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# Synthesis of the Proposed Structure of Pentahydroxylated Pyrrolizidine Hyacinthacine $C_5$ and Its $C_6$,$C_7$ Epimer

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The synthesis of two pentahydroxylated pyrrolizidines, hyacinthacine $C_5$ (**1**) and 6,7-di-*epi*-hyacinthacine $C_5$ (**12**), from an orthogonally protected pyrrolidine of 2,5-dideoxy-2,5-imino-D-mannitol configuration (i.e., **7**) is described. The analytical and spectroscopic data of synthetic **1** present some differences with those of natural hyacinthacine $C_5$ that exceed the previously observed variations in similar compounds. On this respect, additional studies on chemical derivatives of synthetic **1** support our initially proposed structure and establish the absolute configuration of putative (+)-hyacinthacine $C_5$ as that shown in **1**. These studies lead us to conclude that the natural compound originally labeled as (+)-hyacinthacine $C_5$ might be a different isomer.

## Introduction

Hyacinthacine $C_5$ (**1**) was first isolated by Kato et al.[1] in 2007 from the bulbs of *Scilla Socialis* and has shown moderate inhibitory activity against rat intestinal maltase, *Caldocellum saccharolyticum* β-glucosidase, and *Aspergillus niger* amiloglucosidase with an $IC_{50}$ value of 77, 48, and 57 μM, respectively. This natural compound belongs to one of the five structural classes utilized to classify iminosugars:[2] polyhydroxylated pyrrolizidines. Hyacinthacines C, a subclass of this group, present the characteristic five hydroxy groups along their bicyclic ring, one of them being a hydroxymethyl group adjacent to the ring nitrogen at C-3 (Figure 1). Not many hyacinthacines C have been described to date,[1,3] and only six compounds presenting a substitution pattern similar to that of hyacinthacine $C_5$ (**1**) and hyacinthacine $C_1$ (**2**) have been published, including a very recent synthesis of proposed **1**.[1,3a,3b,3d–3f] Recently, we described the synthesis of two pentahydroxylated pyrrolizidines (compounds **4** and **5**), which are epimers of hyacinthacine $C_1$, by using suitably protected α,β-unsaturated ketone **6** as the starting material.[3a] This ketone was in turn obtained from a 2,5-dideoxy-2,5-imino-D-altritol (DALDP) derivative.[4] In our synthesis, a highly stereoselective bishydroxylation of ketone **6** was the key step to achieve highly functionalized hyacinthacine $C_1$ epimers **4** and **5**.

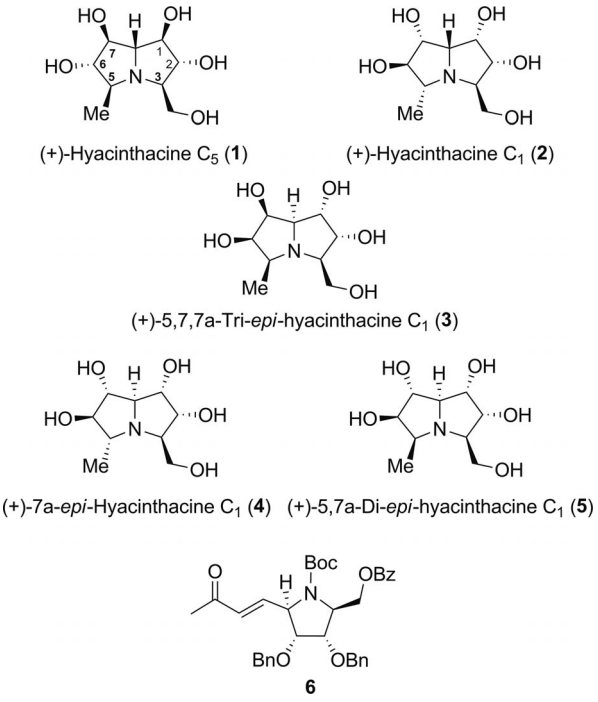


Figure 1. Some examples of hyacinthacine $C_1$ and $C_5$-type alkaloids **1**–**5**.

Related to this work, and as part of our studies concerned with the synthesis of polyhydroxylated pyrrolizidines alkaloids (PHPAs),[3a,5] we decided to approach the synthesis of hyacinthacine $C_5$ (**1**). In this case, an orthogonally protected pyrrolidine of DMDP (2,5-dideoxy-2,5-imino-D-mannitol) configuration (i.e., **7**),[5e,6] previously used by our group for the synthesis of (+)-casuarine (**8**),[5e] was the intermediate chosen as the starting material. Orthogonally

