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Synthesis of 1-homoaustraline

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Dedicated to Professor Janusz Jurczak on the occassion of his 65th birthday

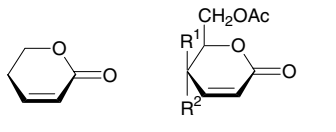
Abstract—The 1,3-dipolar cycloaddition of a five-membered cyclic nitrone derived from malic acid and unsaturated D-*threo*-hexono-lactone leads to a single adduct, which was transformed into 1-homoaustraline *via* a reaction sequence involving rearrangement of the six-membered lactone ring into the five-membered one, removal of the terminal carbon atom from the sugar chain, reduction of the lactone fragment into triol, protection of primary hydroxy groups, mesylation of the secondary one, cleavage of the N–O bond, and the intramolecular alkylation of the nitrogen atom.

Keywords: Iminosugars; Homoaustraline; Nitrones; Aldono-1,5-lactone; 1,3-Dipolar cycloaddition; Glucosidases

1. Introduction

Recently, we have reported on the cycloaddition of 2,3-unsaturated δ-lactones **1**–**3** and the five-membered cyclic nitrones **4** or **5**, which proceeds exclusively in the exo mode and results in a high preference for the anti addition to both the acetoxymethyl group of the lactone and the 3-*tert*-butoxy group of the nitrone.[1–3] In the case of mismatched pairs (syn either to acetoxymethyl or to 3-*tert*-butoxy group), the 4-*O*-acetyl group of the lactone assumes a decisive role in the control of the stereochemical outcome of the cycloaddition. This stereochemical preferences leads, in many cases, to formation of a single adduct or at least a high preponderance of a single adduct.[3] Particularly attractive are the exclusive formation of adducts **6** and **7** from the nitrone **4** and the D-*threo* 4-*O*-acetyl-lactone **2** and D-*erythro* 4-*O*-acetyl-lactone **3**, respectively.[3]

We have shown that application of the known methodology[4] to cycloadduct **8** offers a convenient approach to the indolizidine alkaloids. This has been demonstrated by the synthesis of 7-hydroxy-lentiginosine (**9**) and the formal synthesis of lentiginosine (**10**).[5] The straightforward access to adducts **6** and **7** enables



1 **2**: R^1 = OAc, R^2 = H; **3**: R^1 = H, R^2 = OAc **4** **5**

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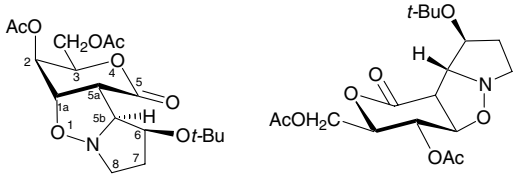
convenient entry to the corresponding pyrrolizidines and indolizidines with an (*R*) or (*S*) configuration at the bridgehead carbon atom.[6]



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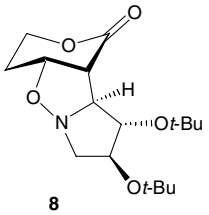

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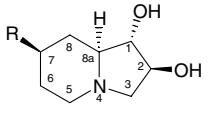
Both components of the cycloaddition, the nitrone and the unsaturated lactone, carry over their own substituents (such as protected hydroxyl groups) with their original configurations, whereas the configuration at C-1a, C-5a, and C-5b of the cycloadduct is established during the reaction. Adduct **6** is particularly interesting because it has anti located *tert*-butoxy group and the bridgehead proton H-5b,[3] which corresponds to an anti rearrangement of OH-1 and H-8a in indolizidines, or OH-1 and H-7a in pyrrolizidines. Such a geometry, found in many indolizidines and pyrrolizidines, for example, castanospermine (**11**),[6d] swainsonine (**12**),[7] or australine (**13**),[8] cannot be achieved by the cycloaddition of simple olefins to the nitrone **4** or by its alkylation with nucleophiles since this direction of approach is highly hindered by the unfavorable steric interactions. In order to force the syn approach of the dipolarophile to the substituent at C-3 of the nitrone Brandi's group[9] performed 1,3-dipolar cycloaddition as an intramolecular process. In the case of cycloaddition of the nitrone **4** to the lactone **2**, syn approach of **2** to the *tert*-butoxy group was coerced by substituents in the lactone.

