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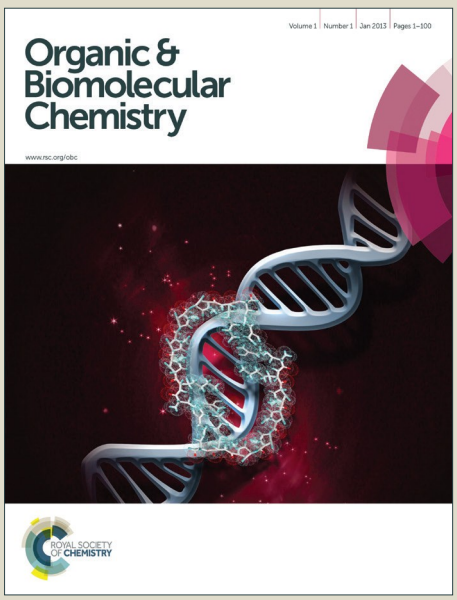

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First Total Synthesis of (+)-Broussonetine W: Glycosidase Inhibition of Natural Product & Analogs

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The first total synthesis of (+)-broussonetine W (**4**), a naturally-occurring pyrrolidine iminosugar isolated from the traditional Chinese medical plant *Broussonetia kazinoki* SIEB (Moraceae), has been completed through a concise synthetic route starting from the readily available D-arabinose derived cyclic nitrone **10** in 11 steps and 31% overall yield, with regioselective installation of the α,β-unsaturated ketone functional group by the elimination of HBr from α-bromoketone as the key step. A number of analogs of (+)-broussonetine W (**4**) with variable side chain length, different polyhydroxylated pyrrolidine core configurations or saturated cyclohexanones have also been prepared to explore the glycosidase inhibition and the preliminary structure-activity relationship of this intriguing class of compounds. Glycosidase inhibition studies identified the natural product (+)-broussonetine W (**4**) as a selective and potent inhibitor of β-galactosidase (IC_{50} = 0.03 μM), while its enantiomer was a selective and potent inhibitor of α-glucosidase (IC_{50} = 0.047μM). It was found that the configuration of the polyhydroxylated pyrrolidine ring played a key role on their glycosidase inhibitory activities. The length of side chain and α,β-unsaturated ketone functional group also exhibited some effect on their glycosidase inhibition.

Introduction

Broussonetines, a family of naturally-occurring iminosugar alkaloids with a polyhydroxylated pyrrolidine ring as its core structural segment, have been isolated from the branches of *Broussonetia kazinoki* SIEB (Moraceae),[1] which is a raw material for handmade Japanese paper and traditional Chinese medicines. Thus far, more than 30 of this class of alkaloids have been isolated and characterized, namely broussonetines A-X, J_1, J_2, M_1, U_1, and broussonetinines A and B, *etc*. (Figure 1).[2]

With broussonetines N (pyrrolizidine ring), U, and U_1 (pyrroline ring) as exceptions, broussonetines and broussonetinines share a common polyhydroxylated pyrrolidine core[3] and a 13-carbon-atom side chain that contains various functional groups at the C-5 position of the pyrrolidine ring. Although a subset has been assigned as 2*R*, 3*S*, 4*R*, 5*R* configuration, most of these alkaloids have 2*R*, 3*R*, 4*R*, 5*R* pyrrolidine rings. Therefore, these compounds could be viewed as homologues of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB, **5**)[4] or 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, **6**)[4d,5].

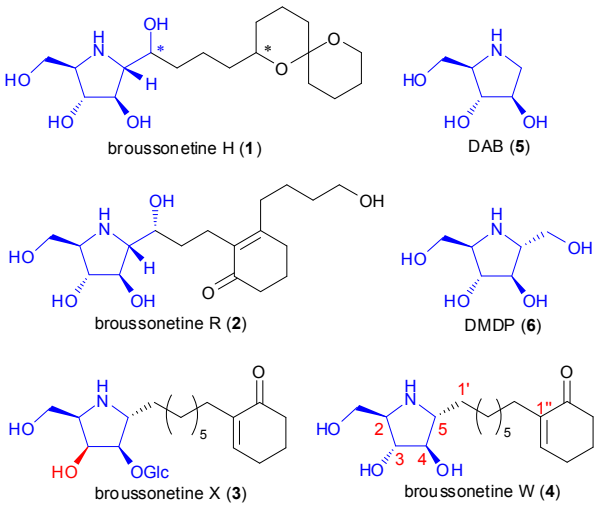

Figure 1. Representative examples of broussonetines.

Broussonetines have been attracted intense interest due to their glycosidase inhibition activities and potential therapeutic applications in diseases including cancer, HIV[1e,1f,2,6] and lysosomal storage disorders[7]. In particular, many

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Electronic Supplementary Information (ESI) available: Copies of ^1H, ^{13}C and 2D NMR spectra and results of the bioassay. See DOI: 10.1039/x0xx00000x

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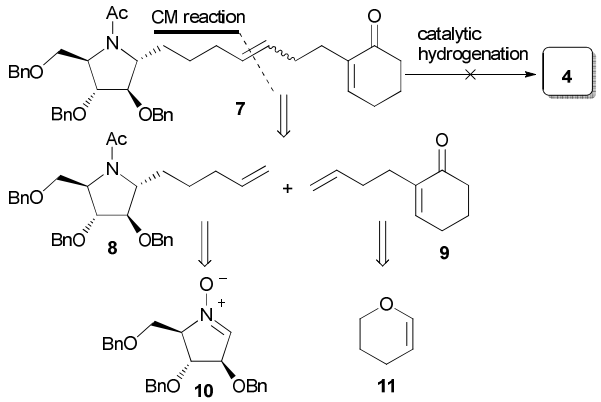
broussonetines showed potent and selective inhibition against *β*-glycosidases (*β*-glucosidases, *β*-galactosidases, or *β*-mannosidases); for example, broussonetine H (**1**) is a potent inhibitor of *β*-galactosidases (IC_{50} = 0.002 μM, from bovine liver) and *β*-glucosidase (IC_{50} = 0.036 μM, from sweet almond). Moreover, synthetic L-enantiomers of some DMDP-related iminosugars have been attractive targets in recent years due to their potent and selective *α*-glucosidase inhibition.[5b,9] Our previous study on the synthesis and glycosidase inhibition of broussonetines[8], showed that the L-enantiomers of broussonetine I and J_2 showed potent and selective inhibition of *α*-glucosidases, and as such may have chemotherapeutic potential in the treatment of type-II diabetes[9g,10], cancer[11], and viral infections[3f,12]. In view of the interesting structures and biological activities of the broussonetines family, efficient synthetic methods for these alkaloids and their analogs, including their enantiomers, need to be developed. However, to date, relatively few syntheses have been reported.[8,13]

Broussonetine W (**4**) was isolated from *Broussonetia* in 2001 by Kusano and co-workers.[1h] The relative configuration of broussonetine W was established on the basis of NOE experiments and the absolute configuration was assigned as (2*R*,3*R*,4*R*,5*R*) by analogy with the $[\alpha]_D$ value (+16.0) of broussonetine W with those of broussonetines C (+25.0) and D (+22.9).[1a] However, the proposed structure can only be determined unless unequivocally confirmed by total synthesis. No biological evaluation has been reported for broussonetine W (**4**). Because of the potent glycosidase inhibition of the closely related broussonetine I and J_2[8], we became interested in the synthesis of broussonetine W to establish both the relative and absolute configurations of broussonetine W and to study its biological activity.

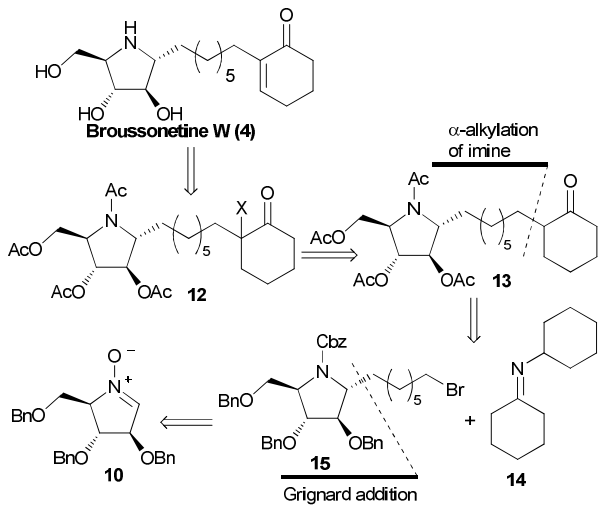
Results and discussion

Our initial synthetic strategy for the total synthesis of broussonetine W (**4**) is presented in Scheme 1. Construction of the long side chain between the pyrrolidine and cyclohexenone moieties could be accomplished by CM reactions[14], which proved to be a flexible strategy in the synthesis of broussonetine I and J_2.[8] Therefore, the precursor compound **7** can be synthesized through CM reaction of pyrrolidine fragment **8** and cyclohexenone **9**. Clearly, pyrrolidine **8** can be obtained from D-arabinose derived cyclic nitrone **10**, which was easily prepared on a large scale by our improved approach,[15] while cyclohexenone **9** can be prepared from 3, 4-2*H*-dihydropyran (**11**).[16] Unfortunately, all attempts at the regioselective hydrogenation[17] of the C4'–C5' double bond in compound **7**, proved to be unsuccessful. It was not possible to reduce the carbon-carbon double bond of the side chain whilst retaining the *α,β*-unsaturated ketone group. Hydrogenation of **7** always resulted in the formation of a mixture of products with poor regioselectivity.

Thus, the synthetic strategy was modified so that the *α,β*-unsaturated ketone group could be introduced at the last step, thereby avoiding the troublesome regioselective reduction of the C4'–C5' double bond. The cyclohexanone derivative **13** could be synthesized first and the protecting groups on the hydroxyl and amino groups can be converted to acetyl groups for easy deprotection in the final step (Scheme 2).



Scheme 1. Initial synthetic strategy for the synthesis of broussonetine W (**4**).



Scheme 2. Retrosynthesis of broussonetine W (**4**).

The *α,β*-unsaturated keto function[18] in the target product could be introduced by regioselective *α*-halogenation of ketone **13**,[18b-d,19] followed by elimination of HX from *α*-haloketone **12**. The key intermediate **13** could be synthesized by the *α*-alkylation of the imine **14** with bromide **15**, and subsequent conversion of the protecting groups to acetyl groups. Pyrrolidine fragment **15** could be obtained from cyclic nitrone **10** by successive Grignard reaction,[15,20] hydroboration/oxidation and Appel halogenations of the resulting alcohol.[21]

Accordingly, the polyhydroxylated pyrrolidine moiety **17** was first synthesized from D-arabinose derived cyclic nitrone **10** (Scheme 3). The addition of hept-6-en-1-ylmagnesium bromide to the cyclic nitrone **10** at 0 °C afforded hydroxylamine **16** as the only product,[8,20f,22] which was used in the next step without further purification. The newly formed chiral centre

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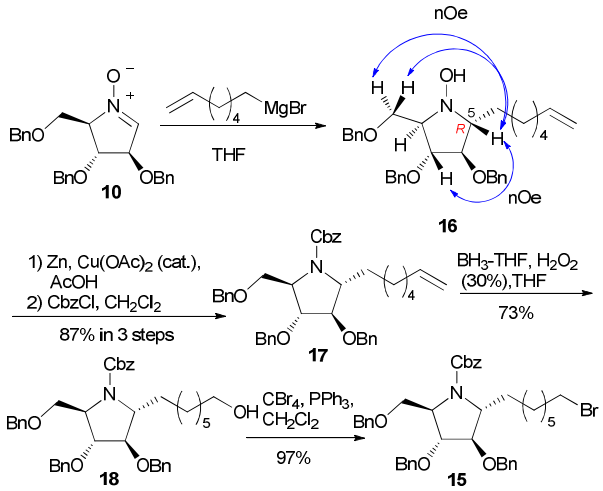
was determined as *R*-configuration by NOE experiments. Reduction of hydroxylamine **16** by Zn-Cu(OAc)$_2$-AcOH system gave the corresponding amine, which was treated with CbzCl to form the *N*-Cbz derivative **17** in 87% yield (3 steps). Hydroboration of **17** with BH_3-THF and subsequent oxidation by H_2O_2 (30%) gave the primary alcohol **18** in 73% yield, which on treatment with CBr_4 and PPh_3 afforded the corresponding bromide **15** in 97% yield.



Scheme 3. Synthesis of pyrrolidine **15**.

In order to determine unambiguously the relative and absolute configurations of the natural product broussonetine W, both broussonetine W (**4**) and *ent*-broussonetine W (***ent*-4**) were synthesized. Furthermore, in order to verify the generality of this synthetic method for the synthesis of broussonetine W-related compounds and explore the preliminary structure-activity relationship of broussonetine W, several analogs of broussonetine W (**4**) with varied side chain length (***ent*-4a**, ***ent*-4b**) and different polyhydroxylated pyrrolidine core configurations (**3-*epi*-4**, ***ent*-3-*epi*-4**) were prepared (Figure 2).

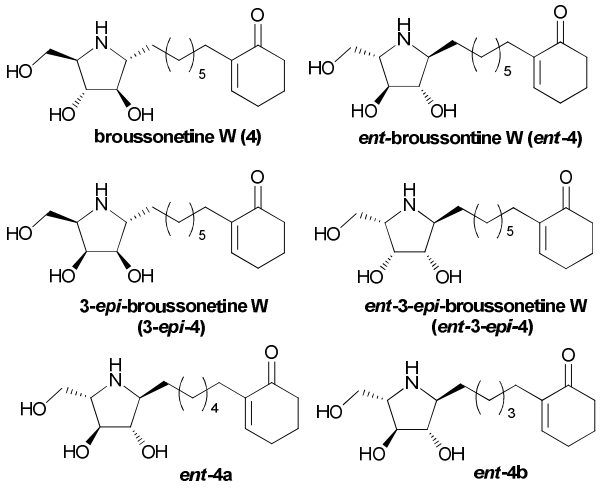
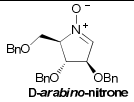
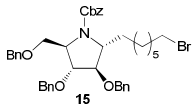
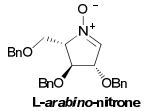
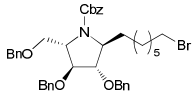
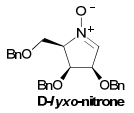
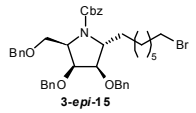
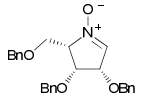
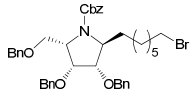
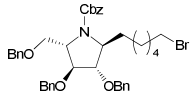
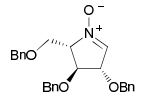
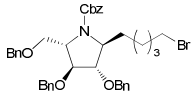


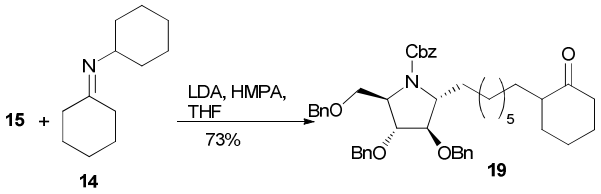
Figure 2. Broussonetine W (**4**) and its analogs.

Therefore, pyrrolidines fragments with a terminal bromide, i.e. ***ent*-15**, **3-*epi*-15**, ***ent*-3-*epi*-15**, ***ent*-15a** and ***ent*-15b**, have also been prepared by the same methodology as that for the synthesis of **15**, starting from the various corresponding cyclic nitrones and Grignard reagents (Table 1).

Table 1. Pyrrolidine fragments derived from different cyclic nitrones or different Grignard reagents.

