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Total Synthesis and Glycosidase Inhibition of Broussonetine I and J_2

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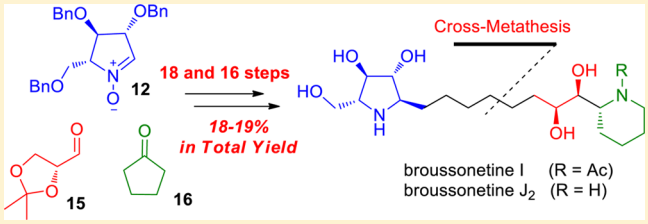
Supporting Information

ABSTRACT: The first total synthesis of both broussonetine I and J_2 together with their enantiomers have been accomplished via the same synthetic route through 18 and 16 steps in excellent overall yields (18% and 19%, respectively), starting from *R*-glyceraldehyde. Broussonetine I was found to be a potent inhibitor of *β*-glucosidase (IC_{50} = 2.9 *μ*M), while *ent*-broussonetine I and *ent*-broussonetine J_2 were found to be potent inhibitors of *α*-glucosidase (IC_{50} = 0.33 and 0.53 *μ*M, respectively).



INTRODUCTION

Broussonetines are a family of naturally occurring iminosugars, or polyhydroxylated pyrrolidine alkaloids, isolated from the branches of the deciduous tree *Broussonetia kazinoki* SIEB (Moraceae),[1] which is widely growing in several Far East countries, especially in Japan and China. *Broussonetia kazinoki* has been used as a folk medicine in China since ancient times and was found to possess some important functions, such as diuretic, detoxicating, hemostatic, tonic, and antiedema functions.[2] To date, 29 congeners of this family of alkaloids, broussonetines A–J, J_2, K–M, M_2, O, P, and R–Z, have been isolated by Kusano and co-workers.[1h] Most of these compounds show potent glycosidase inhibitory activities and as such have enormous therapeutic potential as antitumor and anti-HIV agents.[1h,3] Therefore, the synthesis and biological evaluation of these alkaloids have attracted much attention.[4]

Studies have shown that polyhydroxypyrrolidine core and/or piperidine core play an important role in natural alkaloids with important biological activities.[5] Broussonetines I (**6**), J (**7**), J_1 (**8**), and J_2 (**9**) possess unique structures in the broussonetine family (Figure 1), i.e., a polyhydroxylated pyrrolidine connected with a chiral piperidine through a long hydrocarbon chain. This intriguing structure may have unexpected effects on bioactivities. Herein, we report the total synthesis and glycosidase inhibition of broussonetine I (**6**) and J_2 (**9**).

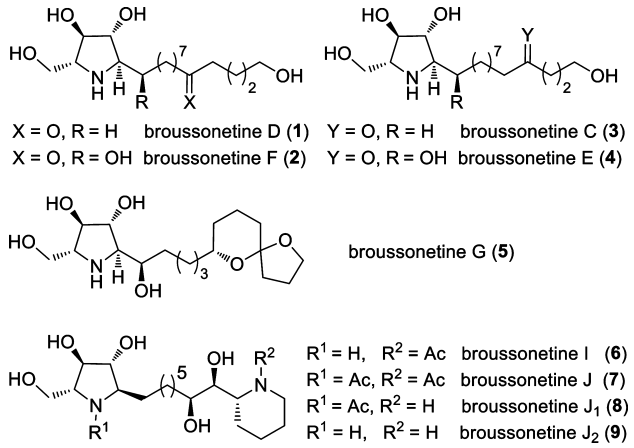


Figure 1. Representative broussonetines.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. Our retrosynthetic analysis is presented in Scheme 1. The first challenge is how to construct the long side chain which connects the pyrrolidine and piperidine moieties. Cross-metathesis or CM reaction[6] seems to be the best method to connect the pyrrolidine ring and the piperidine ring because broussonetine I (**6**) and J_2 (**9**) could be efficiently synthesized through the same method starting from suitable pyrrolidine and piperidine substrates. The disconnection between C4′′–C5′′ was based on the previously modeled reactions, which showed that disconnection at this position may give the best results of the CM reaction. Thus, the target compound **6** can be synthesized through CM reaction of pyrrolidine **10** and piperidine **11**. Pyrrolidine **10** can be prepared from the sugar-derived cyclic nitrone **12**.[7] Piperidine **11**, containing a terminal olefinic bond, can be prepared by addition of vinylmagnesium bromide to the terminal epoxide derived from **13**. The piperidine **13** can be synthesized starting from **14**, which can be prepared from the aldol reaction between *R*-glyceraldehyde (**15**)[8] and cyclopentanone (**16**), through four critical steps: (1) Baeyer–Villiger oxidation; (2)

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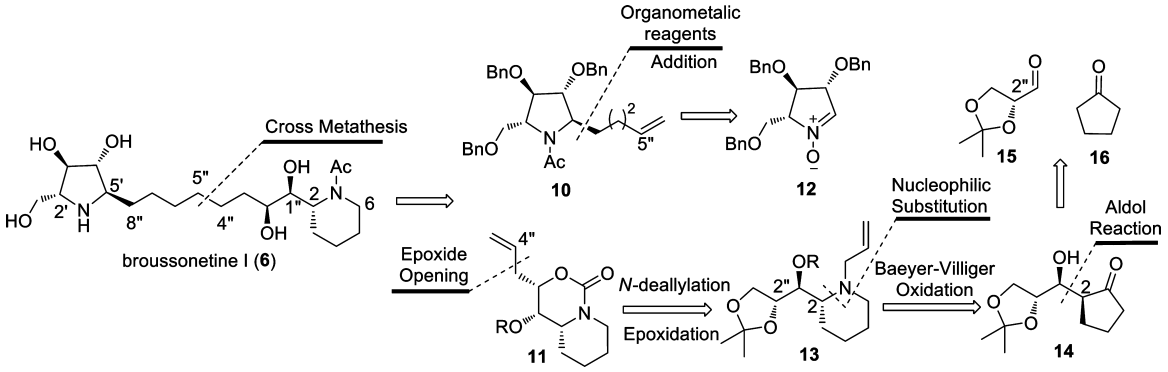
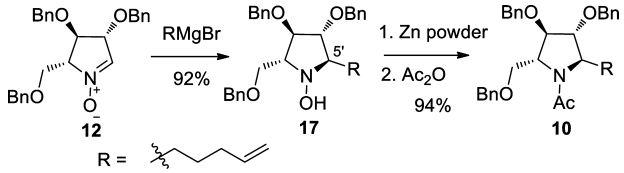
Scheme 1. Retrosynthesis of Broussonetine I (6)



reduction by lithium aluminum hydride; (3) dimesylation; and (4) nucleophilic substitution by allylamine.[9]

Synthesis of Pyrrolidine 10. To execute the synthesis of pyrrolidine **10**, as depicted in Scheme 2, D-arabinose derived