2. Results and discussion

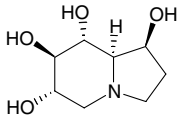
Recently we have shown that the adduct **6** with identical configurations at C-1a, 2, 5a, 5b, and 6 carbon atoms, which is the same as in castanospermine (**11**) at C-7, 6, 8, 8a, and C-1 atoms, can be easily transformed into the iminosugars related to **11**, especially into 8-homocastanospermine (**14**).[10] The same adduct **6** opens also an easy access to australine **13**[8] and related compounds *via* intramolecular alkylation of the nitrogen atom by the activated C-2 carbon atom. It should be stressed that the configuration at C-2 of the adduct **6** undergoes inversion during the nitrogen alkylation step, consequently leading to the correct configuration at C-3 of australine-related compounds. The present paper describes the synthesis of a derivative of australine in which the 1-hydroxy group was replaced by the hydroxymethyl substituent (1-homoaustraline; **15**). Synthesis of a number of 7-hydroxymethyl-indolizidines using intramolecular 1,3-dipolar cycloaddition has been reported recently by the Brandi's group.[9b]

Aldehydo-lactone **16**, the substrate for the synthesis, was obtained from adduct **6** following a earlier reported two-step procedure,[10] which involves rearrangement of the six-membered lactone ring into the five-membered one by deacetylation of **6** followed by glycolic cleavage of the terminal diol group. Subsequently, the aldehydo-lactone **16** was reduced to the triol **17** and both primary hydroxy groups were protected with *tert*-butyldiphenylsilyl ethers to afford **19**. The remaining secondary hydroxy group was mesylated to give compound **21** (Scheme 1).

Hydrogenolysis of the N–O bond over Pd/C caused prompt intramolecular alkylation of the nitrogen atom, which proceeded with inversion of configuration at the carbon atom bearing the mesyloxy group to afford **22**, which was characterized as the acetate **23**. The configuration of **23** was confirmed by ^{1}H NMR spectroscopy. The coupling constants $J_{1,2}$ and $J_{2,3}$ (both 8.2 Hz) confirmed the axial position of H-1, H-2, and H-3 protons. NOEs measurements showed a spin–spin interaction between H-1 (δ 2.59 ppm) and H-3 (δ 2.90 ppm) protons.



9: R=OH
10: R=H



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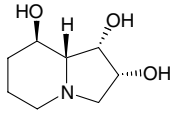

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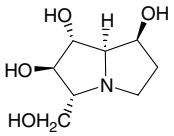

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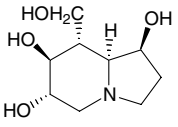

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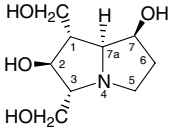

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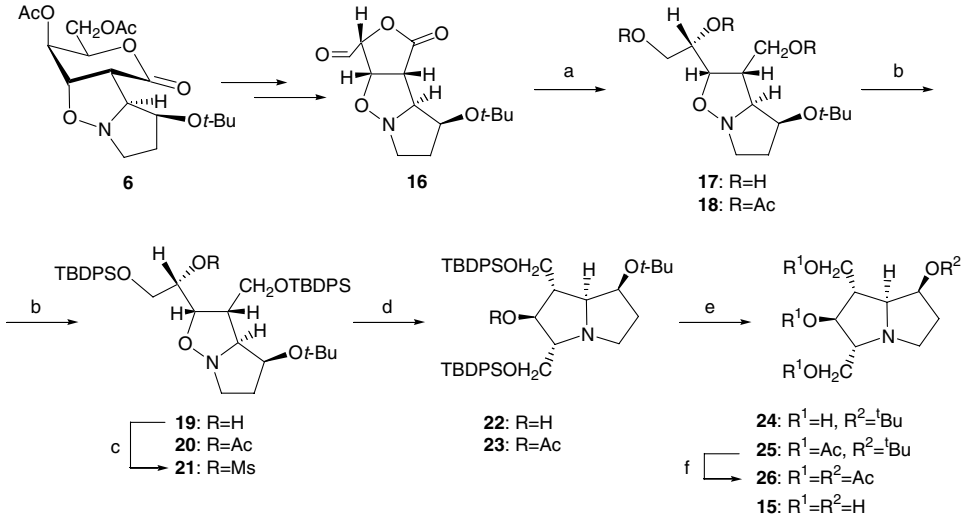