Entry	Cyclic Nitrone	Product	Yield[a] (%)
1	 D-*arabino*-nitrone (10)	 15	62
2	 L-*arabino*-nitrone (*ent*-10)	 *ent*-15	77
3	 D-*lyxo*-nitrone (3-epi-10)	 3-*epi*-15	58
4	 L-*lyxo*-nitrone (*ent*-3-*epi*-10)	 *ent*-3-*epi*-15	53
5	 L-*arabino*-nitrone (*ent*-10)	 *ent*-15a	70
6	 L-*arabino*-nitrone (*ent*-10)	 *ent*-15b	79

[a]Total yield in 5 steps starting from cyclic nitrones to the corresponding bromide



Scheme **4**. Synthesis of ketone **19.**

With the pyrrolidine fragments in hand, the next task was the installation of cyclohexanone into the molecules. As an example, α-alkylation of imine **14**, which had been prepared from the reaction of cyclohexanone and cyclohexylamine,[23] with pyrrolidine bromide **15,** followed by aqueous work-up gave ketone **19** in 73% yield (Scheme 4).[24] By the same sequence, analogs of ketone **19**, i.e. ***ent*-19**, **3-*epi*-19**, ***ent*-3-**

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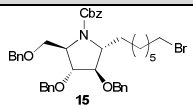
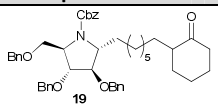
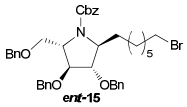
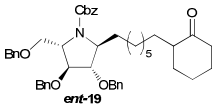
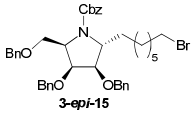
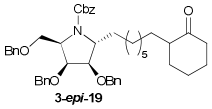
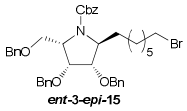
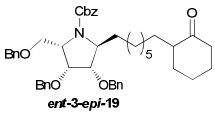
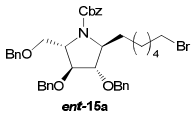
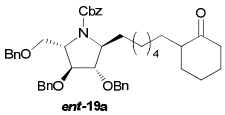
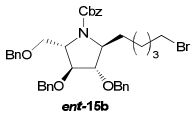
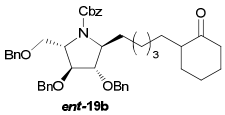
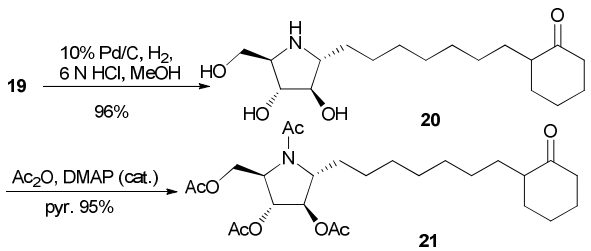
***epi*-19**, ***ent*-19a** and ***ent*-19b**, were synthesized from the corresponding bromides (Table 2).

Table 2. Ketones derived from the corresponding bromides.

Entry	Substrate	product	Yield (%)[a]
1			73
2			71
3			60
4			71
5			68
6			71

[a]Isolated yield.

The last challenge in the synthesis of broussonetine W analogs was the formation of α,β-unsaturated ketone group *via* *α*-halogenation-elimination of the cyclohexanone. In order to avoid the potential side reactions that may be caused by *N*-Cbz group in the *α*-halogenations of ketone **19** and also to prevent the reduction of the *α,β*-unsaturated ketone group during the debenzylation process, the protecting groups were first converted to acetyl groups, which allowed final deprotection easily without any of the above side reactions. Thus, Pd-catalyzed hydrogenolysis of ketone **19** gave the broussonetine W analog **20** containing a saturated cyclohexanone group at the end of the side chain, in 96% yield. A series of analogs with saturated cyclohexanone group (**20**, ***ent*-20**, **3-*epi*-20**, ***ent*-3-*epi*-20**, ***ent*-20a** and ***ent*-20b**) were obtained easily by this process (Figure 3). Treatment of compound **20** with conventional acetylation methods provided fully protected compound **21** in 95% yield (Scheme 5).



Scheme 5. Transformation of the protecting-groups.

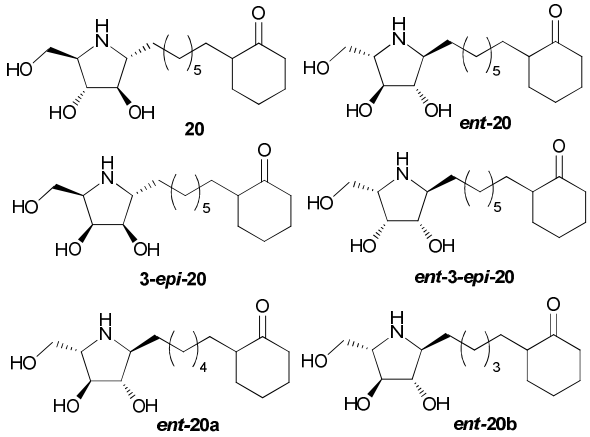
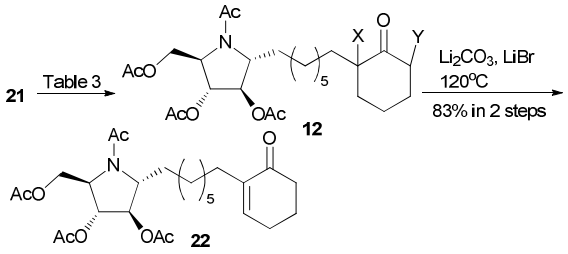


Figure 3. Cyclohexanone analogs of broussonetine W.

The final problem in the total synthesis of broussonetine W was the introduction of *α,β*-unsaturated ketone group at the end of the side chain,[18] by an elimination reaction on a corresponding *α*-haloketone. A number of reagents and reaction conditions were screened to optimize the regioselective α-halogenation of ketone **21** (Table 3).[18b,18d] Treatment of ketone **21** with $(TMS)_2NH$/NaI/TMSCl system followed by NBS was the best method which produced the desired *α*-bromoketone **12b** (X=Br, Y=H) in excellent isolated yield. Thus, α-bromination of ketone **21** and β-elimination of the resulted α-bromoketone **12b** yielded the acetyl-protected broussonetine W (**22**) in 83% yield in two steps (Scheme 6). Analogs of acetyl-protected broussonetine W, *i.e.* compounds **22**, ***ent*-22**, **3-*epi*-22**, ***ent*-3-*epi*-22**, ***ent*-22a** and ***ent*-22b**, were also synthesized by the same method (Table 4).



Scheme 6. Synthesis of **22**.

Table 3. Screening the *α*-halogenation conditions.

Entry	Reagent	Solvent/ °C	result	yield [a]
1	NBS	CCl_4/rt	No reaction	-
2	NBS	CCl_4/80	No reaction	-
3	NBS	CCl_4/120	No reaction	-
4	SO_2Cl_2	CCl_4/rt	**12a**:X=Y=Cl	100%
5	SO_2Cl_2	CCl_4/0	**12a**:X=Y=Cl	100%
6	$(TMS)_2NH$, NaI, TMSCl, then NBS	CH_3CN/ 0, then -20	**12b**:X=Br Y=H	95%

[a]Conversion of **21**.

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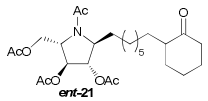
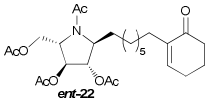
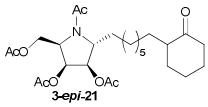
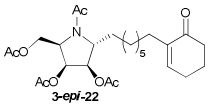
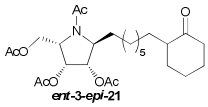
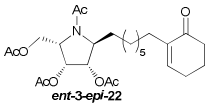
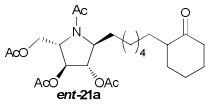
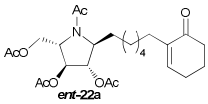
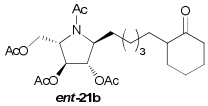
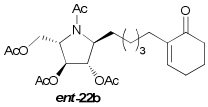
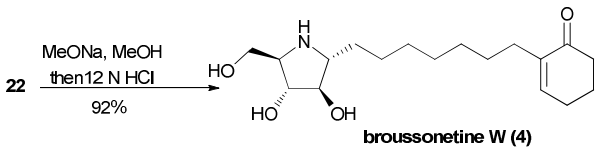
Table 4. *α,β*-Unsaturated ketones derived from the corresponding ketones.

Entry	Substrate	Product	Yield (%)[a]
1	 *ent*-21	 *ent*-22	80
2	 3-*epi*-21	 3-*epi*-22	59
3	 *ent*-3-*epi*-21	 *ent*-3-*epi*-22	78
4	 *ent*-21a	 *ent*-22a	69
5	 *ent*-21b	 *ent*-22b	67

[a]Isolated yield.



Scheme 7. Completion of the total synthesis of broussonetine W (**4**).

Completion of the total synthesis was then achieved smoothly by removal of the acetyl protecting groups from the hydroxyl and amino groups. Thus, treatment of **22** with MeONa/MeOH followed by concentrated hydrochloric acid provided broussonetine W (**4**) in 92% yield (Scheme 7).[25] The synthetic broussonetine W (**4**) displayed identical spectral properties (^{1}H NMR, ^{13}C NMR) to those reported in the literature for the natural product (see the Supplementary Information for the details); the specific rotation of the synthetic broussonetine W (**4**) {$[\alpha]_D^{20}$ +15.0 (*c* 0.4, MeOH)} was consistent with that of the natural broussonetine W {$[\alpha]_D$ +16.0 (*c* 0.07, MeOH)}.[1h] These measurements confirmed that both the reported relative and absolute configurations of natural broussonetine W were correct.

The NMR spectra of the natural product were performed in pyridine in order to compare with the literature data reported in pyridine. Other analogues were all new compounds without reported NMR data, and therefore were carried out in CD_3OD to obtain relatively better peak splits.

A similar synthetic approach to ***ent*-4**, **3-*epi*-4** and ***ent*-3-*epi*-4** (Figure 2 and Figure 3) allowed a preliminary study of the structure-activity relationship of broussonetine W and its analogs. In addition, analogs with different side chain length (***ent*-4a**, ***ent*-4b**) were prepared.

Glycosidase Inhibition.

Broussonetine W and its analogs were assayed[26] as potential glycosidase inhibitors of a range of enzymes (Table 5 and 6). The synthetic D-broussonetine W (**4**) showed very powerful inhibition of *β*-glucosidase from bovine liver (IC_{50} = 0.12 μM), *β*-galactosidase from bovine liver (IC_{50} = 0.03 μM), and it also showed potent inhibition toward *β*-glucuronidase from *E.coli* (IC_{50} = 3.3 μM). In contrast, its enantiomer L-broussonetine W (***ent*-4**) showed remarkable enhancements in *α*-glucosidases from rice, rat intestinal maltase, rat intestinal sucrose (IC_{50} = 0.73 μM, 0.047 μM, 0.20 μM, respectively), whereas ***ent*-4** clearly decreased the inhibition of these *β*-glycosidases. The enhanced *α*-glucosidase inhibition parallels that of L-DMDP in the core pyrrolidine structure. **3-*Epi*-4** was a much weaker inhibitor than natural product (+)-broussonetine W (**4**). This result indicated that the C3 configuration of polyhydroxylated pyrrolidine ring played a key role on their glycosidase inhibitory activity. However, it is noteworthy that dramatic changes in the spectrum and potency of inhibition were found for its enantiomer ***ent*-3-*epi*-4**. This compound still showed potent inhibition of bovine liver *β*-glucosidase, bovine liver *β*-galactosidase, with IC_{50} values 0.99 and 0.18 μM, respectively. Furthermore, its inhibition toward *α*-glucosidases from rat intestinal maltase and sucrose were clearly increased relative to the natural product (+)-broussonetine W (**4**), with IC_{50} values 3.5 and 3.4 μM, respectively.

Variations in the length of the side chain did not have a significant effect on their glycosidase inhibition through comparison of *ent*-broussonetine W related (***ent*-4**, ***ent*-4a**, ***ent*-4b**). The glycosidase inhibition activity was slightly weakened, when the side chain length was shortened.

The terminal substituents fixed at the end of the side chain did not show significant effect on the patterns of glycosidase inhibitory activities. However, some changes have a small effect on the potency of inhibition against the same enzyme. Compounds containing the saturated cylohexanone group (**20**, ***ent*-20**, **3-*epi*-20**, ***ent*-3-*epi*-20**, ***ent*-20a**, ***ent*-20b**) were slightly weaker inhibitors against the same enzyme than natural product (+)-broussonetine W (**4**) and its analogs containing the same α,β-unsaturated cylohexenone group (***ent*-4**, **3-*epi*-4**, ***ent*-3-*epi*-4**, ***ent*-4a**, ***ent*-4b**). However, **3-*epi*-20** was notably found to be a much stronger inhibitor of *α*-glucosidases than **3-*epi*-4** which has the unsaturated cylohexenone group.

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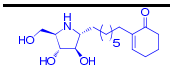
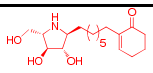
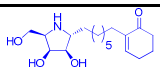
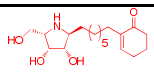
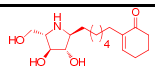
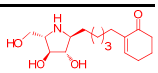
Table 5. The glycosidase inhibition of Broussonetine W and Its Analogs (**4**, ***ent*-4**, **3-*epi*-4**, ***ent*-3-*epi*-4**, ***ent*-4a**, ***ent*-4b**)

	IC$_{50}$ (μM)					
						
enzyme	**4**	***ent*-4**	**3-*epi*-4**	***ent*-3-*epi*-4**	***ent*-4a**	***ent*-4b**
α-glucosidase						
yeast	22	407	NI[a] (23.7%)[b]	310	758	622
rice	119	0.73	63	24	1.1	1.3
rat intestinal maltase	67	0.047	NI (43.9%)	3.5	0.19	0.2
intestinal isomaltase	NI (29.3%)	1.5	NI (0%)	114	3.0	5.1
rat intestinal sucrase	216	0.20	111	3.4	0.25	0.28
ER α-glucosidase II	NI (43.5%)	7.5	NI (13.2%)	200	15	21
β-glucosidase						
almond	9.8	NI (39.5%)	NI (31.8%)	92	NI (27.2%)	NI (13.4%)
bovine liver	0.12	180	44	0.99	59	263
α-galactosidase						
coffee bean	NI (19.6%)	NI (4.2%)	NI (46.9%)	NI (15.8%)	NI (1.1%)	NI (19.1%)
β-galactosidase						
bovine liver	0.03	127	11	0.18	11	105
α-mannosidase						
jack bean	NI (15.1%)	NI (0%)	385	NI (5.4%)	NI (0%)	NI (6.5%)
β-mannosidase						
snail	282	NI (0%)	NI (7.7%)	NI (0%)	NI (0%)	NI (1.2%)
α-L-fucosidase						
bovine kidney	NI (16.8%)	NI (0%)	NI (12.3%)	20.4	NI (0%)	NI (43.3%)
α, α-trehalase						
porcine kidney	NI (0.8%)	NI (8.3%)	NI (2.2%)	NI (3.3%)	NI (16.4%)	NI (10.0%)
amyloglucosidase						
Aspergilusniger	30	NI (0%)	NI (2.8%)	448	NI (16.2%)	NI (0%)
α-L-rhamnosidase						
Penicillium decumbens	NI (35.1%)	174	NI (47.3%)	166	591	1000
β-glucuronidase						
E.coli	3.3	38	14	83.3	25	60
bovine liver	NI (46.1%)	379	27	NI (40.2%)	NI (46.7%)	186

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

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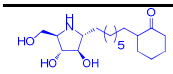
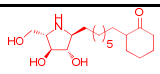
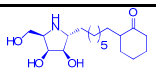
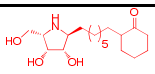
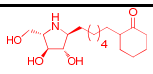
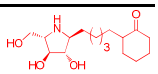
Table 6. The glycosidase inhibition of Broussonetine W's Analogs (**20**, ***ent*-20**, **3-*epi*-20**, ***ent*-3-*epi*-20**, ***ent*-20a**, ***ent*-20b**).

