synthesis of compound **1a**, the reductive alkylation of lactam **10**[24] (219 mg, 1.00 mmol) with ethylmagnesium bromide and LAH gave, after flash chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/100), pyrrolidine **11** and its diastereomer (dr = 6/1, determined by ^1H NMR of the crude product) in a combined yield of 73%. **11**: colorless oil; $[\alpha]_D^{20}$ +4.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3062, 3027, 2959, 2925, 2873, 2854, 1494, 1454, 1115, 746, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.83 (dd, J = 7.4, 7.4 Hz, 3H), 1.14−1.89 (m, 4H), 2.53−2.62 (m, 1H),

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2.86−2.95 (m, 1H), 3.02−3.14 (m, 2H), 3.20 (s, 3H), 3.71 (d, J = 14.0 Hz, 1H), 3.88 (d, J = 14.0 Hz, 1H), 7.19−7.35 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.5, 27.4, 27.7, 29.1, 29.7, 57.9, 58.9, 64.0, 67.0, 65.8, 126.6, 128.0 (2C), 129.0 (2C), 140.5 ppm; MS (ESI) m/z 234 (M + H$^+$, 100%); HRESIMS calcd for $[C_{15}H_{24}NO]^+$ (M + H$^+$) 234.1852, found 234.1853.

(2*S*,3*R*,6*R*)-3-(Benzyloxy)-6-[8-(*tert*-butyldimethylsilyloxy)-octyl]-1-(4-methoxybenzyl)-2-methylpiperidine (14a). Tf_2O (101 μL, 0.60 mmol) was added dropwise to a cooled (−78 °C) solution of the known lactam **12**[25] (170 mg, 0.50 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (123 mg, 0.60 mmol) in CH_2Cl_2 (5 mL), and the resultant mixture was allowed to warm to 0 °C over 1 h. After being cooled to −78 °C, a solution of freshly prepared Grignard reagent **13** (0.30 M in THF, 1.67 mL, 0.50 mmol) was added dropwise to the resultant mixture. The mixture was allowed to warm slowly to room temperature and stirred for 1 h. The resulting mixture was concentrated under reduced pressure to give a residue, which, without further purification, was dissolved in EtOAc (1 mL) and hydrogenolyzed in the presence of 20% $Pd(OH)_2/C$ (80 mg) under a hydrogen atmosphere (1 atm, balloon) at room temperature for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/10) to afford compound **14a** (170 mg, yield: 60%) (dr = 20/1, determined by ^{1}H NMR) as a colorless oil. $[\alpha]_D^{20}$ −13.8 (c 1.0, $CHCl_3$); IR (KBr) 2928, 2855, 1511, 1463, 1248, 1098, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.92 (s, 9H), 1.24 (d, J = 6.3 Hz, 3H), 1.15−1.83 (m, 17H), 2.14−2.23 (m, 1H), 2.43−2.52 (m, 1H), 2.66 (dq, J = 8.4, 6.3 Hz, 1H), 3.10−3.21 (m, 1H), 3.61 (t, J = 6.5 Hz, 2H), 3.75 (d, J = 14.7 Hz, 1H), 3.79 (d, J = 14.7 Hz, 1H), 3.81 (s, 3H), 4.49 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.26−7.39 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.3 (2C), 17.7, 18.4, 25.8, 26.0 (3C), 26.5, 27.5, 29.0, 29.4, 29.6, 29.9, 32.9, 34.3, 51.6, 55.2, 61.3, 61.6, 63.3, 70.8, 79.1, 113.3 (2C), 127.4, 127.7 (2C), 128.3 (2C), 128.9 (2C), 134.0, 128.9, 158.0 ppm; MS (ESI) m/z 568 (M + H$^+$, 100%); HRESIMS calcd for $[C_{35}H_{58}NO_3Si]^+$ (M + H$^+$) 568.4180, found 568.4187.