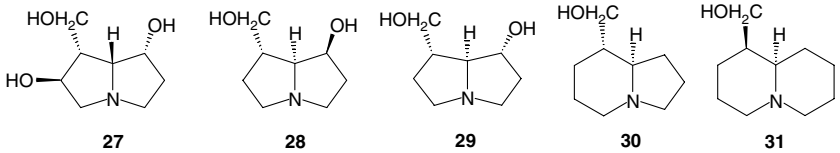
Scheme 1. Reagents and conditions: (a) $LiBH_4$, THF, rt, 24 h, 68% after acetylation; (b) TBDPSiCl, Et_3N, DMAP, 24 h, 58%; (c) MsCl, CH_2Cl_2, Et_3N, 2 h, −5 °C, 89%; (d) 10% Pd/C, AcOEt, H_2, 24 h, 65% after acetylation; (e) Bu_4NF, THF, 24 h, 87% after acetylation; (f) TFA, 2 h, 67% after acetylation.

Irradiation of the H-1 signal caused enhancement of the H-3 signal by 2.5% and conversely, the signal due to H-1 was enhanced by 3.1% when H-3 was irradiated.

In order to get the free iminosugar **15**, the stepwise deprotection was carried out. Initially the two primary hydroxy groups were desilylated and acetylated. Subsequently the *tert*-butyl group in **23** was removed using trifluoroacetic acid and the resulting hydroxyl was acetylated yielding the tetra-acetate of 1-homoaustraline **15**.

The discrimination between hydroxymethyl groups at earlier stage of the synthesis, followed by oxidative decarboxylation of the carboxylic group derived from the lactone should provide a simple way to australine **13**.

The biological activity of **15** toward commercially available α- and β-glucosidases was tested. Surprisingly, **15** showed only a weak inhibition of the α-glucosidase activity at a concentration of 0.02 M and no inhibition of β-glucosidase. Low biological activity of both 8-homocastanospermine (**14**) and 1-homoaustraline (**15**) is worth to note since the hydroxymethyl group at the carbon atom next to the bridgehead junction occurs in many natural iminosugars and related alkaloids, for example: (−)-rosmarinecine (**27**),[11] (+)-turneforcidine (**28**),[12] (−)-hastanecine (**29**),[12a,13] lupinine (30),[14] or (+)-tashiromine (**31**).[15]



In summary, we have reported the simple synthesis of 1-homoaustraline **15** in which a proper selection of readily available components of the 1,3-dipolar cycloaddition controls the absolute stereochemistry at all five stereogenic centers present in the target molecule. The reported synthesis demonstrated an exceptional effectiveness of the 1,3-dipolar cycloaddition of nitrones and sugar unsaturated δ-lactones, which led to only one diastereo-isomer with defined configuration at all stereogenic centers.

3. Experimental

3.1. General methods

^1H NMR spectra were recorded on a Bruker DRX 500 Avance Spectrometer. IR spectra were obtained on an FT-IR-1600 Perkin–Elmer spectrophotometer. The optical rotations were measured with a JASCO Dip-360 digital polarimeter. Mass spectra were recorded using an AMD-604 instrument and HPLC-MS were recorded with Mariner and API 356 detectors. Column chromatography was carried out using E. Merck Kiesel Gel (230–400 mesh). Adduct **6** was obtained according to known procedure.[2,3]

Enzymes and substrates were purchased from Sigma: α-glucosidase from rice, type V, 63.43 U/mg, 1.34 mg/mL; β-glucosidase from almonds, 25.8 U/mg, 95.4% protein.