	IC_{50} (μM)					
						
enzyme	**20**	***ent*-20**	**3-*epi*-20**	***ent*-3-*epi*-20**	***ent*-20a**	***ent*-20b**
α-glucosidase						
yeast	80	NI[a] (32.7%)[b]	NI (44.0%)	NI (16.7%)	NI (46.8%)	NI (39.1%)
rice	70	1.7	7.9	33	1.4	3.7
rat intestinal maltase	32	0.15	1.6	13	0.11	0.14
intestinal isomaltase	663	3.7	40.3	366	2.1	3.8
rat intestinal sucrase	80	0.36	3.1	18	0.14	0.17
ER α-glucosidase II	NI (46.9%)	14	157	458	12	25
β-glucosidase						
almond	43	NI (37.2%)	NI (25.4%)	NI (35.5%)	NI (35.8%)	NI (39.0%)
bovine liver	0.10	14	27	40	237	372
α-galactosidase						
coffee bean	NI (13.8%)	NI (14.6%)	NI (29.4%)	NI (13.5%)	NI (0%)	NI (0.7%)
β-galactosidase						
bovine liver	0.046	8.5	35	14	42	129
α-mannosidase						
jack bean	NI (33.7%)	NI (0%)	245	NI (2.4%)	NI (1.2%)	NI (0%)
β-mannosidase						
snail	224	NI (15.2%)	NI (0%)	NI (0%)	NI (0.9%)	NI (0%)
α-L-fucosidase						
bovine kidney	NI (25.2%)	NI (0.7%)	NI (18.9%)	28	NI (35.7%)	NI (7.6%)
α, α-trehalase						
porcine kidney	NI (0.8%)	NI (3.3%)	NI (0%)	NI (0%)	NI (10.0%)	NI (13.2%)
amyloglucosidase						
Aspergilusniger	41	NI (28.3%)	NI (7.7%)	NI (8.6%)	NI (4.6%)	NI (1.5%)
α-L-rhamnosidase						
Penicillium decumbens	NI (31.4%)	152	895	443	330	410
β-glucuronidase						
E.coli	9.5	79	21	45	428	435
bovine liver	NI (39.7%)	NI (45.2%)	NI (39.0%)	NI (12.3%)	NI (31.9%)	597

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

Conclusion:

In summary, the first total synthesis of broussonetine W has been achieved in 11 steps and 31% total yield, starting from D-arabinose derived cyclic nitrone **10**; the key step of this synthetic method is the regioselective installation of the *α,β*-unsaturated ketone group by elimination of *α*-bromoketone. The relative and absolute configurations of natural product broussonetine W have been confirmed unambiguously through the synthesis of both enantiomers of broussonetine W, by the clear study of their ^{1}H and ^{13}C NMR spectra and a comparison of the specific rotations of the synthetic broussonetine W with that of the natural product. Furthermore, in order to explore the structure-activity relationship of broussonetine W and related compounds, a number of analogs of broussonetine W have also been synthesized *via* the same synthetic procedure starting from different cyclic nitrones. Glycosidase inhibition study revealed that natural product (+)-broussonetine W (**4**) and its enantiomer ***ent*-4** showed clearly different inhibition specificities. ***Ent*-4** showed enhancements in *α*-glucosidases, whereas it decreased the inhibition of these *β*-glycosidases. The side chain length and *α,β*-unsaturated ketone group do

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not have significant effect on their glycosidase inhibition. This concise and efficient synthetic strategy shows the value of sugar nitrones in a general approach to this class of alkaloids which will allow the detailed study of their structure-activity relationship.

Experimental section

Material and methods

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Acetonitrile and pyridine were dried with activated 4-Å molecular sieves before use. Tetrahydrofuran was distilled from sodium and benzophenone immediately before use. TLC plates were visualized by ultraviolet light or by treatment with a 0.5% solution of $KMnO_4$ in acetone or a spray of Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O). Chromatographic purification of products was carried out by flash column chromatography on silica gel (200–300 mesh). Acidic ion exchange chromatography was performed on Dowex 50WX8-400, H^+ form. Infrared spectra were recorded on a JASCO FT/IR-480 plus Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard), Methanol-d_4 or Pyridine-d_5 on a Bruker AV300 (^{1}H at 300 MHz, ^{13}C at 75 MHz), a Bruker AV400 (^{1}H at 400MHz, ^{13}C at 101 MHz) or a Bruker AV500 (^{1}H at 500 MHz, ^{13}C at 126 MHz) magnetic resonance spectrometer. 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 a Thermo Scientific LTQ/FT mass spectrometer or a GCT mass spectrometer. Polarimetry was carried out using an Optical Activity AA-10R polarimeter and the measurements were made at the sodium D-line with a 0.5 dm path length cell. Concentrations (c) are given in gram per 100 mL.

General procedures for synthesis of compound **17**, *ent*-**17**, **3-*epi*-17**, ***ent*-3-*epi*-17**, ***ent*-17a** and ***ent*-17b**, with compound **17** as an example.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-1-benzyloxycarbonyl-5-(hept-6-en-1-yl)pyrrolidine (17)

To a stirred solution of cyclic nitrone **10** (2.00 g, 4.79 mmol) in anhydrous THF (10 mL) was added a solution of Grignard reagent hept-6-en-1-ylmagnesium bromide in THF [prepared by stirring Mg turnings (240 mg, 10.06 mmol) and 7-bromohept-1-ene (1.46 mL, 9.58 mmol) in THF (5 mL)] at 0 °C, under argon atmosphere. The reaction mixture was stirred for 30 min, quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extracts were dried and the solvents were removed *in vacuo* to give the crude product hydroxylamine **16**, which was used directly in the next step of reaction without further purification. [The sample for structure characterization was obtained *via* purification by flash column chromatography (silica gel, petroleum ether/EtOAc = 5/1) as a light yellow syrup. Data for **16**: $[\alpha]_D^{20}$ -8.0 (c 0.5, CH_2Cl_2); IR (KBr, cm^{-1}): 3238, 3064, 3030, 2926, 2856, 1497, 1454, 1363, 1100, 736, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.16 (m, 15H), 6.02–5.55 (m, 2H), 4.95–4.82 (m, 2H), 4.50–4.35 (m, 6H), 3.88–3.85 (m, 1H), 3.74–3.68 (m, 2H), 3.54–3.48 (m, 1H), 3.45 (dd, J = 10.5, 5.3 Hz, 1H), 3.10 (dt, J = 7.9, 5.5 Hz, 1H), 1.95 (q, J = 6.8 Hz, 2H), 1.78 (s, 1H), 1.45–1.36 (m, 1H), 1.35–1.17 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 138.3, 138.2, 128.50, 128.48, 128.47, 128.1, 128.0, 127.84, 127.81, 127.75, 114.4, 86.9, 84.8, 73.5, 71.81, 71.77, 70.2, 70.1, 68.5, 33.9, 29.4, 29.0, 26.5. HRMS ESI: calcd for $C_{33}H_{41}NO_4H^+$ [M + H]$^+$ 516.31084, found 516.31133.]

Zinc powder (3.07 g, 47.90 mmol) and $Cu(OAc)_2$ (88 mg, 0.48 mmol) was added to acetic acid (20 mL), and the mixture was stirred at room temperature for 15 min after which the color turned to brown. Crude product hydroxylamine **16** was added, and the reaction mixture was stirred at room temperature for 8 h. After the starting material disappeared, acetic acid was removed under reduced pressure, then EtOAc was added and the reaction mixture filtered to remove the solid. The filtrate was washed with saturated aqueous solution of $NaHCO_3$ until the mixture became neutral. The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*.

To a solution of the crude product in THF (about 20 mL, including 1~2 mL secondary H_2O) at 0 °C was added $NaHCO_3$ (0.80 g, 9.58 mmol) and CbzCl (0.8 mL, 5.75 mmol) slowly, and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The residuewas purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 15/1) to afford **17** (2.64 g, 4.16 mmol, 87% in 3 steps) as a light yellow syrup.

Data for **17**: $[\alpha]_D^{20}$ -27.6 (c 1.5, CH_2Cl_2); IR (KBr, cm^{-1}): 3064, 3031, 2926, 2857, 1699, 1496, 1455, 1409, 1347, 1205, 1097, 735, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.14 (m, 20H), 5.84–5.70 (m, 1H), 5.23–5.14 (m, 1H), 5.03 (d, J = 12.3 Hz, 1H), 5.01–4.89 (m, 2H), 4.67–4.56 (m, 1.5H), 4.49–4.41 (m, 2H), 4.41–4.31 (m, 2.5H), 4.25 (d, J = 10.0 Hz, 0.5H), 4.18–4.12 (m, 1.5H), 4.08–4.03 (m, 0.5H), 3.87–3.70 (m, 2.5H), 3.51–3.44 (m, 1H), 2.09–1.91 (m, 2.5H), 1.77–1.51 (m, 1.5H), 1.42–1.09 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 154.3, 139.2, 139.1, 138.6, 138.4, 138.1, 138.0, 137.79, 137.75, 136.74, 136.69, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.87, 127.85, 127.80, 127.76, 127.72, 127.67, 127.6, 114.4, 114.3, 84.5, 83.4, 83.2, 82.1, 73.13, 73.06, 71.3, 71.1, 70.9, 68.9, 67.9, 67.0, 66.9, 65.1, 64.8, 63.0, 62.7, 33.8, 33.7, 31.5, 30.2, 29.0, 28.9, 28.8, 26.51, 26.47. HRMS ESI: calcd for $C_{41}H_{47}NO_5H^+$ [M + H]$^+$ 634.35270, found 634.35182.

***Ent*-17**: light yellow syrup, 2.98 g, 4.69 mmol, 98% yield in 3 steps, starting from the corresponding cyclic nitrone ***ent*-10** (2.00 g, 4.79 mmol).

Data for ***ent*-16**: colorless syrup, $[\alpha]_D^{20}$ +10.9 (c 0.55, CH_2Cl_2); IR (KBr, cm^{-1}): 3244, 2927, 2857, 1639, 1497, 1454, 1363, 1100, 735, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.24 (m, 15H), 6.13 (s, br, 1H), 5.84–5.74 (m, 1H), 5.01–4.95 (m, 1H), 4.94–4.90 (m, 1H), 4.57–4.42 (m, 6H), 3.94 (dd, J = 3.8, 2.7 Hz, 1H), 3.82–3.75

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(m, 2H), 3.58 (dd, *J* = 9.4, 6.9 Hz, 1H), 3.54–3.50 (m, 1H), 3.19–3.14 (m, 1H), 2.05–1.99 (m, 2H), 1.78 (s, 1H), 1.45–1.36 (m, 1H), 1.35–1.17 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 138.3, 138.21, 138.20, 128.49, 128.47, 128.46, 128.1, 128.0, 127.83, 127.80, 127.7, 114.4, 86.9, 84.7, 73.5, 71.8, 71.7, 70.2, 70.1, 68.4, 33.9, 29.4, 29.0, 26.5. HRMS ESI: calcd for $C_{33}H_{41}NO_4H^+$ $[M + H]^+$ 516.31084, found 516.31077.

Data for ***ent*-17**: $[\alpha]_D^{20}$ +41.4 (*c* 1.4, CH_2Cl_2); IR (KBr, cm^{-1}): 3064, 3031, 2927, 2857, 1699, 1497, 1454, 1409, 1348, 1205, 1112, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.13 (m, 20H), 5.87–5.65 (m, 1H), 5.18 (t, *J* = 12.6 Hz, 1H), 5.06–4.88 (m, 3H), 4.66–4.53 (m, 1.5H), 4.48–4.39 (m, 2H), 4.39–4.22 (m, 3H), 4.20–4.11 (m, 1.5H), 4.07 (dd, *J* = 8.5, 3.9 Hz, 0.5H), 3.90–3.69 (m, 2.5H), 3.48 (t, *J* = 9.6 Hz, 1H), 2.13–1.89 (m, 2.5H), 1.79–1.47 (m, 1.5H), 1.41–1.07 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 154.3, 139.1, 139.0, 138.6, 138.3, 138.0, 137.9, 137.72, 137.69, 136.7, 136.6, 128.54, 128.48, 128.41, 128.37, 128.2, 128.1, 128.0, 127.80, 127.75, 127.70, 127.66, 127.62, 127.56, 114.34, 114.30, 84.4, 83.3, 83.2, 82.0, 73.1, 73.0, 71.2, 71.0, 70.9, 68.8, 67.8, 66.9, 66.8, 65.0, 64.7, 62.9, 62.6, 33.74, 33.69, 31.4, 30.1, 28.94, 28.88, 28.7, 26.5, 26.4. HRMS ESI: calcd for $C_{41}H_{47}NO_5H^+$ $[M + H]^+$ 634.35270, found 634.35204.

3-*Epi*-17: light yellow syrup, 5.01 g, 7.90 mmol, 66% yield in 3 steps, starting from the corresponding cyclic nitrone **3-*epi*-10** (5.00 g, 11.98 mmol).

Data for **3-*epi*-16**: colorless syrup, $[\alpha]_D^{20}$ -8.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 3270, 2926, 2857,1639, 1497, 1454, 1362, 1097, 734, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 15H), 5.84–5.75 (m, 1H), 5.49 (s, br, 1H), 5.01–4.95 (m, 1H), 4.95–4.90 (m, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 8.9 Hz, 1H), 4.56 (d, *J* = 9.0 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.20 (t, *J* = 4.9 Hz, 1H), 3.86 (dd, *J* = 9.7, 7.1 Hz, 1H), 3.81 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.66 (dd, *J* = 7.0, 4.9 Hz, 1H), 3.50–3.45 (m, 1H), 3.33–3.27 (m, 1H), 2.06–1.99 (m, 2H), 1.69–1.62 (m, 1H), 1.50–1.41 (m, 2H), 1.41–1.26 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 138.4, 138.3, 138.2, 128.53, 128.52, 128.48, 128.02, 127.98, 127.97, 127.89, 127.82, 127.80, 114.3, 83.5, 73.8, 73.6, 72.9, 71.3, 68.8, 67.4, 33.9, 30.7, 29.4, 29.0, 26.9. HRMS ESI: calcd for $C_{33}H_{41}NO_4H^+$ $[M + H]^+$ 516.31084, found 516.31103.

Data for **3-*epi*-17**: $[\alpha]_D^{20}$ -2.2 (*c* 0.9, CH_2Cl_2); IR (KBr, cm^{-1}): 3064, 3031, 2927, 2858, 1703, 1454, 1407, 1351, 1094, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.14 (m, 20H), 5.86–5.66 (m, 1H), 5.26–5.03 (m, 2H), 5.03–4.88 (m, 2H), 4.86–4.71 (m, 1H), 4.71–4.49 (m, 4H), 4.44–4.34 (m, 1H), 4.33–4.20 (m, 2H), 4.19–4.07 (m, 1H), 3.85–3.73 (m, 2H), 3.70 (d, *J* = 8.6 Hz, 0.5H), 3.58 (d, *J* = 7.2 Hz, 0.5H), 2.07–1.83 (m, 2.5H), 1.79–1.56 (m, 0.5H), 1.41–1.17 (m, 4H), 1.17–0.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 154.6, 139.0, 138.9, 138.8, 138.4, 138.3, 136.8, 136.6, 128.5, 128.4, 128.3, 128.03, 127.99, 127.8, 127.7, 127.5, 127.44, 127.38, 127.3, 114.47, 114.44, 81.1, 79.9, 78.0, 77.4, 73.0, 72.7, 72.5, 72.3, 71.9, 70.6, 69.1, 67.0, 66.9, 62.7, 62.3, 57.9, 57.8, 33.7, 33.2, 31.9, 28.92, 28.86, 28.7, 26.5, 26.4. HRMS ESI: calcd for $C_{41}H_{47}NO_5H^+$ $[M + H]^+$ 634.35270, found 634.35168.

***Ent*-3-*epi*-17**: light yellow syrup, 3.46 g, 5.46 mmol, 76% yield in 3 steps, starting from the corresponding cyclic nitrone ***ent*-3-*epi*-10** (3.00 g, 7.19 mmol).

Data for ***ent*-3-*epi*-16**: colorless syrup, $[\alpha]_D^{20}$ +7.3 (*c* 1.1, CH_2Cl_2); IR (KBr, cm^{-1}): 3269, 2926, 2857, 1640, 1497, 1454, 1363, 1100, 734, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.24 (m, 15H), 5.85 (s, br, 1H), 5.83–5.75 (m, 1H), 5.01–4.95 (m, 1H), 4.95–4.90 (m, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.20 (t, *J* = 5.0 Hz, 1H), 3.85 (dd, *J* = 9.7, 7.0 Hz, 1H), 3.80 (dd, *J* = 9.7, 6.4 Hz, 1H), 3.67 (dd, *J* = 7.0, 5.0 Hz, 1H), 3.51–3.47 (m, 1H), 3.32–3.26 (m, 1H), 2.06–1.98 (m, 2H), 1.72–1.62 (m, 1H), 1.50–1.41 (m, 2H), 1.41–1.25 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 138.4, 138.3, 138.2, 128.50, 128.49, 127.99, 127.97, 127.94, 127.86, 127.79, 127.77, 114.3, 83.3, 77.3, 73.7, 73.6, 72.8, 70.9, 68.9, 67.4, 33.9, 30.5, 29.4, 29.0, 26.9. HRMS ESI: calcd for $C_{33}H_{41}NO_4H^+$ $[M + H]^+$ 516.31084, found 516.3112.

