Cope–House Cyclization Strategy for the Synthesis of Pyrrolizidines: An Expedient Route to 5-*epi*-Hyacinthacine A_3 and 5-*epi*-Hyacinthacine A_5

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Abstract: An expedient Cope–House cyclization strategy is reported here for the synthesis of several polyhydroxy pyrrolizidine alkaloids starting from sugar-derived nitrones.

Key words: nitrone, Grignard reaction, Cope–House cyclization, hydrogenation, hyacinthacine

Natural products having polyhydroxylated pyrrolizidine ring as their structural subunit are quite abundant and many of them show remarkable inhibitory activity against different kinds of glycoprotein-processing glycosidases and hence have high potential as chemotherapeutic agents.[1] Among them, densely polyhydroxylated pyrrolizidines namely hyacinthacines (Figure 1) having one carbon branch both at C(3) and at C(5) show significant activity against viral infections, cancer and diabetes.[1b,2] In view of their promising biological activity coupled with interesting structures, considerable efforts have been directed towards the isolation of new pyrrolizidine-type alkaloids as well as the development of new stereocontrolled synthetic routes[3] for the synthesis of these alkaloids and their unnatural analogues.

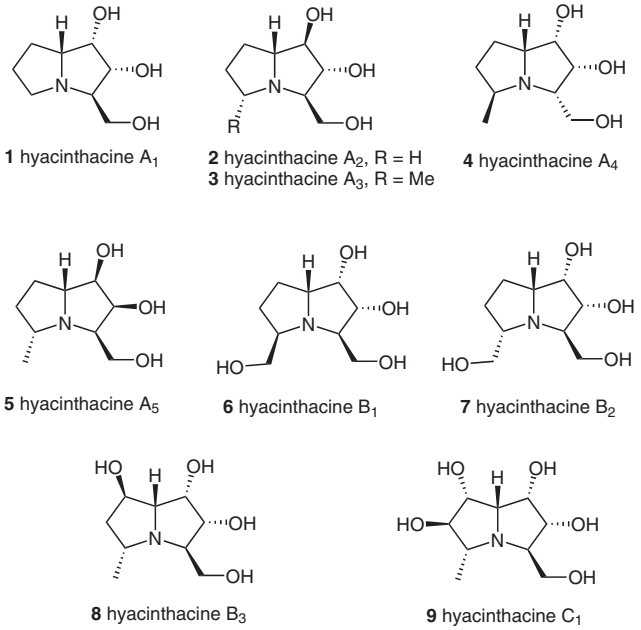

Figure 1 Hyacinthacine family

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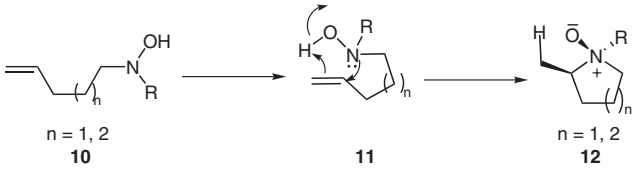
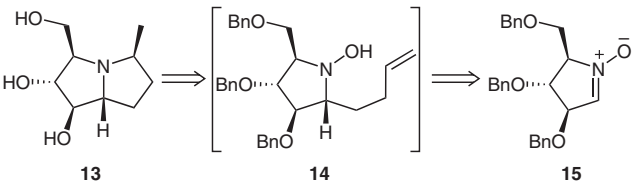
In continuation of our ongoing program directed towards the synthesis of natural products and natural-product-like molecules,[4] we developed interest in devising a simple and straightforward strategy to some of these alkaloids. While investigating novel approaches as compared with the aforementioned syntheses[5] for hyacinthacines, it occurred to us that Cope–House cyclization[6] could be an ideal reaction to construct the key five-membered ring in a single step. Cope–House cyclization, believed to be the reverse of Cope elimination (Scheme 1), was serendipitously observed by House and co-workers,[7] and well studied by Oppolzer[8] and Ciganek.[9] Though this reaction offers an excellent path to 2-substituted pyrrolidines, it has seldom been exploited in the total synthesis of natural products. In this communication, we present a short and efficient synthesis of 5-*epi*-hyacinthacine A_3 and 5-*epi*-hyacinthacine A_5 and also of a few closely related alkaloids using Cope–House cyclization[6] as the key step.



