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Total synthesis of the proposed structure for pochonicine and determination of its absolute configuration

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ABSTRACT

Pochonicine is a polyhydroxylated pyrrolizidine alkaloid with a powerful inhibitory activity against β-*N*-acetylglucosaminidases. The proposed structure for pochonicine and the three diastereomers concerning its C-1 and/or C-3 positions were synthesized from *N*-acetyl-D-glucosamine through construction of the pyrrolizidine skeleton by two intramolecular amino cyclizations as key steps. This synthetic study not only revised the structure of the natural product to the corresponding 1,3-di-*epi*-form but also determined the absolute configuration as 1*R*, 3*S*, 5*R*, 6*R*, 7*S*, 7a*R*.

Pochonicine was isolated from a solid fermentation culture of the fungal strain *Pochonia suchlasporia* var. *suchlasporia* TAMA 87 by Usuki et al.[1] The structure was shown to be a new polyhydroxylated pyrrolizidine alkaloid **1** with an acetamide group by using the NMR and MS technique (Fig. 1). Its relative stereochemistry was deduced by NOE correlations and $^{3}J_{H,H}$ coupling constants while the absolute configuration has not been determined. This natural product exhibited a potent inhibitory activity against β-*N*-acetylglucosaminidases (GlcNAcases) of various organisms including insects, fungi, mammals, and a plant but no inhibition against β-glucosidase of almond, β-glucosidase of yeast, or chitinase of *Bacillus* sp. Its inhibition potency was comparable to that of a potent GlcNAcase inhibitor, nagstatin.[2] Recent studies have revealed that GlcNAcases may be associated with several diseases such as diabetes mellitus, leukemia, and cancer.[3] Therefore, GlcNAcase inhibitors are potentially useful tools not only for biochemical studies but also in the design of therapeutic drugs. In connection with our synthetic studies on enzyme inhibitors,[4] described herein is the total synthesis of **1** and its three types of diastereomers, which dictates revision of the formula to *ent*-**4**.

Since the absolute configuration of pochonicine was unknown, the structure **1** shown in Figure 1 of the original paper[1] was tentatively chosen as the synthetic target. The retrosynthetic plan of **1** is shown in Scheme 1. Cleavage of the C–N bond (position a) in **1** leads it back to **5**. This would be prepared from **6** via OsO_4 oxidation and selective *O*-protection. The allyl unit in **6** might be introduced by the α-chelation controlled addition of an allylic metal to **7**. The pyrrolidine ring could be constructed by an intramolecular cyclization (position b) of an amine obtainable from **8**. We therefore selected a *N*-acetyl-D-glucosamine derivative **9**[5] as the starting material. This route also enabled us to prepare three diastereomers concerning the C-1 and/or C-3 positions[6] of **1**.

Synthesis of **1** began with the configurational inversion[4a,7] of **9** at the 3-position (Scheme 2). The D-allosamine derivative **10** thus obtained was hydrolyzed to give **11** after benzyloxycarbonylation. Regioselective cleavage of the benzylidene group in **11** was accomplished by treating it with $Me_3N{\cdot}BH_3$–$AlCl_3$ in the presence of MS4A in tetrahydrofuran (THF)[8] to provide the corresponding 6-*O*-benzyl derivative in high yield.[9] The 1,2-diol moiety was protected by an acetonide to afford **12**. Treatment of **12** with *N*-bromosuccinimide and subsequent reduction with sodium borohydride gave an acyclic diol **13**. This compound was transformed into the 5-*O*-mesylate **8** in 2 steps. Removal of the *N*-protecting group by hydrogenation was accompanied by the intramolecular cyclization to give a pyrrolidine derivative, which was isolated as the corresponding *tert*-butylcarbamate **14**. After debenzylation of **14**, the resulting alcohol was oxidized by Swern's method to afford an aldehyde **7**. Introduction of the allyl group into **7** was performed by the action of allylmagnesium chloride in the presence of $ZnCl_2$ in dichloromethane–THF at −78 °C to afford a 77:23 of mixture of a *threo* alcohol **6** and an *erythro* isomer **15** in 87% yield.[10,11]