Data for ***ent*-3-*epi*-17**: $[\alpha]_D^{20}$ +10.0 (*c* 0.8, CH_2Cl_2); IR (KBr, cm^{-1}): 3064, 3031, 2927, 2857, 1699, 1499, 1454, 1407, 1351, 1215, 1095, 735, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.14 (m, 20H), 5.83–5.69 (m, 1H), 5.26–5.01 (m, 2H), 5.01–4.90 (m, 2H), 4.85–4.74 (m, 1H), 4.73–4.51 (m, 4H), 4.42–4.34 (m, 1H), 4.34–4.22 (m, 2H), 4.17–4.11 (m, 1H), 3.84–3.74 (m, 2H), 3.70 (d, *J* = 6.9 Hz, 0.5H), 3.58 (d, *J* = 8.4 Hz, 0.5H), 2.04–1.87 (m, 2.5H), 1.70–1.59 (m, 0.5H), 1.39–1.18 (m, 4H), 1.18–0.97 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.5, 139.0, 138.9, 138.7, 138.4, 138.3, 136.7, 136.6, 128.5, 128.4, 128.2, 128.1, 128.00, 127.96, 127.74, 127.66, 127.5, 127.40, 127.35, 127.2, 114.5, 114.4, 81.0, 79.8, 78.0, 77.6, 73.0, 72.9, 72.7, 72.5, 72.2, 71.9, 70.5, 69.1, 66.93, 66.85, 62.6, 62.3, 57.9, 57.8, 33.7, 33.6, 33.2, 31.8, 28.9, 28.8, 28.7, 26.5, 26.3. HRMS ESI: calcd for $C_{41}H_{47}NO_5H^+$ $[M + H]^+$ 634.35270, found 634.35187.

***Ent*-17a**: light yellow syrup, 2.49 g, 4.02 mmol, 84% yield in 3 steps, starting from the corresponding cyclic nitrone ***ent*-10** (2.00 g, 4.79 mmol), and Grignard reagent was hex-5-en-1-ylmagnesium bromide [prepared by heating Mg turnings (0.24 g, 10.07 mmol) and 6-bromohex-1-ene (1.29 mL, 9.60 mmol)].

Data for ***ent*-16a**: $[\alpha]_D^{20}$ +10.7 (*c* 0.75, CH_2Cl_2); IR (KBr, cm^{-1}): 3240, 2926, 2860, 1640, 1497, 1454, 1362, 1099, 735, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.16 (m, 15H), 6.24–5.86 (m, 1H), 5.85–5.71 (m, 1H), 5.03–4.87 (m, 2H), 4.59–4.38 (m, 6H), 3.93 (s, 1H), 3.83–3.73 (m, 2H), 3.61–3.54 (m, 1H), 3.52 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.20–3.12 (m, 1H), 2.08–1.99 (m, 2H), 1.93–1.80 (m, 1H), 1.55–1.44 (m, 1H), 1.44–1.31 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.3, 138.2, 128.50, 128.47, 128.1, 128.0, 127.84, 127.80, 127.7, 114.5, 86.8, 84.7, 73.5, 71.82, 71.76, 70.2, 70.1, 68.5, 33.8, 29.2, 28.6, 26.2. HRMS ESI: calcd for $C_{32}H_{39}NO_4H^+$ $[M + H]^+$ 502.29519, found 502.29523.

Data for ***ent*-17a**: $[\alpha]_D^{20}$ +37.4 (*c* 1.6, CH_2Cl_2); IR (KBr, cm^{-1}): 3064, 3031, 2926, 2858, 1699, 1497, 1454, 1409, 1348, 1206, 1093, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.01 (m, 20H), 5.75–5.52 (m, 1H), 5.16–5.01 (m, 1H), 4.93 (d, *J* = 12.3 Hz, 1H), 4.88–4.76 (m, 2H), 4.58–4.43 (m, 1.5H), 4.36 (d, *J* = 5.8 Hz, 1H), 4.32 (d, *J* = 5.5 Hz, 1H), 4.30–4.20 (m, 2.5H), 4.17 (dd, *J* = 10.5, 4.0 Hz, 0.5H), 4.10–4.02 (m, 1.5H), 3.97 (dd, *J* = 8.7, 4.2 Hz, 0.5H), 3.80–3.59 (m, 2.5H), 3.38 (td, *J* = 9.7, 1.7 Hz, 1H),

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2.03–1.87 (m, 1H), 1.81 (q, *J* = 6.9 Hz, 1H), 1.72–1.39 (m, 2H), 1.37–0.98 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 154.2, 138.8, 138.7, 138.5, 138.3, 137.94, 137.89, 137.7, 137.6, 136.63, 136.58, 128.5, 128.45, 128.38, 128.3, 128.2, 128.1, 128.0, 127.8, 127.72, 127.69, 127.64, 127.59, 127.5, 114.5, 84.4, 83.3, 83.1, 81.9, 73.03, 72.96, 71.2, 71.0, 70.8, 68.7, 67.8, 66.9, 66.8, 65.0, 64.6, 62.9, 62.6, 33.7, 33.5, 31.3, 29.9, 28.6, 28.4, 25.9. HRMS ESI: calcd for $C_{40}H_{45}NO_5H^+$ $[M + H]^+$ 620.33705, found 620.33613.

***Ent*-17b**: light yellow syrup, 2.70 g, 4.46 mmol, 93% yield, starting from the corresponding cyclic nitrone ***ent*-10** (2.00 g, 4.79 mmol), Grignard reagent was pent-4-en-1-ylmagnesium bromide [prepared by heating Mg turnings (0.24 g, 10.07 mmol) and 5-bromopent-1-ene (1.14 mL, 9.60 mmol)].

Data for ***ent*-16b**: colorless syrup, $[\alpha]_D^{20}$ +8.9 (*c* 0.9, CH_2Cl_2); IR (KBr, cm^{-1}): 3239, 2924, 2862, 1640, 1496, 1454, 1363, 1098, 735, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 15H), 5.84–5.74 (m, 1H), 5.09 (s, br, 1H), 5.03–5.97 (m, 1H), 4.96–4.92 (m, 1H), 4.58–4.42 (m, 6H), 3.93 (dd, *J* = 4.0, 2.7 Hz, 1H), 3.81–3.74 (m, 2H), 3.59 (dd, *J* = 9.5, 6.6 Hz, 1H), 3.53 (dd, *J* = 10.4, 5.8 Hz, 1H), 3.22–3.16 (m, 1H), 2.11–2.03 (m, 2H), 1.91–1.80 (m, 1H), 1.54–1.41 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.3, 138.21, 138.17, 128.47, 128.45, 128.43, 128.1, 128.0, 127.80, 127.77, 127.7, 114.7, 86.8, 84.6, 73.4, 71.8, 71.7, 70.2, 69.9, 68.3, 34.0, 28.5, 25.9. HRMS ESI: calcd for $C_{31}H_{37}NO_4H^+$ $[M + H]^+$ 488.27954, found 488.27954.Data for ***ent*-17b**: $[\alpha]_D^{20}$ +36.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 3064, 3031, 2925, 2861, 1699, 1497, 1455, 1410, 1348, 1097, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.13 (m, 20H), 5.86–5.59 (m, 1H), 5.19 (t, *J* = 11.9 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.97–4.84 (m, 2H), 4.67–4.54 (m, 1.5H), 4.47 (d, *J* = 6.2 Hz, 1H), 4.42 (d, *J* = 5.8 Hz, 1H), 4.40–4.30 (m, 2.5H), 4.26 (dd, *J* = 10.1, 2.9 Hz, 0.5H), 4.20–4.12 (m, 1.5H), 4.06 (dd, *J* = 7.8, 3.4 Hz, 0.5H), 3.92–3.69 (m, 2.5H), 3.48 (t, *J* = 9.8 Hz, 1H), 2.17–1.98 (m, 1.5H), 1.98–1.85 (m, 1H), 1.83–1.53 (m, 1.5H), 1.49–1.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 154.3, 138.6, 138.43, 138.37, 138.02, 137.98, 137.7, 136.7, 128.51, 128.47, 128.4, 128.22, 128.18, 128.1, 127.83, 127.76, 127.72, 127.69, 127.63, 127.57, 114.71, 114.66, 84.5, 83.5, 83.2, 82.0, 73.1, 73.0, 71.3, 71.1, 70.9, 68.8, 67.9, 67.0, 66.9, 65.0, 64.7, 63.0, 62.7, 33.6, 33.4, 31.1, 29.9, 26.01, 25.96. HRMS ESI: calcd for $C_{39}H_{43}NO_5H^+$ $[M + H]^+$ 606.32140, found 606.32083.

General procedures for synthesis of compound **18**, ***ent*-18**, ***3-epi*-18**, ***ent*-3-*epi*-18**, ***ent*-18a** and ***ent*-18b**, with compound **18** as an example.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-1-benzyloxycarbonyl-5-(7-hydroxyheptyl)pyrrolidine (18).

To a stirred solution of olefin **17** (2.40 g, 3.79 mmol) in 20 mL dry THF was slowly added a 1 M solution of BH_3-THF in THF (7.6 mL, 7.57 mmol) at 0 °C, under argon; the solution was stirred at room temperature for 3 h. Then, the reaction was cooled to 0 °C and an aqueous solution of NaOH (10 M, 2 mL) was added to get an alkaline reaction environment, followed by the addition of an aqueous solution of H_2O_2 (30%, 9 mL). The reaction mixture was stirred for 1 h at room temperature. After the reaction was completed, it was quenched with a solution of HCl (10% in water) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 6/1) to afford alcohol **18** (1.80 g, 2.76 mmol, 73%) as a colorless syrup.

Data for **18**: $[\alpha]_D^{20}$ -35.4 (*c* 1.3, CH_2Cl_2); IR (KBr, cm^{-1}): 3445, 3064, 3031, 2929, 2857, 1699, 1497, 1455, 1417, 1349, 1115, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.15 (m, 20H), 5.18 (t, *J* = 12.4 Hz, 1H), 5.03 (d, *J* = 12.3 Hz, 1H), 4.68–4.55 (m, 1.5H), 4.50–4.41 (m, 2H), 4.40–4.29 (m, 2.5H), 4.25 (dd, *J* = 10.6, 4.0 Hz, 0.5H), 4.19–4.11 (m, 1.5H), 4.05 (dd, *J* = 8.7, 4.2 Hz, 0.5H), 3.89–3.69 (m, 2.5H), 3.60 (q, 6.5 Hz, 2H), 3.52–3.43 (m, 1H), 2.10–1.96 (m, 0.5H), 1.79–1.60 (m, 1.5H), 1.59–1.46 (m, 2H), 1.38–1.09 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 154.4, 138.6, 138.3, 138.02, 137.96, 137.74, 137.72, 136.6, 128.6, 128.52, 128.45, 128.4, 128.2, 128.1, 127.83, 127.80, 127.75, 127.70, 127.67, 127.6, 127.2, 84.5, 83.4, 83.2, 82.0, 73.12, 73.05, 71.2, 71.1, 70.9, 68.8, 67.8, 67.0, 65.1, 64.8, 63.05, 63.02, 62.99, 62.7, 32.8, 31.5, 30.0, 29.3, 29.2, 26.5, 26.4, 25.7, 25.6. HRMS ESI: calcd for $C_{41}H_{49}NO_6H^+$ $[M + H]^+$ 652.36326, found 652.36241.

Data for ***ent*-18**: colorless syrup, 2.87 g, 4.40 mmol, 93% yield, derived from the corresponding olefin ***ent*-17** (3.00 g, 4.73 mmol).

$[\alpha]_D^{20}$ +34.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 3451, 3063, 3030, 2927, 2856, 1698, 1497, 1454, 1410, 1348, 1093, 736, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.14 (m, 20H), 5.22–5.13 (m, 1H), 5.03 (dd, *J* = 12.3, 1.5 Hz, 1H), 4.66–4.55 (m, 1.5H), 4.49–4.40 (m, 2H), 4.40–4.30 (m, 2.5H), 4.29–4.23 (m, 0.5H), 4.18–4.12 (m, 1.5H), 4.08–4.03 (m, 0.5H), 3.88–3.70 (m, 2.5H), 3.56 (q, *J* = 6.8 Hz, 2H), 3.47 (t, *J* = 9.6 Hz, 1H), 2.09–1.99 (m, 0.5H), 1.86 (s, br, 1H), 1.76–1.61 (m, 1H), 1.61–1.43 (m, 2.5H), 1.37–1.09 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.3, 138.5, 138.3, 137.94, 137.88, 137.7, 137.6, 136.6, 128.5, 128.43, 128.36, 128.3, 128.1, 128.03, 127.98, 127.75, 127.71, 127.66, 127.62, 127.58, 127.5, 84.4, 83.3, 83.1, 81.9, 73.03, 72.96, 71.1, 71.0, 70.8, 68.7, 67.8, 66.9, 66.8, 65.0, 64.7, 62.9, 62.8, 62.6, 32.71, 32.69, 31.4, 30.0, 29.3, 29.2, 26.45, 26.38, 25.63, 25.60. HRMS ESI: calcd for $C_{41}H_{49}NO_6H^+$ $[M + H]^+$ 652.36326, found 652.36254.

Data for **3-*epi*-18**: colorless syrup, 0.93 g, 1.42 mmol, 100% yield, derived from the corresponding olefin **3-*epi*-17** (0.90 g, 1.42 mmol).

$[\alpha]_D^{20}$ -2.9 (*c* 0.7, CH_2Cl_2); IR (KBr, cm^{-1}): 3447, 3063, 3031, 2929, 2857, 1698, 1497, 1454, 1409, 1352, 1097, 735, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.11 (m, 20H), 5.25–4.99 (m, 2H), 4.84–4.73 (m, 1H), 4.72–4.58 (m, 2.5H), 4.57–4.50 (m, 1.5H), 4.42–4.34 (m, 1H), 4.33–4.21 (m, 2H), 4.13 (s, 1H), 3.83–3.74 (m, 2H), 3.70 (d, *J* = 6.9 Hz, 0.5H), 3.61–3.54 (m, 2.5H), 1.96–1.89 (m, 0.5H), 1.82 (s, br, 1H), 1.67–1.58 (m, 0.5H), 1.56–1.43 (m, 2H), 1.35–1.19 (m, 5H), 1.18–0.95 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 154.5, 138.9, 138.6, 138.3, 138.2, 136.6, 136.5, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 81.0, 79.8, 77.9, 77.5, 73.0, 72.9, 72.6, 72.4, 72.2, 71.8, 70.5, 69.0, 66.8, 62.8, 62.6, 62.3, 57.8, 57.7, 33.2, 32.7, 31.7, 29.22, 29.18, 26.4, 25.6. HRMS ESI: calcd for $C_{41}H_{49}NO_6H^+$ $[M + H]^+$ 652.36326, found 652.36229.

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Data for ***ent*-3-*epi*-18**: colorless syrup, 1.43 g, 2.19 mmol, 73% yield, derived from the corresponding olefin ***ent*-3-*epi*-17** (1.90 g, 3.00 mmol).

$[\alpha]_D^{20}$ +5.9 (*c* 1.4, CH_2Cl_2); IR (KBr, cm^{-1}): 3459, 3063, 3031, 2929, 2857, 1694, 1497, 1455, 1410, 1352, 1215, 1111, 735, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.14 (m, 20H), 5.24–4.99 (m, 2H), 4.84–4.74 (m, 1H), 4.72–4.58 (m, 2.5H), 4.57–4.51 (m, 1.5H), 4.42–4.34 (m, 1H), 4.34–4.21 (m, 2H), 4.16–4.12 (m, 1H), 3.83–3.75 (m, 2H), 3.70 (d, *J* = 9.2 Hz, 0.5H), 3.61–3.55 (m, 2.5H), 1.96–1.87 (m, 0.5H), 1.74 (s, br, 1H), 1.67–1.54 (m, 0.5H), 1.57–1.44 (m, 2H), 1.36–1.19 (m, 5H), 1.19–0.96 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.5, 138.9, 138.7, 138.3, 138.2, 136.7, 136.6, 128.5, 128.4, 128.21, 128.16, 128.05, 127.97, 127.95, 127.7, 127.64, 127.62, 127.5, 127.4, 127.3, 127.2, 81.0, 79.8, 78.0, 77.5, 77.4, 73.0, 72.9, 72.7, 72.4, 72.2, 71.8, 70.5, 69.0, 66.9, 62.8, 62.6, 62.3, 57.8, 57.7, 33.2, 32.7, 31.7, 29.24, 29.20, 26.4, 25.63, 25.59. HRMS ESI: calcd for $C_{41}H_{49}NO_6H^+$ $[M + H]^+$ 652.36326, found 652.36266.

Data for ***ent*-18a**: colorless syrup, 1.40 g, 2.20 mmol, 91% yield, derived from the corresponding olefin ***ent*-17a** (1.50 g, 2.42 mmol).