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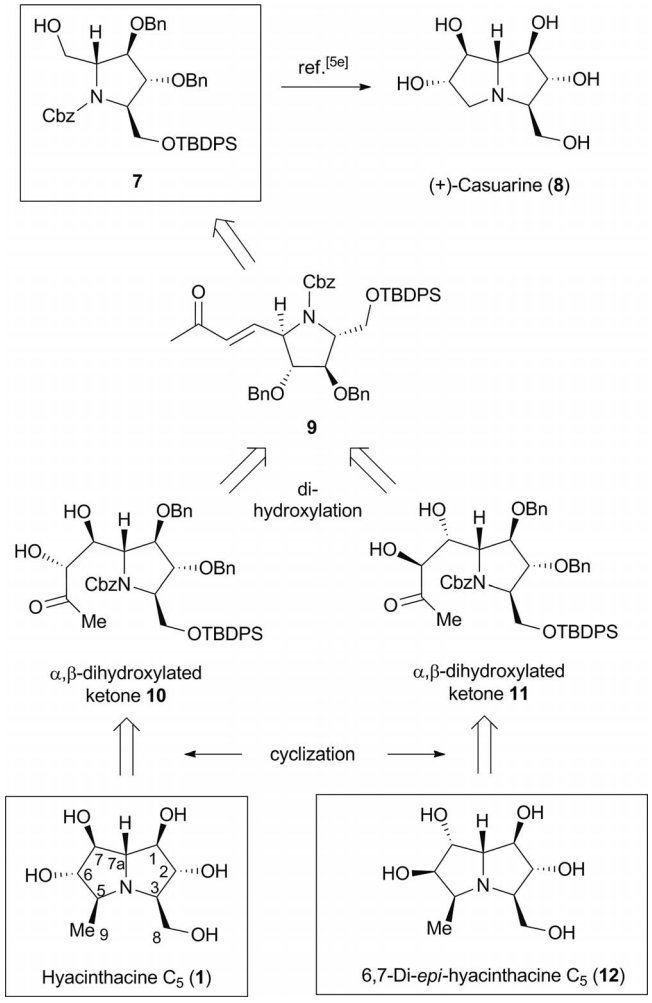
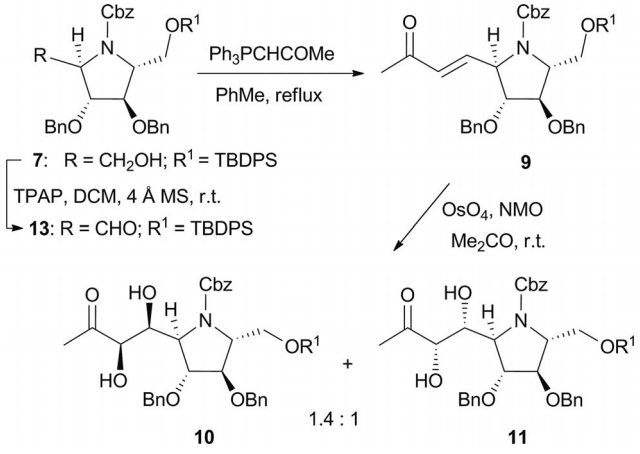
protected α,β-unsaturated ketone **9**, derived from **7**, would be a desirable intermediate that, when subjected to dihydroxylation, could led us to pentahydroxylated pyrrolidines **10** and **11**, which are precursors of the desired hyacinthacine $C_5$-type bicyclic ring when subjected to the appropriate chemical transformations (Scheme 1). In this article, we report on the synthesis of putative (+)-hyacinthacine $C_5$ (**1**) and (+)-6,7-di-*epi*-hyacinthacine $C_5$ (**12**) by using the orthogonally protected pyrrolidine of DMDP configuration (i.e., **7**) as the starting chiral building block. Following the synthesis of putative hyacinthacine $C_5$ (**1**) and 6,7-di-*epi*-hyacinthacine $C_5$ (**12**), we describe an exhaustive structural study by NMR spectroscopic analysis of final compound **1** and its hydrochloride salt, as well as some of its chemical precursors and derivatives. Analytical and spectroscopic data for synthetic **1** and its hydrochloride salt, however, did not match those reported by Kato for the natural product,[1] but did however match those reported by Yu in a recent synthesis of *ent*-**1**.[3a] Moreover, NOE studies on synthetic **1** and **1**·HCl together with those of the chemical precursors of synthetic **1** prompt us to conclude, together with the work of Yu, that the natural compound initially labeled as (+)-hyacinthacine $C_5$ is in fact a different isomer.




Scheme 1. Previous synthesis of (+)-casuarine (**8**) from DMDP precursor **7** and retrosynthetic analysis of hyacinthacine $C_5$ (**1**) and 6,7-di-*epi*-$C_5$ (**12**).

## Results and Discussion

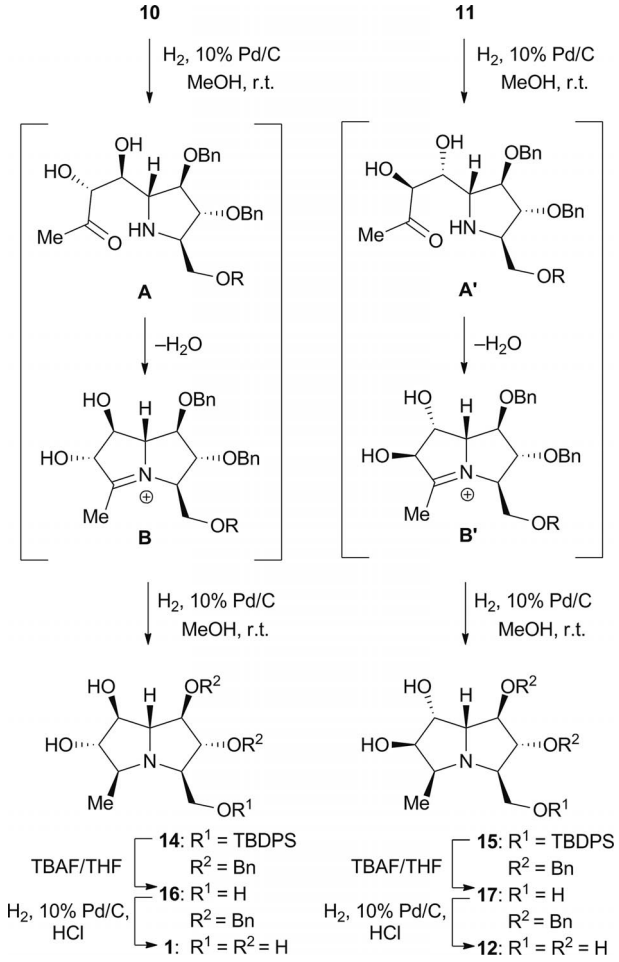
According to the retrosynthetic analysis shown in Scheme 1, the synthesis started with previously described pyrrolidine **7**.[5e,6] Oxidation of the free OH group in **7** produced aldehyde **13**,[5e] which was treated in situ with 1-triphenylphosphoranylidene-2-propanone to afford key intermediate α,β-unsaturated ketone **9** (Scheme 2). Dihydroxylation of **9** with aqueous 1% $OsO_4$ yielded diol intermediates **10**/**11** as a 1.4:1 mixture[7] that was easily separated by flash chromatography. The configurations of the two new generated stereogenic centers were not established at this point but later in the synthesis, because their $^1$H NMR spectra appeared as an irresolvable mixture of rotamers. Catalytic hydrogenation of **10** and **11** in the presence of Pd/C yielded pyrrolizidines **14** and **15**, respectively, as the only isomers (Scheme 3). The absolute configurations of **14** and **15** were established on the basis of spectroscopic analysis carried out on their corresponding *O*-desilylation derivatives **16** and **17**, respectively (Scheme 3). Their proposed structures were confirmed by NOE experiments, which showed positive interactions between 1-H–7-H, 6-H–7a-H, 6-H–Me, 1-H–5-H, and 5-H–7-H in **16** and between 1-H–3-H, 1-H–5-H, 5-H–6-H, and 7-H–7a-H in **17** (Figure 2).




Scheme 2. Synthesis of pyrrolidines **10** and **11**.

In this sense, it is worth noting the stereoselectivity observed in the hydrogenation reactions of **10** and **11**. As suggested by Scheme 3, initial *N*-Cbz removal affords intermediates **A** and **A′**, which upon intramolecular reductive amination form intermediate bicyclic iminium ions **B** and **B′**. Highly stereoselective hydrogenation of such intermediates through the α-face yields pyrrolizidines **14** and **15**, which both present the *S* configuration at C-5 (Figure 3). According to this description, the stereochemistry at C-6 remains unaffected during the reaction, and consequently pyrrolizidine **14** shows a *trans* disposition between the OH group at C-6 and the Me group at C-5, and pyrrolizidine **15** adopts a *cis* disposition. These experimental facts




Scheme 3. Synthesis of pyrrolizidines **1** and **12** from pyrrolidines **10** and **11** respectively.