3.2. (1′*S*,2*S*,3*S*,3a*S*,4*S*)-4-*tert*-Butoxy-2-(1′,2′-dihydroxyethyl)-3-hydroxymethyl-pyrrolidino[1,2-*b*]isoxazolidine (17)

The crude aldehyde **16** (0.12 g, 0.45 mmol), obtained by the earlier reported procedure,[10] was dissolved in dry THF (15 mL) and reduced with 2 mol equiv of $LiBH_4$. After 24 h, 1 M HCl was added by drops until pH 7. Then the mixture was diluted with THF, filtered through Celite, and evaporated to afford crude triol **17** (0.09 g, 74% yield), which was used for the next steps without purification. The triol **17** was characterized as the triacetate **18**, which was obtained by acetylation with Ac_2O–pyridine and a catalytic amount of DMAP. After standard work up, the product was purified on a silica gel column using 1:1 hexane–EtOAc as an eluent to afford (1′*S*,2*S*,3*S*,3a*S*,4*S*)-3-acetoxymethyl-4-*tert*-butoxy-2-(1′,2′-diacetoxyethyl)-pyrrolidino[1,2-*b*]isoxazolidine (**18**); $[\alpha]_D$ +31.5 (*c* 1.0, CH_2Cl_2); IR (film): *v* 1746 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 5.65 (ddd, 1H, *J* 3.7, 6.2, 6.3 Hz, H-1′), 4.59 (dd, 1H, *J* 3.7, 11.9 Hz, H-2′a), 4.35 (dd, 1H, *J* 8.3, 11.1 Hz, CH*H*OAc), 4.32 (dd, 1H, *J* 5.6, 6.2 Hz, H-2), 4.30 (dd, 1H, *J* 6.3, 11.9 Hz, H-2′b), 4.26 (dd, 1H, *J* 6.8, 11.1 Hz, C*H*HOAc), 3.60 (m, 1H, H-4), 3.32 (dd, 1H, *J* 2.7, 6.7 Hz, H-3a), 3.12 (m, 1H, H-6), 3.03 (dddd, 1H, *J* 2.7, 5.6, 6.8, 8.3 Hz, H-3), 2.99 (m, 1H, H-6′), 1.78, 1.71, 1.70 (3s, 9H, OAc), 1.56 (m, 1H, H-5), 1.43 (m, 1H, H-5′), 0.94 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 170.7, 170.6, 170.2, 76.9, 74.2, 71.1, 70.9, 69.3, 63.5, 62.8, 54.1, 45.2, 33.1, 28.2, 21.1, 20.8, 20.7; HRESIMS: calcd for $C_{19}H_{31}NO_8Na$: 424.1942; found: 424.1964 $[M+Na]^+$.

3.3. (1′*S*,2*S*,3*S*,3a*S*,4*S*)-4-*tert*-Butoxy-2-(2′-*tert*-butyldiphenylsiloxy-1′-hydroxyethyl)-3-*tert*-butyldiphenylsiloxymethyl-pyrrolidino[1,2-*b*]isoxazolidine (19)