$[\alpha]_D^{20}$ +44.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 3462, 3063, 3031, 2930, 2858, 1699, 1497, 1454, 1410, 1349, 1206, 1096, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.13 (m, 20H), 5.18 (t, *J* = 12.6 Hz, 1H), 5.03 (d, *J* = 12.3 Hz, 1H), 4.68–4.55 (m, 1.5H), 4.47 (d, *J* = 5.9 Hz, 1H), 4.43 (d, *J* = 5.8 Hz, 1H),4.40–4.29 (m, 2.5H), 4.25 (dd, *J* = 10.4, 3.9 Hz, 0.5H), 4.19–4.10 (m, 1.5H), 4.06 (dd, *J* = 8.7, 4.1 Hz, 0.5H), 3.89–3.69 (m, 2.5H), 3.59 (d, *J* = 6.5 Hz, 1H), 3.54 (d, *J* = 6.7 Hz, 1H), 3.47 (d, *J* = 9.8 Hz, 1H), 2.11–1.97 (m, 0.5H), 1.80–1.39 (m, 4.5H), 1.39–1.08 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 154.3, 138.6, 138.4, 138.0, 137.8, 136.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.84, 127.79, 127.76, 127.71, 127.67, 127.6, 84.5, 83.5, 83.2, 82.1, 73.13, 73.07, 71.3, 71.1, 71.0, 68.8, 67.9, 66.9, 65.0, 64.8, 63.0, 62.9, 62.7, 32.7, 31.4, 30.0, 29.1, 29.0, 26.5, 26.4, 25.6, 25.5. HRMS ESI: calcd for $C_{40}H_{47}NO_6H^+$ $[M + H]^+$ 638.34761, found 638.34723.

Data for ***ent*-18b**: colorless syrup, 2.72 g, 4.36 mmol, 91% yield, derived from the corresponding olefin ***ent*-17b** (2.90 g, 4.79 mmol).

$[\alpha]_D^{20}$ +32.6 (*c* 1.4, CH_2Cl_2); IR (KBr, cm^{-1}): 3462, 3064, 3031, 2932, 2860, 1698, 1497, 1455, 1410, 1349, 1206, 1093, 737, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.10 (m, 20H), 5.23–5.13 (m, 1H), 5.03 (dd, *J* = 12.4, 2.7 Hz, 1H), 4.66–4.56 (m, 1.5H), 4.50–4.40 (m, 2H), 4.40–4.29 (m, 2.5H), 4.25 (d, *J* = 10.0 Hz, 0.5H), 4.18–4.11 (m, 1.5H), 4.06 (dd, *J* = 8.0, 3.2 Hz, 0.5H), 3.85 (d, *J* = 10.9 Hz, 0.5H), 3.81–3.70 (m, 2H), 3.57 (t, *J* = 6.4 Hz, 1H), 3.51–3.43 (m, 2H), 2.09–1.99 (m, 0.5H), 1.86–1.63 (m, 1H), 1.62–1.46 (m, 2H), 1.44–1.28 (m, 3H), 1.24–1.11 (m, 2.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.3, 138.6, 138.3, 138.0, 137.9, 137.72, 137.69, 136.65, 128.6, 128.52, 128.45, 128.4, 128.2, 128.1, 127.86, 127.85, 127.78, 127.72, 127.67, 127.65, 127.6, 84.5, 83.5, 83.1, 82.0, 73.12, 73.05, 71.2, 71.1, 70.9, 68.8, 67.8, 67.0, 66.9, 64.9, 64.7, 63.0, 62.9, 62.8, 62.7, 32.7, 32.5, 31.4, 30.1, 26.31, 26.28, 25.44, 25.35. HRMS ESI: calcd for $C_{39}H_{45}NO_6H^+$ $[M + H]^+$ 624.33196, found 624.33119.

General procedures for synthesis of compound **15**, ***ent*-15**, **3-*epi*-15**, ***ent*-3-*epi*-15**, ***ent*-15a** and ***ent*-15b**, with compound **15** as an example.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-1-benzyloxycarbonyl-5-(7-bromoheptyl)pyrrolidine (15).

Alcohol **18** (1.70 g, 2.61 mmol) and CBr_4 (2.16 g, 6.52 mmol) were dissolved in dry CH_2Cl_2 (20 mL) and PPh_3 (1.37 g, 5.22 mmol) was added to the solution in portions at 0 °C. After complete addition, the solution was stirred for 5 min at 0 °C, then warmed to room temperature slowly and stirred for 2 h at the same temperature. When the starting material had disappeared, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated to 20 mL under reduced pressure, then 10 mL of petroleum ether was added, a white precipitate was formed and removed by filtration through celite. After concentration, this crude material was purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 15/1) to afford the corresponding bromide **15** (1.81 g, 2.53 mmol, 97%) as a light yellow syrup.

Data for **15**: $[\alpha]_D^{20}$ -29.6 (*c* 1.2, CH_2Cl_2); IR (KBr, cm^{-1}): 3063, 3031, 2929, 2856, 1699, 1496, 1454, 1409, 1348, 1096, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.15 (m, 20H), 5.25–5.13 (m, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.68–4.55 (m, 1.5H), 4.50–4.41 (m, 2H), 4.41–4.30 (m, 2.5H), 4.25 (dd, *J* = 10.3, 3.8 Hz, 0.5H), 4.19–4.11 (m, 1.5H), 4.06 (dd, *J* = 8.5, 4.0 Hz, 0.5H), 3.88–3.69 (m, 2.5H), 3.48 (t, *J* = 9.8 Hz, 1H), 3.36 (q, *J* = 6.8 Hz, 2H), 2.10–1.97 (m, 0.5H), 1.87–1.61 (m, 3H), 1.60–1.49 (m, 0.5H), 1.43–1.08 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 154.3, 138.6, 138.4, 138.0, 137.7, 136.7, 128.6, 128.52, 128.45, 128.4, 128.23, 128.15, 128.09, 127.84, 127.78, 127.73, 127.69, 127.66, 127.6, 84.5, 83.5, 83.2, 82.1, 73.1, 71.3, 71.1, 70.9, 68.8, 67.9, 66.94, 66.89, 65.1, 64.8, 63.0, 62.7, 34.1, 34.0, 32.9, 32.8, 31.4, 30.1, 29.2, 29.0, 28.7, 28.6, 28.12, 28.09, 26.5. HRMS ESI: calcd for $C_{41}H_{48}{}^{79}BrNO_5H^+$ $[M + H]^+$ 714.27886, found 714.27750.

Data for ***ent*-15**: light yellow syrup, 2.42 g, 3.39 mmol, 85% yield, derived from the corresponding alcohol ***ent*-18** (2.60 g, 3.99 mmol).

$[\alpha]_D^{20}$ +28.8 (*c* 1.6, CH_2Cl_2); IR (KBr, cm^{-1}): 3063, 3031, 2929, 2856, 1699, 1497, 1454, 1409, 1348, 1096, 737, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.15 (m, 20H), 5.23–5.14 (m, 1H), 5.03 (dd, *J* = 12.3, 2.7 Hz, 1H), 4.66–4.55 (m, 1.5H), 4.48–4.40 (m, 2H), 4.40–4.30 (m, 2.5H), 4.26 (dd, *J* = 10.5, 4.0 Hz, 0.5H), 4.18–4.13 (m, 1.5H), 4.07 (dd, *J* = 8.7, 4.2 Hz, 0.5H), 3.87–3.70 (m, 2.5H), 3.51–3.45 (m, 1H), 3.36–3.30 (m, 2H), 2.09–1.99 (m, 0.5H), 1.83–1.62 (m, 3H), 1.61–1.52 (m, 0.5H), 1.40–1.08 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 154.2, 138.5, 138.3, 137.94, 137.89, 137.7, 137.6, 136.62, 136.58, 128.5, 128.44, 128.41, 128.36, 128.3, 128.14, 128.05, 128.0, 127.76, 127.75, 127.70, 127.65, 127.60, 127.57, 127.5, 84.4, 83.3, 83.1, 81.9, 73.02, 72.95, 71.1, 71.0, 70.8, 68.7, 67.8, 66.84, 66.79, 65.0, 64.6, 62.9, 62.6, 34.00, 33.95, 32.74, 32.69, 31.3, 30.0, 29.1, 28.9, 28.6, 28.4, 28.01, 27.97, 26.4, 26.3. HRMS ESI: calcd for $C_{41}H_{48}{}^{79}BrNO_5H^+$ $[M + H]^+$ 714.27886, found 714.27784.

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Data for **3-*epi*-15**: light yellow syrup, 0.79 g, 1.11 mmol, 88% yield, derived from the corresponding alcohol **3-*epi*-18** (0.82 g, 1.26 mmol).

$[\alpha]_D^{20}$ -2.2 (*c* 0.9, CH_2Cl_2); IR (KBr, cm^{-1}): 3063, 3031, 2929, 2856, 1698, 1497, 1454, 1408, 1352, 1096, 736, 697; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.14 (m, 20H), 5.25–5.98 (m, 2H), 4.84–4.74 (m, 1H), 4.72–4.57 (m, 2.5H), 4.57–4.49 (m, 1.5H), 4.41–4.35 (m, 1H), 4.34–4.22 (m, 2H), 4.16–4.10 (m, 1H), 3.84–3.74 (m, 2H), 3.70 (d, *J* = 8.1 Hz, 0.5H), 3.59 (d, *J* = 8.0 Hz, 0.5H), 3.37–3.28 (m, 2H), 1.96–1.87 (m, 0.5H), 1.82–1.69 (m, 2H), 1.68–1.56 (m, 0.5H), 1.39–1.31 (m, 1H), 1.31–1.18 (m, 4H), 1.17–0.97 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 154.3, 138.8, 138.6, 138.2, 138.1, 136.6, 136.4, 128.3, 128.2, 128.1, 128.0, 127.83, 127.80, 127.6, 127.50, 127.48, 127.3, 127.23, 127.19, 127.1, 80.8, 79.7, 77.9, 77.4, 72.8, 72.7, 72.5, 72.3, 72.1, 71.7, 70.4, 68.9, 66.8, 66.75, 66.69, 62.5, 62.1, 57.7, 57.6, 33.9, 33.8, 33.0, 32.6, 32.5, 31.6, 29.6, 29.0, 28.8, 28.4, 28.3, 27.8, 26.3, 26.2. HRMS ESI: calcd for $C_{41}H_{48}{}^{79}BrNO_5H^+$ $[M + H]^+$ 714.27886, found 714.27789.

Data for ***ent*-3-*epi*-15**: light yellow syrup, 1.0 g, 1.40 mmol, 96% yield, derived from the corresponding alcohol ***ent*-3-*epi*-18** (0.95 g, 1.46 mmol)**.**

$[\alpha]_D^{20}$ +7.1 (*c* 0.9, CH_2Cl_2); IR (KBr, cm^{-1}): 3063, 3030, 2929, 2856, 1699, 1497, 1454, 1407, 1351, 1096, 735, 697; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.14 (m, 20H), 5.25–4.99 (m, 2H), 4.84–4.74 (m, 1H), 4.73–4.58 (m, 2.5H), 4.58–4.51 (m, 1.5H), 4.42–4.34 (m, 1H), 4.34–4.22 (m, 2H), 4.14 (dd, *J* = 6.4, 4.0Hz, 1H), 3.82–3.75 (m, 2H), 3.70 (d, *J* = 8.1 Hz, 0.5H), 3.58 (d, *J* = 8.3 Hz, 0.5H), 3.39–3.32 (m, 2H), 1.95–1.86 (m, 0.5H), 1.85–1.71 (m, 2H), 1.69–1.59 (m, 0.5H), 1.40–1.33 (m, 1H), 1.33–1.18 (m, 4H), 1.17–0.97 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 154.4, 138.9, 138.7, 138.3, 138.2, 136.7, 136.5, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.35, 127.30, 127.2, 81.0, 79.8, 78.0, 77.5, 73.0, 72.95, 72.87, 72.6, 72.4, 72.2, 71.8, 70.5, 69.0, 66.9, 66.8, 62.6, 62.2, 57.8, 57.7, 34.0, 33.9, 33.1, 32.70, 32.65, 31.7, 29.7, 29.1, 28.9, 28.5, 28.4, 28.0, 26.4, 26.3. HRMS ESI: calcd for $C_{41}H_{48}{}^{79}BrNO_5H^+$ $[M + H]^+$ 714.27886, found 714.27774.

Data for ***ent*-15a**: light yellow syrup, 1.32 g, 1.88 mmol, 92% yield, derived from the corresponding alcohol ***ent*-18a** (1.30 g, 2.04 mmol).

$[\alpha]_D^{20}$ +36.5 (*c* 1.2, CH_2Cl_2); IR (KBr, cm^{-1}): 3063, 3031, 2929, 2857, 1701, 1496, 1454, 1408, 1348, 1094, 736, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.13 (m, 20H), 5.26–5.12 (m, 1H), 5.03 (dd, *J* = 12.4, 1.9 Hz, 1H), 4.68–4.55 (m, 1.5H), 4.47 (d, *J* = 5.3 Hz, 1H), 4.43 (d, *J* = 4.8 Hz, 1H), 4.40–4.29 (m, 2.5H), 4.26 (dd, *J* = 10.4, 3.8 Hz, 0.5H), 4.20–4.11 (m, 1.5H), 4.06 (dd, *J* = 8.6, 4.0 Hz, 0.5H), 3.88–3.69 (m, 2.5H), 3.48 (t, *J* = 9.7 Hz, 1H), 3.35 (t, *J* = 6.8 Hz, 1H), 3.29 (t, *J* = 6.8 Hz, 1H), 2.11–1.96 (m, 0.5H), 1.86–1.57 (m, 3.5H), 1.46–1.20 (m, 4H), 1.20–1.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 154.3, 138.6, 138.4, 138.0, 137.7, 136.6, 128.5, 128.43, 128.39, 128.20, 128.17, 128.1, 127.9, 127.7, 127.6, 84.5, 83.4, 83.1, 82.0, 73.1, 73.0, 71.3, 71.1, 70.9, 68.8, 67.9, 67.0, 66.9, 65.0, 64.7, 63.0, 62.7, 34.0, 33.9, 32.8, 32.7, 31.4, 30.1, 28.6, 28.3, 28.1, 27.9, 26.4, 26.3. HRMS ESI: calcd for $C_{40}H_{46}{}^{79}BrNO_5H^+$ $[M + H]^+$ 700.26321, found 700.26222.

Data for ***ent*-15b**: light yellow syrup, 3.07 g, 4.47 mmol, 93% yield, derived from the corresponding alcohol ***ent*-18b** (3.00 g, 4.81 mmol).

$[\alpha]_D^{20}$ +40.0 (*c* 1.1, CH_2Cl_2); IR (KBr, cm^{-1}): 3063, 3031, 2934, 2860, 1698, 1496, 1454, 1409, 1348, 1093, 737, 698; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.14 (m, 20H), 5.25–5.12 (m, 1H), 5.06–4.98 (m, 1H), 4.67–4.55 (m, 1.5H), 4.48–4.39 (m, 2H), 4.39–4.29 (m, 2.5H), 4.28–4.21 (m, 0.5H), 4.18–4.11 (m, 1.5H), 4.09–4.03 (m, 0.5H), 3.86–3.70 (m, 2.5H), 3.51–3.43 (m, 1H), 3.33 (t, *J* = 6.8 Hz, 1H), 3.24 (t, *J* = 6.6 Hz, 1H), 2.09–1.99 (m, 0.5H), 1.86–1.75 (m, 1H), 1.74–1.60 (m, 2H), 1.61–1.52 (m, 0.5H), 1.51–1.34 (m, 1H), 1.34–1.08 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.3, 138.6, 138.3, 138.0, 137.9, 137.7, 137.6, 136.7, 136.6, 128.6, 128.52, 128.46, 128.4, 128.3, 128.22, 128.15, 128.1, 127.9, 127.82, 127.77, 127.7, 127.6, 84.4, 83.4, 83.1, 81.9, 73.1, 73.0, 71.3, 71.1, 70.9, 68.8, 67.8, 67.0, 66.9, 64.9, 64.5, 63.0, 62.7, 33.9, 33.8, 32.7, 32.4, 31.2, 29.9, 27.9, 27.6, 25.7, 25.6. HRMS ESI: calcd for $C_{39}H_{44}{}^{79}BrNO_5H^+$ $[M + H]^+$ 686.24756, found 686.24651.