Scheme 1 Cope–House cyclization

As depicted in the Scheme 2, our retrosynthetic analysis revealed that the pyrrolizidine alkaloid **15** could be synthesized from **14** by Cope–House cyclization followed by hydrogenolysis. The unsaturated cyclic hydroxylamine **14** could then be easily furnished by the addition of 3-butenylmagnesium bromide to cyclic nitrone **15**, which could in turn be derived from L-xylose.



Scheme 2 Retrosynthesis

This strategy is more viable and attractive as several cyclic nitrones, as shown in Figure 2, could be easily made from various sugars using well-established procedures.[5a,10]

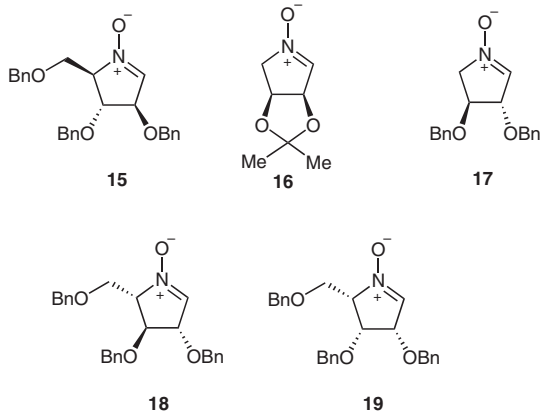
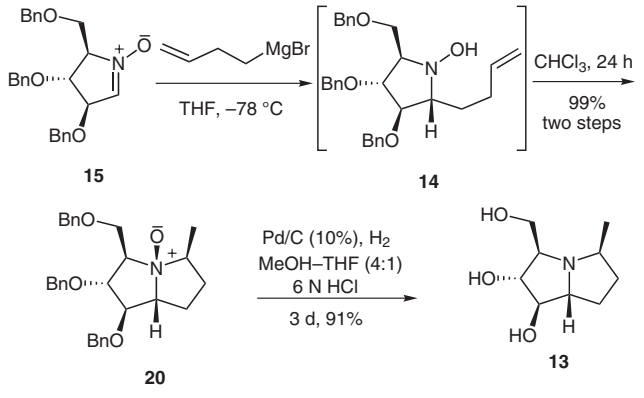


Figure 2 Nitrones

Our synthesis of hyacinthacine A_3 was started with the addition of 3-butenylmagnesium Grignard reagent to a previously cooled solution of nitrone **15** in THF at –78 °C to furnish the hydroxylamine **14** as a single diastereomer. The stereochemistry of the hydroxylamine **14** could be easily explained by the *anti* attack of the organometallic reagent with respect to the adjacent benzyl ether, as a result of steric and stereoelectronic effects.[11] This hydroxylamine was then subjected to Cope–House cyclization[12] without further purification by dissolving it in chloroform and stirring the solution for 24 hours. TLC analysis showed complete consumption of the starting material as well as the formation of a highly polar compound, which was later proved from the spectral data[13] to be the Cope–House cyclized product **20** (quantitative yield for two steps) as a single diastereomer (Scheme 3).



Scheme 3 Synthesis of 5-(+)-*epi*-hyacinthacine A_3 (**13**)

It is noteworthy to mention here that the corresponding Cope–House cyclization of acyclic unsaturated hydroxylamine often gives a mixture of diastereomers.[14] The stereochemistry of the Cope–House cyclized product **20** could be assigned on the assumption that it proceeds via a planar five-membered transition state, wherein the double bond occupies the pseudoequatorial position (Figure 3). Hence, in the product **20**, the *N*-oxide function and the newly formed alkyl (methyl) group were found to be *cis* with respect to each other.

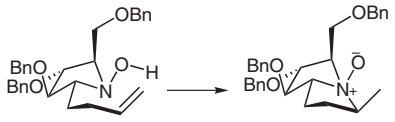


Figure 3

To complete the synthesis, the cyclized product **20** was subjected to global hydrogenolysis, which effectively removed the benzyl groups as well as cleaved the N–O bond in the presence of 6 N HCl, 10% Pd/C and a hydrogen atmosphere to provide the pyrrolizidine **13** in good yield (91%).[15,16]

The configuration of newly generated C-5 center was determined on the basis of extensive NOE experiment. The distinct NOE effects (see Figure 4) between C(5)H and C(3)H, and also between C(9)H and C(8)H indicated that the exocyclic methyl group at C-5 was *syn* to the hydroxymethyl group at C-3. Hence, the configuration at C-5 was determined to be *S* and we successfully accomplished the synthesis of 5-(+)-*epi*-hyacinthacine A_3.