Scheme 2. Construction of the Polyhydroxylated Pyrrolidine Moiety 10

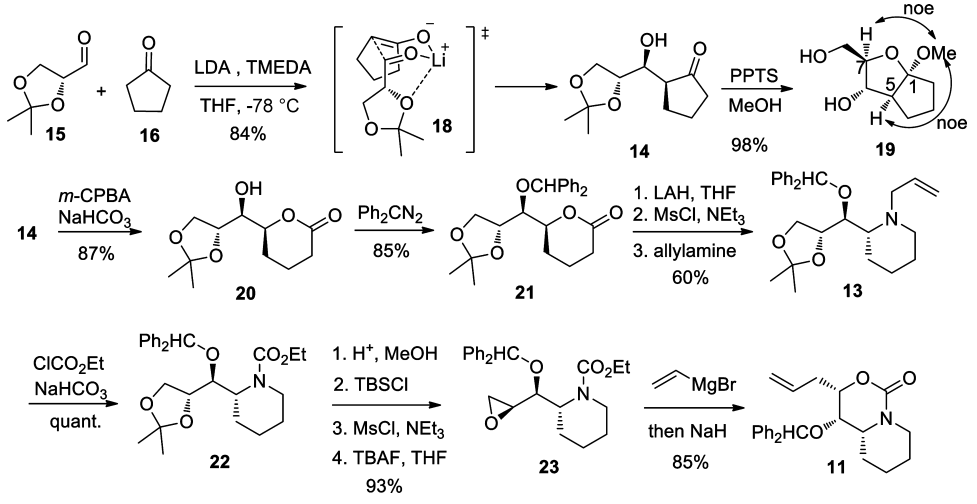


cyclic nitrone **12** was treated with Grignard reagent pent-4-en-1-ylmagnesium bromide to furnish hydroxylamine **17** in 92% yield as the only product of the reaction.[10] Reduction of hydroxylamine **17** with Zn/Cu(OAc)$_2$/AcOH and acylation of the resulting secondary amine afforded the desired product **10** in 94% yield over two steps.

Synthesis of Piperidine 11. To execute the synthesis of piperidine **11**, as depicted in Scheme 3, cyclopentanone derivative **14** was prepared from *R*-glyceraldehyde (**15**) and commercially available cyclopentanone (**16**) in 84% yield with excellent diastereoselectivity (Scheme 3). NOESY study (interaction between H-5 and OMe, H-7 and OMe) of the ketal **19**, prepared by treating **14** with PPTS in methanol, indicated that the aldol reaction proceeded in nonclassical way to give the desired *syn* product, which could be explained with the model proposed by Heathcock et al. in 1991.[11] Then, ketone **14** underwent *m*-CPBA promoted Baeyer–Villiger oxidation smoothly to afford lactone **20**. Protection of the free hydroxyl group turned out to be a tricky task. Many attempts of trying to protect the free hydroxyl group of lactone **20** failed to give decent results, such as protecting with TBS, MOM, etc. Finally, it was found that diphenylmethyl[12] works well as protecting group for lactone **20**. The protected lactone **21** was then treated with lithium aluminum hydride and methanesulfonyl chloride successively, followed by nucleophilic substitution of allylamine, to give *N*-allyl piperidine **13** in excellent overall yields. A number of reagents and conditions had been attempted to remove the allylic group, including α-chloroethyl carbonochloridate[13] or Pd(PPh$_3$)$_4$,[14] but were not successful. Fortunately, deprotection of **13** employing ethyl chloroformate with sodium bicarbonate as additives worked well to give *N*-carbamate **22**. Then, removal of the acetonide in acidic methanol and conversion of dihydroxyl to epoxide by conventional procedure afforded the epoxide **23** in excellent overall yields.[15] Treatment of **23** with vinylmagnesium bromide, followed by sodium hydride, provided the desired bicyclic compound **11**.[16]

Completion of the Total Synthesis. With both key intermediates in hand, we started attempts on the coupling reaction of **10** and **11**. After screening a number of conditions,

Scheme 3. Synthesis of Fragment 11



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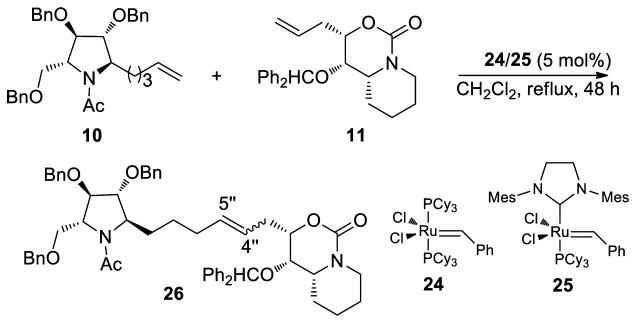
it was found that CM reaction of **10** and **11** proceeded well in the presence of the Grubbs' reagent **25** in refluxing dichloromethane to give product **26** (inseparable mixture of *E*/*Z* isomers) in 80.5% yield (Table 1). The spectacular increase in

Table 1. CM Coupling of 10 and 11

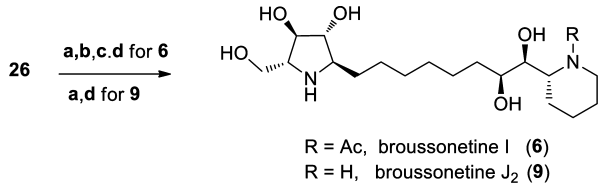


entry	10/11	Grubbs' reagent	solvent	yield[a] (%)
1	1:1	**25**	CH_2Cl_2	12
2	2:1	**25**	CH_2Cl_2	80.5
3	2:1	**24**	CH_2Cl_2	<5
4	2:1	**25**	$ClCH_2CH_2Cl$	trace

[a]Isolated yield.

yield from entry 1 to entry 2 (Table 1) might be attributed to that the homodimers of compound **10** (Type I olefin) could participate in CM reaction again, which precluded the dimerization of compound **11** (Type II olefin).[6a] Then, conversion of the *N*-carbamate to *N*-acyl derivative proceeded efficiently in three conventional steps: (1) using 2 M KOH-EtOH to destroy oxazine ring;[17] (2) acylated the second amine and hydroxyl; (3) selective removal of the acyl group from oxygen. At last, broussonetine I (**6**) was obtained after hydrogenation in the presence of 12 N HCl (Scheme 4).

Scheme 4. Completion of the Total Synthesis of Broussonetine I (6) and J_2 (9)[a]



[a]Reagents and conditions: (a) 2 M KOH−EtOH, 90 °C; (b) Ac_2O (2.5 equiv), NEt_3 (5 equiv), DMAP (cat.), CH_2Cl_2, rt; (c) MeONa (1 M in MeOH, 1 equiv), MeOH, rt; (d) 10% Pd/C (0.3 equiv), H_2, 12 N HCl, MeOH, rt, 83% over four steps.