(2*S*,3*R*,6*R*)-3-(Benzyloxy)-6-(8-bromooctyl)-1-(4-methoxybenzyl)-2-methylpiperidine (15). Bromine (31 μL, 0.60 mmol) was added to a cooled (0 °C) solution of Ph_3P (157 mg, 0.60 mmol) in CH_2Cl_2 (6 mL). After being stirred at rt for 20 min, a solution of compound **14a** (227 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) was added, and the resultant mixture was stirred at rt for 30 min. The reaction was quenched with water (5 mL), and the mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/5) to afford bromide **15** (170 mg, yield: 82%) as a colorless oil. $[\alpha]_D^{20}$ −22.1 (c 1.0, $CHCl_3$); IR (KBr) 3064, 3025, 2929, 2854, 1510, 1454, 1243, 735, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.3 Hz, 3H), 1.18−1.60 (m, 14H), 1.74−1.85 (m, 3H), 2.12−2.20 (m, 1H), 2.40−2.49 (m, 1H), 2.63 (dq, J = 8.4, 6.3 Hz, 1H), 3.09−3.17 (m, 1H), 3.38 (t, J = 6.8 Hz, 2H), 3.71 (d, J = 14.8 Hz, 1H), 3.75 (d, J = 14.8 Hz, 1H), 3.78 (s, 3H), 4.45 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 7.26−7.36 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 26.3, 27.4, 28.0, 28.6, 28.9, 29.3, 29.7, 32.7, 33.9, 34.2, 51.6, 55.2, 61.3, 61.6, 70.7, 78.9, 113.3 (2C), 127.4, 127.6 (2C), 128.2 (2C), 128.8 (2C), 133.9, 138.8, 158.0 ppm; MS (ESI) m/z 516 (M + H$^+$, 100%); HRESIMS calcd for $[C_{29}H_{43}BrNO_2]^+$ (M + H$^+$) 516.2472, found 516.2456.

Benzyl 12-[(2*R*,5*R*,6*S*)-5-(Benzyloxy)-1-(4-methoxybenzyl)-6-methylpiperidin-2-yl]-3-oxododecanoate (16). To a cooled (0 °C) suspension of NaH (13 mg, 0.33 mmol) in THF (1 mL) under N_2 was added a solution of benzyl acetoacetate (58 mg, 0.30 mmol) in THF (1 mL). The resultant mixture was stirred at 0 °C for 30 min before *n*-BuLi (0.12 mL, 0.30 mmol) was added dropwise. After being stirred at 0 °C for 30 min, a solution of **15** (78 mg, 0.15 mmol) in THF (1 mL) was added, and the mixture was warmed to rt and stirred for 1 h. The reaction was then quenched with a saturated NH_4Cl solution (3 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/2) to afford compound **16** (69 mg, yield: 73%) as a colorless oil. $[\alpha]_D^{20}$ −24.2 (c 1.0, $CHCl_3$); IR (KBr) 2927, 2854, 2854, 1744, 1716, 1510, 1454, 1243, 1096, 737, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.2 Hz, 3H), 1.16−1.81 (m, 19H), 2.12−2.21 (m, 1H), 2.40−2.48 (m, 1H), 2.48 (t, J = 7.3 Hz, 2H), 2.62 (dq, J = 8.6, 6.2 Hz, 1H), 3.13 (ddd, J = 8.7, 8.6, 4.4 Hz, 1H), 3.46 (s, 2H), 3.71 (d, J = 16.4 Hz, 1H), 3.75 (d, J = 16.4 Hz, 1H), 3.77 (s, 3H), 4.45 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 5.16 (s, 2H), 6.81 (d, J = 8.6 Hz, 2H), 7.23−7.35 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 23.4, 26.4, 27.4, 28.9 (2C), 29.2, 29.3, 29.4, 29.8, 34.3, 43.0, 49.2, 51.5, 52.2, 61.3, 61.6, 70.7, 79.0, 113.3 (2C), 127.4, 127.6 (2C), 128.1, 128.2 (2C), 128.3 (2C), 128.4, 128.5 (2C), 128.8 (2C), 135.3, 138.9, 158.0, 167.0, 202.6 ppm; MS (ESI) m/z 628 (M + H$^+$, 100%); HRESIMS calcd for $[C_{40}H_{54}NO_5]^+$ (M + H$^+$) 628.3997, found 628.4001.

Benzyl (*R*)-12-[(2*R*,5*R*,6*S*)-5-(Benzyloxy)-1-(4-methoxybenzyl)-6-methylpiperidin-2-yl]-3-hydroxydodecanoate (17). Preparation of the HCl salt of compound **16**: acetyl chloride (0.2 mL) was added at 0 °C to MeOH (2 mL), and the mixture was stirred at 0 °C for 5 min. Compound **16** (63 mg, 0.10 mmol) was added. After being stirred at rt for 30 min, the solvent was evaporated. The crude oily product was used in the next step.