The crude triol **17** (0.082 g, 0.30 mmol) was dissolved in Et_3N (15 mL), then *tert*-butyl(chloro)diphenylsilane (0.20 g, 0.72 mmol) and DMAP (0.06 mmol) were added. The soln was left under argon, at room temperature for 24 h and subsequently refluxed for 3 h. The mixture was then cooled, washed with water, brine, and again with water. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column using 4:1 hexane–ethyl acetate as eluent to afford **19** (0.13 g, 58% yield); $[\alpha]_D$ +16.5 (*c* 1.1, CH_2Cl_2); IR (film): *v* 3468, 1112 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 7.85, 7.25 (2m, 20H, Ph), 5.05 (d, 1H, *J* 7.7 Hz, H-2), 4.61 (dd, 1H, *J* 5.2, 9.1 Hz, H-1′), 4.45 (dd, 1H, *J* 9.8, 10.5 Hz, C*H*HOSi), 4.22 (dd, 1H, *J* 9.1, 9.2 Hz, H-2′a), 4.14 (dd, 1H, *J* 5.2, 9.2 Hz, H-2′b), 4.00 (dd, 1H, *J* 5.7, 9.8 Hz, CH*H*OSi), 3.68 (dddd, 1H, *J* 5.7, 6.0, 7.7, 10.5 Hz, H-3), 3.54 (ddd, 1H, *J* 6.7, 7.8, 8.0 Hz, H-4), 3.14 (ddd, 1H, *J* 2.6, 6.9, 13.3 Hz, H-6), 2.98 (dd, 1H, *J* 6.0, 7.8 Hz, H-3a), 2.42 (ddd, 1H, *J* 5.8, 11.7, 13.3 Hz, H-6′), 1.90 (m, 1H, H-5), 1.35 (m, 1H, H-5′), 1.22, 1.19, 0.86 (3s, 27H, *t*-Bu); ^{13}C NMR without aromatic carbons (125 MHz, C_6D_6) *δ*: 78.9, 73.3, 72.9, 72.1, 69.4, 65.5, 64.0, 52.9, 48.4, 32.4, 28.2, 27.2, 27.2, 19.6, 19.5; HRESIMS: calcd for $C_{45}H_{62}NO_5Si_2$: 752.4161; found: 752.4191 $[M+H]^+$.

3.4. (1′*S*,2*S*,3*S*,3a*S*,4*S*)-2-(1′-Acetoxy-2′-*tert*-butyldiphenylsiloxyethyl)-4-*tert*-butoxy-3-*tert*-butyldiphenylsiloxymethyl-pyrrolidino[1,2-*b*]isoxazolidine (20)

Disilyl derivative **19** (0.13 g, 0.173 mmol) was dissolved in Et_3N (15 mL), then Ac_2O (15 mL) and DMAP (0.02 mmol) were added. After 30 min the mixture was washed with water, brine, and again with water. The organic layer was dried over $MgSO_4$ and evaporated. Crude product was purified on silica gel column using hexane–ethyl acetate 3:1 v/v as an eluent to afford **20** (0.115 g, 84% yield); $[\alpha]_D$ +14.4 (*c* 1.4, CH_2Cl_2); IR (film): *v* 1744, 1112 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 7.80, 7.22 (2m, 20H, Ph), 5.70 (m, 1H, H-1′), 4.86 (dd, 1H, *J* 4.8, 5.8 Hz, H-2), 4.08 (d, 2H, *J* 5.8 Hz, H-2′a, H-2′b), 4.06 (dd, 1H, *J* 8.1, 9.9 Hz, C*H*HOSi), 4.00 (dd, 1H, *J* 7.8, 9.9 Hz, CH*H*OSi), 3.76 (m, 1H, H-4), 3.68 (dd, 1H, *J* 3.5, 6.9 Hz, H-3a), 3.25 (m, 2H, H-3, H-6), 3.00 (ddd, 1H, *J* 6.6, 7.6, 12.0 Hz, H-6′), 1.71 (m, 1H, H-5), 1.62 (s, 3H, OAc), 1.50 (m, 1H, H-5′), 1.19, 1.18, 0.94 (3s, 27H, *t*-Bu); ^{13}C NMR without aromatic carbons (125 MHz, C_6D_6) *δ*: 169.6, 77,0, 73.5, 72.3, 72.2, 70.6, 63.4, 63.3, 54.4, 49.3, 33.3, 28.3, 27.2, 27.1, 20.8, 19.5, 19.5; HRESIMS: calcd for $C_{47}H_{64}NO_6Si_2$: 794.42667; found: 794.4273 $[M+H]^+$.