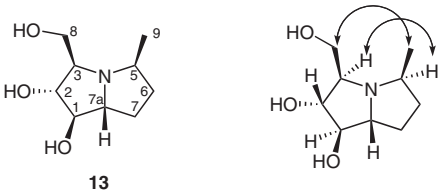
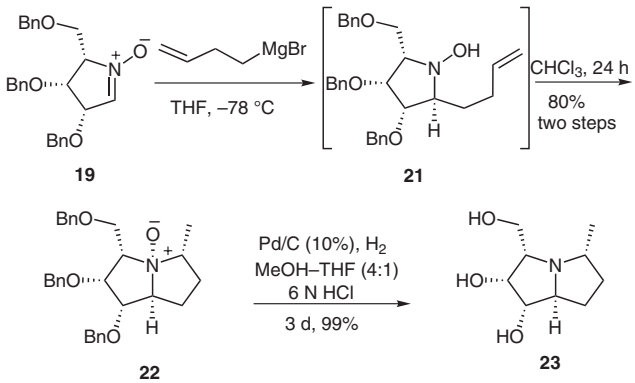


Figure 4 NOE interactions in **13**

After successfully synthesizing the 5-(+)-*epi*-hyacinthacine A_3 we wanted to extend this strategy to the synthesis of hyacinthacine A_5 starting from D-ribose-derived nitrone **19** where the stereochemistry of all protected hydroxy groups were *syn* to each other.

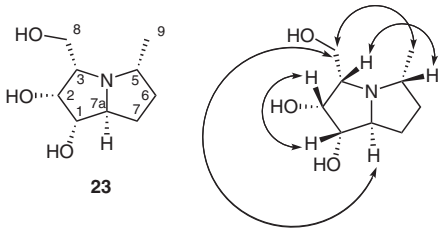


Scheme 4 Synthesis of 5-(–)-*epi*-hyacinthacine A_5 (**23**)

The nucleophilic addition of 3-butenylmagnesium bromide to nitrone **19** afforded again only one diastereomer **21**, which was subjected to the Cope–House cyclization in $CHCl_3$ at room temperature to provide **22** (80% yield over two steps). The *N*-oxide compound **22** was then hydrogenated under acidic conditions in the presence of 10% Pd/

C for three days to afford the pyrrolizidine **23** in 99% yield (Scheme 4).[15,16]

NOE experiments were again used to assign the stereochemistry at the newly generated center C(5) (Figure 5). The observed NOE effects between C(5)H and C(3)H, C(9)H and C(8)H, C(8)H and C(7a)H and C(1)H and C(2)H suggested that C(1)H, C(2)H, C(3)H, C(7a) and C(5)H, were on the same side of the molecule. Thus, the configuration was tentatively assigned as *R* at C(5) and utilizing this strategy, we completed the synthesis of 5-(–)-*epi*-hyacinthacine A_5.

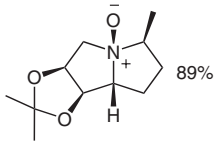
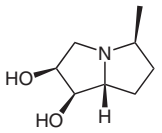
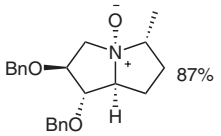
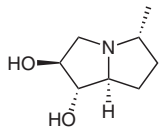
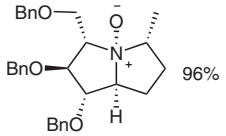
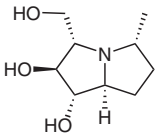


23

Figure 5 NOE interactions in **23**

In view of its simplicity and potential diversity in synthesizing several analogues of these alkaloids, this strategy was then extended to synthesize a range of unnatural pyrrolizidine alkaloids as shown in Table 1. The yields of Cope–House cyclization as well as the hydrogenation steps were consistently excellent.

Table 1 Synthesis of Unnatural Pyrrolizidine Alkaloids

Entry	Nitrones	Cope–House product	Pyrrolizidines
1	**16**	 89% **24**	 98% **25**
2	**17**	 87% **26**	 96% **27**
3	**18**	 96% **28**	 99% **29**

In summary, we have successfully accomplished the synthesis of 5-*epi*-hyacinthacine A_3 and 5-*epi*-hyacinthacine A_5 in three steps using Cope–House cyclization as the key step. This strategy is general and has very good potential to synthesize several simpler analogues of hyacinthacine alkaloids.