A vial containing the HCl salt of compound **16** (63 mg, 0.10 mmol) and catalyst [(*R*)-BINAP]$RuCl_2$ (4 mg, 0.005 mmol, 5 mol %) in MeOH (2 mL) was placed in an autoclave. After being purged with hydrogen for 5 min, the pressure of hydrogen was raised to 6 atm, and the mixture was stirred at 65 °C for 4 h. The reaction was then stopped, and the mixture was diluted with CH_2Cl_2 (5 mL). The resulting mixture was passed through a pad of silica gel, and the collected solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-hexane = 1/1) to afford compound **17** (46 mg, yield: 73%) as a colorless oil. $[\alpha]_D^{20}$ −24.8 (c 1.0, $CHCl_3$); IR (KBr) 3436, 2927, 2853, 1736, 1511, 1455, 1245, 1096, 737, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.3 Hz, 3H), 1.10−1.84 (m, 21H), 2.11−2.21 (m, 1H), 2.40−2.48 (m, 1H), 2.45 (dd, J = 16.4, 9.0 Hz, 1H), 2.55 (dd, J = 16.4, 3.2 Hz, 1H), 2.62 (dq, J = 8.5, 6.3 Hz, 1H), 2.86 (br s, 1H, D_2O exchangeable), 3.13 (ddd, J = 8.7, 8.5, 4.3 Hz, 1H), 3.72 (d, J = 13.4 Hz, 1H), 3.75 (d, J = 13.4 Hz, 1H), 3.78 (s, 3H), 3.97−4.05 (m, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 5.15 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.23−7.38 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 25.4, 26.4, 27.4, 29.0, 29.4, 29.5, 29.5, 29.5, 29.9, 34.3, 36.5, 41.4, 51.6, 55.2, 61.3, 61.6, 66.4, 68.0, 70.8, 79.1, 113.3 (2C), 127.4, 127.7 (2C), 128.2 (2C), 128.3 (2C), 128.3, 128.6 (2C), 128.8 (2C), 134.0, 135.6, 138.9, 158.0, 172.8 ppm; MS (ESI) m/z 630 (M + H$^+$, 100%); HRESIMS calcd for $[C_{40}H_{56}NO_5]^+$ (M + H$^+$) 630.4153, found 630.4157.

(*R*)-3-Hydroxy-12-[(2*R*,5*R*,6*S*)-5-hydroxy-6-methylpiperidin-2-yl]dodecanoic Acid, (−)-Morusimic Acid D (7). A suspension of **17** (35 mg, 0.06 mmol) and 20% $Pd(OH)_2/C$ (15 mg) in MeOH (2 mL) was stirred under a hydrogen atmosphere (6 atm) at room temperature for 24 h. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure, affording compound **7** (14 mg, yield: 85%) as a white solid. mp 230 °C (decomposed); $[\alpha]_D^{20}$ −13.9 (c 0.25, MeOH) {lit.[7] $[\alpha]_D^{20}$ −14.6 (c 0.25, MeOH)}; IR (KBr) 3381, 2924, 2851, 1566, 1415, 1342, 1066 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.37 (d, J = 6.3 Hz, 3H), 1.28−1.52 (m, 17H), 1.64−1.72 (m, 1H), 2.02 (d, J = 12.4 Hz, 1H), 2.08 (d, J = 12.4 Hz, 1H), 2.20−2.41 (m, 2H), 2.80−2.90 (m, 1H), 2.92−3.02 (m, 1H), 3.36−3.42 (m, 1H), 3.84−3.96 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 16.5, 26.5, 26.6, 29.1, 30.3, 30.3, 30.4, 30.4, 30.5, 33.4, 34.9, 38.1, 45.4, 58.1, 59.2, 70.4, 71.6, 180.5 ppm; MS m/z (ESI) 330 (M + H$^+$, 100%); HRESIMS calcd for $[C_{18}H_{36}NO_4]^+$ (M+H$^+$) 330.2639, found 330.2633.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds and NOESY spectra of compounds **11** and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Guo-Qiang Lin on the occasion of his 70th Birthday.

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