Synthesis of 8-homocastanospermine[1]

Konrad Paśniczek, Dariusz Socha, Margarita Jurczak, Jolanta Solecka, and Marek Chmielewski

Abstract: The 1,3-dipolar cycloaddition of a five-membered cyclic nitrone derived from malic acid (**4**) and unsaturated D-*threo*-hexaldonolactone (**1**) leads to a single adduct **6**, which can be transformed into the 8-homocastanospermine (**13**) via a sequence involving rearrangement of the six-membered lactone ring into the five-membered one, removal of the terminal carbon atom from the sugar chain, cleavage of the N—O bond, and the intramolecular alkylation of the nitrogen atom. The iminosugar (**13**) does not show any interesting inhibitory activity towards α- and β-glucosidases.

Key words: iminosugars, homocastanospermine, nitrones, aldono-1,5-lactone, 1,3-dipolar cycloaddition, glucosidases.

Résumé : La cycloaddition 1,3-dipolaire d'une nitrone cyclique à cinq chaînons dérivée de l'acide malique (**4**) et de la D-*thréo*-hexaldonolactone insaturée (**1**) conduit à la formation d'un seul adduit qui peut être transformé en 8-homocastanospermine (**13**), par le biais d'une séquence impliquant le réarrangement de la lactone à six chaînons en une lactone à cinq chaînons, l'élimination de l'atome de carbone terminal de la chaîne du sucre, le clivage de la liaison N—O et d'une alkylation intramoléculaire de l'atome d'azote. L'iminosucre (**13**) ne présente pas d'activité inhibitrice intéressante vis-à-vis des α- et des β-glucosidases.

Mots clés : iminosucres, homocatanospermine, nitrones, aldono-1,5-lactone, cycloaddition 1,3-dipolaire, glucosidases.

[Traduit par la Rédaction]

Introduction

Recently, we have reported that the cycloaddition of 2,3-unsaturated aldono-1,5-lactones (**1** or **2**) and the five-membered cyclic nitrones (**3** or **4**) (Chart 1) 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, the 4-acetoxy group of the lactone assumes a decisive role in the control of the stereochemical pathway of cycloaddition. The stereochemical preferences are the underlying reason that, in many cases, a single adduct or at least a high preponderance of a single adduct is observed. This observation has been well-illustrated by the exclusive formation of adducts **6** and **7** from D-*threo* 4-*O*-acetyl-lactone (**1**) and D-*erythro* 4-*O*-acetyl-lactone (**2**), respectively (Chart 2) (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-hydroxylentiginosine (**9**) and the formal synthesis of lentiginosine (**10**) (5). The easy access to adducts **6** and **7** opens an entry to the corresponding indolizidines with an (*R*) or (*S*) configurations at the bridgehead carbon atom, which are closely related to the castanospermine (**11**) and swainsonine (**12**) (Chart 3) (6).

Both components of the cycloaddition, the nitrone and the unsaturated lactone, carry over their own substituents (protected hydroxyls) with their original configuration, whereas the configurations at C-1a, C-4a, and C-4b of the cycloadduct are established during the reaction. Adduct **6** is particularly interesting because it can be easily transformed into the compounds related to the castanospermine (**11**) and especially the 8-homocastanospermine (**13**). The castanospermine (**11**) (7) itself displays a range of interesting therapeutic properties (8), however, it is very toxic, therefore its use has a limited value. The present paper describes the synthesis of imino sugar **13** from adduct **6**.

Results and discussion

Adduct **6** (2, 3) was deacetylated with sodium methoxide in methanol to afford compound **14**. The reaction proceeds with rearrangement of the six-membered lactone ring into a five-membered one. The glycolic cleavage of the terminal diol group in **14** with $NaIO_4$ followed by the reduction of the aldehyde group with sodium triacetoxyborohydride gave compound **16** in 83% yield. The use of sodium borohydride resulted in the reduction of both carbonyl functions of the aldehyde **15**, whereas the sodium cyanoborohydride gave the desired product **16** in a low yield (Scheme 1).

The activation of the terminal hydroxymethyl group by the introduction of a halogen or sulfonyl as a leaving group, followed by the direct alkylation of the isoxazolidine nitrogen atom, led to an unattractive mixture of products. Therefore, we decided to form the indolizidine skeleton in a stepwise manner. First, the hydroxymethyl group was pro-

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Chart 1.