3.5. (1′*S*,2*S*,3*S*,3a*S*,4*S*)-2-(2′-*tert*-Butyldiphenylsiloxy-1′-methanesulfonyloxyethyl)-4-*tert*-butoxy-3-*tert*-butyldiphenylsiloxymethyl-pyrrolidino[1,2-*b*]isoxazolidine (21)

A soln of alcohol **19** (0.13 g, 0.173 mmol), dry CH_2Cl_2 (15 mL), and Et_3N (0.04 g, 0.4 mmol) was cooled to −5 °C. Subsequently mesyl chloride (0.027 g, 0.24 mmol) was added and the temperature of the mixture was allowed to rise to room temperature. After 2 h the mixture was washed with brine (10 mL) and water (10 mL), dried over $MgSO_4$, and evaporated. The crude product was purified on a silica gel column using hexane–ethyl acetate 1:1 v/v as an eluent to afford **21** (0.13 g, 89% yield); $[\alpha]_D$ +15.9 (*c* 1.9, CH_2Cl_2); IR (film): *v* 1112 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 7.90–7.18 (m, 20H, Ph), 5.36 (m, 1H, H-1′), 4.84 (dd, 1H, *J* 5.9, 7.0 Hz, H-2), 4.28–4.21 (m, 2H, H-2′a, H-2′b), 4.16 (dd, 1H, *J* 8.3, 10.4 Hz, C*H*HOSi), 3.92 (dd, 1H, *J* 6.6, 10.4 Hz, CH*H*OSi), 3.68 (m, 1H, H-4), 3.56 (dd, 1H, *J* 3.5, 7.0 Hz, H-3a), 3.22 (dddd, 1H, *J* 3.5, 5.9, 6.6, 8.3 Hz, H-3), 3.14 (m, 1H, H-6), 2.95 (ddd, 1H, *J* 6.5, 8.4, 12.3 Hz, H-6′), 2.60 (s, 3H, Ms), 1.65 (m, 1H, H-5), 1.46 (m, 1H, H-5′), 1.20, 1.13, 0.89 (3s,

27H, *t*-Bu); ^{13}C NMR without aromatic carbons (125 MHz, C_6D_6) δ: 81.4, 77.8, 73.6, 72.0, 70.1, 64.8, 63.0, 54.6, 48.7, 38.8, 33.3, 28.2, 27.2, 27.1, 19.6, 19.4; HRESIMS: calcd for $C_{46}H_{64}NO_7Si_2S$: 830.3937; found: 830.3942 $[M+H]^+$.

3.6. (1*S*,2*S*,3*R*,7*S*,7a*S*)-2-Acetoxy-1,3-bis-(*tert*-butyldiphenylsiloxymethyl)-7-*tert*-butoxy-pyrolizidine (23)

To a soln of **21** (0.138 g, 0.154 mmol) in AcOEt (10 mL), a catalytic amount of 10% Degussa Pd/C was added and the mixture was held under hydrogen atmosphere. After 24 h, the catalyst was filtered and the solvent evaporated. The crude **22** was dissolved in Et_3N (10 mL) and Ac_2O (10 mL) and DMAP (0.02 mmol) were added. After 1 h, solvents were evaporated and a crude product was purified on a silica gel column (1:1 hexane–EtOAc) to afford **23** (0.11 g, 91% yield); $[\alpha]_D$ −15.9 (*c* 0.22, $CHCl_3$); IR (film): ν 1741, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.31 (m, 20H, Ph), 5.27 (t, 1H, *J* 8.2 Hz, H-2), 3.90 (m, 1H, H-7), 3.67 (dd, 1H, *J* 4.9, 10.5 Hz, C-3C*H*HOSi), 3.66 (dd, 1H, *J* 6.5, 10.5 Hz, C-3CH*H*OSi), 3.64 (m, 2H, C-1CH_2OSi), 3.38 (dd, 1H, *J* 5.1, 7.9 Hz, H-7a), 3.08 (m, 1H, H-5), 2.90 (ddd, 1H, *J* 4.9, 6.5, 8.2 Hz, H-3), 2.78 (m, 1H, H-5′), 2.59 (m, 1H, H-1), 1.89 (s, 3H, Ac), 1.85 (m, 2H, H-6,6′), 1.09, 1.04, 1.03 (3s, 27H, 3*t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.0, 135.7, 135.7, 135.7, 135.7, 133.8, 133.8, 133.7, 133.5, 129.5, 129.5, 129.5, 129.4, 127.6, 127.6, 127.6, 127.5, 77.6, 73.3, 72.3, 71.5, 67.6, 67.1, 62.9, 52.8, 44.7, 35.5, 28.4, 26.9, 26.8, 21.1, 19.2, 19.2; HRESIMS: calcd for $C_{47}H_{64}NO_5Si_2$: 778.4318; found: 778.4352 $[M+H]^+$.