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References and Notes

(1) (a) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48*, 1091. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (c) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (d) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

(2) (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159. (b) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.

(3) (a) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875. (b) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887. (c) Yoda, H.; Katoh, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 7661. (d) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785. (e) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129. (f) Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Argyropoulou, E. C. *Tetrahedron Lett.* **2000**, *41*, 4819. (g) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276.

(4) (a) Kaliappan, K. P.; Ravikumar, V. *Synlett* **2007**, 977. (b) Kaliappan, K. P.; Gowrisankar, P. *Synlett* **2007**, 1537. (c) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417. (d) Kaliappan, K. P.; Ravikumar, V. *J. Org. Chem.* **2007**, *72*, 6116. (e) Kaliappan, K. P.; Subrahmanayam, A. V. *Org. Lett.* **2007**, *9*, 1121.

(5) (a) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (b) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Rodríguez, M.; Martos, A. *Tetrahedron* **2006**, *62*, 6006. (c) Zhou, L.; Chen, J.; Cao, X.-P. *Synthesis* **2007**, 1359.

(6) (a) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243. (b) Brainbridge, N. P.; Currie, A. C.; Cooper, N. J.; Muir, J. C.; Knight, D. W.; Walton, J. M. *Tetrahedron Lett.* **2007**, *48*, 7782.

(7) (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

(8) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

(9) (a) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. (b) Ciganek, E.; Read, J. M.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795. (c) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803.

(10) (a) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274. (b) Tamura, O.; Toyao, A.; Ishibashi, H. *Synlett* **2002**, 1344.

(11) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776.

(12) **General Procedure for the Cope–House Cyclization**: To a stirred solution of nitrone (1.2 mmol) in anhyd THF (20 mL), a previously prepared (4.8 mmol of 4-bromobutene and 7.2 mmol Mg in 15 mL anhyd THF) Grignard solution was slowly added under a nitrogen atmosphere at –78 °C and allowed to come to r.t. Then the reaction mixture was quenched by sat. NH_4Cl solution and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, washed with brine and filtered. The filtrate was evaporated under vacuum to afford the hydroxylamine. Without further purification, the hydroxylamine was dissolved in $CHCl_3$ (15 mL) and stirred for 24 h at r.t. to

provide the cyclized product which upon purification by silica gel column chromatography (MeOH in $CHCl_3$) afforded the product.