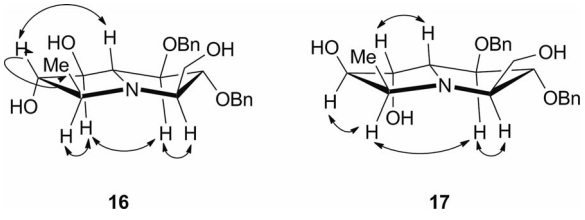



Figure 2. Main NOE interactions in **16** and **17**.

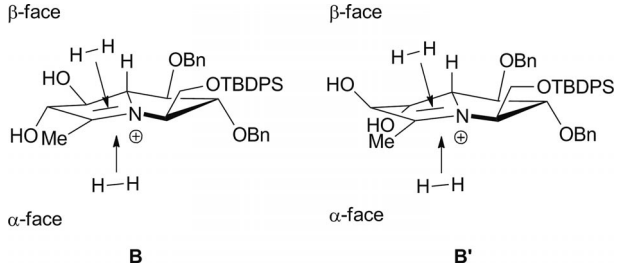



Figure 3. Proposed iminium intermediates **B** and **B′** in the catalytic hydrogenation of **10** and **11**.

prompt us to state that iminium intermediates **B** and **B′** are the chemical species subjected to hydrogenation and therefore to conclude that α,β-dihydroxylated ketone **10** is the precursor of **14** having the 1′*S*,2′*R* configuration, whereas **11**, with a 1′*R*,2′*S* configuration, is the precursor of **15**.

To finish the synthesis, the transformation of **16** and **17** into target molecules **1** and **12** was achieved by *O*-debenzylation to proposed hyacinthacine $C_5$ (**1**) and 6,7-di-*epi*-hyacinthacine $C_5$ (**12**, Scheme 3).

The analytical and spectroscopic data of compounds **1** and **12** were established by careful studies and confirmed by extensive $^1H$, $^{13}C$, and NOE NMR experiments. As previously described by different authors,[8] analytical and spectroscopic data of synthetic alkaloids can vary with those of natural compounds. Metal ions, ionic strength of the solvent, pH, and purification methodology can be responsible for these differences, especially in their NMR chemical shift values.

In our case, the analytical and spectroscopic data of synthetic **1** and **1**·HCl are inconsistent with those data described for natural hyacinthacine $C_5$. $^1H$ and $^{13}C$ NMR experiments carried out on synthetic **1** and **1**·HCl under the same conditions as those described by Kato[1] [$D_2O$ and 3-(trimethylsilyl)propionate (TSP) as an internal standard, see the Supporting Information] do not match those reported for hyacinthacine $C_5$ (see Tables 1 and 2). Especially significant are the $^{13}C$ NMR spectroscopic data. In both compounds, the chemical shifts of C-2 and C-8 appear upfield with respect to those of natural hyacinthacine $C_5$ (Table 2,

Table 1. $^1H$ NMR spectroscopic data of synthetic **1**, **1**·HCl, and natural **1** at 500 MHz in $D_2O$.[a]

| Entry | Proton | **1**·HCl | Synthetic **1** | Natural **1** |
|---|---|---|---|---|
| 1 | 1-H | 4.42 | 4.19 | 4.01 |
| 2 | 2-H | 4.15 | 3.99 | 3.80 |
| 3 | 3-H | 3.73 | 2.97–2.93 | 3.01 |
| 4 | 5-H | 3.64 | 2.97–2.93 | 2.81 |
| 5 | 6-H | 3.93–3.96 | 3.72–3.66 | 3.60 |
| 6 | 7-H | 4.38 | 4.15 | 3.99 |
| 7 | 7a-H | 3.82–3.86 | 3.08 | 3.24 |
| 8 | 8-H | 3.93–3.96 | 3.72–3.66 | 3.50 |
| 9 | 8′-H | 3.82–3.86 | 3.72–3.66 | 3.55 |

[a] Chemical shifts are expressed in ppm downfield from sodium TSP.

Table 2. $^{13}C$ NMR spectroscopic data of synthetic **1**, **1**·HCl, and natural **1** at 125 MHz in $D_2O$.[a]

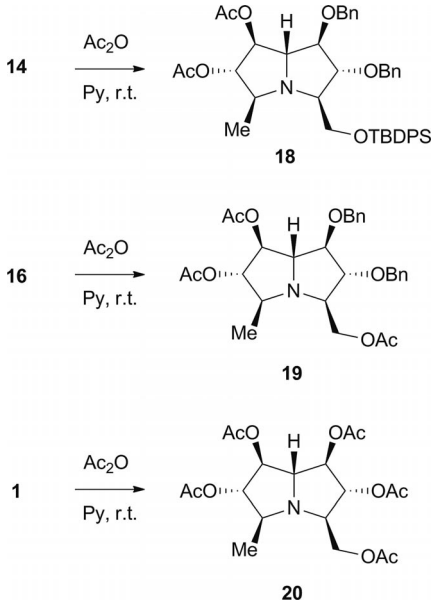
| Entry | Carbon | **1**·HCl ($x$) | ($x - z$) | Synthetic **1** ($y$) | ($y - z$) | Natural **1** ($z$) |
|---|---|---|---|---|---|---|
| 1 | C-1 | 80.0 | +1.8 | 79.6 | +1.4 | 78.2 |
| 2 | C-2 | 79.1 | –1.9 | 78.7 | –2.3 | 81.0 |
| 3 | C-3 | 76.6 | +11.5 | 65.3 | +0.2 | 65.1 |
| 4 | C-5 | 71.1 | +9.7 | 70.4 | +9 | 61.4 |
| 5 | C-6 | 82.5 | +0.8 | 82.3 | +0.6 | 81.7 |
| 6 | C-7 | 79.5 | +1.7 | 79.0 | +1.2 | 77.8 |
| 7 | C-7a | 76.1 | +6.9 | 70.5 | +1.3 | 69.2 |
| 8 | C-8 | 60.9 | –4.8 | 62.2 | –3.5 | 65.7 |
| 9 | C-9 | 17.0 | +1.3 | 17.2 | +1.5 | 15.7 |

[a] Chemical shifts are expressed in ppm downfield from sodium TSP.