3.7. (1*S*,2*S*,3*R*,7*S*,7a*S*)-2-Acetoxy-1,3-diacetoxymethyl-7-*tert*-butoxy-pyrrolizidine (25)

To compound **23** (0.078 g, 0.100 mmol) in THF (10 mL), 1 equiv of Bu_4NF was added. After 24 h, pyridine (1.5 mL) and Ac_2O (1 mL) were added to the mixture. After 3 h, the reaction mixture was concentrated and a crude product was purified on a silica gel (1:1 hexane–EtOAc) to afford **25** (0.034 g, 87% yield); $[\alpha]_D$ +9.61 (*c* 1.05, CH_2Cl_2); IR (film): ν 1743, 1237 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 5.53 (t, 1H, *J* 8.6 Hz, H-2), 4.37 (dd, 1H, *J* 4.6, 11.3 Hz, C-3C*H*HOAc), 4.27 (dd, 1H, *J* 5.6, 11.2 Hz, C-1C*H*HOAc), 4.21 (dd, 1H, *J* 7.27, 11.2 Hz, C-1CH*H*OAc), 4.19 (dd, 1H, *J* 7.1, 11.3 Hz, C-3CH*H*OAc), 3.55 (m, 1H, H-7), 3.16 (dd, 1H, *J* 4.6, 8.0 Hz, H-7a), 3.06 (m, 2H, H-3, H-5), 2.89 (m, 1H, H-1), 2.67 (m, 1H, H-5′), 1.72, 1.71, 1.66 (3s, 9H, 3 × Ac), 1.67 (m, 1H, H-6), 1.57 (m, 1H, H-6′), 0.98 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) δ: 170.0, 169.9, 169.6, 77.6, 73.5, 71.1, 69.3, 68.5, 65.3, 64.0, 52.1, 41.7, 36.2, 28.3, 20.5, 20.5, 20.4; HRESIMS: calcd for $C_{19}H_{32}NO_7$: 386.21733; found: 386.2179 $[M+H]^+$.

3.8. (1*S*,2*S*,3*R*,7*S*,7a*S*)-2,7-Diacetoxy-1,3-diacetoxymethyl-pyrrolizidine (26)

Compound **23** (0.034 g, 0.088 mmol) was dissolved in TFA (8 mL) and stirred for 5.5 h. Subsequently the solvent was carefully evaporated. The crude product was dissolved in Et_3N (5 mL), Ac_2O (5 mL), and DMAP was added. After 1 h the solvents were evaporated and the residue was purified by chromatography (1:1 hexane–EtOAc) to afford **26** (0.022 g, 67% yield); $[\alpha]_D$ +10.7 (*c* 0.61, CH_2Cl_2); IR (film): ν 1734 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ: 5.34 (t, 1H, *J* 8.8 Hz, H-2), 5.10 (ddd, 1H, *J* 1.3, 4.1, 4.1 Hz, H-7), 4.32 (dd, 1H, *J* 4.4, 11.3 Hz, C-3C*H*HOAc), 4.31 (dd, 1H, *J* 5.1, 11.2 Hz, C-1C*H*HOAc), 4.09 (dd, 1H, *J* 5.6, 11.3 Hz, C-3CH*H*OAc), 3.97 (dd, 1H, *J* 7.7, 11.2 Hz, C-1CH*H*OAc), 3.22 (dd, 1H, *J* 4.1, 8.4 Hz, H-7a), 2.98 (m, 2H, H-3, H-5), 2.58 (dddd, 1H, *J* 5.1, 7.7, 8.4, 8.8 Hz, H-1), 2.49 (ddd, 1H, *J* 6.1, 9.3, 11.5 Hz, H-5′), 1.76 (m, 1H, H-6), 1.74, 1.71, 1.65, 1.62 (4s, 12H, 4 × OAc), 1.66 (m, 1H, H-6′); ^{13}C NMR (125 MHz, C_6D_6) δ: 170.0, 169.8, 169.5, 169.2, 77.2, 73.6, 69.1, 68.9, 65.3, 64.3, 52.0, 42.1, 34.7, 20.5, 20.4, 20.4, 20.3; HRESIMS: calcd for $C_{17}H_{26}NO_8$: 372.16529; found: 372.1650 $[M+H]^+$.