(13) Spectral data for selected compounds: Compound **20**: R_f 0.65 ($CHCl_3$–MeOH, 3:0.5); $[\alpha]_D^{25}$ 8.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.36 (m, 15 H), 4.42–4.61 (m, 6 H), 4.35 (t, J = 3.9 Hz, 1 H), 4.24 (dd, J = 5.8, 10.1 Hz, 1 H), 4.07–4.12 (m, 1 H), 3.86 (dd, J = 6.4, 10.1 Hz, 1 H), 3.76 (dd, J = 3.4, 6.4 Hz, 1 H), 3.66–3.73 (m, 1 H), 3.61 (dd, J = 5.8, 10.4 Hz, 1 H), 2.36–2.41 (m, 1 H), 2.03–2.09 (m, 2 H), 1.71–1.95 (m, 1 H), 1.32 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 136.8, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 86.7, 83.5, 83.4, 74.3, 73.0, 72.5, 72.0, 71.5, 65.9, 29.5, 26.2, 12.7. IR (neat): 3063, 3031, 2933, 2868, 1650, 1496, 1454, 1367, 1107, 1027, 740, 699 cm^{-1}. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_{30}H_{36}NO_4$: 474.2644; found: 474.2632. Compound **22**: R_f 0.63 ($CHCl_3$–MeOH, 3:0.5); $[\alpha]_D^{25}$ –13.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.36 (m, 15 H), 4.78–4.81 (m, 2 H), 4.52–4.69 (m, 5 H), 4.36 (t, J = 3.6 Hz, 1 H), 4.14 (dd, J = 5.8, 10.4 Hz, 1 H), 3.83–3.93 (m, 3 H), 3.43–3.45 (m, 1 H), 2.01–2.28 (m, 2 H), 1.96–1.99 (m, 1 H), 1.69–1.71 (m, 1 H), 1.31 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 137.6, 137.1, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 83.3, 82.1, 78.3, 77.5, 76.2, 73.8, 73.1, 72.3, 64.2, 32.2, 25.5, 11.7. IR (neat): 3064, 3031, 2936, 2873, 1650, 1497, 1454, 1368, 1153, 1073, 1028, 748, 698 cm^{-1}. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_{30}H_{36}NO_4$: 474.2644; found: 474.2641. Compound **24**: R_f 0.63 ($CHCl_3$–MeOH, 2:1); $[\alpha]_D^{25}$ –1.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (q, J = 6.4 Hz, 1 H), 4.44 (dd, J = 4.9, 6.7 Hz, 1 H), 4.15–4.19 (m, 1 H), 3.99 (dd, J = 6.7, 13.1 Hz, 1 H), 3.70 (dd, J = 6.1, 12.8 Hz, 1 H), 3.06–3.15 (m, 1 H), 2.51–2.60 (m, 1 H), 2.15–2.25 (m, 1 H), 2.05–2.13 (m, 1 H), 1.85–1.93 (m, 1 H), 1.60 (s, 3 H), 1.39 (d, J = 6.4 Hz, 3 H), 1.32 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.7, 85.1, 84.4, 76.3, 71.9, 68.7, 30.0, 27.0, 25.1, 24.9, 12.2. IR (neat): 2988, 2934, 1659, 1460, 1385, 1214, 1160, 1054, 992, 854, 758 cm^{-1}. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_{11}H_{20}NO_3$: 214.1443; found: 214.1435. Compound **26**: R_f 0.67 ($CHCl_3$–MeOH, 2:1); $[\alpha]_D^{25}$ –8.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.39 (m, 10 H), 4.44–4.58 (m, 4 H), 4.30–4.35 (m, 1 H), 4.27 (d, J = 5.8 Hz, 1 H), 3.94 (dd, J = 6.1, 13.4 Hz, 1 H), 3.82 (br d, J = 3.4 Hz, 1 H), 3.66–3.77 (m, 2 H), 2.37–2.45 (m, 1 H), 2.14–2.25 (m, 1 H), 1.98–2.03 (m, 1 H), 1.68–1.78 (m, 1 H), 1.37 (d, J = 6.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7, 136.4, 128.4, 128.3, 128.1, 127.8, 127.6, 127.5, 86.7, 86.3, 81.8, 72.9, 71.8, 71.4, 68.1, 30.7, 26.8, 11.9. IR (neat): 3060, 3027, 2925, 2851, 1660, 1495, 1454, 1368, 1113, 1026, 753, 700 cm^{-1}. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_{22}H_{28}NO_3$: 354.2069; found: 354.2081. Compound **28**: R_f 0.60 ($CHCl_3$–MeOH, 3:0.5); $[\alpha]_D^{25}$ –9.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.36 (m, 15 H), 4.42–4.61 (m, 6 H), 4.36 (t, J = 3.9 Hz, 1 H), 4.26 (dd, J = 5.5, 10.1 Hz, 1 H), 4.16–4.21 (m, 1 H), 3.87 (dd, J = 6.4, 10.1 Hz, 1 H), 3.76 (dd, J = 3.4, 6.4 Hz, 1 H), 3.66–3.72 (m, 1 H), 3.62 (dd, J = 5.8, 10.4 Hz, 1 H), 2.36–2.44 (m, 1 H), 2.00–2.15 (m, 2 H), 1.69–1.78 (m, 1 H), 1.33 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 136.9, 36.9, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.4, 86.9, 83.5, 83.4, 74.5, 73.2, 72.6, 72.1, 71.6, 66.0, 29.6, 26.3, 12.8. IR (neat): 3060, 3030, 2928, 2867, 1655, 1496, 1454, 1367, 1105, 1028, 740, 698 cm^{-1}. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_{30}H_{36}NO_4$: 474.2644; found: 474.2658.

(14) (a) Palmer, A. M.; Jäger, V. *Eur. J. Org. Chem.* **2001**, 2547. (b) Palmer, A. M.; Jäger, V. *Synlett* **2000**, 1405. (c) Palmer, A. M.; Jäger, V. *Eur. J. Org. Chem.* **2001**, 1293.