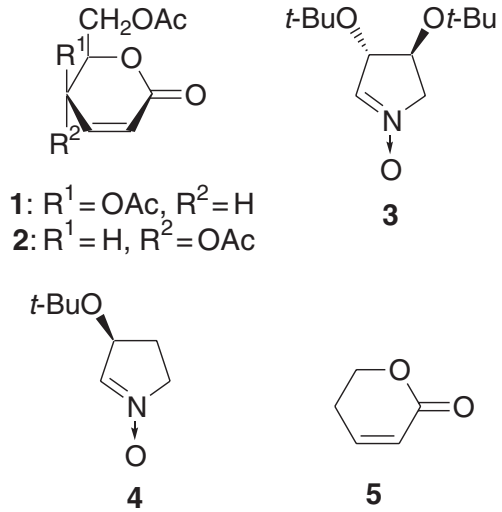
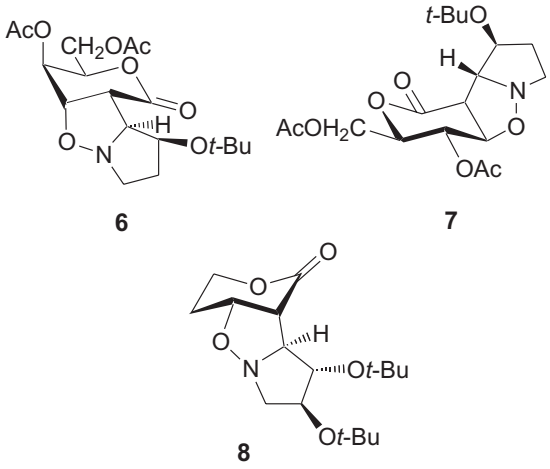
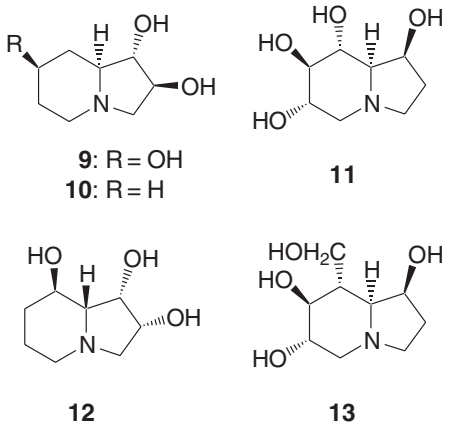


Chart 2.



tected as a *tert*-butyldiphenylsilyl derivative **17** and lactone was reduced with sodium borohydride to give diol **18**. Both hydroxy groups in **18** were masked by the formation of an isopropylidene moiety. The desilylation of **19** with tetrabutylammonium fluoride led to alcohol **20**. Due to the low stability of the isopropylidene fragment and the tendency of the terminal mesyloxymethyl group to undergo intramolecular alkylation, the next three steps were performed with only a partial purification of intermediary products. Alcohol **20** was mesylated to afford **21**, the isopropylidene protection was removed using 80% acetic acid, and the sequence was completed by the hydrogenolysis of the N—O bond over Pd/C and intramolecular alkylation of the nitrogen atom. The final product of this reaction sequence (indolizidine **22**) was acetylated and characterized as the triacetate **23**. The *tert*-butyl protection in **23** was subsequently removed with trifluoroacetic acid and the liberated hydroxy group was acetylated affording tetraacetate **24**. The complete deacetylation of **24** with ammonia in methanol furnished the **13**. Synthesis of a number of 8-hydroxymethylindolizidines using intramolecular 1,3-dipolar cycloaddition has been reported recently by Brandi's group (9).

Chart 3.



Note that the oxidation of the hydroxymethyl group in suitably protected **13** or **23** to the carboxylic function followed by an oxidative decarboxylation, for example, by the methodology recently reported by us for the other indolizidine (5), should provide **11**.

The biological activity of compound **13** toward commercially available α- and β-glucosidases was tested and compared with the corresponding data measured for commercially available **11**. Surprisingly, compound **13** showed only a trace inhibition of α-glucosidase activity in a concentration of 0.02 mol/L and no inhibition of β-glucosidase.