Broussonetine J_2 (**9**) was also obtained after oxazine ring-opening, followed by catalytic hydrogenation involving 12 N HCl. The ^1H and ^{13}C NMR spectra of the synthetic broussonetine I (**6**) and J_2 (**9**) were identical to those reported for the natural products (see the Supporting Information for the details). The optical rotation of the synthetic broussonetine I (**6**) $[[\alpha]^{20}_D$ +3.7 (c = 0.3, in MeOH)] and broussonetine J_2 (**9**) $[[\alpha]^{20}_D$ +3.6 (c = 0.5, in MeOH)] were similar to those of the natural broussonetine I $[[\alpha]^{25}_D$ +2.9 (c = 0.26, in MeOH)] and broussonetine J_2 $[[\alpha]^{25}_D$ +2.7 (c = 0.43, in MeOH)].[1d,g]

Evaluation of Glycosidase Inhibition. In order to study the basic structure−activity relationship of this class of natural products, the enantiomers of these two natural products, i.e., *ent*-broussonetine I (***ent*-6**) and J_2 (***ent*-9**), had also been synthesized starting from ***ent*-12** and ***ent*-15** via the same synthetic procedure (Figure 2). Broussonetine I (**6**) and J_2 (**9**)

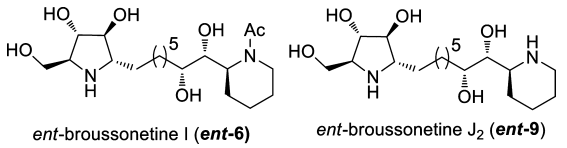


Figure 2. Enantiomers of broussonetine I and J_2.

together with *ent*-broussonetine I (***ent*-6**) and J_2 (***ent*-9**) were assayed as potential glycosidase inhibitors of a range of enzymes (Table 2).[18] It was found that the natural products and their

Table 2. Concentration of Iminosugars Giving 50% Inhibition of Various Glycosidases[a,b]

	IC_{50} (μM)			
enzyme	**6**	**9**	***ent*-6**	***ent*-9**
α-glucosidase				
yeast	NI (33.7%)	NI (12.0%)	NI (15.8%)	NI (18.8%)
rice	NI (43.7%)	NI (18.6%)	2.2	5
rat intestinal maltase	NI (28.4%)	NI (15.9%)	0.33	0.53
β-glucosidase				
almond	652	1000	NI (36.6%)	NI (5.6%)
bovine liver	2.9	10	327	120
α-galactosidase				
coffee beans	NI (8.2%)	NI (12.3%)	NI (15.3%)	NI (16.6%)
β-galactosidase				
bovine liver	2.7	10	250	72
α-mannosidase				
jack beans	408	NI (17%)	NI (0%)	NI (22%)
β-mannosidase				
Helix pomatia	NI (44%)	NI (33%)	NI (0%)	NI (0%)
α-L-fucosidase				
bovine kidney	NI (5.9%)	NI (7.9%)	NI (8.7%)	NI (18.7%)
amyloglucosidase				
Aspergillus niger	52	54	NI (16.7%)	NI (24.9%)
α-L-rhamnosidase				
Penicillium decumbens	NI (5.8%)	NI (0%)	193	214

[a]NI: No inhibition (less than 50% inhibition at 1000 μM). [b]Parentheses: inhibition % at 1000 μM.

enantiomers showed different inhibition patterns of glycosidases. Broussonetine I (**6**) showed potent inhibition of β-glucosidase (IC_{50} = 2.9 μM, against bovine liver), while *ent*-broussonetine I (***ent*-9**) of α-glucosidase (IC_{50} = 0.33 μM, against rat intestinal maltase). Although, broussonetine J_2 (**9**) gave moderate inhibition of β-glucosidase (IC_{50} = 10 μM, against bovine liver), *ent*-broussonetine J_2 (***ent*-9**) was a little better of α-glucosidase (IC_{50} = 0.53 μM, against rat intestinal maltase). The natural products also showed inhibition of β-galacosidase (IC_{50} = 2.7 μM and 10 μM, respectively for I and J_2, against bovine liver), but their enantiomers showed weak inhibition or no inhibition at all. It seemed that the enantiomers of the natural products inhibited α-glucosidase selectively.

■ CONCLUSIONS

In summary, the first total synthesis of broussonetine I and J_2 have been accomplished via a same synthetic route through 18 and 16 steps in excellent overall yields (18% and 19%,

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respectively) starting from *R*-glyceraldehyde. In order to study the basic structure−activity relationship of this class of natural products, the enantiomers (***ent*-6** and ***ent*-9**) had also been synthesized starting from ***ent*-12** and ***ent*-15** *via* the same synthetic procedure. The synthetic strategy developed for this class of natural products will be useful for the synthesis of a variety of analogues of these alkaloids, and therefore, are significant for the future work on the discovery of new lead compounds of selective and potent glycosidase inhibitors. Furthermore, the method for the construction of the homochiral 2-substituted piperidine **11** provided an efficient way for the synthesis of this kind of compounds. The results obtained from the preliminary structure−activity relationship study are valuable for future work on the design and synthesis of iminosugar-based glycosidase inhibitors.

EXPERIMENTAL SECTION

General Methods. All reagents were used as received from commercial sources or prepared as described in the literature. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O} or a solution 0.5% ninhydrin in acetone. Acidic ion exchange chromatography was performed on Amberlite IR-120 (H^+) or Dowex 50WX8-400, H^+ form. Melting points were determined using an electrothermal melting point apparatus. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or D_2O on a magnetic resonance spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on an LTQ/FT linear ion trap mass spectrometer. Concentrations (c) are given in gram per 100 mL. The presence of impurities in the sample, indicated by ^1H NMR, are the "best" quality spectra available.

*(2R,3R,4R,5R)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(pent-4-en-1-yl)pyrrolidin-1-ol (**17**).* To a stirred solution of Mg (150 mg, 6.25 mmol) and I_2 (cat.) in THF (10 mL) under N_2 atmosphere was quickly added 0.05 mL of 5-bromopent-1-ene (0.681 mL, 6 mmol, in 5 mL THF), and then the resulting mixture was heated by hairdryer until the color of the mixture disappeared and the remaining 5-bromopent-1-ene added slowly. After addition was complete, the mixture was heated to reflux for 1 h, and then the resulting mixture was cooled to room temperature. To a stirred solution of **12** (2 g, 5 mmol) in THF, the prepared Grignard reagent was added slowly by syringe at 0 °C under N_2 atmosphere. Saturated NH_4Cl was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/petroleum ether = 1:5) to afford compound **17** (2.149 g, 92% yield) as a colorless oil. $[\alpha]^{25}_D$ = −7.36 (c 1.9, CH_2Cl_2). IR (KBr, cm^{-1}): 3232, 2934, 1454. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30−7.09 (m, 15H), 6.65 (s, 1H), 5.70 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 4.94−4.84 (m, 2H), 4.50−4.34 (m, 6H), 3.92−3.83 (m, 1H), 3.77−3.63 (m, 2H), 3.57−3.37 (m, 2H), 3.08 (dd, J = 12.0, 5.8 Hz, 1H), 1.97 (dd, J = 12.9, 6.3 Hz, 2H), 1.1.82−1.79 (m, 1H), 1.50−1.30 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.2, 138.14, 138.11, 128.39, 128.37, 128.36, 128.0, 127.9, 127.72, 127.69, 127.6, 114.6, 86.8, 84.6, 73.4, 71.7, 71.6, 70.1, 69.8, 68.2, 33.9, 25.9. HRMS ESI: calcd for $C_{31}H_{38}NO_4$ $[M + H]^+$ 488.27954, found 488.27951.