3.9. (1*S*,2*S*,3*R*,7*S*,7a*S*)-1,3-Dihydroxymethyl-2,7-dihydroxy-indolizidine (1-homoaustraline, 15)

Compound **26** (0.022 g, 0.059 mmol) was dissolved in 1.3% soln of ammonia in MeOH (8 mL) and left for 24 h at room temperature. Subsequently, MeOH was evaporated and the residue was purified by chromatography (MeOH) to afford **15** (0.01 g, 83% yield); $[\alpha]_D$ −3.7 (*c* 0.44, CH_3OH); IR (film): ν 3402 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ: 4.15 (ddd, 1H, *J* 2.3, 4.1, 4.2 Hz, H-7), 3.88 (dd, 1H, *J* 4.2, 10.8 Hz, C-1C*H*HOH), 3.77 (t, 1H, *J* 9.0 Hz, H-2), 3.74 (dd, 1H, *J* 3.4, 11.1 Hz, C-3C*H*HOH), 3.58 (dd, 1H, *J* 7.2, 10.8 Hz, C-1CH*H*OH), 3.53 (dd, 1H, *J* 6.4, 11.1 Hz, C-3CH*H*OH), 3.24 (dd, 1H, *J* 4.2, 8.7 Hz, H-7a), 3.14 (ddd, 1H, *J* 2.4, 7.3, 10.0 Hz, H-5), 2.80 (ddd, 1H, *J* 6.2, 10.0, 11.0 Hz, H-5′), 2.68 (ddd, 1H, *J* 3.4, 6.4, 9.0 Hz, H-3), 2.41 (dddd, 1H, *J* 4.2, 7.2, 8.7, 9.0 Hz, H-1), 2.00 (dddd, 1H, *J* 2.3, 2.4, 6.2, 13.0 Hz, H-6), 1.93 (dddd, 1H, *J* 4.1, 7.3, 11.0, 13.0 Hz, H-6′); ^{13}C NMR (125 MHz, CD_3OD) δ: 76.6, 75.4, 71.7, 71.2, 64.3, 63.0, 53.3, 46.8, 37.2; HRESIMS: calcd for $C_9H_{18}NO_4$: 204.12303; found: 204.1240 $[M+H]^+$.

3.10. Biological tests

The β-glucosidase activity of pyrrolizidine **15** was measured by modification of procedures described previously.[16,17] The reaction mixture consisted of: 100 μL of 0.014 M *p*-nitrophenyl β-D-glucopyranoside, 250 μL of

0.2 M acetate buffer (pH 4.6), 50 μL of inhibitor soln (either water or MeOH), and 100 μL of enzyme soln (3 μg/mL). After incubation for 15 min at 30 °C, the reaction was terminated by addition of 1 mL of 2% sodium carbonate. The absorbance of liberated *p*-nitrophenol was measured at 405 nm.

The α-glucosidase activity of **15** was measured by modification of the procedures described previously.[18,19] The reaction mixture consisted of: 25 μL of 0.0165 M *p*-nitrophenyl α-D-glucopyranoside, 403 μL of 0.1 M acetate buffer (pH 4.0), 50 μL of inhibitor soln (either water or MeOH), and 22 μL of enzyme soln (10 × diluted). After incubation for 15 min at 37 °C, the reaction was terminated by addition of 1 mL of 2% sodium carbonate. The absorbance of liberated *p*-nitrophenol was measured at 405 nm.

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