(15) **General Procedure for Hydrogenation**: To a solution of *N*-oxide (0.65 mmol) in a mixture of MeOH and THF (4:1, 20 mL) was added 10% Pd/C (111 mg). After the reaction flask was purged with H_2, 10 drops of 6 N HCl were added and the reaction mixture was stirred for 3 d at r.t. under a H_2 atmosphere. The mixture was then filtered through a pad of Celite, and the filtrate was concentrated under vacuum. The residue was dissolved in minimum amount of H_2O and stirred with IRA450 resin (OH^- form) until pH 11. After filtration, the filtrate was concentrated in vacuo to give the pure pyrrolizidine.

(16) Spectral data for selected compounds: Compound **13**: R_f 0.46 ($CHCl_3$–MeOH, 2:1); $[\alpha]_D^{25}$ 24.8 (c = 1.00, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 3.89–3.94 (m, 2 H), 3.81 (dd, J = 4.4, 12.2 Hz, 1 H), 3.72 (dd, J = 6.3, 12.6 Hz, 1 H), 3.57–3.64 (m, 1 H), 3.36–3.42 (m, 1 H), 3.11–3.15 (m, 1 H), 2.10–2.27 (m, 2 H), 1.83–1.95 (m, 1 H), 1.55–1.68 (m, 1 H), 1.20 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 79.2, 77.1, 70.0, 68.5, 65.1, 60.0, 32.5, 27.9, 17.4. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_9H_{18}NO_3$: 188.1287; found: 188.1277. Compound **23**: R_f 0.44 ($CHCl_3$–MeOH, 2:1); $[\alpha]_D^{25}$ –8.0 (c = 1.00, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 4.34 (t, J = 3.7 Hz, 1 H), 4.08 (dd, J = 3.7, 8.4 Hz, 1 H), 3.82–3.98 (m, 3 H), 3.40–3.66 (m, 2 H), 2.11–3.31 (m, 2 H), 1.83–1.94 (m, 1 H), 1.66–1.78 (m, 1 H), 1.24 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 75.6, 72.5, 69.5, 68.7, 65.2, 5.3, 31.8, 26.8, 17.2. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_9H_{18}NO_3$: 188.1287; found: 188.1287. Compound **25**: R_f 0.42 ($CHCl_3$–MeOH, 2:1); $[\alpha]_D^{25}$ 32.5 (c = 1.00, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 4.43 (d, J = 3.4 Hz, 1 H), 4.11 (br m, 1 H), 3.90–3.92 (m, 1 H), 3.18–3.43 (m, 3 H), 2.15–2.28 (m, 2 H), 1.64–1.86 (m, 2 H), 1.27 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (75 MHz, D_2O): δ = 77.7, 73.6, 72.1, 68.0, 57.8, 35.5, 29.9, 18.3. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_8H_{16}NO_2$: 158.1181; found: 158.1186. Compound **27**: R_f 0.46 ($CHCl_3$–MeOH, 2:1); $[\alpha]_D^{25}$ –33.5 (c = 1.00, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.34 (dd, J = 3.1, 7.3 Hz, 1 H), 4.17 (t, J = 2.7 Hz, 1 H), 3.89–3.94 (m, 1 H), 3.52–3.61 (m, 2 H), 3.22 (dd, J = 2.7, 12.9 Hz, 1 H), 2.56–2.33 (m, 1 H), 2.17–2.23 (m, 1 H), 1.96–2.06 (m, 1 H), 1.59–1.69 (m, 1 H), 1.33 (d, J = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 81.2, 79.6, 76.2, 69.8, 58.5, 36.2, 31.1, 18.6. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_8H_{16}NO_2$: 158.1181; found: 158.1176. Compound **29**: R_f 0.59 ($CHCl_3$–MeOH, 2:1); $[\alpha]_D^{25}$ –22.0 (c = 1.00, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 3.98–4.04 (m, 2 H), 3.89 (dd, J = 3.9, 12.4 Hz, 1 H), 3.78–3.85 (m, 2 H), 3.36–3.64 (m, 1 H), 3.33–3.34 (m, 1 H), 2.21–2.35 (m, 2 H), 1.97–2.04 (m, 1 H), 1.67–1.87 (m, 1 H), 1.31 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 81.2, 78.9, 73.1, 72.3, 68.9, 61.2, 35.1, 30.5, 19.1. HRMS (ESI–TOF): m/z [M + 1]$^+$ calcd for $C_9H_{18}NO_3$: 188.1296; found: 188.1287.