*1-((2R,3R,4R,5R)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(pent-4-en-1-yl)pyrrolidin-1-yl)ethanone (**10**).* To a stirred solution of $Cu(OAc)_2$ (82 mg, 0.4 mmol) in AcOH (40 mL) was added Zn (1.335 g, 20.5 mmol) in one portion. After 0.5 h, **17** (2 g, 4.1 mmol) in CH_2Cl_2 (10 mL) was added to the mixture slowly. After the addition was complete, the mixture was stirred for 6 h, then the solid was filtered out, and the resulting mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and was washed with aq $NaHCO_3$ and brine water until the pH turned to neutral. Then the organic layer was dried with $MgSO_4$ and concentrated in vacuo. To a stirred solution of the crude product in CH_2Cl_2 (40 mL) at 0 °C were slowly added $NaHCO_3$ (0.69 g, 8.2 mmol) and Ac_2O (0.47 mL, 4.9 mmol), and then the mixture was stirred at room temperature for 2 h. Saturated $NaHCO_3$ was added to quench the reaction, and then the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/petroleum ether = 1:5) to afford compound **10** (1.98 g, 94% yield) as a red oil. $[\alpha]^{25}_D$ = −26.2 (c 1.45, CH_2Cl_2). IR (KBr, cm^{-1}): 2923, 1644. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.13 (m, 15H), 5.85−5.64 (m, 1H), 4.98 (d, J = 9.9 Hz, 1H), 4.92 (d, J = 9.9 Hz, 1H), 4.64 (dd, J = 12.1, 5.3 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.51−4.37 (m, 4H), 4.32 (dd, J = 12.1, 5.3 Hz, 1H), 4.17 (d, J = 13.6 Hz, 1H), 4.11−3.98 (m, 1H), 3.84 (d, J = 12.5 Hz, 1H), 3.75−3.51 (m, 1.5H), 3.40−3.30 (m, 0.5H), 2.17−1.83 (m, 6H), 1.61−1.18 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 138.7, 138.6, 138.0, 137.9, 137.8, 137.7, 137.6, 137.5, 128.6, 128.5, 128.5, 128.4, 128.3, 127.94, 127.87, 127.79, 127.75, 127.7, 127.6, 127.53, 127.49, 115.2, 114.6, 84.5, 83.6, 83.1, 81.5, 73.0, 71.4, 71.0, 70.9, 69.6, 67.3, 66.0, 64.6, 64.2, 62.7, 33.6, 33.2, 32.3, 29.5, 26.0, 25.9, 23.0, 22.9. HRMS ESI: calcd for $C_{33}H_{40}NO_4$ $[M + H]^+$ 514.2952, found 514.2948.

***ent*-10.** Red oil, 1.98 g, 94% yield. $[\alpha]^{25}_D$ = +17.0 (c 1.65, CH_2Cl_2). IR (KBr, cm^{-1}): 2923, 1644. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.15 (m, 15H), 5.84−5.64 (m, 1H), 4.98 (d, J = 9.7 Hz, 1H), 4.92 (d, J = 9.7 Hz, 1H), 4.64 (dd, J = 12.1, 5.2 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.51−4.37 (m, 4H), 4.32 (dd, J = 12.1, 5.3 Hz, 1H), 4.17 (d, J = 13.7 Hz, 1H), 4.13−3.99 (m, 1H), 3.84 (d, J = 12.4 Hz, 1H), 3.75−3.50 (m, 1.5H), 3.40−3.30 (m, 0.5H), 2.17−1.82 (m, 6H), 1.62−1.16 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.7, 138.7, 138.6, 138.0, 137.8, 137.7, 137.6, 137.5, 128.6, 128.52, 128.49, 128.4, 128.3, 127.94, 127.87, 127.8, 127.8, 127.7, 127.6, 127.54, 127.49, 115.2, 114.6, 84.5, 83.6, 83.1, 81.5, 73.2, 73.0, 71.4, 71.0, 70.9, 69.6, 67.3, 66.0, 64.6, 64.3, 62.7, 33.6, 33.2, 32.3, 29.5, 26.0, 25.9, 23.0, 22.9. HRMS ESI: calcd for $C_{33}H_{40}NO_4$ $[M + H]^+$ 514.2952, found 514.2948.

*(S)-2-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-cyclopentanone (**14**).* To a stirred solution of LDA (151 mL, 2 M in THF, 0.302 mol) in THF (150 mL) was slowly added cyclopentanone (**16**) (25.4 mL, 0.279 mol) at −78 °C under N_2, and then the mixture was stirred at this temperature for 2.5 h and TMEDA (62.8 mL, 0.419 mol) was added in one portion. After 0.5 h, (*R*)-glyceraldehyde (**15**) (30 g, 0.233 mol) in THF (50 mL) was added to the mixture in 5 min. After the addition was complete, the mixture was stirred for 2 h at −78 °C. Saturated NH_4Cl was added to quench the reaction, and then the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/petroleum ether =1:5) to afford compound **14** (42.0 g, 84.1% yield) as a colorless oil. $[\alpha]^{25}_D$ = −29.5 (c 1.1, CH_2Cl_2). IR (KBr, cm^{-1}): 3454, 2985, 2982, 1735. ^1H NMR (300 MHz, $CDCl_3$): δ 4.10−4.04 (m, 2H), 4.03−3.94 (m, 2H), 2.88 (s, 1H), 2.49−2.37 (m, 1H), 2.37−2.25 (m, 1H), 2.19−1.92 (m, 4H), 1.71−1.89 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.1, 109.3, 76.7, 69.8, 66.9, 52.0, 38.8, 26.8, 25.3, 22.8, 20.6. HRMS ESI: calcd for $C_{11}H_{17}O_3$ $[M - H_2O + H]^+$ 197.11722, found 197.11719 (only fragment peaks in MS-ESI).

***ent*-14.** Colorless oil, 41.7 g, 84% yield. $[\alpha]^{25}_D$ = +35.4 (c 1.3, CH_2Cl_2). IR (KBr, cm^{-1}): 3446, 2985, 1733. ^1H NMR (300 MHz, $CDCl_3$) δ 4.13−4.06 (m, 2H), 4.05−3.90 (m, 2H), 2.81 (s, 1H), 2.49−2.37 (m, 1H), 2.37−2.25 (m, 1H), 2.19−1.92 (m, 4H), 1.89−1.74 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.3, 109.3, 76.7, 69.8, 66.8, 52.0, 38.8, 26.8, 25.3, 22.8, 20.6. HRMS ESI: calcd for $C_{11}H_{17}O_3$ $[M - H_2O + H]^+$ 197.11722, found 197.11719 (only fragment peaks in MS-ESI).