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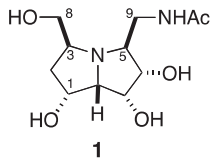
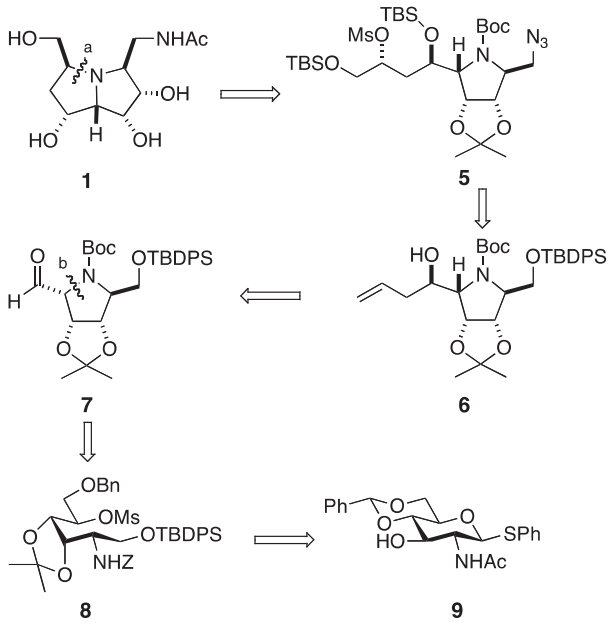
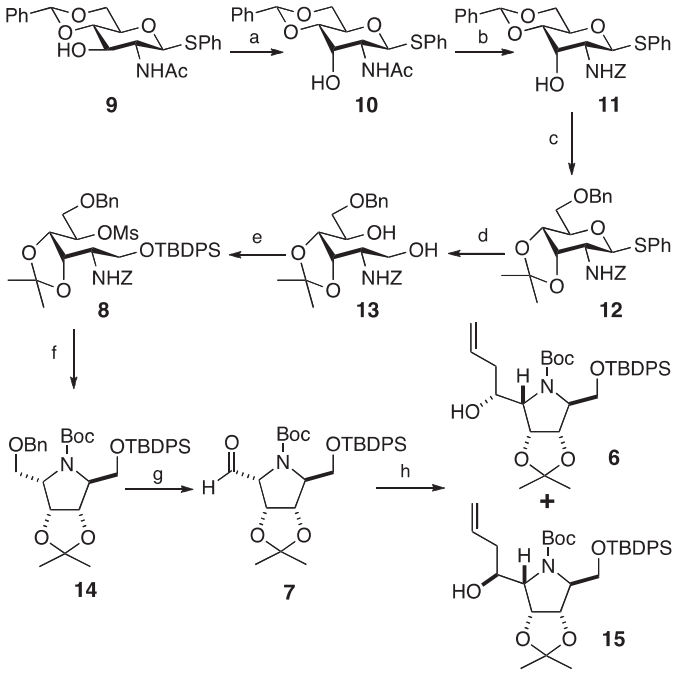


Figure 1. Proposed structure for pochonicine.



Scheme 1. Synthetic plan of the proposed structure **1** for pochonicine.