Entries 2 and 8), whereas the rest of the carbon atoms are moved downfield. In addition, C-5 in synthetic **1** and **1**·HCl shows a 9 and 9.7 ppm downfield shift, respectively, to that of C-5 in natural hyacinthacine $C_5$ (Table 2, Entry 4), whereas the shift for the rest of the carbon atoms ranges from 0.2 to 6.9 ppm (see Table 2). As explained above, certain shifts can be expected between synthetic and natural alkaloids; still, those differences vary evenly for all the signals, which is not the case here. Also significant are the specific rotation values of both synthetic **1** {$[\alpha]_D^{30}$ = +8 (*c* = 1, $H_2O$)} and **1**·HCl {$[\alpha]_D^{28}$ = +18 (*c* = 1, $H_2O$)}, which in concordance with the NMR results do not match those reported for natural **1** {ref.[1] $[\alpha]_D$ = +1.5 (*c* = 0.22, $H_2O$)}.

These results prompted us to consider that the compound initially assigned as hyacinthacine $C_5$ could be a different isomer. To support this conclusion we decided to carry out additional experiments. In this sense, pyrrolizidines **14** and **16**, chemical precursors of synthetic **1**, and synthetic **1** itself were acetylated to **18**, **19**, and peracetylated **20**, respectively (Scheme 4). NOE studies on these compounds showed positive interactions between 1-H–7-H, 1-H–5-H, and 5-H–7-H in all three derivatives **18**, **19**, and **20**.[9] These results definitely support the stereochemistry initially assigned by us to synthetic **1** confirming its structure as the one depicted in Scheme 3 and proving that the natural compound originally described as (+)-hyacinthacine $C_5$ is in fact a different isomer.[3a]




Scheme 4. Synthesis of acetylated derivatives **18**, **19**, and **20**.

## Conclusions

We describe herein the synthesis of two pentahydroxylated pyrrolizidines, putative hyacinthacine $C_5$ (**1**) and 6,7-di-*epi*-hyacinthacine $C_5$ (**12**), from an orthogonally protected pyrrolidine of DMDP configuration (i.e., **7**) as starting chiral building block. The analytical and spectroscopic data of compounds **1** and **12** were established by extensive $^1H$, $^{13}C$, and NOE NMR experiments. Some differences exist between the analytical and spectroscopic data of natural hyacinthacine $C_5$ (**1**) and synthetic **1**, which, although to a certain point expected, exceed the previously observed variations in similar compounds.[8] On this respect, additional studies on chemical derivatives of synthetic **1** support the initially proposed structure and establish the absolute configuration of putative hyacinthacine $C_5$ as that of structure **1**. These results, together with those recently published by Yu, lead us to conclude that the natural compound initially labeled as (+)-hyacinthacine $C_5$ might be a different isomer.

## Experimental Section

**General Remarks:** Solutions were dried with $MgSO_4$ before concentration under reduced pressure. The $^1H$ and $^{13}C$ NMR spectra were recorded with Varian Direct Drive 400 and 500 MHz spectrometers for solutions in $CDCl_3$ (internal $Me_4Si$). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br., broad. IR spectra were recorded with a Perkin–Elmer FTIR Spectrum One instrument, and mass spectra were recorded with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers or a NALDI ionization–time-of-flight (NALDI-TOF) mass spectrometer and EI mass spectrometer. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 $F_{254}$ aluminum sheets and detection by employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulfuric acid containing 0.8% cerium sulfate (w/v) and heating. Column chromatography was performed on silica gel (Merck, 7734). All compounds were shown to be homogeneous by chromatographic methods and characterized by NMR spectroscopy and MS and HRMS.

**(*E*)-4-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-Dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloximethylpyrrolidin-2′-yl]but-3-en-2-one (9):** To a solution of **7** (1.01 g, 1.4 mmol) in dry DCM (15 mL) was added activated powdered 4 Å molecular sieves (200 mg), *N*-methylmorpholine *N*-oxide (250 mg, 2.1 mmol), and tetrapropylammonium perruthenate (TPAP, 100 mg), and the reaction mixture was kept at room temperature for 1 h. TLC ($Et_2O$/hexane, 3:2) then showed a faster-running compound. The reaction was diluted with $Et_2O$ (30 mL), filtered through a bed of Silica gel 60 (230–400 mesh), and thoroughly washed with $Et_2O$. The combined filtrate and washings were concentrated to aldehyde **13** (955 mg, 95%), which was used in the next step. IR (KBr, neat): $\tilde{\nu}$ = 3063 and 3029 (Ph), 1735 (CHO), 1724 (C=O, Cbz) $cm^{-1}$. A solution of **13** (955 mg, 1.34 mmol) and 1-(triphenylphosphoranylidene)-2-propanone (1.35 g, 4.2 mmol) in dry toluene (15 mL) was heated at reflux for 24 h. TLC then showed a slower-running compound. The solvent was eliminated, and the residue was submitted to column chromatography ($Et_2O$/hexane, 3:2) to afford syrup **9** (870 mg, 86%, from **7**). $[\alpha]_D^{30}$ = +8, $[\alpha]_{405}^{30}$ +7 (*c* = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3032 and 2930 (Ph), 1704 and 1677 (C=O) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.73–7.12 (2 m, 25 H, 5Ph), 6.69 (ddd, $J_{3,4}$ = 16.1 Hz, $J_{4,5'}$ = 7.7 Hz, 1 H, 4-H, two rotamers), 6.04 (2 d, 1 H, 3-H, two rotamers), 5.22–4.87 (4 d, *J* = 12.1 Hz, 2 H, $CH_2Ph$, two rotamers), 4.74–3.72 (br. m, 10 H, 2 $CH_2Ph$, 2′,3′,4′,5′,2′′a,2′′b-H,), 2.19 and 2.01 (2 s, 3 H, 1,1,1-H, two rotamers), 1.11 and 1.06 (2 s, 9 H, $CMe_3$, two rotamers) ppm. $^{13}C$ (125 MHz, $CDCl_3$): $\delta$ = 198.2 (C-2), 154.5 (Cbz), 145.2, 144.9, 137.5, 135.5, 133.3, 131.4,

129.7, 127.9, 86.4, and 85.5 (C-3′, two rotamers), 82.4 and 81.4 (C-4′, two rotamers), 71.8, 71.7, 71.4 and 71.2 (2 $CH_2Ph$, two rotamers), 67.3, 67.1 (Cbz, two rotamers), 65.4 and 65.4 (C-2′, two rotamers), 65.1 (C-5′), 62.1 and 61.4 (C-5′′, two rotamers), 27.0, 26.9 ($CMe_3$, two rotamers), 19.4 and 19.2 (Me, two rotamers) ppm. HRMS (NALDI-TOF): calcd. for $C_{47}H_{51}NO_6NaSi$ $[M + H]^+$ 776.3383; found 776.3381 (deviation +0.3 ppm).