In summary, we have reported the simple synthesis of 8-homocastanospermine (**13**) 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 formation of only one diastereomer with a fully defined configuration at all stereogenic centers.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX 500 Avance spectrometer. IR spectra were obtained on a PerkinElmer FT-IR 1600 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 performed with E. Merck Kiesel Gel (230–400 mesh).

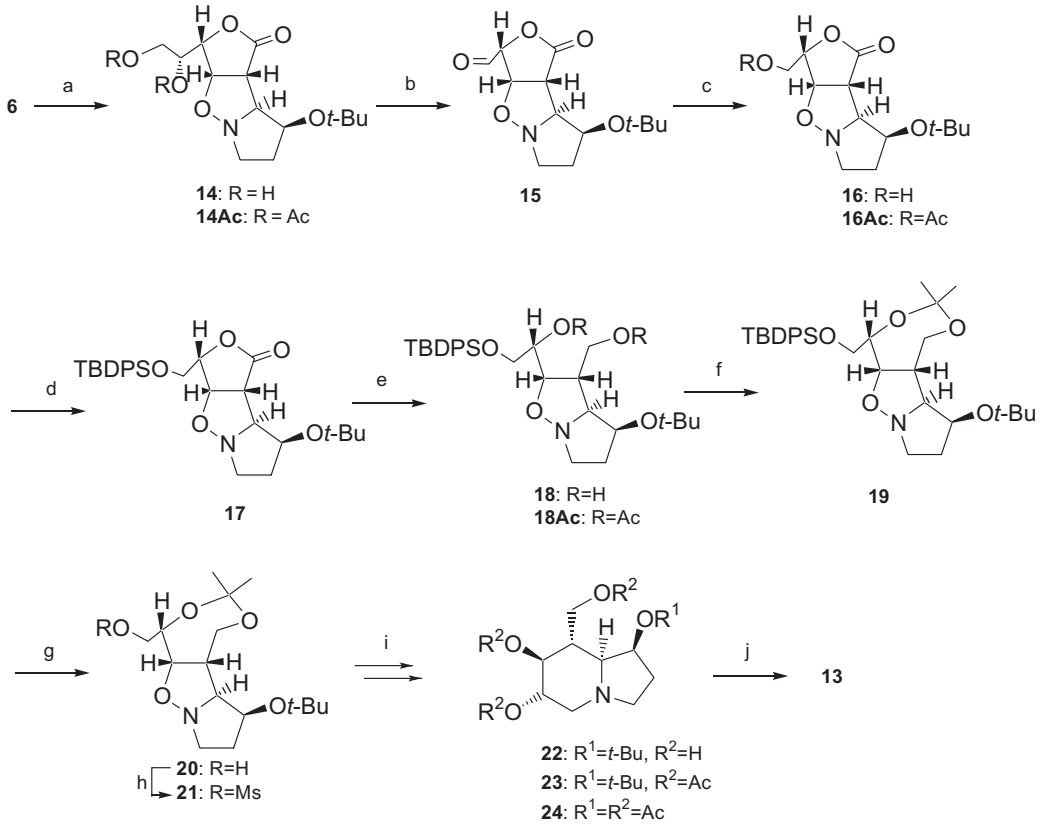
Adduct **6** was obtained according to the known procedure (2, 3).

Enzymes and substrates were purchased from Sigma-Aldrich: 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.

(1a*S*,2*R*,4a*R*,4b*S*,5*S*,1′*R*)-5-*tert*-Butoxy-2-(1′,2′-dihydroxyethyl)-4-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]-tetrahydrofurane (14)

Adduct **6** was dissolved in methanol, treated with 1 molar equiv. of sodium carbonate, and stirred at room temperature

Scheme. 1. (*a*) Na_2CO_3, MeOH (88%); (*b*, *c*) $NaIO_4$, MeOH–H_2O; $NaBH(OAc)_3$, CH_2Cl_2 (74%); (*d*) *tert*-butyldiphenylchlorosilane, DMAP, CH_2Cl_2 (76%); (*e*) $NaBH_4$, MeOH (60%); (*f*) 2,2-dimethoxypropane, *p*-TsOH (87%); (*g*) Bu_4NF, THF (94%); (*h*) MsCl, Et_3N, CH_2Cl_2 (96%); (*i*) 80% AcOH; H_2, 10% Pd/C, MeOH; Ac_2O, Et_3N, DMAP (55%); (*j*) MeOH–NH_3 (91%).