*(2R,3S,3aS,6aS)-2-(Hydroxymethyl)-6a-methoxyhexahydro-2H-cyclopenta[b]furan-3-ol (**19**).* To a stirred solution of **14** (0.163 g, 0.758 mmol) in MeOH (15 mL) was added PPTS (19 mg, 0.19 mmol) at room temperature, and then the mixture was heated to reflux for 6 h. $NaHCO_3$ was added to neutralize the PPTS, and MeOH was

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removed under reduced pressure. The residue was dissolved with water (5 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc) to afford compound **19** (0.139 g, 98% yield) as a colorless oil. $[\alpha]^{25}_D$ = +5.0 (*c* 0.8, CH_2Cl_2). IR (KBr, cm^{-1}): 3389, 2950, 2871. ^1H NMR (600 MHz, $CDCl_3$): δ 3.90 (dt, *J* = 7.5, 3.8 Hz, 1H), 3.85 (d, *J* = 11.9 Hz, 1H), 3.79 (s, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 3.31 (s, 3H), 2.80 (s, 1H), 2.40−2.30 (m, 2H), 1.96−1.93 (m, 1H), 1.93−1.84 (m, 1H), 1.72−1.78 (m, 1H), 1.65−1.55 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 119.3, 83.9, 78.8, 62.0, 56.8, 50.7, 34.7, 29.7, 24.6. HRMS ESI: calcd for $C_8H_{13}O_3$ $[M - CH_4O + H]^+$ 157.08592, found 157.08591 (only fragment peaks in MS-ESI).

*(S)-6-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-tetrahydro-2H-pyran-2-one (**20**).* To a stirred solution of **14** (0.1 g, 0.5 mmol) and $NaHCO_3$ (84 mg, 1 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (0.173 g, 1 mmol) over 5 min at room temperature. After the addition was complete, the mixture was stirred for 2 h, and then the solid in the mixture was filtered out. The solution was concentrated to 10 mL under reduced pressure, and the precipitated solid was filtered out again. The resulting mixture was washed with saturated $NaHCO_3$ (3 × 10 mL), and the combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/petroleum ether = 1:3) to afford compound **20** (91.4 mg, 87% yield) as a colorless oil. $[\alpha]^{25}_D$ = +21.6 (*c* 1.0, CH_2Cl_2). IR (KBr, cm^{-1}): 3427, 2986, 1732. ^1H NMR (300 MHz, $CDCl_3$) δ 4.47−4.42 (m, 1H), 4.08−3.92 (m, 3H), 3.80 (s, 1H), 3.18 (s, 1H), 2.54 (d, *J* = 17.1 Hz, 1H), 2.38 (d, *J* = 17.1 Hz, 1H), 1.80−1.89 (m, 4H), 1.34 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 109.6, 81.3, 74.6, 72.9, 67.1, 29.8, 26.8, 25.1, 21.1, 18.2. HRMS ESI: calcd for $C_{11}H_{19}O_5$ $[M + H]^+$ 231.12270, found 231.12267.

*ent-**20**.* Colorless oil, 92.7 mg, 88% yield. $[\alpha]^{25}_D$ = −24.6 (*c* 1.3, CH_2Cl_2). IR (KBr, cm^{-1}): 3434, 2985, 1732. ^1H NMR (300 MHz, $CDCl_3$) δ 4.55−4.51 (m, 1H), 4.12−4.09 (m, 1H), 4.08−3.96 (m, 2H), 3.85 (dd, *J* = 7.7, 2.8 Hz, 1H), 2.65−2.56 (m, 1H), 2.49−2.37 (m, 1H), 2.04−1.77 (m, 5H), 1.41 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 109.6, 81.4, 74.7, 72.8, 67.2, 29.8, 26.7, 25.1, 20.8, 18.2. HRMS ESI: calcd for $C_{11}H_{19}O_5$ $[M + H]^+$ 231.12270, found 231.12268.

*(S)-6-((S)-(Benzhydryloxy)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-methyl)tetrahydro-2H-pyran-2-one (**21**).* To a stirred solution of **20** (0.1 g 0.4 mmol) in toluene (15 mL) was added freshly prepared diphenyldiazomethane (151 mg, 0.8 mmol) at room temperature, and then the mixture was heated to reflux for 6 h and the color of the mixture was changed from purple to yellow. Toluene was removed in vacuo, and the residue was chromatographed (EtOAc/petroleum ether = 1:10) to afford compound **21** (1.457 g, 85% yield) as a white solid. $[\alpha]^{25}_D$ = +58.4 (*c* 1.2, CH_2Cl_2). Mp: 110−112 °C. IR (KBr, cm^{-1}): 2985, 1739. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45−7.15 (m, 10H), 5.78 (s, 1H), 4.56 (dd, *J* = 7.2, 2.7 Hz, 1H), 4.09 (dd, *J* = 13.7, 6.2 Hz, 1H), 3.96 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.84 (dd, *J* = 7.6, 2.6 Hz, 1H), 3.47 (dd, *J* = 8.3, 6.1 Hz, 1H), 2.53−2.43 (m, 1H), 2.23−2.10 (m, 1H), 1.96−1.70 (m, 4H), 1.29 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 142.3, 141.8, 128.5, 128.3, 127.9, 127.7, 127.3, 126.9, 109.4, 83.8, 81.8, 78.8, 74.5, 67.5, 29.8, 26.5, 25.3, 21.8, 18.3. HRMS ESI: calcd for $C_{24}H_{28}O_5Na$ $[M + Na]^+$:419.1829, found 419.1827.

*ent-**21**.* White solid, 1.47 g, 85% yield. $[\alpha]^{25}_D$ = −55.4 (*c* 1.1, CH_2Cl_2). Mp: 109−111 °C. IR (KBr, cm^{-1}): 2985, 1739. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.19 (m, 10H), 5.78 (s, 1H), 4.64−4.49 (m, 1H), 4.09 (dd, *J* = 13.4, 6.3 Hz, 1H), 4.04−3.90 (m, 1H), 3.84 (dd, *J* = 7.6, 2.2 Hz, 1H), 3.47 (dd, *J* = 8.1, 6.2 Hz, 1H), 2.53−2.43 (m, 1H), 2.26−2.09 (m, 1H), 2.23−2.10 (m, 1H), 1.99−1.70 (m, 4H), 1.29 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 142.3, 141.8, 128.5, 128.2, 127.9, 127.7, 127.3, 126.9, 109.5, 83.8, 81.8, 78.8, 74.5, 67.5, 29.8, 26.5, 25.3, 21.8, 18.3. HRMS ESI: calcd for $C_{24}H_{28}O_5Na$ $[M + Na]^+$ 419.1829, found 419.1827.