**(2*R*,3*R*,4*R*,5*R*)-3,4-Dibenzyloxy-*N*-benzyloxycarbonyl-2-*tert*-butyldiphenylsilyloxymethyl-5-[(1′*S*,2′*R*)-1′-2′-dihydroxy-3′-oxobutyl]pyrrolidine (10) and (2*R*,3*R*,4*R*,5*R*)-3,4-Dibenzyloxy-*N*-benzyloxycarbonyl-2-*tert*-butyldiphenylsilyloxymethyl-5-[(1′*R*,2′*S*)-1′-2′-dihydroxy-3′-oxobutyl]pyrrolidine (11):** To a stirred solution of **9** (855 mg, 1.13 mmol) in acetone/water (8:1, 13.5 mL) was added NMO (332 mg, 2.83 mmol) and aqueous 1% $OsO_4$ (2.5 mL). The mixture was left at room temperature for 20 h. TLC ($Et_2O$/hexane, 3:2) then revealed the presence of two new products of lower mobility. The mixture was concentrated to a residue that was submitted to chromatography ($Et_2O$/hexane, 1:1) to afford first **10** as a syrup. Yield: 328 mg (37%). $[a]_D^{24} = -25$ ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3435 (OH), 1702 and 1679 (C=O) $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.73–7.07 (2 m, 25 H, 5Ph), 5.06–4.85 (m, 2 H, $CH_2Ph$), 4.69–4.02 (2 br. m, 11 H, $2CH_2Ph$, 3′,4′,5′,2′′a,2′′b,3,4-H), 3.92 (dd, 1 H, OH, two rotamers), 3.82–3.66 (m, 1 H, 2′-H), 3.53 (dd, 1 H, OH, two rotamers), 2.25 and 1.79 (2 s, 3 H, 1,1,1-H, two rotamers), 1.08 and 1.01 (2 s, 9 H, $CMe_3$, two rotamers) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 208.1 (C-2), 155.4 (Cbz), 137.7, 136.7, 135.9, 135.5, 133.3, 129.8, 128.2, 127.8, 82.1 (C-3′), 81.3 (C-4′), 78.3 (C-3), 71.6 (C-4), 69.8 (C-2′), 68.0 (C-5′), 67.3, 65.2 and 61.8 ($2CH_2Ph$ and Cbz), 26.8 ($CMe_3$), 25.9 (Me) and 19.2 ($CMe_3$) ppm. HRMS (NALDI-TOF): calcd. for $C_{47}H_{54}NO_8Si$ $[M + H]^+$ 788.3619; found 788.3607 (deviation –1.5 ppm). Eluted second was **11** (246 mg, 28%) as a syrup. $[a]_D^{26} = -5$, $[a]_{546}^{27} = -6$ ($c$ 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3389 (OH), 1721 and 1672 (C=O) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.61–7.12 (2 m, 25 H, 5Ph), 5.00 (m, 2 H, $CH_2Ph$), 4.63 (m, 2 H, $CH_2Ph$), 4.50 (m, 2 H, 3,4-H), 4.40 (m, 2 H, $CH_2Ph$), 4.17 (m, 3 H, 2′′a,2′′b,3′-H), 4.04 (m, 1 H, 2′-H), 3.78 (m, 2 H, 4′,5′-H), 2.01 (s, 3 H, Me), 1.04 (s, 9 H, $CMe_3$) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 207.0 (C-2), 157.9 (Cbz), 137.6, 137.5, 135.6, 135.4, 133.4, 133.3, 129.8, 128.5, 127.7, 82.6 (C-3′), 81.7 (C-4′), 78.4 (C-3), 74.6 (C-4), 71.5 and 71.1 (C-2′, two rotamers), 67.8 (C-5′), 67.6, 65.2 and 61.7 (2 $CH_2Ph$, Cbz), 26.8 ($CMe_3$), 25.0 (Me) and 19.2 ($CMe_3$) ppm. HRMS (NALDI-TOF): calcd. for $C_{47}H_{54}NO_8Si$ $[M + H]^+$ 788.3619; found 788.3616 (deviation –0.4).