General procedures for synthesis of compound **19**, ***ent*-19**, **3-*epi*-19**, ***ent*-3-*epi*-19**, ***ent*-19a** and ***ent*-19b**, with compound **19** as an example.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-1-benzyloxycarbonyl-5-(7-(2-cyclohexanone)heptyl)pyrrolidine (19)

A solution of cyclohexanone (20 g, 204 mmol) and cyclohexylamine (20 g, 204 mmol) in 150 mL of ether was allowed to stand over 4-Å molecular sieves for 12 h. Filtration and removal of solvent followed by distillation afforded *N*-cyclohexylidenecyclohexanamine (**14**, 35.4 g, 89%) as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 3.34–3.25 (m, 1H), 2.36–2.23 (m, 4H), 1.81–1.69 (m, 4H), 1.68–1.56 (m, 7H), 1.48–1.13 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 57.9, 40.3, 34.2, 34.2, 29.1, 27.9, 27.6, 26.2, 25.7, 25.1, 25.1.

To a solution of DIPA (0.12 mL, 0.84 mmol) in THF (10 mL) at 0°C was added n-BuLi (2.4 M in THF; 0.29 mL, 0.70 mmol). To this reaction mixture was added a solution of *N*-cyclohexylidenecyclohexanamine (**14**; 0.10 g, 0.56 mmol) in THF (1 mL) dropwise, and the solution was stirred for 1 h at 0 °C. To the resulting mixture were added HMPA (0.12mL, 0.70 mmol) and followed by a solution of bromide **15** (0.20 g, 0.28 mmol) in THF (2 mL) at 0 °C; the resulting solution was stirred for 2 h at room temperature. After the starting material disappeared, the reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 15/1) to afford ketone **19** (0.15 g, 73%) as a light yellow syrup.

Data for **19**: $[\alpha]_D^{20}$ -30.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 3031, 2929, 2856, 1704, 1497, 1454, 1409, 1348, 1313, 1206, 1094, 1028, 737, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.06 (m, 20H), 5.17–5.05 (m, 1H), 4.96 (d, *J* = 12.2 Hz, 1H), 4.60–4.47 (m, 1.5H), 4.43–4.31 (m, 2.5H), 4.30–4.22 (m, 2H), 4.17 (dd, *J* = 10.5, 4.1 Hz, 0.5H), 4.10–4.02 (m, 1.5H), 3.97 (dd, *J* = 8.7, 4.1 Hz, 0.5H), 3.80–3.61 (m, 2.5H), 3.44–3.34 (m, 1H), 2.35–2.26

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(m, 1H), 2.25–2.10 (m, 2H), 2.07–1.86 (m, 2H), 1.82–1.43 (m, 6H), 1.29–0.99 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 213.6, 154.8, 154.3, 138.6, 138.4, 138.1, 138.0, 137.79, 137.75, 136.73, 136.71, 128.6, 128.5, 128.44, 128.41, 128.2, 128.1, 128.0, 127.82, 127.77, 127.72, 127.69, 127.64, 127.58, 84.5, 83.4, 83.2, 82.1, 73.1, 73.0, 71.2, 71.1, 70.9, 68.8, 67.9, 66.91, 66.87, 65.1, 64.8, 63.0, 62.7, 50.9, 42.1, 33.95, 33.92, 31.5, 30.2, 29.8, 29.6, 29.52, 29.48, 29.3, 28.1, 27.3, 26.7, 24.9. HRMS ESI: calcd for $C_{47}H_{57}NO_6H^+$ $[M + H]^+$ 732.42587, found 732.42474.

Data for ***ent*-19**: light yellow syrup, 100 mg, 0.14 mmol, 71% yield, derived from the corresponding bromide ***ent*-15** (137 mg, 0.19 mmol).

$[\alpha]_D^{20}$ +34.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 3031, 2928, 2856, 1704, 1496, 1454, 1408, 1348, 1313,1206, 1094, 1028, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.07 (m, 20H), 5.16–5.05 (m, 1H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.59–4.47 (m, 1.5H), 4.42–4.30 (m, 2.5H), 4.30–4.22 (m, 2H), 4.17 (dd, *J* = 10.5, 3.9 Hz, 0.5H), 4.10–4.03 (m, 1.5H), 3.97 (dd, *J* = 8.6, 4.1 Hz, 0.5H), 3.79–3.62 (m, 2.5H), 3.44–3.35 (m, 1H), 2.34–2.26 (m, 1H), 2.24–2.10 (m, 2H), 2.05–1.88 (m, 2H), 1.82–1.41 (m, 6H), 1.24–0.99 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.7, 213.6, 154.7, 154.3, 138.6, 138.4, 138.1, 138.0, 137.78, 137.74, 136.72, 136.70, 128.6, 128.5, 128.43, 128.40, 128.2, 128.1, 128.0, 127.82, 127.77, 127.72, 127.69, 127.64, 127.58, 84.5, 83.4, 83.2, 82.1, 73.1, 73.0, 71.2, 71.1, 70.9, 68.8, 67.9, 66.90, 66.86, 65.1, 64.8, 63.0, 62.7, 50.9, 42.1, 33.95, 33.92, 31.5, 30.2, 29.8, 29.6, 29.51, 29.47, 29.3, 28.1, 27.3, 26.7, 24.9. HRMS ESI: calcd for $C_{47}H_{57}NO_6H^+$ $[M + H]^+$ 732.42587, found 732.42468.

Data for **3-*epi*-19**: light yellow syrup, 270 mg, 0.37 mmol, 60% yield, derived from the corresponding bromide **3-*epi*-15** (440 mg, 0.62 mmol).

$[\alpha]_D^{20}$ –11.4 (*c* 0.7, CH_2Cl_2); IR (KBr, cm^{-1}): 2928, 2856, 1705, 1454, 1407, 1352, 1096, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.11 (m, 20H), 5.27–4.99 (m, 2H), 4.85–4.71 (m, 1H), 4.70–4.49 (m, 4H), 4.43–4.34 (m, 1H), 4.34–4.20 (m, 2H), 4.19–4.10 (m, 1H), 3.85–3.74 (m, 2H), 3.70 (d, *J* = 7.9 Hz, 0.5H), 3.58 (d, *J* = 7.3 Hz, 0.5H), 2.43–2.16 (m, 3H), 2.15–1.54 (m, 7H), 1.46–0.96 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 154.6, 138.8, 138.4, 136.8, 128.5, 128.4, 128.2, 128.0, 127.64, 127.59, 127.4, 127.3, 81.1, 79.9, 78.1, 77.4, 73.0, 72.7, 72.5, 72.2, 71.9, 70.6, 69.1, 66.8, 62.7, 62.4, 57.9, 50.8, 42.0, 33.9, 33.3, 31.9, 29.7, 29.5, 28.1, 27.2, 26.6, 24.9. HRMS ESI: calcd for $C_{47}H_{57}NO_6H^+$ $[M + H]^+$ 732.42587, found 732.42491.

Data for ***ent*-3-*epi*-19**: light yellow syrup, 580 mg, 0.79 mmol, 71% yield, derived from the corresponding bromide ***ent*-3-*epi*-15** (800 mg, 1.12 mmol).

$[\alpha]_D^{20}$ +8.6 (*c* 0.7, CH_2Cl_2); IR (KBr, cm^{-1}): 2928, 2856, 1705, 1454, 1408, 1352, 1098, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.12 (m, 20H), 5.28–4.98 (m, 2H), 4.85–4.70 (m, 1H), 4.69–4.50 (m, 4H), 4.43–4.35 (m, 1H), 4.34–4.20 (m, 2H), 4.19–4.10 (m, 1H), 3.84–3.74 (m, 2H), 3.71 (d, *J* = 7.3 Hz, 0.5H), 3.58 (d, *J* = 7.3 Hz, 0.5H), 2.43–2.15 (m, 3H), 2.14–1.54 (m, 7H), 1.46–0.96 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 154.6, 138.7, 138.3, 136.7, 128.4, 128.3, 128.1, 127.9, 127.6, 127.5, 127.4, 127.3, 81.0, 79.9, 78.0, 77.4, 72.9, 72.6, 72.4, 72.2, 71.9, 70.5, 69.0, 66.8, 62.6, 62.3, 57.9, 50.8, 42.0, 33.9, 33.2, 31.8, 29.6, 29.4, 28.0, 27.1, 26.5, 24.8. HRMS ESI: calcd for $C_{47}H_{57}NO_6H^+$ $[M + H]^+$ 732.42587, found 732.42444.

Data for ***ent*-19a**, light yellow syrup, 140 mg, 0.20 mmol, 68% yield, derived from the corresponding bromide ***ent*-15a** (200 mg, 0.21 mmol).

$[\alpha]_D^{20}$ +31.7 (*c* 1.2, CH_2Cl_2); IR (KBr, cm^{-1}): 2928, 2857, 1704, 1454, 1409, 1348, 1096, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.14 (m, 20H), 5.24–5.13 (m, 1H), 5.03 (d, *J* = 12.3 Hz,1H), 4.67–4.55 (m, 1.5H), 4.50–4.29 (m, 4.5H), 4.25 (dd, *J* = 10.5, 4.0 Hz, 0.5H), 4.18–4.10 (m, 1.5H), 4.05 (dd, *J* = 8.7, 4.2 Hz, 0.5H), 3.88–3.69 (m, 2.5H), 3.52–3.42 (m, 1H), 2.46–2.15 (m, 3H), 2.13–1.95 (m, 2H), 1.90–1.46 (m, 6H), 1.45–1.02 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 213.6, 154.8, 154.3, 138.6, 138.4, 138.0, 137.79, 137.75, 136.7, 128.6, 128.51, 128.45, 128.4, 128.2, 128.1, 127.8, 127.70, 127.65, 127.6, 84.5, 83.4, 83.2, 82.1, 73.1, 73.0, 71.2, 71.1, 70.9, 68.8, 67.9, 66.9, 65.1, 64.8, 63.0, 62.7, 50.8, 42.1, 34.0, 31.5, 30.2, 29.8, 29.7, 29.5, 29.3, 28.2, 27.2, 26.6, 24.9. HRMS ESI: calcd for $C_{46}H_{55}NO_6H^+$ $[M + H]^+$ 718.41021, found 718.40914.

Data for ***ent*-19b**, light yellow syrup, 73 mg, 0.10 mmol, 71% yield, derived from the corresponding bromide ***ent*-15b** (100 mg, 0.15 mmol).

$[\alpha]_D^{20}$ +36.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 2932, 2858, 1704, 1497, 1454, 1409, 1348, 1095, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.12 (m, 20H), 5.25–5.15 (m, 1H), 5.03 (d, *J* = 12.2 Hz, 1H), 4.69–4.54 (m, 1.5H), 4.52–4.29 (m, 4.5H), 4.25 (dd, *J* = 10.5, 3.9 Hz, 0.5H), 4.19–4.09 (m, 1.5H), 4.05 (dd, *J* = 8.5, 4.0 Hz, 0.5H), 3.88–3.68 (m, 2.5H), 3.47 (t, *J* = 9.8 Hz, 1H), 2.43–2.33 (m, 1H), 2.32–2.12 (m, 2H), 2.12–1.94 (m, 3H), 1.91–1.76 (m, 1H), 1.77–1.51 (m, 4H), 1.44–1.05 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 154.7, 154.3, 138.6, 138.4, 138.0, 137.7, 136.7, 128.52, 128.47, 128.4, 128.2, 128.0, 127.8, 127.7, 127.60, 127.56, 84.5, 83.4, 83.2, 82.1, 73.1, 73.0, 71.2, 71.1, 70.9, 68.8, 66.8, 65.1, 64.8, 63.0, 62.7, 50.7, 42.0, 33.9, 30.1, 29.6, 29.3, 28.1, 27.1, 26.5, 24.9. HRMS ESI: calcd for $C_{45}H_{53}NO_6H^+$ $[M + H]^+$ 704.39456, found 704.39369.

General procedures for synthesis of compound **20**, ***ent*-20**, **3-*epi*-20**, ***ent*-3-*epi*-10**, ***ent*-10a** and ***ent*-10b**, with compound **20** as an example.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dihydroxy-2-hydroxymethyl-5-[7-(2-cyclohexanone)heptyl]pyrrolidine (20)

10% Pd/C (30 mg) and 6 N HCl (0.5 mL) were added to a solution of **19** (100 mg, 0.14 mmol) in MeOH (10 mL, replaced with argon 3 times). After the resulting suspension was stirred under an atmosphere of H_2 at room temperature for 8 h, TLC (EtOAc/MeOH: 3/1) revealed the formation of a polar compound. The Pd/C was filtered off, and the solution was concentrated *in vacuo*, the residue was dissolved in MeOH and neutralized with aqueous ammonium solution, concentrated *in vacuo*. The above procedure was repeated for three times to ensure complete neutralization. The residue was purified by an acid resin column (DOWEX 50W × 8, 100-200 mesh), eluting with distilled water (100 mL) and then 6N NH_4OH (50 mL), affording **20** (43 mg, 0.13 mmol, 96%) as a light yellow syrup.

Data for **20**: $[\alpha]_D^{20}$ +17.8 (*c* 0.7, MeOH); IR (KBr, cm^{-1}): 3357, 2927, 2855, 1701, 1131, 1076, 1042; ^{1}H NMR (300 MHz, MeOD) δ 3.87 (t, *J* = 6.4 Hz, 1H), 3.82–3.65 (m, 3H), 3.17–3.09

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(m, 1H), 3.06–2.95 (m, 1H), 2.54–2.32 (m, 2H), 2.27–2.05 (m, 2H), 2.01–1.89 (m, 1H), 1.89–1.65 (m, 4H), 1.63–1.21 (m, 14H). ^{13}C NMR (75 MHz, MeOD) δ 216.1, 83.1, 79.2, 64.6, 62.9, 62.7, 51.8, 42.8, 35.3, 34.8, 30.8, 30.7, 30.6, 30.5, 29.3, 28.2, 27.6, 25.8. HRMS ESI: calcd for $C_{18}H_{33}NO_4H^+$ [M + H]$^+$ 328.24824, found 328.24796.

Data for ***ent*-20**: light yellow syrup, 75 mg, 0.23 mmol, 84% yield, derived from the corresponding ketone ***ent*-19** (200 mg, 0.27 mmol).

$[\alpha]_D^{20}$ -13.3 (*c* 1.5, MeOH); IR (KBr, cm^{-1}): 3357, 2927, 2855, 1701, 1132, 1076, 1042; ^{1}H NMR (400 MHz, MeOD) δ 3.81 (t, *J* = 6.3 Hz, 1H), 3.75–3.61 (m, 3H), 3.14–3.07 (m, 1H), 3.02–2.94 (m, 1H), 2.42–2.26 (m, 2H), 2.19–1.98 (m, 2H), 1.90–1.81 (m, 1H), 1.79–1.58 (m, 4H), 1.57–1.12 (m, 14H). ^{13}C NMR (101 MHz, MeOD) δ 217.0, 83.6, 79.7, 65.5, 63.9, 63.1, 52.6, 43.7, 36.2, 35.2, 31.7, 31.52, 31.46, 31.3, 30.2, 29.1, 28.4, 26.7. HRMS ESI: calcd for $C_{18}H_{33}NO_4H^+$ [M + H]$^+$ 328.24824, found 328.24786.

Data for **3-*epi*-20**: light yellow syrup, 60 mg, 0.18 mmol, 75% yield, derived from the corresponding ketone **3-*epi*-19** (180 mg, 0.25 mmol).

$[\alpha]_D^{20}$ +25.7 (*c* 0.7, MeOH); IR (KBr, cm^{-1}): 3394, 2927, 2855, 1701, 1112, 618; ^{1}H NMR (300 MHz, MeOD) δ 4.20 (s, 1H), 4.07–3.90 (m, 3H), 3.75 (s, 1H), 3.54–3.40 (m, 1H), 2.54–2.28 (m, 2H), 2.25–2.02 (m, 2H), 2.00–1.61 (m, 6H), 1.60–1.17 (m, 14H). ^{13}C NMR (75 MHz, MeOD) δ 216.3, 77.5, 71.8, 63.4, 62.0, 59.4, 51.8, 42.8, 35.3, 32.0, 30.8, 30.6, 30.33, 30.33, 29.3, 28.2, 27.5, 25.8. HRMS ESI: calcd for $C_{18}H_{33}NO_4H^+$ [M + H]$^+$ 328.24824, found 328.24799.

Data for ***ent*-3-*epi*-20**: light yellow syrup, 180 mg, 0.55 mmol, 79% yield, derived from the corresponding ketone ***ent*-3-*epi*-19** (520 mg, 0.71 mmol).