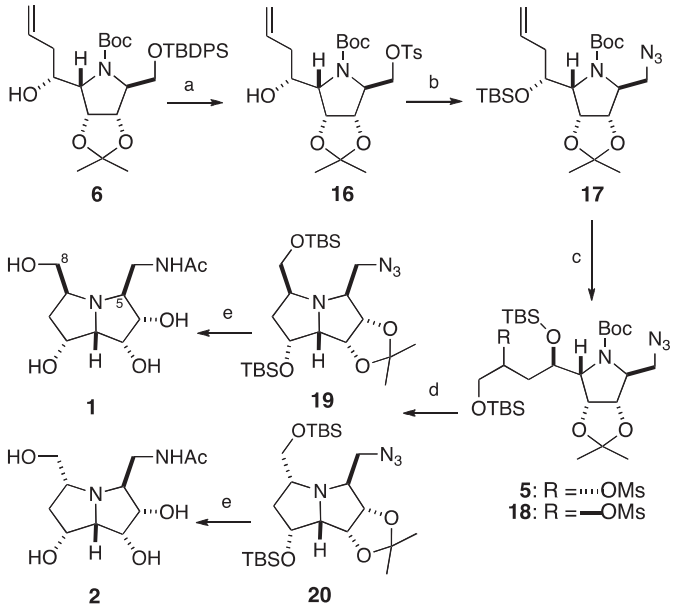


Scheme 2. Reagents and conditions: (a) (i) MsCl, pyridine, 0 °C–>rt, 94%; (ii) NaOAc, 2-methoxyethanol–water, 120 °C, 95%; (b) (i) NaOH, 2-methoxyethanol–water, 120 °C, 74%; (ii) ZCl, Na_2CO_3, CH_2Cl_2–MeOH–water, 0 °C–>rt, 95%; (c) (i) $Me_3N{\cdot}BH_3$, $AlCl_3$, MS4A, THF, rt, 89%; (ii) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, 90%; (d) (i) NBS, THF–water, 0 °C; (ii) $NaBH_4$, EtOH, 0 °C, 78% in 2 steps; (e) (i) TBDPSCl, imidazole, DMF, 0 °C–>rt; (ii) MsCl, DMAP, pyridine, 0 °C–>rt, 96% in 2 steps; (f) (i) 10% Pd/C, H_2, EtOH, rt; (ii) Boc_2O, DIPEA, DMF, rt, 63% in 2 steps; (g) (i) 20% $Pd(OH)_2$/C, H_2, EtOH, 98%; (ii) Swern oxid., quant.; (h) allylMgCl, $ZnCl_2$, CH_2Cl_2–THF, −78 °C, 87% (**6**/**15** = 77/23).

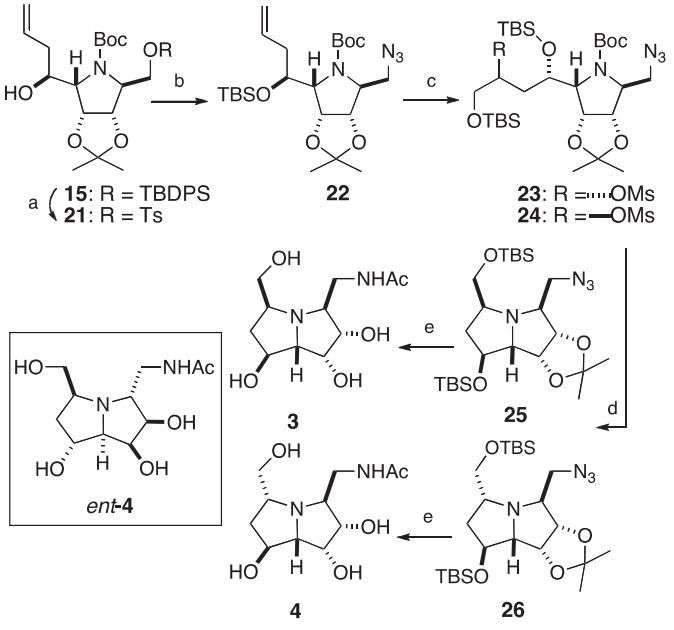
These isomers could be separated by chromatography on silica gel. The stereochemistry was determined by the modified Mosher method[12] of the corresponding MTPA esters of **6**.[13]

As we secured the key intermediate **6**, our attention next turned to the construction of the pyrrolizidine ring system (Scheme 3). Prior to the cyclization, the second nitrogen functional group was introduced through the nucleophilic displacement reaction of a primary tosylate **16** with sodium azide. Since diastereoselective dihydroxylation of **17** with AD-mix[15] could not be achieved, the olefin was oxidized with OsO_4-*N*-methylmorpholine *N*-oxide to provide a ca. 1:1 mixture of diols, which were transformed into the corresponding mesylates **5** and **18**. Each isomer was separated by chromatography on silica gel, and their stereochemistry was determined by the detailed NMR analysis of the following pyrrolizidine derivatives **19** and **20**.[16] Formation of the second ring system was effected by the treatment of **5** (the less polar isomer) with TMSOTf-2,6-lutidine[17] followed by heating in the presence of triethylamine, affording **19** in high yield. Finally, installation of the acetamide group and deprotection with HCl yielded **1**[10] as a hydrochloride salt. ^1H, and ^{13}C NMR data of **1**·HCl or **1** were inconsistent with those of the natural product. Furthermore, the reported NOEs between H-5/H-8 and H-5/H-8′ were not observed. These results suggest that the structure of natural pochonicine should be revised. With the expectation of the NOE reported, we prepared the 3-epimer **2** from the more polar isomer **18**. However, ^1H, and ^{13}C NMR data of **2**[10] did not match those of the natural product.