*(R)-1-Allyl-2-((S)-(benzhydryloxy)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)piperidine (**13**).* To a stirred solution of **21** (0.1 g, 0.25 mmol) in THF (20 mL) was slowly added $LiAlH_4$ (62 mg, 1.5 mmol) at 0 °C. After the addition was complete, the mixture was stirred for 0.5 h. NaOH (10%) was added to quench the reaction, and the solid was filtered out. The solvent was removed under reduced pressure. To a stirred mixture of the crude product in CH_2Cl_2 (20 mL) were added TEA (0.175 mL, 1.3 mmol) and DMAP (5 mg) at 0 °C, then MsCl (59 μL, 0.8 mmol) was added slowly. After the addition was complete, the mixture was stirred at room temperature for 2 h. Saturated $NaHCO_3$ was added to quench the reaction, and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. To a stirred solution of the crude product in MeOH (20 mL) was added allylamine (94 μL, 1.3 mmol), and the mixture was heated to reflux for 12 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (EtOAc/petroleum ether = 1:10) to afford compound **13** (67 mg, 63% yield) as a white solid. $[\alpha]^{25}_D$ = +4.2 (*c* 1.1, CH_2Cl_2). Mp: 54−56 °C. IR (KBr, cm^{-1}): 2933, 1454, 1093. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.07 (m, 10H), 5.76 (s, 1H), 5.44 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 4.92−4.80 (m, 2H), 4.43 (t, *J* = 7.2 Hz, 1H), 4.21 (d, *J* = 4.1 Hz, 1H), 4.13 (t, *J* = 7.4 Hz, 1H), 3.96 (t, *J* = 7.3 Hz, 1H), 3.04 (dd, *J* = 14.5, 6.1 Hz, 1H), 2.87 (dd, *J* = 14.5, 7.3 Hz, 1H), 2.74 (d, *J* = 11.4 Hz, 1H), 2.17 (d, *J* = 11.4 Hz, 1H), 2.05 (dt, *J* = 11.8, 2.6 Hz, 1H), 1.91 (d, *J* = 12.5 Hz, 1H), 1.67 (d, *J* = 12.8 Hz, 1H), 1.50 (d, *J* = 12.4 Hz, 1H), 1.43−1.32 (m, 4H), 1.28 (s, 3H), 1.95−0.95 (m, 1H), 0.82−0.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 142.5, 132.9, 128.4, 128.1, 127.9, 127.6, 127.1, 126.8, 118.2, 107.2, 100.0, 83.0, 75.7, 74.2, 64.6, 61.7, 56.5, 53.6, 26.6, 26.4, 25.8, 24.5. HRMS ESI: calcd for $C_{27}H_{36}NO_3$ $[M + H]^+$ 422.2690, found 422.2686.

*ent-**13**.* White solid, 68 mg, 63% yield. $[\alpha]^{25}_D$ = −2.9 (*c* 0.7, CH_2Cl_2). Mp: 53−54 °C. IR (KBr, cm^{-1}): 2933. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.07 (m, 10H), 5.81 (s, 1H), 5.61−5.39 (m, 1H), 4.92 (dd, *J* = 13.5, 7.2 Hz, 2H), 4.48 (t, *J* = 7.1 Hz, 1H), 4.26 (d, *J* = 4.0 Hz, 1H), 4.17 (t, *J* = 7.4 Hz, 1H), 4.01 (t, *J* = 7.3 Hz, 1H), 3.09 (dd, *J* = 14.5, 6.1 Hz, 1H), 2.92 (dd, *J* = 15.0, 7.9 Hz, 1H), 2.79 (d, *J* = 11.4 Hz, 1H), 2.22 (d, *J* = 11.2 Hz, 1H), 2.10 (dt, *J* = 11.8, 2.5 Hz, 1H), 1.96 (d, *J* = 12.5 Hz, 1H), 1.72 (d, *J* = 12.7 Hz, 2H), 1.53 (t, *J* = 15.0 Hz, 1H), 1.43 (s, 4H), 1.33 (s, 4H), 1.16−1.03 (m, 1H), 0.86−0.70 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 142.5, 133.0, 128.3, 128.1, 127.9, 127.6, 127.1, 126.8, 118.1, 107.2, 83.0, 75.7, 74.2, 64.6, 61.7, 56.5, 53.6, 26.6, 26.4, 25.8, 24.5, 24.5. HRMS ESI: calcd for $C_{27}H_{36}NO_3$ $[M + H]^+$ 422.2690, found 422.2686.

*(R)-Ethyl 2-((S)-(Benzhydryloxy)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)piperidine-1-carboxylate (**22**).* To a stirred solution of **8** (63 mg, 0.15 mmol) and $NaHCO_3$ (25 mg, 0.3 mmol) in $ClCH_2CH_2Cl$ (10 mL) was added ethyl chloroformate (28 μL, 0.3 mmol) at room temperature, and the mixture was heated to reflux for 12 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (EtOAc/petroleum ether = 1:10) to afford compound **22** (68 mg, quant) as a colorless oil. $[\alpha]^{25}_D$ = −69.4 (*c* 1.7, CH_2Cl_2). IR (KBr, cm^{-1}): 2934,1694. ^1H NMR (300 MHz, $CDCl_3$): δ 7.41−7.14 (m, 10H), 6.02 (s, 1H), 4.29 (t, *J* = 7.2 Hz, 1H), 4.19−4.13 (m, 4H), 4.09 (t, *J* = 8.0 Hz, 1H), 4.01−3.93 (m, 1H), 3.75−3.60 (m, 1H), 2.05 (s, 1H), 1.58−1.38 (m, 4H), 1.36 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 4H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 143.1, 141.9, 129.0, 128.3, 128.0, 127.7, 126.7, 126.2, 108.5, 82.9, 78.0, 72.6, 64.3, 61.2, 52.4, 39.6, 26.5, 26.3, 25.3, 25.0, 20.0, 14.8. HRMS ESI: calcd for $C_{27}H_{36}NO_5$ $[M + H]^+$ 454.25880, found 454.25876.

*(R)-Ethyl 2-((S)-(Benzhydryloxy)((S)-oxiran-2-yl)methyl)-piperidine-1-carboxylate (**23**).* To a stirred solution of **22** (0.1 g, 0.2 Mmol) in MeOH (10 mL) was added DOWEX 50 H^+ (cat.), and then the resulting mixture was heated to reflux for 12 h. Acidic resin was filtered out, and MeOH was removed in vacuo. To a stirred solution of the crude product in CH_2Cl_2 (10 mL) were added TEA (92 μL, 0.7 mmol), DMAP (5 mg), and TBSCl (50 mg, 0.3 mmol) at 0 °C, and then the mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ was added to quench the reaction, and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. To a stirred solution of the crude product in pyridine (10 mL)

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were added DMAP (5 mg) and MsCl (26 μL, 0.3 mmol) at 0 °C, and then the resulting mixture was stirred at room temperature for 2 h. Saturated $NaHCO_3$ was added to quench the reaction, and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. To a stirred solution of the crude product THF (10 mL) was added TBAF (173 mg, 0.7 mmol), and the mixture was stirred at room temperature for 1 h. NaOH (10%) was added to the mixture, and after 0.5 h, the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/petroleum ether = 1:15) to afford compound **23** (81 mg, 93% yield) as a colorless oil. $[\alpha]^{25}_D$ = −73.4 (*c* 1.2, CH_2Cl_2). IR (KBr, cm^{-1}): 2934, 1693. ^1H NMR (300 MHz, $CDCl_3$): δ 7.41−7.14 (m, 10H), 5.91 (s, 1H), 4.52 (s, 1H), 4.28−4.12 (m, 2H), 3.93 (s, 1H), 3.34 (t, *J* = 7.8 Hz, 1H), 3.13−3.06 (m, 1H), 2.81 (t, *J* = 4.5 Hz, 1H), 2.52 (dd, *J* = 4.8, 2.7 Hz, 1H), 2.35 (s, 1H), 1.75−1.61 (m, 2H), 1.61−1.48 (m, 3H), 1.48−1.30 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 143.1, 141.7, 128.4, 128.4, 128.1, 127.7, 126.9, 126.2, 81.0, 61.3, 53.9, 52.3, 43.5, 39.9, 26.3, 25.1, 20.2, 14.8. HRMS ESI: calcd for $C_{24}H_{30}NO_4$ $[M + H]^+$ 396.21693, found 396.21704.