$[\alpha]_D^{20}$ -20.0 (*c* 0.4, MeOH); IR (KBr, cm^{-1}): 3370, 2929, 2855, 1706, 1124, 618; ^{1}H NMR (300 MHz, MeOD) δ 4.15 (s, 1H), 3.94–3.71 (m, 3H), 3.52 (s, 1H), 3.29–3.18 (m, 1H), 2.45–2.27 (m, 2H), 2.20–2.00 (m, 2H), 1.99–1.56 (m, 6H), 1.56–1.09 (m, 14H). ^{13}C NMR (75 MHz, MeOD) δ 216.2, 78.2, 72.6, 62.5, 62.0, 60.7, 51.8, 42.8, 35.3, 33.6, 30.8, 30.59, 30.59, 30.4, 29.3, 28.2, 27.7, 25.8. HRMS ESI: calcd for $C_{18}H_{33}NO_4H^+$ [M + H]$^+$ 328.24824, found 328.24800.

Data for ***ent*-20a**: light yellow oil, 36 mg, 0.11 mmol, 82% yield, derived from the corresponding ketone ***ent*-19a** (100 mg, 0.14 mmol).

$[\alpha]_D^{20}$ -13.3 (*c* 0.2, MeOH); IR (KBr, cm^{-1}): 3374, 2927, 2855, 1701, 1076, 1042;^{1}H NMR (300 MHz, MeOD) δ 3.66 (t, *J* = 6.5 Hz, 1H), 3.58 (dd, *J* = 11.3, 4.2 Hz, 1H), 3.54–3.46 (m, 2H), 2.91 (q, *J* = 6.2 Hz, 1H), 2.79 (q, 7.1 Hz, 1H), 2.33–2.15 (m, 3H), 2.08–1.88 (m, 2H), 1.82–1.48 (m, 5H), 1.43–1.02 (m, 11H). ^{13}C NMR (75 MHz, MeOD) δ 216.1, 83.4, 79.4, 64.5, 63.0, 62.8, 51.7, 42.8, 35.3, 35.0, 30.8, 30.7, 30.6, 29.3, 28.2, 27.6, 25.8. HRMS ESI: calcd for $C_{17}H_{31}NO_4H^+$ [M + H]$^+$ 314.23258, found 314.23196.

Data for ***ent*-20b**: light yellow oil, 390 mg, 1.30 mmol, 83% yield, derived from the corresponding ketone ***ent*-19b** (1.10 g, 1.56 mmol).

$[\alpha]_D^{20}$ -16.0 (*c* 0.5, MeOH); IR (KBr, cm^{-1}): 3370, 2931, 2858, 1699, 1124, 1076; ^{1}H NMR (300 MHz, D_2O) δ 3.83 (t, *J* = 7.0 Hz, 1H), 3.75–3.59 (m, 3H), 3.18–3.09 (m, 1H), 3.04–2.94(m, 1H), 2.45–2.25 (m, 1H), 2.11–1.88 (m, 2H), 1.81–1.55 (m, 5H), 1.55–1.11 (m, 11H). ^{13}C NMR (126 MHz, MeOD) δ 216.2, 82.1, 78.3, 64.9, 63.3, 61.6, 51.7, 42.8, 35.3, 33.7, 30.8, 30.5, 29.3, 28.1, 27.3, 25.8. HRMS ESI: calcd for $C_{16}H_{29}NO_4H^+$ [M + H]$^+$300.21693, found 300.21679.

General procedures for synthesis of compound **21**, ***ent*-21**, **3-*epi*-21**, ***ent*-3-*epi*-21**, ***ent*-21a** and ***ent*-21b**, with compound **21** as an example.

(2*R*,3*R*,4*R*,5*R*)-3,4-Diyldiacetate-2-(acetoxymethyl)-1-acetyl-5-(7-(2-cyclohexanone)heptyl)pyrrolidine (21).

To a solution of **20** (130 mg, 0.40 mmol) in pyrdine (10 mL) were added DMAP (cat. 10 mg) and Ac_2O (0.2 mL, 2.40 mmol); the solution was stirred for 5h at room temperature. After the starting material had disappeared, the reaction was quenched with H_2O and extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 3/1) to afford ketone **21** (191 mg, 0.39 mmol, 95%) as a yellow syrup.

Data for **21**: $[\alpha]_D^{20}$ -31.6 (*c* 0.6, CH_2Cl_2); IR (KBr, cm^{-1}): 2930, 2857, 1747, 1708, 1652, 1371, 1221, 1040, 882, 604; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.08 (d, *J* = 5.6 Hz, 1H), 4.51 (dd, *J* = 10.1, 2.8 Hz, 0.5H), 4.40 (dd, *J* = 10.1, 2.6 Hz, 0.5H), 4.32–4.16 (m, 1H), 4.12–3.94 (m, 1.5H), 3.74 (d, *J* = 10.1 Hz, 0.5H), 2.41–2.16 (m, 4H), 2.15–1.89 (m, 13H), 1.88–1.57 (m, 5H), 1.49–1.11 (m, 13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.7, 213.6, 171.0, 170.9, 169.9, 169.7, 169.6, 169.5, 169.2, 169.1, 78.6, 77.8, 77.5, 76.3, 65.8, 65.4, 63.0, 62.8, 62.3, 60.5, 50.8, 42.04, 42.01, 34.0, 33.91, 33.88, 33.3, 30.1, 29.72, 29.68, 29.5, 29.4, 29.3, 28.1, 27.2, 26.3, 26.2, 24.90, 24.86, 22.9, 21.09, 21.05, 21.0, 20.9, 20.8. HRMS ESI: calcd for $C_{26}H_{41}NO_8H^+$ [M + H]$^+$496.29049, found 496.28962.

Data for ***ent*-21**: light yellow syrup, 325 mg, 0.66 mmol, 94% yield, derived from the corresponding compound ***ent*-20** (230 mg, 0.70 mmol).

$[\alpha]_D^{20}$ +38.6 (*c* 1.5, CH_2Cl_2); IR (KBr, cm^{-1}): 2931, 2857, 1747, 1709, 1652, 1373, 1220, 1042, 882, 604; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 1H), 5.09 (s, 1H), 4.52 (d, *J* = 9.7 Hz, 0.5H), 4.41 (d, *J* = 9.5 Hz, 0.5H), 4.34–4.15 (m, 1H), 4.14–3.95 (m, 1.5H), 3.75 (d, *J* = 11.5 Hz, 0.5H), 2.43–2.17 (m, 4H), 2.17–1.95 (m, 13H), 1.93–1.56 (m, 5H), 1.54–1.10 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 213.5, 171.0, 170.9, 169.8, 169.6, 169.4, 169.2, 169.0, 78.6, 77.8, 77.5, 76.3, 65.7, 65.4, 62.9, 62.8, 62.3, 60.5, 50.8, 42.01, 41.98, 34.0, 33.89, 33.85, 33.3, 30.0, 29.70, 29.65, 29.45, 29.37, 29.3, 28.1, 27.2, 26.3, 26.2, 24.9, 24.8, 22.8, 21.1, 21.03, 20.96, 20.9, 20.8. HRMS ESI: calcd for $C_{26}H_{41}NO_8H^+$ [M + H]$^+$ 496.29049, found 496.28975.

Data for **3-*epi*-21**: light yellow syrup, 173 mg, 0.35 mmol, 76% yield, derived from the corresponding compound **3-*epi*-20** (150 mg, 0.46 mmol).

$[\alpha]_D^{20}$ +3.5 (*c* 1.2, CH_2Cl_2); IR (KBr, cm^{-1}): 2929, 2857, 1745, 1708, 1654, 1393, 1368, 1225, 1107, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (dd, *J* = 7.7, 4.0 Hz, 0.5H), 5.38–5.30 (m, 1.5H), 4.55 (t, *J* = 8.2 Hz, 0.5H), 4.51–4.43 (m, 1H), 4.37–4.28 (m, 1.5H), 3.97 (d, *J* = 10.2 Hz, 0.5H), 3.73 (d, *J* = 10.6 Hz, 0.5H),

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2.42–2.19 (m, 5H), 2.19–1.93 (m, 12H), 1.90–1.59 (m, 5H), 1.54–1.11 (m, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.73, 213.65, 170.4, 170.3, 170.1, 170.0, 169.8, 169.7, 169.6, 75.2, 74.1, 70.1, 68.9, 63.6, 63.5, 62.7, 60.9, 56.7, 55.1, 50.8, 42.1, 42.0, 34.7, 34.0, 33.9, 31.3, 29.8, 29.70, 29.66, 29.5, 29.40, 29.35, 29.3, 28.1, 27.2, 26.4, 26.3, 24.92, 24.89, 23.1, 22.2, 21.1, 21.0, 20.8, 20.7, 20.5. HRMS ESI: calcd for $C_{26}H_{41}NO_8H^+$ $[M + H]^+$ 496.29049, found 496.28902.

Data for ***ent*-3-*epi*-21**: light yellow syrup, 142 mg, 0.29 mmol, 94% yield, derived from the corresponding compound ***ent*-3-*epi*-20** (100 mg, 0.31 mmol).

$[\alpha]_D^{20}$ -3.6 (*c* 0.6, CH_2Cl_2); IR (KBr, cm^{-1}): 2931, 2857, 1747, 1708, 1652, 1395, 1368, 1225, 1107, 1043; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (dd, *J* = 7.7, 4.4 Hz, 0.5H), 5.42–5.25 (m, 1.5H), 4.59–4.40 (m, 1.5H), 4.40–4.25 (m, 1.5H), 3.97 (d, *J* = 9.9 Hz, 0.5H), 3.75 (d, *J* = 10.4 Hz, 0.5H), 2.45–2.19 (m, 5H), 2.18–1.92 (m, 12H), 1.90–1.57 (m, 5H), 1.51–1.12 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 213.2, 170.1, 170.0, 169.75, 169.72, 169.6, 169.41, 169.35, 75.0, 73.9, 69.9, 68.7, 63.4, 63.2, 62.5, 60.6, 56.5, 54.9, 50.5, 41.8, 34.4, 33.8, 33.7, 31.0, 29.44, 29.39, 29.22, 29.18, 29.12, 29.08, 29.0, 27.9, 26.9, 26.1, 26.0, 24.7, 24.6, 22.8, 21.9, 20.8, 20.7, 20.5, 20.4, 20.3. HRMS ESI: calcd for $C_{26}H_{41}NO_8H^+$ $[M + H]^+$ 496.29049, found 496.28986.

Data for ***ent*-21a**: light yellow syrup, 628 mg, 1.30 mmol, 93% yield, derived from the corresponding compound ***ent*-20a** (440 mg, 1.40 mmol).

$[\alpha]_D^{20}$ +25.0 (*c* 0.8, CH_2Cl_2); IR (KBr, cm^{-1}): 2932, 2858, 1745, 1708, 1652, 1371, 1222, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 1H), 5.09 (d, *J* = 3.9 Hz, 1H), 4.52 (dd, *J* = 9.7, 3.4 Hz, 0.5H), 4.41 (dd, *J* = 9.4, 2.9 Hz, 0.5H), 4.33–4.17 (m, 1H), 4.14–3.96 (m, 1.5H), 3.75 (dd, *J* = 11.6, 2.6 Hz, 0.5H), 2.44–2.18 (m, 4H), 2.14–1.97 (m, 13H), 1.95–1.56 (m, 5H), 1.55–1.10 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 213.5, 171.0, 170.9, 169.9, 169.6, 169.5, 169.2, 169.1, 78.6, 77.8, 76.4, 65.8, 65.4, 63.0, 62.8, 62.3, 60.5, 50.8, 42.1, 42.0, 34.0, 33.9, 33.3, 30.1, 29.6, 29.4, 29.3, 28.1, 27.1, 26.3, 26.2, 25.0, 24.9, 22.9, 21.09, 21.06, 21.0, 20.9, 20.8. HRMS ESI: calcd for $C_{25}H_{39}NO_8H^+$ $[M + H]^+$ 482.27484, found 482.27417.

Data for ***ent*-21b**: light yellow syrup, 610 mg, 1.30 mmol, 90% yield, derived from the corresponding compound ***ent*-20b** (430 mg, 1.44 mmol).

$[\alpha]_D^{20}$ +20.0 (*c* 1.1, CH_2Cl_2); IR (KBr, cm^{-1}): 2934, 2859, 1744, 1708, 1652, 1371, 1221, 1039; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.86 (s, 1H), 4.29 (d, *J* = 7.5 Hz, 0.5H), 4.19 (d, *J* = 7.7 Hz, 0.5H), 4.09–3.95 (m, 1H), 3.94–3.80 (m, 1H), 3.76 (d, *J* = 8.9 Hz, 0.5H), 3.57 (d, *J* = 10.4 Hz, 0.5H), 2.23–1.73 (m, 17H), 1.72–1.34 (m, 5H), 1.34–0.84 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 212.4, 170.3, 170.2, 169.3, 169.0, 168.9, 168.8, 168.6, 168.5, 78.1, 77.4, 77.2, 77.0, 75.8, 65.1, 64.8, 62.5, 62.3, 61.8, 59.9, 50.1, 41.5, 33.6, 33.5, 33.4, 32.6, 29.4, 28.9, 28.8, 27.6, 26.4, 25.5, 24.4, 24.3, 22.3, 20.43, 20.37, 20.3, 20.2.HRMS ESI: calcd for $C_{24}H_{37}NO_8H^+$ $[M + H]^+$ 468.25919, found 468.25892.

General procedures for synthesis of compound **22**, ***ent*-22**, ***3-epi*-22**, ***ent*-3-*epi*-22**, ***ent*-22a** and ***ent*-22b**, with compound **22** as an example.

(2*R*,3*R*,4*R*,5*R*)-3,4-Diyldiacetate-2-(acetoxymethyl)-1-acetyl-5-[7-(cyclohexy-2-on-1(6)-enyl)heptyl]pyrrolidine (22).

$(TMS)_2NH$ (0.1 mL, 0.47 mmol) was added to a solution of **21** (130 mg, 0.26 mmol) in CH_3CN (10 mL) at 0°C. After 10 min, NaI (50 mg, 0.34 mmol) and TMSCl (40 µL, 0.34 mmol) were successively added and the resulting mixture was stirred for 3 h. The mixture was cooled to -20 °C, and NBS (49 mg, 0.28 mmol) was added. After 30 min, the reaction was allowed to reach room temperature, and the mixture was stirred for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated to afford the corresponding bromo compound, which was used in the next step of reaction without further purification.

LiBr (27 mg, 0.31 mmol) and Li_2CO_3 (23 mg, 0.31 mmol) were successively added to a solution of bromo compound (0.26 mmol) in DMF (10 mL). The reaction mixture was heated at 120 °C°Cfor 4 h and then quenched by addition of water; the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with brine. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 3/1) to afford the corresponding *α,β*-unsaturated ketone **22** (107 mg, 0.22 mmol, 83%) as a yellow syrup.

Data for **22**: $[\alpha]_D^{20}$ -26.7 (*c* 1.4, CH_2Cl_2); IR (KBr, cm^{-1}): 2928, 2856, 1746, 1652, 1373, 1221, 1096, 1039; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73–6.67 (m, 1H), 5.16 (s, 1H), 5.10 (d, *J* = 3.5 Hz, 1H), 4.53 (dd, *J* = 9.7, 3.4 Hz, 0.5H), 4.41 (dd, *J* = 9.4, 2.9 Hz, 0.5H), 4.34–3.95 (m, 2.5H), 3.76 (dd, *J* = 11.5, 2.3 Hz, 0.5H), 2.46–2.29 (m, 4H), 2.24–2.03 (m, 13H), 2.03–1.91 (m, 2H), 1.91–1.56 (m, 2H), 1.54–1.19 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.59, 199.57, 170.94, 170.87, 169.9, 169.60, 169.56, 169.4, 169.2, 169.0, 145.0, 144.9, 139.91, 139.88, 78.6, 77.8, 77.5, 76.3, 65.7, 65.4, 62.9, 62.7, 62.3, 60.5, 38.6, 33.2, 30.0, 29.6, 29.5, 29.33, 29.28, 29.2, 28.64, 28.55, 26.3, 26.2, 26.1, 23.2, 22.8, 21.1, 21.0, 20.95, 20.9, 20.7. HRMS ESI: calcd for $C_{26}H_{39}NO_8H^+$ $[M + H]^+$ 494.27484, found 494.27398.

Data for ***ent*-22**: yellow syrup, 338 mg, 0.68 mmol, 85% yield, derived from the corresponding compound ***ent*-21** (400 mg, 0.81mmol).