until the disappearance of the substrate (1 h). Subsequently, the solution was neutralized with Amberlite IR-1200 [H^+], diluted with dichloromethane, filtered through Celite, and evaporated. The crude product was purified by chromatography using CH_2Cl_2–MeOH (20:1 *v*/*v*) as the eluent to afford **14** in 88% yield. $[\alpha]_D$ +5.3° (*c* 0.5, CH_2Cl_2). IR (film, cm^{-1}): 3392, 1773. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.90 (dd, 1H, *J* = 6.3, 8.1 Hz, H-1a), 4.64 (dd, 1H, *J* = 2.8, 6.3 Hz, H-2), 4.23 (dt, 1H, *J* = 5.8, 7.3, 7.5 Hz, H-5), 4.20 (ddd, 1H, *J* = 2.8, 5.0, 6.4 Hz, C*H*OH), 3.93 (bd, 1H, *J* = 7.3 Hz, H-4b), 3.90 (dd, 1H, *J* = 0.9, 8.1 Hz, H-4a), 3.81 (dd, 1H, *J* = 6.4, 11.1 Hz, C*H*HOH), 3.72 (dd, 1H, *J* = 5.0, 11.1 Hz, CH*H*OH), 3.47 (ddd, 1H, *J* = 2.6, 7.8, 14.0 Hz, H-7), 2.90 (dddd, 1H, *J* = 0.6, 7.4, 10.8, 14.0 Hz, H-7′), 2.12 (ddt, 1H, *J* = 2.6, 7.4, 7.5, 13.1 Hz, H-6), 1.99 (dddd, 1H, *J* = 5.8, 7.8, 10.8, 13.1 Hz, H-6′), 1.21 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.4, 82.5, 78.5, 74.6, 73.5, 71.2, 69.4, 63.9, 53.1, 50.7, 34.0, 28.4. HRMS (ESI) *m*/*z* calcd. for $C_{14}H_{23}NO_6Na$: 324.1418 [M + Na]$^+$; found: 324.1430.

(1a*S*,2*R*,4a*R*,4b*S*,5*S*,1′*R*)-2-(1′,2′-Diacetoxyethyl)-5-*tert*-butoxy-4-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]-tetrahydrofurane (14Ac)

Melting point 81–83 °C. $[\alpha]_D$ –4.7° (*c* 0.3, CH_2Cl_2). IR (film, cm^{-1}): 1781, 1745. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.49 (ddd, 1H, *J* = 2.9, 3.7, 8.8 Hz, CHOAc), 4.75 (dd, 1H, *J* = 4.6, 6.7 Hz, H-1a), 4.66 (dd, 1H, *J* = 4.6, 8.8 Hz, H-2), 4.54 (dd, 1H, *J* = 2.9, 12.6 Hz, C*H*HOAc), 4.31 (dd, 1H, *J* = 3.7, 12.6 Hz, CH*H*OAc), 4.21 (dt, 1H, *J* = 5.5, 7.2, 7.3 Hz, H-5), 3.94 (bd, 1H, *J* = 7.3 Hz, H-4b), 3.83 (dd, 1H, *J* = 0.8, 6.7 Hz, H-4a), 3.35 (ddd, 1H, *J* = 3.5, 7.7, 13.6 Hz, H-7). 2.92 (ddd, 1H, *J* = 7.2, 10.4, 13.6 Hz, H-7′), 2.10, 2.09 (2s, 6H, 2Ac), 2.06 (ddt, 1H, *J* = 3.5, 13.1, 7.2, 7.2 Hz, H-6), 1.90 (dddd, 1H, *J* = 5.5, 7.2, 10.4, 13.1 Hz, H-6″), 1.22 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.0, 170.5, 169.8, 80.1, 77.9, 74.6, 73.3, 71.1, 70.0, 62.7, 53.9, 52.0, 34.3, 28.4, 20.9, 20.7. HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{28}NO_8$: 386.1809 [M + H]$^+$; found: 386.1827.