In re-examining the NMR data reported, we found that the signals derived from H-1 and 3 of the natural product were observed at the low-filed rather than those of our synthetic samples, and investigated the NMR data of the related pyrrolizidine alkaloids. The papers reported by Kato et al.[18] and Yoda and co-workers[19] suggested that the chemical shift of such protons in the pyrrolizidine alkaloids was affected by the stereochemistry of C-1 as well as C-3. These results prompted us to compare the NMR data of the



Scheme 3. Reagents and conditions: (a) (i) TBAF, AcOH, THF, rt, 92%; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C–>rt, 97%; (b) (i) NaN_3, DMF, 60 °C, 72%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 91%; (c) (i) OsO_4, NMO, acetone–water, rt, 98%; (ii) TBSCl, imidazole, DMF, rt; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C–>rt, 45% for **5** and 35% for **18** (2 steps); (d) (i) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C–>rt; (ii) Et_3N, THF, rt–>70 °C, 84% from **5** for **19** and 85% from **18** for **20** (2 steps); (e) (i) Ph_3P, THF–water, 60 °C; (ii) Ac_2O, pyridine, rt; (iii) HCl–MeOH, CH_2Cl_2, rt, 79% for **1** and 67% for **2** (3 steps).



Scheme 4. Reagents and conditions: (a) (i) TBAF, AcOH, THF, rt, 84%; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C–>rt, 92%; (b) (i) NaN_3, DMF, 60 °C, 75%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.; (c) (i) OsO_4, NMO, acetone–water, rt, 92% in 2 steps; (ii) TBSCl, imidazole, DMF, rt, 90%; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C–>rt, 38% for **23** and 36% for **24** (2 steps); (d) (i) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C–>rt; (ii) Et_3N, THF, 70 °C, 82% from **23** for **25** and 87% from **24** for **26** (2 steps); (e) (i) 10% Pd/C, H_2, EtOAc, rt; (ii) Ac_2O, pyridine, rt; (iii) HCl–MeOH, CH_2Cl_2, rt, 50% for **3** and 66% for **4** (3 steps).

Table 1
Inhibition of **4** against a couple of GlcNAcases

Origin of enzymes	IC_{50} (nM)		
	4	Pochonicine[a]	PUGNAc[b]
Spodoptera litura[c]	>14200	5.96	714
Jack bean	3130	0.288	678

[a] These data were referred from the previous paper.[1]
[b] *O*-(2-Acetamido-2-deoxy-D-glucopyranosylidene)amino *N*-phenylcarbamate (PUGNAc)[24] was used as a positive control.
[c] A crude enzyme was employed for the assay.

1-epimers of **1** and **2** with that of the natural product. The epimers **3** and **4** were synthesized via **25** and **26** from alcohol **15** according to the method described for the preparation of **1** and **2** (Scheme 4).[16] Comparing the data of both compounds with those of the natural product, we found that the NMR data of **4** were consistent with those of natural pochonicine.[20] However, the sign of the specific rotation value of **4**·HCl was opposite to that of natural pochonicine·HCl.[21] Furthermore, we examined the inhibitory activity of **4** against a couple of GlcNAcases.[22] As shown in Table 1, the inhibitory potency of **4** against GlcNAcases from *Spodoptera litura*, and Jack bean was very weak compared to that of the natural product. Based on these results, we concluded that **4** was an enantiomer of the natural product, and that the structure of pochonicine should be revised to be *ent*-**4**.

In conclusion, the structural revision of pochonicine and determination of the absolute configuration were achieved by total synthesis of the proposed structure for pochonicine and its three types of diastereomers concerning the C-1 and/or C-3 positions.

Acknowledgement

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Supplementary data

Supplementary data (^{1}H NMR data for MTPA esters of **6**, ^{1}H- and ^{13}C NMR spectra of synthetic **4** and natural pochonicine) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.015.