**(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*R*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-6,7-dihydroxy-5-methylpyrrolizidine (14):** Compound **10** (230 mg, 0.29 mmol) in MeOH (4 mL) was hydrogenated (60 psi $H_2$) in the presence of 10% Pd/C (35 mg) overnight. TLC (AcOEt/hexane, 3:1) then showed a slower-running compound. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were concentrated to a residue that was submitted to chromatography (AcOEt/hexane, 1:1) to afford pure **14** (121 mg, 65%) as a colorless viscous syrup. $[a]_D^{25} = -5$ ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3368 (OH) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.70–7.22 (2 m, 20 H, 4Ph), 4.52 (2 d, 4 H, $2CH_2Ph$), 4.23 (t, $J_{1,2} = J_{2,3}$ = 2.3 Hz, 1 H, 2-H), 4.13–4.07 (m, 1 H, 1-H), 3.99 (t, $J_{6,7} = J_{7,7a}$ = 7.5 Hz, 1 H, 7-H), 3.72–3.56 (m, 3 H, 6,8,8′-H), 3.40 (m, 1 H, 7a-H), 3.18 (m, 1 H, 3-H), 2.95 (m, 1 H, 5-H), 1.08 (d, $J_{Me,5}$ = 6.2 Hz, 3 H, Me), 1.04 (s, 9 H, $CMe_3$) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 138.0, 135.6, 135.6, 133.6, 133.5, 129.6, 129.6, 128.4, 128.4, 127.7, 127.6, 127.6, 127.5, 87.1 (C-1), 86.0 (C-2), 83.0 (C-6), 80.1 (C-7), 72.8 (C-7a), 71.6 ($CH_2Ph$), 71.5 ($CH_2Ph$), 71.3 (C-3), 65.2 (C-5), 65.1 (C-8), 26.9 ($CMe_3$), 19.2 (Me), 19.2 ($CMe_3$) ppm. HRMS (NALDI-TOF): calcd. for $C_{39}H_{48}NO_5Si$ $[M + H]^+$ 638.3302; found 638.3307 (deviation +0.5 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*R*)-1,2-Dibenzyloxy-6,7-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine (16):** To a stirred solution of **14** (51 mg, 0.08 mmol) in THF (2.5 mL) was added TBAF·$3H_2O$ (76 mg, 0.24 mmol). The mixture was kept at 50 °C for 16 h. TLC ($AcOEt/H_3CCN/MeOH/H_2O$, 70:10:10:5) then showed a new slower-running compound. The reaction mixture was evaporated and subjected to chromatography ($AcOEt/H_3CCN/MeOH/H_2O$, 95:10:4:2) to afford pure **16** (30 mg, 94%). $[a]_D^{28} = -14$ ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3368 (OH) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.23 (m, 10 H, 2 Ph), 4.63 and 4.60 (2 d, $J$ = 3.1 Hz, 2 H, $CH_2Ph$), 4.52 and 4.47 (2 d, $J$ = 11.8 Hz, 2 H, $CH_2Ph$), 4.10 (t, $J_{1,7a} = J_{1,2}$ = 3.7 Hz, 1 H, 1-H), 4.00 (t, $J_{6,7} = J_{7,7a}$ = 7.55 Hz, 1 H, 7-H), 3.96 (t, $J_{2,3}$ = 3.7 Hz, 1 H, 2-H), 3.86 (br. s, 1 H, OH), 3.73 (t, $J_{5,6}$ = 7.55 Hz, 1 H, 6-H), 3.59–3.43 (m, 3 H, 7a,8,8′-H), 3.19 (m, 1 H, 3- H), 2.96 (m, 1 H, 5-H), 1.21 (d, $J_{Me,5}$ = 6.22 Hz, 3 H, Me) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 131.2, 131.2, 130.6, 130.5, 130.5, 130.3 (Ph), 89.4 (C-1), 87.9 (C-2), 85.2 (C-6), 82.7 (C-7), 74.9 ($CH_2Ph$), 74.6 (C-7a), 74.5 ($CH_2Ph$), 73.7 (C-3), 67.5 (C-5), 63.3 (C-8), 20.9 (Me) ppm. HRMS (NALDI-TOF): calcd. for $C_{23}H_{30}NO_5$ $[M + H]^+$ 400.2124; found 400.2115 (deviation –2.2 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*R*)-1,2,6,7-Tetrahydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-hyacinthacine $C_5$, 1]:** Compound **16** (41 mg, 0.10 mmol) in MeOH (4.5 mL) and conc. HCl (four drops) was hydrogenated (70 psi $H_2$) in the presence of 10% Pd/C (16 mg) for 27 h. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were treated with Amberlite IRA-400 resin ($OH^-$ form). Evaporation of the solvent afforded pure **1** (16 mg, 73%) as a colorless viscous syrup. $[a]_D^{28} = +8$ ($c$ = 1, $H_2O$). IR (neat): $\tilde{\nu}$ = 3363 (OH) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$): $\delta$ = 4.19 (t, $J_{1,2} = J_{1,7a}$ = 6.9 Hz, 1 H, 1-H), 4.15 (t, $J_{6,7} = J_{7,7a}$ = 6.9 Hz, 1 H, 7-H), 3.99 (t, $J_{2,3}$ = 6.9 Hz, 1 H, 2-H), 3.72–3.66 (m, 3 H, 6,8,8-H), 3.08 (t, 1 H, 7a-H), 2.97–2.93 (m, 2 H, 3,5-H), 1.24 (d, $J_{Me,5}$ = 6.3 Hz, 3 H, Me) ppm. $^{13}C$ NMR (125 MHz, $D_2O$): $\delta$ = 82.3 (C-6), 79.6 (C-1), 79.0 (C-7), 78.7 (C-2), 70.5 (C-7a), 70.4 (C-5), 65.3 (C-3), 62.2 (C-8), 17.2 (Me) ppm. HRMS (NALDI-TOF): calcd. for $C_9H_{18}NO_5$ $[M + H]^+$ 220.1185; found 220.1182 (deviation –1.4 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*R*)-1,2,6,7-Tetrahydroxy-3-hydroxymethyl-5-methylpyrrolizidine Hydrochloride [1·HCl]:** Conc. HCl (three drops) was added to a solution of **1** (16 mg, 0.073 mmol) in $H_2O$ (4 mL). Evaporation of the solvent afforded **1**·HCl (18 mg, quantitative). $[a]_D^{28} = +18$ ($c$ = 1, $H_2O$). $^1H$ NMR (500 MHz, $D_2O$): $\delta$ = 4.42 (t, $J_{1,2} = J_{1,7a}$ = 5.1 Hz, 1 H, 1-H), 4.38 (t, $J_{6,7} = J_{7,7a}$ = 6.6 Hz, 1 H, 7-H), 4.15 (t, $J_{2,3}$ = 5.2 Hz, 1 H, 2-H), 3.96–3.93 (m, 2 H, 6,8-H), 3.86–3.82 (m, 2 H, 7a,8′-H), 3.73 (m, 1 H, 3-H), 3.64 (quint., $J_{5,6}$ = 6.9 Hz, 1 H, 5-H), 1.50 (d, $J_{Me,5}$ = 6.8 Hz, 3 H, Me) ppm. $^{13}C$ NMR (125 MHz, $D_2O$): $\delta$ = 82.5 (C-6), 80.0 (C-1), 79.5 (C-7), 79.1 (C-2), 76.6 (C-3), 76.1 (C-7a), 71.1 (C-5), 60.9 (C-8), 17.0 (Me) ppm.

**(1*R*,2*R*,3*R*,5*S*,6*R*,7*R*,7a*R*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-6,7-dihydroxy-5-methylpyrrolizidine (15):** Compound **11** (200 mg, 0.25 mmol) in MeOH (3.5 mL) was hydrogenated (60 psi $H_2$) in the presence of 10% Pd/C (40 mg) overnight. TLC (AcOEt/hexane, 3:1) then showed a slower-running compound. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were concentrated to a residue that was submitted to chromatography (AcOEt/hexane, 3:2) to afford pure **15** (91 mg, 56%) as a colorless viscous syrup. $[a]_D^{25} = +14$ ($c$