(1a*S*,2*S*,4a*R*,4b*S*,5*S*)-5-*tert*-Butoxy-2-hydroxymethyl-4-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydrofurane (16)

Compound **14** (0.051 g, 0.17 mmol) was dissolved in methanol–water (6:1 *v*/*v*, 5 mL) and treated at room temperature with 2 molar equiv. of sodium metaperiodate (0.072 g). After 1 h the reaction was completed. The crude product (**15**) was passed through a short silica gel column using dichloromethane–methanol (20:1 *v*/*v*) as the eluent. After evaporation of the solvent, the product was dissolved in dry CH_2Cl_2 (15 mL) and reduced with 2 molar equiv. of $NaBH(OAc)_3$. Standard work up provided a product that was purified on a silica gel column (hexane – ethyl acetate, 1:2 *v*/*v*) to afford **16** (0.034 g, 74%). $[\alpha]_D$ +11.0° (*c* 0.4, CH_2Cl_2). IR (film, cm^{-1}): 3409, 1774. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.90 (dd, 1H, *J* = 6.1, 7.9 Hz, H-1a), 4.66 (ddd, 1H, *J* = 3.7, 4.9, 6.0 Hz, H-2), 4.23 (dt, 1H, *J* = 5.7, 7.3, 7.5 Hz, H-5), 4.06 (dd, 1H, *J* = 3.7, 12.4 Hz, C*H*HOH), 3.96 (dd, 1H, *J* = 5.0, 12.4 Hz, CH*H*OH), 3.95 (d, 1H, *J* =

7.5 Hz, H-4b), 3.89 (d, 1H, *J* = 7.9 Hz, H-4a), 3.46 (ddd, 1H, *J* = 2.8, 7.8, 14.0 Hz, H-7), 2.93 (ddd, 1H, *J* = 7.4, 10.6 14.0 Hz, H-7′), 2.13 (ddt, 1H, *J* = 2.8, 13.2, 7.3, 7.4 Hz, H-6), 1.98 (dddd, 1H, *J* = 5.7, 7.8, 10.6, 13.2 Hz, H-6′), 1.22 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.5, 82.5, 78.4, 74.5, 73.6, 71.3, 60.3, 53.3, 51.1, 34.1, 28.3. HRMS (ESI) *m*/*z* calcd. for $C_{13}H_{22}NO_5$: 272.1492 $[M + H]^+$; found: 272.1486.

(1a*S*,2*S*,4a*R*,4b*S*,5*S*)-2-Acetoxymethyl-5-*tert*-butoxy-4-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydrofurane (16Ac)

$[\alpha]_D$ –8.7° (*c* 0.4, CH_2Cl_2). IR (film, cm^{-1}): 1779, 1742. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.81 (dd, 1H, *J* = 4.8, 6.8 Hz, H-1a), 4.72 (ddd, 1H, *J* = 3.8, 4.8, 8.3 Hz, H-2), 4.56 (dd, 1H, *J* = 3.8, 12.4 Hz, C*H*HOAc), 4.41 (dd, 1H, *J* = 8.3, 12.4 Hz, CH*H*OAc), 4.23 (dt, 1H, *J* = 5.3, 7.1, 7.3 Hz, H-5), 3.95 (d, 1H, *J* = 7.3 Hz, H-4b), 3.82 (d, 1H, *J* = 6.8 Hz, H-4a), 3.40 (ddd, 1H, *J* = 3.5, 7.7, 13.6 Hz, H-7), 2.94 (ddd, 1H, *J* = 7.3, 10.0, 13.6 Hz, H-7′), 2.13 (s, 3H, Ac), 2.10 (dddd, 1H, *J* = 3.5, 7.1, 7.3, 13.1 Hz, H-6), 1.95 (dddd, 1H, *J* = 5.3, 7.7, 10.0, 13.1 Hz, H-6′), 1.24 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, C_6D_6) δ: 176.2, 169.9, 80.1, 77.6, 73.8, 73.7, 71.6, 63.0, 53.4, 51.6, 34.5, 28.2, 20.2. HRMS (ESI) *m*/*z* calcd. for $C_{15}H_{24}NO_6$: 314.15981 $[M + H]^+$; found: 314.1613.