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6. The carbon-numbering system was conveniently according to the original Letter.[1]
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9. The regioisomer was not detected by TLC analysis.
10. *Spectral data of representative compounds:*
1: $[\alpha]_D^{24}$ −13.6 (*c* = 0.34, MeOH); ^{1}H NMR (600 MHz, CD_3OD): δ 4.44 (1H, ddd, *J* = 5.0, 5.0, 3.3 Hz, H-1), 4.27 (1H, dd, *J* = 5.5, 5.0 Hz, H-7), 3.77 (1H, dd, *J* = 6.5, 5.0 Hz, H-6), 3.53 (1H, dd, *J* = 5.5, 5.0 Hz, H-7a), 3.50 (1H, dd, *J* = 11.0, 4.2 Hz, H-8), 3.40 (1H, dd, *J* = 11.0, 6.0 Hz, H-8′), 3.31 (2H, m, H-9 and 9′), 3.27 (1H, dddd, *J* = 8.7, 6.9, 6.0, 4.2 Hz, H-3), 3.02 (1H, ddd, *J* = 6.5, 5.1, 5.1 Hz, H-5), 2.02 (1H, ddd, *J* = 12.9, 6.9, 3.3 Hz, H-2), 1.95 (3H, s, *Me*CO), 1.75 (1H, ddd, *J* = 12.9, 8.7, 5.0 Hz, H-2′); ^{13}C NMR (150 MHz, CD_3OD): δ 173.5 (CO), 76.8 (C-6), 74.4 (C-1), 74.1 (C-7), 71.4 (C-5), 70.7 (C-7a), 68.4 (C-3), 66.6 (C-8), 43.1 (C-9), 40.0 (C-2), 22.6 (Me); HRMS (ESI$^+$) calcd for $C_{11}H_{21}N_2O_5$ $[M+H]^+$ 261.1450, found: 261.1458.
2: $[\alpha]_D^{25}$ −16.9 (*c* = 0.36, MeOH); ^{1}H NMR (600 MHz, CD_3OD): δ 4.42 (1H, ddd, *J* = 6.0, 5.5, 4.1 Hz, H-1), 4.19 (1H, dd, *J* = 4.2, 4.1 Hz, H-7), 3.98 (1H, dd, *J* = 11.5, 7.3 Hz, H-8), 3.79 (1H, dd, *J* = 7.8, 4.2 Hz, H-6), 3.78 (1H, dd, *J* = 11.5, 3.7 Hz, H-8′), 3.51 (1H, m, H-5), 3.49 (1H, dd, *J* = 6.0, 4.1 Hz, H-7a), 3.45 (1H, dd, *J* = 13.3, 5.1 Hz, H-9), 3.39 (1H, m, H-3), 3.28 (1H, dd, *J* = 13.3, 5.0 Hz, H-9′), 2.12 (1H, ddd, *J* = 12.8, 7.3, 6.0 Hz, H-2), 1.87 (1H, ddd, *J* = 12.8, 5.5, 4.1 Hz, H-2′), 1.95 (3H, s, *Me*CO); ^{13}C NMR (150 MHz, CD_3OD): δ 173.6 (CO), 78.8 (C-6), 74.0 (C-7), 73.8 (C-1), 68.9 (C-7a), 63.4 (C-8), 62.4 (C-3), 61.6 (C-5), 43.7 (C-9), 40.8 (C-2), 22.6 (Me); HRMS (ESI$^+$) calcd for $C_{11}H_{21}N_2O_5$ $[M+H]^+$ 261.1450, found: 261.1455.
3·*HCl*: $[\alpha]_D^{26}$ −10.4 (*c* = 0.53, MeOH); ^{1}H NMR (600 MHz, CD_3OD): δ 4.74 (1H, ddd, *J* = 6.0, 4.4, 2.5 Hz, H-1), 4.25 (1H, dd, *J* = 3.6, 3.6 Hz, H-7), 4.06 (1H, dd, *J* = 9.5, 3.6 Hz, H-6), 4.03 (1H, dd, *J* = 3.6, 2.5 Hz, H-7a), 3.95 (1H, dd, *J* = 15.1, 3.3 Hz, H-9), 3.86 (3H, m, H-3, 8, and 8′), 3.56 (1H, ddd, *J* = 9.5, 6.0, 3.3 Hz, H-5), 3.49 (1H, br dd, *J* = 15.1, 6.0 Hz, H-9′), 2.52 (1H, ddd, *J* = 13.8, 7.4, 6.0 Hz, H-2), 2.02 (3H, s, *Me*CO), 1.90 (1H, ddd, *J* = 13.8, 6.0, 4.4 Hz, H-2′); ^{13}C NMR (150 MHz, CD_3OD): δ 175.9 (CO), 78.1 (C-7a), 75.0 (C-6), 74.1 (C-3), 70.9 (C-7), 70.7 (C-5), 70.2 (C-1), 61.8 (C-8), 39.6 (C-9), 38.3 (C-2), 22.3 (Me); HRMS (ESI$^+$) calcd for $C_{11}H_{21}N_2O_5$ $[M+H]^+$ 261.1450, found: 261.1454.