*(3S,4S,4aR)-3-Allyl-4-(benzhydryloxy)hexahydropyrido[1,2-c][1,3]oxazin-1(3H)-one (**11**).* To a stirred solution of **23** (230 mg, 0.6 mmol) and CuI (12 mg, 0.06 mmol) in THF (10 mL) was slowly added vinylmagnesium bromide (0.64 mL, 0.64 mmol) at 0 °C under N_2 atmosphere, and then the resulting mixture was stirred at room temperature for 2 h. Saturated NH_4Cl was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (3 × 5 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved again in THF (10 mL), and then NaH (48 mg, 60% with oil, 1.2 mmol) was added slowly to the stirred mixture at 0 °C and the resulting mixture was stirred at room temperature for 2 h. Cold water was added to quench the reaction, and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/petroleum ether =1:3) to afford compound **11** (192 mg, 85% yield) as a white solid. $[\alpha]^{25}_D$ = −11.2 (*c* 1.1, CH_2Cl_2). Mp: 135−137 °C. IR (KBr, cm^{-1}): 2933, 1683. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.14 (m, 10H), 5.61−5.42 (m, 2H), 5.06−4.85 (m, 2H), 4.48 (dd, *J* = 13.2, 1.9 Hz, 1H), 4.11 (t, *J* = 7.1 Hz, 1H), 3.81 (d, *J* = 3.9 Hz, 1H), 3.38−3.22 (m, 1H), 2.64 (td, *J* = 12.9, 3.0 Hz, 1H), 2.44 (ddd, *J* = 14.5, 7.1, 6.0 Hz, 1H), 2.12 (dt, *J* = 14.7, 7.4 Hz, 1H), 1.73 (d, *J* = 7.2 Hz, 1H), 1.61 (d, *J* = 14.5 Hz, 1H), 1.52−1.34 (m, 2H), 1.32−1.22 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 141.6, 141.5, 133.0, 128.4, 128.3, 127.9, 127.8, 127.6, 118.2, 84.7, 77.9, 71.3, 59.6, 45.0, 34.9, 27.8, 24.6, 23.6. HRMS ESI: calcd for $C_{24}H_{28}NO_3$ $[M + H]^+$ 378.2070, found 378.2062.

*ent-**11**.* White solid, 194 mg, 85% yield. $[\alpha]^{25}_D$ = +9.5 (*c* 1.0, CH_2Cl_2). Mp: 134−135 °C. IR (KBr, cm^{-1}): 2933, 1683. ^1H NMR (300 MHz, $CDCl_3$): δ 7.43−7.16 (m, 10H), 5.63−5.44 (m, 2H), 5.00−4.88 (m, 2H), 4.50 (d, *J* = 13.2 Hz, 1H), 4.12 (t, *J* = 7.1 Hz, 1H), 3.83 (d, *J* = 3.9 Hz, 1H), 3.42−3.24 (m, 1H), 2.66 (td, *J* = 12.9, 2.8 Hz, 1H), 2.50−2.41 (m, 1H), 2.19−2.05 (m, 1H), 1.76 (d, *J* = 13.3 Hz, 1H), 1.63 (d, *J* = 13.6 Hz, 1H), 1.58−1.36 (m, 2H), 1.36−1.21 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 141.61, 141.55, 133.1, 128.4, 128.3, 127.9, 127.8, 127.6, 118.1, 84.7, 77.9, 71.3, 70.6, 59.6, 45.0, 34.9, 27.8, 24.7, 23.6. HRMS ESI: calcd for $C_{24}H_{28}NO_3$ $[M + H]^+$ 378.2070, found 378.2062.

*(3S,4S,4aR)-3-(6-((2R,3R,4R,5R)-1-Acetyl-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)pyrrolidin-2-yl)hex-2-en-1-yl)-4-(benzhydryloxy)hexahydropyrido[1,2-c][1,3]oxazin-1(3H)-one (**26**).* To a stirred solution of **10** (0.272 g, 0.5 mmol) and **11** (0.1 g, 0.3 mmol) in CH_2Cl_2 (10 mL) was added Grubbs' reagent (11 mg, 0.01 mmol) in CH_2Cl_2 (3 mL) at room temperature, and then the resulting mixture was heated to reflux for 24 h. The mixture was purified by column chromatography (EtOAc/petroleum ether = 1:3) to afford **26** (211 mg, 80.5% yield) as a gray oil. $[\alpha]^{32}_D$ = −14.3 (*c* 0.7, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.46−7.14 (m, 25H), 5.56−5.47 (m, 1H), 5.25−4.94 (m, 2H), 4.72−4.29 (m, 8H), 4.24−4.07 (m, 2H), 4.02 (t, *J* = 8.7 Hz, 2H), 3.93−3.77 (m, 2H), 3.75−3.62 (m, 1H), 3.62−3.55 (m, 0.5H), 3.42−3.22 (m, 2H), 2.66 (t, *J* = 11.9 Hz, 1H), 2.46−2.30 (m, 1H), 2.20−2.01 (m, 5H), 2.01−1.83 (m, 3H), 1.83−1.71 (m, 1H), 1.71−1.10 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 160.5, 153.6, 147.0, 141.9, 141.7, 141.6, 141.5, 141.1, 138.6, 138.2, 137.9, 137.8, 137.7, 137.6, 137.5, 136.0, 133.8, 133.3, 133.0, 131.3, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 125.4, 125.2, 124.8, 124.5, 123.9, 123.8, 84.5, 83.4, 81.5, 73.2, 73.0, 71.4, 71.0, 69.6, 67.2, 64.7, 64.2, 62.7, 59.7, 45.0, 32.4, 27.7, 26.2, 24.7, 23.6, 23.0, 22.9. HRMS ESI: calcd for $C_{55}H_{63}N_2O_7$ $[M + H]^+$ 863.4635, found 863.4631.