(1a*S*,2*R*,4a*R*,4b*S*,5*S*)-5-*tert*-butoxy-2-formyl-4-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydrofurane (15)

A small sample of **15** was partially purified by chromatography using hexane – ethyl acetate (1:2 *v*/*v*) as the eluent; mp 60.5–63.5 °C. $[\alpha]_D$ +29.1° (*c* 0.4, CH_2Cl_2). IR (film, cm^{-1}): 1773, 1728. ^{1}H NMR (500 MHz, C_6D_6) δ: 9.57 (d, 1H, *J* = 2.2 Hz, CHO), 4.29 (bt, 1H, *J* = 6.3, 7.4 Hz, H-1a), 3.94 (dd, 1H, *J* = 2.2, 6.3 Hz, H-2), 3.51 (bd, 1H, *J* = 7.6 Hz, H-4b), 3.42 (dt, 1H, *J* = 5.8, 7.2, 7.6 Hz, H-5), 3.23 (dd, 1H, *J* = 1.0, 7.4 Hz, H-4a), 3.04 (ddd, 1H, *J* = 2.2, 7.8, 13.9 Hz, H-7), 2.26 (dddd, 1H, *J* = 0.7, 7.4, 11.0, 13.9 Hz, H-7′), 1.60 (m, 1H, H-6), 1.35 (m, 1H, H-6′), 0.90 (s, 9H, *t*-Bu). HRMS (ESI) *m*/*z* calcd. for $C_{14}H_{23}NO_6Na$: 324.14176 [M + MeOH + Na]$^+$; found: 324.1408. HRMS (ESI) *m*/*z* calcd. for $C_{15}H_{25}NO_6Na$: 338.15741 [M + EtOH + Na]$^+$; found: 338.1590.

(1a*S*,2*S*,4a*R*,4b*S*,5*S*)-5-*tert*-Butoxy-2-*tert*-butyldiphenylsiloxymethyl-4-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]-tetrahydrofurane (17)

Alcohol **16** (0.043 g, 0.16 mmol) was dissolved in dichloromethane (15 mL), and treated with *tert*-butyldiphenylchlorosilane (0.057 g, 0.2 mmol) and DMAP (0.2 mmol). The solution was left under argon at room temperature for 24 h and then it was refluxed for 3 h. Subsequently, the mixture was cooled, washed with water, brine, and water again. The organic layer was dried and evaporated. The residue was purified on a silica gel column using hexane – ethyl acetate (4:1 *v*/*v*) as the eluent to afford **17** (0.062 g, 76% yield). $[\alpha]_D$ –0.9° (*c* 0.5, CH_2Cl_2). IR (film, cm^{-1}): 1779. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (m, 4H, Ph), 7.39 (m, 6H, Ph), 4.70 (dd, 1H, *J* = 4.2, 6.3 Hz, H-1a), 4.61 (ddd, 1H, *J* = 4.2, 5.8, 6.5 Hz, H-2), 4.17 (dt, 1H, *J* = 5.6, 7.0, 7.1 Hz, H-5), 4.04 (dd, 1H, *J* = 5.8, 11.2 Hz, C*H*HOH), 4.02 (dd, 1H, *J* = 6.5, 11.2 Hz, CH*H*OH), 3.94 (dd, 1H, *J* = 1.2, 7.1 Hz, H-4b), 3.76 (dd, 1H, *J* = 1.2, 6.3 Hz, H-4a), 3.22 (ddd, 1H, *J* = 4.5, 7.5, 13.0 Hz, H-7), 2.92 (ddd, 1H, *J* = 6.9, 9.3, 13.0 Hz, H-7′), 1.97 (dddd, 1H, *J* = 4.5, 6.9, 7.0, 13.0 Hz, H-6), 1.83 (dddd, 1H, *J* = 5.6, 7.5, 9.3, 13.0 Hz, H-6′), 1.20, 1.06 (2s, 18H, 2*t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.1, 135.62, 135.61, 133.4, 133.2, 129.72, 129.70, 127.7, 127.6, 82.8, 77.8, 74.4, 72.9, 71.1, 61.7, 53.7, 52.0, 34.0, 28.4, 26.8, 19.2. HRMS (ESI) *m*/*z* calcd. for $C_{29}H_{39}NO_5NaSi$: 532.2490 $[M + H]^+$; found: 532.2516.