4: $[\alpha]_D^{26}$ +3.0 (*c* = 1.74, MeOH) [21] [lit. [1]: $[\alpha]_D^{17}$ +9.2 (*c* = 0.89, MeOH)]; ^{1}H NMR (600 MHz, CD_3OD): δ 4.55 (1H, ddd, *J* = 6.8, 6.4, 5.0 Hz, H-1), 3.94 (1H, dd, *J* = 3.7, 3.7 Hz, H-7), 3.80 (1H, dd, *J* = 8.2, 3.7 Hz, H-6), 3.77 (1H, dd, *J* = 11.9, 3.6 Hz, H-8), 3.61 (1H, dd, *J* = 11.9, 5.1 Hz, H-8′), 3.43 (1H, m), 3.38 (1H, dd, *J* = 13.3, 5.5 Hz, H-9), 3.33 (1H, dd, *J* = 5.0, 3.7 Hz, H-7a), 3.28 (1H, dd, *J* = 13.3, 5.0 Hz, H-9′), 3.19 (1H, ddd, *J* = 8.2, 5.5, 5.0 Hz, H-5), 2.09 (1H, ddd, *J* = 12.4, 6.4, 4.6 Hz, H-2), 1.95 (1H, ddd, *J* = 12.4, 7.4, 6.8 Hz, H-2′), 1.94 (3H, s, *Me*CO); ^{13}C NMR (150 MHz, CD_3OD): δ 173.6 (CO), 79.0 (C-6), 75.2 (C-7a), 72.2 (C-7), 69.1 (C-1), 62.9 (C-8), 62.2 (C-3), 60.7 (C-5), 43.4 (C-9), 40.4 (C-2), 22.6 (Me); HRMS (ESI$^+$) calcd for $C_{11}H_{21}N_2O_5$ $[M+H]^+$ 261.1450, found: 261.1447.
4·*HCl*: $[\alpha]_D^{26}$ −30.6 (*c* = 0.82, MeOH) [natural pochonicine·HCl[23]: $[\alpha]_D^{27}$ +33.3 (*c* = 0.09, MeOH)]; ^{1}H NMR (600 MHz, CD_3OD): δ 4.60 (1H, br d, *J* = 4.1 Hz, H-1), 4.22 (1H, dd, *J* = 4.6, 4.1 Hz, H-7), 4.14 (1H, dddd, *J* = 12.8, 8.2, 5.5, 2.7 Hz, H-3), 4.06 (1H, br d, *J* = 4.6 Hz, H-7a), 4.06 (1H, dd, *J* = 13.3, 2.7 Hz, H-8), 4.03 (1H, dd, *J* = 15.1, 3.7 Hz, H-9), 4.01 (1H, dd, *J* = 9.7, 4.1 Hz, H-6), 3.93 (1H, dd, *J* = 13.3, 8.2 Hz, H-8′), 3.91 (1H, ddd, *J* = 9.7, 4.1, 3.7 Hz, H-5), 3.53 (1H, dd, *J* = 15.1, 4.1 Hz, H-9′), 2.25 (1H, ddd, *J* = 12.8, 12.8, 4.1 Hz, H-2), 2.03 (3H, s, *Me*CO), 1.96 (1H, br dd, *J* = 12.8, 5.5 Hz, H-2′); ^{13}C NMR (150 MHz, CD_3OD): δ 176.6 (CO), 79.3 (C-7a), 74.3 (C-6), 70.0 (C-7), 69.8 (C-1), 67.8 (C-3), 63.5 (C-5), 59.1 (C-8), 39.4 (C-9), 37.5 (C-2), 22.2 (Me).
6: $[\alpha]_D^{26}$ +19.0 (*c* = 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65–7.60 (4H, m), 7.46–7.36 (6H, m), 6.41 (1H, s), 6.07 (1H, m), 5.14 (1H, br d, *J* = 17.1 Hz), 5.07 (1H, br d, *J* = 10.2 Hz), 4.70 (2H, br s), 4.17 (1H, br s), 4.03 (1H, br s), 3.79 (1H, br dd, *J* = 7.9, 2.5 Hz), 3.75–3.69 (2H, m), 2.66 (br d, *J* = 14.2 Hz), 2.42 (1H, m), 1.44