*Broussonetine I (**6**).* Compound **26** (0.1 g, 0.1 mmol) was dissolved in 2 M KOH−EtOH (8 mL), and the mixture was stirred at 90 °C for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved with CH_2Cl_2 and water. The resulting mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic layer was dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/MeOH = 1:5). To a stirred solution of the crude product in CH_2Cl_2 (8 mL) were added TEA (49 μL, 0.3 mmol), DMAP (2 mg), and Ac_2O (26 μL, 0.3 mmol) at 0 °C, and then the mixture was stirred at room temperature for 2 h. Saturated $NaHCO_3$ was added to quench the reaction, and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in MeOH (5 mL), and MeONa (1 mL, 1 M in MeOH) was added to the stirred mixture at room temperature. After 2 h, MeOH was removed under reduced pressure, and the residue was dissolved with CH_2Cl_2 and water.The resulting mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic layer was dried with $MgSO_4$. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether = 3:1). To a stirred solution of the crude product in MeOH (8 mL) and 12 N HCl (1 mL) was added 10% Pd/C (10 mg), and the resulting mixture was stirred under H_2 atmosphere at room temperature for 48 h.The solid was filtered, and MeOH was removed under reduced pressure. The residue was dissolved in MeOH (1 mL) and $NH_3{\cdot}H_2O$ (4 mL, 17 N), and the mixture was concentrated again under reduced pressure. The residue was purified by column chromatography (acidic ion-exchange resin) to afford compound **6** (39 mg, 83% yield) as a colorless oil. $[\alpha]^{25}_D$ = +3.7 (*c* 0.3, MeOH). IR (KBr, cm^{-1}): 3348, 2929, 1607. ^1H NMR (300 MHz, pyr): δ 4.96 (d, *J* = 13.2 Hz, 1H), 4.75 (t, *J* = 6.3 Hz, 1H), 4.58 (s, 1H), 4.47 (t, *J* = 6.5 Hz, 1H), 4.30−4.20 (m, 3H), 3.94 (s, 2H), 3.67 (s, 1H), 2.85 (t, *J* = 11.9 Hz, 1H), 2.42 (s, 3H), 2.09 (s, 4H), 1.90 (s, 4H), 1.80−1.46 (m, 10H), 1.38 (s, 6H). ^{13}C NMR (75 MHz, pyr): δ 172.5, 84.8, 80.8, 73.0, 72.8, 70.8, 66.7, 64.4, 64.1, 57.8, 52.4, 38.7, 37.1, 31.8, 31.7, 28.7, 28.3, 28.1, 27.5, 24.3, 21.8.. HRMS ESI: calcd for $C_{20}H_{39}N_2O_6$ $[M + H]^+$ 403.2803, found 403.2801.

*ent-Broussonetine I (ent-**6**).* Colorless oil, 37 mg, 83% yield. $[\alpha]^{25}_D$ = −4.2 (*c* 0.4, MeOH). IR (KBr, cm^{-1}): 3348, 2929, 1607. ^1H NMR (300 MHz, MeOD): δ 4.49 (d, *J* = 12.8 Hz, 1H), 4.14 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.80 (t, *J* = 6.4 Hz, 2H), 3.71 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.65 (dd, *J* = 9.4, 3.9 Hz, 2H), 3.62−3.55 (m, 2H), 3.34−3.31 (m, 1H), 3.09−3.02 (m, 1H), 2.98−2.90 (m, 1H), 2.75−2.65 (m, 1H), 2.16 (s, 2H), 2.14 (s, 1H), 1.92−1.83 (m, 1H), 1.81−1.33 (m, 20H). ^{13}C NMR (75 MHz, MeOD): δ 173.7, 83.3, 79.3, 71.6, 69.8, 64.6, 62.9, 62.8, 57.1, 38.3, 35.4, 34.9, 30.7, 27.6, 27.1, 27.0, 26.5, 22.2, 20.6. HRMS ESI: calcd for $C_{20}H_{39}N_2O_6$ $[M + H]^+$ 403.2803, found 403.2801.

*Broussonetine J_2 (**9**).* Compound **26** (0.1 g, 0.1 mmol) was dissolved in 2 M KOH−EtOH (8 mL), and the mixture was stirred at 90 °C for 2 h. The solvent was removed under reduced pressure, and then the residue was dissolved with CH_2Cl_2 and water. The resulting mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic layer was dried with $MgSO_4$. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (EtOAc/MeOH = 1:5). To a stirred solution of the crude product in MeOH (8 mL) and 12 N HCl (1 mL), 10% Pd/C (10 mg) was added, and the resulting mixture was stirred under H_2 atmosphere at room temperature for 12 h. The catalyst was filtered

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out, and MeOH was removed under reduced pressure. The residue was dissolved in MeOH (1 mL) and $NH_3 \cdot H_2O$ (4 mL, 17 N), and the mixture was concentrated again under reduced pressure. The residue was purified by column chromatography (acidic ion-exchange resin) to afford compound **9** (40 mg, 95% yield) as a colorless oil. $[\alpha]^{25}_D$ = +3.6 (*c* 0.5, MeOH). IR (KBr, cm^{-1}): 3309, 2929. ^1H NMR (300 MHz, pyr) δ 4.70 (t, *J* = 6.5 Hz, 1H), 4.45−4.37 (m, 1H), 4.32−4.16 (m, 2H), 4.06−3.94 (m, 1H), 3.91−3.81 (m, 1H), 3.63−3.53 (m, 1H), 3.32−3.27 (m, 1H), 2.75 (t, *J* = 12.1 Hz, 1H), 2.13−1.20 (m, 16H). ^{13}C NMR (75 MHz, pyr) δ 83.8, 79.8, 75.1, 72.7, 65.3, 63.2, 62.9, 60.5, 46.1, 35.1, 34.9, 31.1, 30.1, 29.2, 28.5, 28.3, 27.9, 27.2, 26.8, 26.4, 25.9, 25.5, 24.7, 24.3. HRMS ESI: calcd for $C_{18}H_{37}N_2O_5$ $[M + H]^+$ 361.2697, found 361.2695.

ent-Broussonetine J$_2$ *(ent-**9**).* Colorless oil, 39 mg, 95% yield. $[\alpha]^{25}_D$ = −4.5 (*c* 0.7, MeOH). IR (KBr, cm^{-1}): 3309, 2929. ^1H NMR (400 MHz, MeOD) δ 3.79−3.73 (m, 1H), 3.69−3.56 (m, 4H), 3.32−3.32 (m, 1H), 3.25 (dd, *J* = 7.2, 1.3 Hz, 1H), 3.19−3.11 (m, 1H), 3.00−2.95 (m, 1H), 2.89−2.79 (m, 2H), 2.76−2.66 (m, 1H), 1.84 (d, *J* = 11.9 Hz, 1H), 1.78 (d, *J* = 13.1 Hz, 1H), 1.68 (d, *J* = 8.2 Hz, 2H), 1.64−1.24 (m, 15H). ^{13}C NMR (101 MHz, MeOD) δ 82.4, 78.4, 74.7, 70.9, 63.1, 62.0, 61.3, 58.9, 45.5, 33.9, 33.5, 29.4, 29.3, 27.2, 26.3, 25.5, 24.4, 23.3. HRMS ESI: calcd for $C_{18}H_{37}N_2O_5$ $[M + H]^+$ 361.2697, found 361.2696.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR spectra for all new compounds. 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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