$[\alpha]_D^{20}$ +27.2 (*c* 1.3, CH_2Cl_2); IR (KBr, cm^{-1}): 2930, 2856, 1747, 1655, 1370, 1220, 1123, 1042; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (s, 1H), 5.16 (s, 1H), 5.09 (s, 1H), 4.52 (d, *J* = 6.9 Hz, 0.5H), 4.41 (d, *J* = 7.9 Hz, 0.5H), 4.35–3.95 (m, 2.5H), 3.76 (d, *J* = 10.7 Hz, 0.5H), 2.51–2.29 (m, 4H), 2.26–2.05 (m, 13H), 2.05–1.91 (m, 2H), 1.90–1.55 (m, 2H), 1.54–1.18 (m, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.74, 199.71, 171.1, 171.0, 170.0, 169.74, 169.69, 169.5, 169.3, 169.1, 145.1, 145.0, 140.1, 140.0, 78.7, 77.9, 77.6, 77.4, 76.4, 65.9, 65.5, 63.0, 62.9, 62.4, 60.6, 38.7, 33.4, 30.1, 29.7, 29.6, 29.5, 29.41, 29.36, 28.8, 28.7, 26.4, 26.3, 26.2, 23.3, 22.9, 21.2, 21.12, 21.05, 21.0, 20.9. HRMS ESI: calcd for $C_{26}H_{39}NO_8H^+$ $[M + H]^+$ 494.27484, found 494.27416.

Data for ***3-epi*-22**: yellow syrup, 140 mg, 0.28 mmol, 78% yield, derived from the corresponding compound ***3-epi*-21** (180 mg, 0.36 mmol).

$[\alpha]_D^{20}$ +8.9 (*c* 0.5, CH_2Cl_2); IR (KBr, cm^{-1}): 2927, 2856, 1747, 1655, 1369, 1226, 1107, 1043; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73–6.68 (m, 1H), 5.46 (dd, *J* = 8.0, 4.4 Hz, 0.5H), 5.40–5.27

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(m, 1.5H), 4.58–4.51 (m, 0.5H), 4.51–4.42 (m, 1H), 4.38–4.26 (m, 1.5H), 4.00–3.93 (m, 0.5H), 3.77–3.69 (m, 0.5H), 2.42 (t, *J* = 6.5 Hz, 1.5H), 2.39–2.31 (m, 1.5H), 2.22 (s, 2H), 2.19–2.09 (m, 6H), 2.09–2.02 (m, 5H), 2.02–1.92 (m, 2.5H), 1.86–1.58 (m, 1.5H), 1.49–1.13 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 170.5, 170.3, 170.09, 170.05, 169.9, 169.71, 169.66, 145.1, 145.0, 140.01, 139.97, 75.2, 74.1, 70.1, 69.0, 63.7, 63.5, 62.7, 60.9, 56.7, 55.1, 38.7, 34.7, 31.3, 29.6, 29.5, 29.4, 29.3, 28.7, 28.6, 26.5, 26.3, 26.2, 23.3, 23.1, 22.2, 21.1, 21.0, 20.8, 20.7, 20.5. HRMS ESI: calcd for $C_{26}H_{39}NO_8H^+$ $[M + H]^+$ 494.27484, found 494.27396.

Data for ***ent*-3-*epi*-22**: yellow syrup, 149 mg, 0.30 mmol, 83% yield, derived from the corresponding compound ***ent*-3-*epi*-21** (180 mg, 0.36 mmol).

$[\alpha]_D^{20}$ -6.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 2928, 2856, 1747, 1655, 1369, 1226, 1107, 1042; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 4.0 Hz, 1H), 5.45 (dd, *J* = 7.9, 4.5 Hz, 0.5H), 5.41–5.25 (m, 1.5H), 4.57–4.51 (m, 0.5H), 4.50–4.41 (m, 1H), 4.39–4.24 (m, 1.5H), 3.97 (d, *J* = 8.5 Hz, 0.5H), 3.78–3.69 (m, 0.5H), 2.41 (t, *J* = 6.6 Hz, 1.5H), 2.38–2.30 (m, 1.5H), 2.22 (s, 2H), 2.19–2.09 (m, 6H), 2.09–2.01 (m, 5H), 2.01–1.91 (m, 2.5H), 1.89–1.57 (m, 1.5H), 1.50–1.11 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 170.4, 170.3, 170.1, 170.0, 169.9, 169.7, 169.6, 145.1, 145.0, 140.00, 139.96, 75.2, 74.1, 70.1, 68.9, 63.7, 63.5, 62.7, 60.9, 56.7, 55.1, 38.7, 34.7, 31.3, 29.6, 29.5, 29.4, 29.3, 28.7, 28.65, 28.56, 26.4, 26.3, 26.2, 23.3, 23.1, 22.2, 21.1, 21.0, 20.8, 20.7, 20.5. HRMS ESI: calcd for $C_{26}H_{39}NO_8H^+$ $[M + H]^+$ 494.27484, found 494.27396.

Data for ***ent*-22a**: yellow syrup, 147 mg, 0.31 mmol, 74% yield, derived from the corresponding compound ***ent*-21a** (200 mg, 0.42 mmol).

$[\alpha]_D^{20}$ +24.0 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 2929, 2857, 1744, 1670, 1373, 1222, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 5.15 (s, 1H), 5.09 (s, 1H), 4.56–4.47 (m, 0.5H), 4.44–4.37 (m, 0.5H), 4.32–4.25 (m, 0.5H), 4.24–4.16 (m, 0.5H), 4.14–3.94 (m, 1.5H), 3.75 (d, *J* = 11.6 Hz, 0.5H), 2.40 (s, 2H), 2.34 (s, 2H), 2.18–2.02 (m, 14H), 1.97 (s, 2H), 1.89–1.76 (m, 0.5H), 1.69–1.56 (m, 0.5H), 1.51–1.19 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 171.0, 170.9, 170.0, 169.7, 169.6, 169.5, 169.2, 169.1, 145.1, 145.0, 139.9, 139.8, 78.6, 77.8, 76.3, 65.8, 65.4, 62.9, 62.8, 62.3, 60.5, 38.6, 33.3, 30.1, 29.7, 29.6, 29.5, 29.2, 28.5, 26.3, 26.2, 26.1, 23.2, 22.8, 21.04, 20.97, 20.9, 20.8. HRMS ESI: calcd for $C_{25}H_{37}NO_8H^+$ $[M + H]^+$ 480.25919, found 480.25848.

Data for ***ent*-22b**: yellow syrup, 368 mg, 0.79 mmol, 74% yield, derived from the corresponding compound ***ent*-21b** (500 mg, 1.07 mmol).

$[\alpha]_D^{20}$ +25.9 (*c* 0.9, CH_2Cl_2); IR (KBr, cm^{-1}): 2934, 2859, 1744, 1716, 1652, 1371, 1223, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74–6.66 (m, 1H), 5.16 (s, 1H), 5.09 (d, *J* = 3.3 Hz, 1H), 4.53 (dd, *J* = 9.7, 3.3 Hz, 0.5H), 4.41 (d, *J* = 8.0 Hz, 0.5H), 4.23–4.19 (m, 1H), 4.19–4.03 (m, 1H), 3.99 (d, *J* = 9.6 Hz, 0.5H), 3.75 (d, *J* = 9.9 Hz, 0.5H), 2.46–2.29 (m, 4H), 2.25–2.04 (m, 14H), 2.03–1.56 (m, 4H), 1.55–1.23 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.54, 199.47, 170.94, 170.87, 169.9, 169.7, 169.6, 169.4, 169.2, 169.0, 145.2, 145.0, 139.9, 139.8, 78.7, 77.8, 77.6, 76.4, 65.8, 65.4, 63.0, 62.8, 62.3, 60.5, 38.6, 33.2, 30.0, 29.7, 29.51, 29.48, 29.1, 28.6, 28.5, 26.11, 26.05, 26.0, 23.2, 22.8, 21.04, 21.01, 20.94, 20.88, 20.7. HRMS ESI: calcd for $C_{24}H_{35}NO_8H^+$ $[M + H]^+$ 466.24354, found 466.24285.

General procedures for synthesis of **broussonetine W (4)** and its analogs ***ent*-4**, **3-*epi*-4**, ***ent*-3-*epi*-4**, ***ent*-4a** and ***ent*-4b**, with broussonetine W (**4**) as an example.

Broussonetine W (**4**)

To a solution of **22** (200 mg, 0.41 mmol) in MeOH (10 mL) was added a 1 M solution of MeONa in MeOH (1 mL); the solution was stirred for 5 h at room temperature. Then concentrated HCl (about 1 mL) was slowly added dropwise to acidify reaction mixture; the solution was stirred for 8 h at room temperature. After the reaction was complete, the solution was concentrated *in vacuo*, and the residue was dissolved in MeOH and neutralized with aqueous ammonium solution, and the solution was concentrated *in vacuo*. The above procedure was repeated for three times to insure completeneutralization. The residue was purified by an acid resin column (DOWEX 50W × 8, 100-200 mesh), eluting with distilled water (100 mL) and then 6N NH_4OH (50 mL), affording compound **4** (121 mg, 0.37 mmol, 92%) as a light yellow oil.

Data for **4**: $[\alpha]_D^{20}$ +15.0 (*c* 0.4, MeOH); IR (KBr, cm^{-1}): 3358, 2926, 2855, 1655, 1455, 1381, 1047; ^{1}H NMR (500 MHz, Pyr) δ 6.91 (s, br, 3H), 6.57 (s, 1H), 4.70 (t, *J* = 6.2 Hz, 1H), 4.43 (t, *J* = 6.5 Hz, 1H), 4.35–4.17 (m, 2H), 3.94–3.82 (m, 1H), 3.69–3.55 (m, 1H), 2.38 (t, *J* = 6.6 Hz, 2H), 2.24 (t, *J* = 7.2 Hz, 2H), 2.19–2.10 (m, 2H), 2.10–2.00 (m, 1H), 1.90–1.72 (m, 3H), 1.72–1.59 (m, 1H), 1.59–1.48 (m, 1H), 1.46–1.35 (m, 2H), 1.35–1.13 (m, 6H). ^{13}C NMR (126 MHz, Pyr) δ 198.8, 145.2, 139.9, 83.5, 79.6, 65.2, 63.0, 62.8, 38.9, 34.8, 30.14, 30.09, 29.8 (2C), 29.1, 27.2, 26.2, 23.6. HRMS ESI: calcd for $C_{18}H_{31}NO_4H^+$ $[M + H]^+$ 326.23258, found 326.23227.

Data for ***ent*-4**: light yellow oil, 36 mg, 0.11 mmol, 78% yield, derived from the corresponding compound ***ent*-22** (70 mg, 0.14 mmol).

$[\alpha]_D^{20}$ -18.0 (*c* 0.5, MeOH); IR (KBr, cm^{-1}): 3324, 2927, 2856, 1670, 1561, 1410, 1124; ^{1}H NMR (300 MHz, Pyr) δ 6.54 (s, 1H), 6.04 (s, br, 4H), 4.69 (t, *J* = 6.4 Hz, 1H), 4.42 (t, *J* = 6.6 Hz, 1H), 4.33–4.16 (m, 2H), 3.92–3.83 (m, 1H), 3.65–3.53 (m, 1H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.26–2.15 (m, 2H), 2.15–2.07 (m, 2H), 2.07–1.96 (m, 1H), 1.89–1.67 (m, 3H), 1.67–1.43 (m, 2H), 1.42–1.09 (m, 8H). ^{13}C NMR (75 MHz, Pyr) δ 198.8, 145.2, 139.8, 83.2, 79.3, 65.0, 62.8, 62.6, 38.8, 34.5, 30.1, 30.0, 29.7, 28.99, 28.99, 27.1, 26.1, 23.5. HRMS ESI: calcd for $C_{18}H_{31}NO_4H^+$ $[M + H]^+$ 326.23258, found 326.23287.

Data for **3-*epi*-4**: light yellow oil, 59 mg, 0.18 mmol, 89% yield, derived from the corresponding compound **3-*epi*-22** (100 mg, 0.20 mmol).

$[\alpha]_D^{20}$ +24.0 (*c* 0.3, MeOH); IR (KBr, cm^{-1}): 3359, 2926, 2854, 1655, 1119; ^{1}H NMR (300 MHz, MeOD) δ 6.86 (t, *J* = 3.9 Hz, 1H), 4.18–4.12 (m, 1H), 3.94–3.72 (m, 3H), 3.56–3.44 (m, 1H), 3.29–3.18 (m, 1H), 2.46–2.35 (m, 2H), 2.21–2.09 (m, 2H), 2.04–1.90 (m, 2H), 1.83–1.22 (m, 14H). ^{13}C NMR (75 MHz, MeOD) δ 202.2, 148.2, 140.8, 78.5, 72.8, 62.6, 62.1, 60.9, 39.6, 33.8, 30.7, 30.7, 30.52, 30.48, 30.0, 27.9, 27.2, 24.4. HRMS ESI: calcd for $C_{18}H_{31}NO_4H^+$ $[M + H]^+$ 326.23258, found 326.23227.

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Data for ***ent*-3-*epi*-4**: light yellow oil, 48 mg, 0.15 mmol, 77% yield, derived from the corresponding compound ***ent*-3-*epi*-22**(95 mg, 0.19 mmol).

$[\alpha]^{20}_{D}$ -20.0 (*c* 0.1, MeOH); IR (KBr, cm^{-1}): 3358, 2925, 2854, 1659, 1123; ^{1}H NMR (300 MHz, MeOD) δ 6.86 (t, *J* = 4.1 Hz, 1H), 4.13 (t, *J* = 3.6 Hz, 1H), 3.93–3.72 (m, 3H), 3.49–3.39 (m, 1H), 3.24–3.13 (m, 1H), 2.47–2.35 (m, 2H), 2.22–2.13 (m, 2H), 2.04–1.93 (m, 2H), 1.81–1.23 (m, 14H). ^{13}C NMR (75 MHz, MeOD) δ 202.0, 148.0, 140.7, 78.5, 72.8, 62.3, 62.0, 61.0, 39.4, 34.0, 30.60, 30.58, 30.39, 30.36, 29.9, 27.8, 27.0, 24.3. HRMS ESI: calcd for $C_{18}H_{31}NO_4H^+$ $[M + H]^+$ 326.23258, found 326.23232.

Data for ***ent*-4a**: light yellow oil, 56 mg, 0.18 mmol, 86% yield, derived from the corresponding compound ***ent*-22a** (100 mg, 0.21 mmol).

$[\alpha]_D^{20}$ -17.1 (*c* 0.4, MeOH); IR (KBr, cm^{-1}): 3375, 2928, 2857, 1652, 1384, 1076; ^{1}H NMR (300 MHz, MeOD) δ 6.87 (t, *J* = 4.0 Hz, 1H), 3.94 (t, *J* = 5.9 Hz, 1H), 3.88–3.72 (m, 3H), 3.44–3.56 (m, 1H), 3.29–3.19 (m, 1H), 2.66–2.55 (m, 1H), 2.46–2.36 (m, 2H), 2.23–2.13(m, 1H), 2.05–1.94 (m, 1H), 1.94–1.78 (m, 2H), 1.77–1.57 (m, 2H), 1.56–1.24 (m, 9H). ^{13}C NMR (75 MHz, MeOD) δ 202.0, 148.2, 140.6, 81.0, 77.2, 65.2, 63.8, 60.3, 39.4, 32.6, 30.5, 30.2, 30.1, 29.7, 27.1, 27.0, 24.2.HRMS ESI: calcd for $C_{17}H_{29}NO_4H^+$ $[M + H]^+$ 312.21693, found 312.21665.

Data for ***ent*-4b**: light yellow oil, 47 mg, 0.16 mmol, 74% yield, derived from the corresponding compound ***ent*-22b** (100 mg, 0.21 mmol).

$[\alpha]_D^{20}$ -8.0 (*c* 0.3, MeOH); IR (KBr, cm^{-1}): 3363, 2927, 2857, 1662, 1383, 1131, 1076; ^{1}H NMR (300 MHz, MeOD) δ 6.87 (t, *J* = 3.9 Hz, 1H), 3.86 (t, *J* = 6.1 Hz, 1H), 3.83–3.64 (m, 3H), 3.25–3.14 (m, 1H), 3.12–3.01 (m 1H), 2.50–2.33 (m, 3H), 2.23–2.13 (m, 2H), 2.07–1.93 (m, 2H), 1.89–1.25 (m, 10H). ^{13}C NMR (75 MHz, MeOD) δ 202.0, 148.2, 140.6, 82.4, 78.5, 64.9, 63.3, 61.8, 39.4, 33.9, 30.5, 30.3, 29.7, 27.2, 27.0, 24.2. HRMS ESI: calcd for $C_{16}H_{27}NO_4H^+$ $[M + H]^+$ 298.20218, found 298.20101.

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