= 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3459 (OH) $cm^{-1}$. $^1H$ NMR (400 MHz): $\delta$ = 7.70–7.24 (2 m, 20 H, 4 Ph), 4.58 and 4.56 (2 d, $J$ = 12.0 Hz, 2 H, $CH_2Ph$), 4.50 (t, $J$ = 12.0 Hz, 2 H, $CH_2Ph$), 4.36 (m, 1 H, 2-H), 4.28 (m, 1 H, 1-H), 4.01 (m, 1 H, 7-H), 3.97 (m, 1 H, 7a-H), 3.86 (m, 1 H, 6-H), 3.76 (t, $J$ = 10.0 Hz, 1 H, 8-H), 3.61 (m, 1 H, 8′-H), 3.41 (d, 1 H, OH), 3.19 (m, 1 H, 3-H), 3.13 (m, 1 H, 5-H), 1.06 (s, 9 H, $CMe_3$), 1.01 (d, $J_{Me,5}$ = 6.5 Hz, 3 H, Me) ppm. $^{13}C$ NMR (125 MHz): $\delta$ = 140.5, 139.5, 138.2, 136.4, 136.2, 132.3, 132.2, 131.3, 131.1, 130.8, 130.5, 130.3, 130.3, 130.2, 87.7 (C-2), 85.1 (C-1), 83.8 (C-6), 79.7 (C-7), 75.8 (C-7a), 74.5 and 74.5 (2 $CH_2Ph$), 73.4 (C-3), 67.9 (C-8), 65.5 (C-5), 29.5 ($CMe_3$), 21.9 (Me), 17.6 ($CMe_3$) ppm. HRMS (NALDI-TOF): calcd. for $C_{39}H_{48}NO_5Si$ $[M + H]^+$ 638.3302; found 638.3311 (deviation +1.4 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*R*,7*R*,7a*R*)-1,2-Dibenzyloxy-6,7-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine (17):** To a stirred solution of **15** (86 mg, 0.13 mmol) in THF (3 mL) was added TBAF·$3H_2O$ (106 mg, 0.34 mmol). The mixture was kept at 55 °C for 4 h. TLC (AcOEt/MeCN/MeOH/$H_2O$, 70:10:5:5) then showed a new slower-running compound. The reaction mixture was evaporated and subjected to chromatography (AcOEt/MeCN/MeOH/$H_2O$, 70:10:5:5) to afford pure **17** as a syrup (41 mg, 76%). $[\alpha]_D^{28}$ = +39 ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3391 (OH) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.39–7.22 (m, 10 H, 2 Ph), 4.73 and 4.62 (2 d, $J$ = 11.8 Hz, 2 H, $CH_2Ph$), 4.58 and 4.52 (2 d, $J$ = 11.5 Hz, 2 H, $CH_2Ph$), 4.45 (t, $J_{1,2}$ = $J_{1,7a}$ = 5.9 Hz, 1 H, 1-H), 4.15 (m, 1 H, 2-H), 4.00 (m, 1 H, 7-H), 3.94 (m, 1 H, 6-H), 3.71 (t, $J_{7,7a}$ = 5.9 Hz, 1 H, 7a-H), 3.65 (dd, $J_{3,8}$ = 3.9 Hz, $J_{8,8'}$ = 11.4 Hz, 1 H, 8-H), 3.56 (dd, $J_{3,8'}$ = 4.1 Hz, 1 H, 8′-H), 3.20 (m, 1 H, 5-H), 2.99 (m, 1 H, 3-H), 1.19 (d, $J_{Me,5}$ = 6.7 Hz, 3 H, Me) ppm. $^{13}C$ (125 MHz, $CDCl_3$): $\delta$ = 138.2, 127.9, 127.6, 127.5, 127.3, 127.2 (Ph), 84.8 (C-2), 80.7 (C-6), 80.4 (C-1), 75.9 (C-7), 72.2 ($CH_2Ph$), 71.8 ($CH_2Ph$), 71.1 (C-7a), 70.6 (C-3), 63.4 (C-5), 60.3 (C-8), 13.4 (Me) ppm. HRMS (NALDI-TOF): calcd. for $C_{23}H_{30}NO_5$ $[M + H]^+$ 400.2124; found 400.2116 (deviation –0.8 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*R*,7*R*,7a*R*)-1,2,6,7-Tetrahydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-6,7-Di-*epi*-hyacinthacine $C_5$, 12]:** Compound **17** (44 mg, 0.11 mmol) in MeOH (4 mL) and conc. HCl (four drops) was hydrogenated (70 psi $H_2$) in the presence of 10% Pd/C (20 mg) for 20 h. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were treated with Amberlite IRA-400 resin ($OH^-$ form). Evaporation of the solvent afforded pure **12** (24 mg, 99%) as a colorless viscous syrup. $[\alpha]_D^{30}$ = +8 ($c$ = 1, $H_2O$) {ref.[1] $[\alpha]_D$ = +1.5 ($c$ = 0.22, $H_2O$)}. IR (neat): $\tilde{\nu}$ = 3363 (OH) $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$): $\delta$ = 4.31 (t, $J_{1,2}$ = $J_{1,7a}$ = 7.5 Hz, 1 H, 1-H), 4.24 (m, 1 H, 7-H), 4.15 (m, 1 H, 6-H), 3.99 (br. t, $J_{2,3}$ = 7.5 Hz, 1 H, 2-H), 3.80 (br. dd, $J_{3,8}$ = 4.0 Hz, $J_{8,8'}$ = 11.9 Hz, 1 H, 8-H), 3.71 (br. dd, $J_{3,8'}$ = 4.7 Hz, 1 H, 8′-H), 3.49 (m, 1 H, 7a-H), 3.16 (m, 1 H, 5-H), 2.81 (m, 1 H, 3-H), 1.19 (d, $J_{Me,5}$ = 6.7 Hz, 1 H, Me) ppm. $^{13}C$ NMR (125 MHz, $D_2O$): $\delta$ = 79.7 (C-6), 78.7 (C-2), 74.3 (C-7), 73.1 (C-1), 70.6 (C-3), 69.1 (C-7a), 62.7 (C-5), 61.6 (C-8), 14.0 (Me) ppm. HRMS (NALDI-TOF): calcd. for $C_9H_{17}NO_5Na$ $[M + Na]^+$ 242.1004; found 242.1012 (deviation +3.3 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*S*)-6,7-Di-*O*-acetyl-1,2-dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-6,7-dihydroxy-5-methylpyrrolizidine (18):** Compound **14** (43 mg, 0.067 mmol) was acetylated in dry pyridine (1.5 mL), acetic anhydride (32 μL, 0.337 mmol), and DMAP (cat.) at room temperature for 1.5 h. TLC (AcOEt/hexane, 2:1) then showed a faster-running compound. The reaction mixture was supported on silica gel and chromatographed (AcOEt/hexane, 1:5) to afford pure **18** (17 mg, 35%) as a colorless viscous syrup. $[\alpha]_D^{30}$ = –3 ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1743 (C=O) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.67–7.62 and 7.40–7.22 (2 m, 20 H, 4 Ph), 5.29 (dd, $J_{6,7}$ = 6.7 Hz, $J_{7,7a}$ = 5.6 Hz, 1 H, 7-H), 4.97 (dd, $J_{5,6}$ = 5.9 Hz, 1 H, 6-H), 4.59–4.46 (m, 4 H, $2CH_2Ph$), 4.23 (br. t, $J_{1,2}$ = $J_{1,7a}$ = 3.3 Hz, 1 H, 1 H, 1-H), 4.12 (br. t, $J_{2,3}$ = 3.0 Hz, 1 H, 2-H), 3.68 (dd, $J_{8,8'}$ = 9.9 Hz, $J_{3,8}$ = 7.7 Hz, 1 H, 8-H), 3.58 (dd, $J_{3,8'}$ = 6.3 Hz, 1 H, 8′-H), 3.45 (dd, 1 H, 7a-H), 3.24 (quint., $J_{5,9}$ = 5.9 Hz, 1 H, 5-H), 3.19 (m, 1 H, 3-H), 2.04 and 1.99 (2 s, 6 H, 2Ac), 1.04 (d, $J_{Me,5}$ = 6.1 Hz, 3 H, Me), 1.03 (s, 9 H, $CMe_3$) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 173.2 and 173.0 (C=O), 140.8, 140.6, 138.3, 131.0, 130.3, 130.2 (Ph), 89.7 (C-1), 88.6 (C-2), 84.6 (C-6), 82.1 (C-7), 74.8 (C-7a), 74.5 ($CH_2Ph$), 74.4 ($CH_2Ph$), 73.3 (C-3), 68.2 (C-8), 66.4 (C-5), 29.5 ($CMe_3$), 23.6 (2 $CH_3CO$), 22.0 (Me), 21.9 ($CMe_3$) ppm. HRMS (NALDI-TOF): calcd. for $C_{43}H_{52}NO_7Si$ $[M + H]^+$ 722.3505; found 722.3513 (deviation +1.1 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*S*)-6,7-Di-*O*-acetyl-3-acetyloxymethyl-1,2-dibenzyloxy-6,7-dihydroxy-5-methylpyrrolizidine (19):** Compound **16** (46 mg, 0.115 mmol) was acetylated in dry pyridine (2 mL), acetic anhydride (87 μL, 0.92 mmol), and DMAP (cat.) at room temperature for 1 h. TLC (AcOEt/hexane, 2:1) then showed a faster-running compound. The reaction mixture was supported on silica gel and chromatographed (AcOEt/hexane, 1:3) to afford pure **19** (31 mg, 51%) as a colorless viscous syrup. $[\alpha]_D^{27}$ = +2 ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1742 (C=O) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35–7.29 (m, 10 H, 2 Ph), 5.29 (t, $J_{6,7}$ = $J_{7,7a}$ = 5.9 Hz, 1 H, 7-H), 5.02 (t, $J_{5,6}$ = 6.1 Hz, 1 H, 6-H), 4.61 and 4.51 (2 d, $J$ = 11.9 Hz, 2 H, $CH_2Ph$) 4.55 and 4.47 (2 d, $J$ = 11.8 Hz, 2 H, $CH_2Ph$), 4.23 (t, $J_{1,2}$ = $J_{1,7a}$ = 3.5 Hz, 1 H, 1-H), 4.02 (m, 2 H, 8,8′-H), 3.91 (t, $J_{2,3}$ = 3.3 Hz, 1 H, 2-H), 3.53 (br. dd, 1 H, 7a-H), 3.28 (m, 1 H, 3-H), 3.20 (quint., 1 H, 5-H), 2.05, 2.01 and 2.00 (3 s, 9 H, 3Ac), 1.13 (d, $J_{Me,5}$ = 6.1 Hz, 3 H, Me) ppm. $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ = 173.4, 173.2 and 172.9 (C=O), 140.4, 131.10, 131.08, 130.5, 130.4, 130.3 (Ph), 88.8 (C-1), 88.2 (C-2), 84.2 (C-6), 81.8 (C-7), 74.66 ($CH_2Ph$), 74.55 (C-7a), 74.51 ($CH_2Ph$), 70.5 (C-3), 67.9 (C-8), 66.5 (C-5), 23.62 and 23.60 (2 $CH_3CO$), 22.0 (Me) ppm. HRMS (NALDI-TOF): calcd. for $C_{29}H_{36}NO_8$ $[M + H]^+$ 526.2441; found 526.2417 (deviation –4.6 ppm).