(3H, s), 1.33 (12H, br s), 1.04 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 135.7, 135.6, 135.4, 132.7, 132.6, 129.92, 129.87, 127.90, 127.86, 116.5, 111.3, 80.8, 80.6, 79.6, 69.7, 68.3, 66.9, 64.1, 38.1, 28.3, 26.9, 26.8, 25.2, 19.1; HRMS (ESI$^+$) calcd for $C_{33}H_{47}NO_6Si$ [M+Na]$^+$ 604.3070, found: 604.3069.

15: $[\alpha]_D^{26}$ +57.4 (c = 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63–7.57 (4H, m), 7.47–7.37 (6H, m), 5.99 (1H, m), 5.09 (1H, br d, J = 17.3 Hz), 5.04 (1H, br d, J = 10.3 Hz), 4.90 (1H, br d, J = 10.3 Hz), 4.88 (1H, t, J = 6.6 Hz), 4.71 (1H, br d, J = 6.6 HZ), 4.20 (1H, br d, J = 6.4 Hz), 4.12 (1H, br t, J = 10.3 Hz), 4.00 (1H, br s), 3.90 (1H, br d, J = 10.3 Hz), 3.67 (1H, dd, J = 10.5, 2.0 Hz), 2.50 (1H, m), 2.15 (1H, m), 1.52 (3H, s), 1.34 (12H, br s), 1.05 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 136.8, 135.6, 135.5, 132.6, 132.4, 130.0, 129.9, 127.93, 127.89, 115.7, 111.1, 81.1, 80.7, 80.1, 70.1, 68.2, 64.8, 64.5, 38.0, 28.3, 26.9, 25.4, 23.7, 19.1; HRMS (ESI$^+$) calcd for $C_{33}H_{47}NO_6Si$ [M+Na]$^+$ 604.3070, found: 604.3069.

11. The ratio was determined by ^{1}H NMR analyses. The results of allylation under other conditions are as follows; (1) allylMgBr, Et_2O, −78 °C, 84% (**6**/**15** = 62/38); (2) allyltributylstannane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C–>rt, 14% (**6**/**15** = 71/29); (3) allylbromide, indium, [14] THF, −78 °C–>rt, 37% (**6**/**15** = 54/46).
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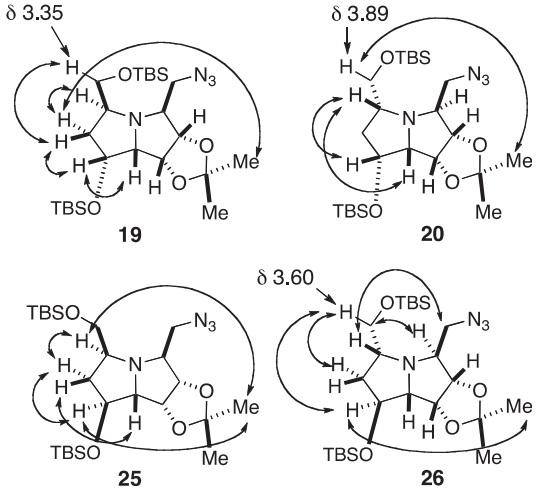
16. Selected NOEs (600 MHz, $CDCl_3$) are shown below.



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20. Since pochonicine is a highly polar basic compound, the chemical shifts of its protons in the ^{1}H NMR spectra readily change in the presence of a trace amount of a base or acid. Therefore, it was very difficult to match the NMR data of **4** or even natural pochonicine with those of the original Letter. [1] For identification by NMR analyses, HPLC treatment of **4** under the same conditions that were used at the final stage of the purification of the authentic sample was needed. Otherwise **4** did not afford the same NMR spectra as those of the natural sample.
21. The specific rotation value of the free amine was small and its data were found to change around ±0 by the pH (see above). On the other hand, the corresponding hydrochloride salt[23] afforded the relatively large and reliable data.
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