**(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*S*)-1,2,6,7-Tetra-*O*-acetyl-3-acetyloxymethyl-1,2,6,7-tetrahydroxy-5-methylpyrrolizidine (20):** Compound 1 (40 mg, 0.812 mmol) was acetylated in dry pyridine (3 mL), acetic anhydride (258 μL, 2.74 mmol), and DMAP (cat.) at room temperature for 1.5 h. TLC (AcOEt/hexane, 2:1) then showed a faster-running compound. The solvent was evaporated, and the residue was supported on silica gel and chromatographed (AcOEt/hexane, 1:2) to afford pure **20** (61 mg, 78%) as a colorless viscous syrup. $[\alpha]_D^{29}$ = +9.3 ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1743 (C=O) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.36 (t, $J_{1,2}$ = $J_{1,7a}$ = 4.7 Hz, 1 H, 1-H), 5.29 (t, $J_{7,7a}$ = $J_{6,7}$ = 5.0 Hz, 1 H, 7-H), 5.18 (t, $J_{2,3}$ = 4.6 Hz, 1 H, 2-H), 5.04 (dd, $J_{5,6}$ = 6.5 Hz, 1 H, 6-H), 4.04 (d, $J_{3,8}$ = 6.6 Hz, 2 H, 8,8-H), 3.45 (t, 1 H, 7a-H), 3.29 (dt, 1 H, 3-H), 3.16 (quint., $J_{Me,5}$ = 6.5 Hz, 1 H, 5-H), 2.09, 2.08, 2.07, 2.07 and 2.06 (5 s, 15 H, 5Ac), 1.16 (d, 3 H, Me) ppm. $^{13}C$ NMR (150 MHz, $CDCl_3$): $\delta$ = 170.8, 170.5, 170.2, 170.2 and 169.9 (C=O), 81.5 (C-6), 79.5 (C-1), 79.25 (C-2), 78.6 (C-7), 71.9 (C-7a), 67.5 (C-3), 64.8 (C-8), 64.5 (C-5), 21.08, 21.06 and 20.97 (5 $CH_3CO$), 19.4 (Me) ppm. HRMS (NALDI-TOF): calcd. for $C_{19}H_{28}NO_{10}$ $[M + H]^+$ 430.1713; found 430.1707 (deviation –1.4 ppm).

**Supporting Information** (see footnote on the first page of this article): Copies of the $^1H$ and $^{13}C$ NMR spectra of compounds **9**, **10**, **11**, **14**, and **15** and copies of the $^1H$, $^{13}C$, COSY, HSQC, and NOE of compounds **16**, **17**, **18**, **19**, **20**, **1**, and **12**.

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[9] See the Supporting Information.

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