(1a*S*,2*S*,3*S*,3a*S*,4*S*)-2-(2′-*tert*-Butyldiphenylsiloxymethyl-1′-hydroxy)-4-*tert*-butoxy-3-hydroxymethyl-pyrrolidino-[1,2-*b*]isoxazolidine (18)

Lactone **17** (0.10 g, 0.2 mmol) was dissolved in methanol (25 mL), treated in portions with $NaBH_4$ (0.015 g, 0.4 mmol), and left for 4 h. Subsequently, 2 drops of water were added and the mixture was filtered through Celite. The solution was evaporated and the residue was purified on a silica gel column using hexane – ethyl acetate (1:3 *v*/*v*) as the eluent to afford **15** (0.062 g, 60%); mp 108.0–109.5 °C. $[\alpha]_D$ +38.2° (*c* 1.23, CH_2Cl_2). IR (film, cm^{-1}): 3392. ^{1}H NMR (500 MHz, C_6D_6) δ: 7.78 (m, 4H, Ph), 7.22 (m, 6H, Ph), 4.57 (d, 1H, *J* = 8.0 Hz, H-1a), 4.06 (dd, 1H, *J* = 8.6, 9.5 Hz, C*H*HOTBDPS), 4.01 (dd, 1H, *J* = 5.2, 9.5 Hz, CH*H*OTBDPS), 3.95 (dd, 1H, *J* = 5.2, 8.6 Hz, H-2), 3.89 (dd, 1H *J* = 5.3, 11.1 Hz, C*H*HOH), 3.83 (dd, 1H, *J* = 5.8, 11.1 Hz, CH*H*OH), 3.69 (q, 1H, *J* = 7.5, 7.5, 7.6 Hz, H-4), 3.57 (dd, 1H, *J* = 5.6, 7.6 Hz, H-3a), 3.26 (m, 1H, *J* = 5.3, 5.6, 5.8, 7.9 Hz, H-3), 3.09 (ddd, 1H, *J* = 2.9, 7.1, 13.3 Hz, H-6), 2.51 (ddd, 1H, *J* = 6.0, 11.0, 13.3 Hz, H-6′), 1.82 (m, 1H, H-5), 1.39 (m, 1H, H-5′), 1.15, 0.97 (2s, 18H, 2*t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.5, 135.5, 133.3, 133.3, 129.7, 129.7, 127.7, 127.7, 78.8, 74.7, 71.4, 71.3, 70.4, 64.6, 60.6, 53.5, 47.6, 31.8, 28.2, 26.8, 19.2. HRMS (ESI) *m*/*z* calcd. for $C_{29}H_{44}NO_5Si$: 514.2983 $[M + H]^+$; found: 514.3003.

(1a*S*,2*S*,3*S*,3a*S*,4*S*)-2-(1′-Acetoxy-2′-*tert*-butyldiphenylsiloxymethyl)-3-acetoxymethyl-4-*tert*-butoxy-pyrrolidino[1,2-*b*]isoxazolidine (18Ac)

$[\alpha]_D$ +21.1° (*c* 1.8, CH_2Cl_2). IR (film, cm^{-1}): 1744. ^{1}H NMR (500 MHz, C_6D_6) δ: 7.82 (m, 4H, Ph), 7.23 (m, 6H, Ph), 5.61 (dt, 1H, *J* = 4.4, 6.1, 6.1 Hz, H-1a), 4.67 (dd, 1H, *J* = 4.4, 5.9 Hz, H-2), 4.35 (dd, 1H, *J* = 8.2, 10.9 Hz, C*H*HOAc), 4.32 (dd, 1H, *J* = 7.1, 10.9 Hz, CH*H*OAc), 4.07 (d, 2H, *J* = 6.1 Hz, CH_2OTBDPS), 3.68 (q, 1H, *J* = 6.0, 6.0, 6.0 Hz, H-4), 3.40 (dd, 1H, *J* = 2.8, 6.8 Hz, H-3a), 3.20 (dt, 1H, *J* = 11.7, 7.1, 7.1 Hz, H-6), 3.14 (m, 1H, *J* = 2.9, 5.9, 7.1, 8.2 Hz, H-3), 3.02 (dt, 1H, *J* = 11.7, 6.8, 6.8 Hz, H-6′), 1.76, 1.71 (2s, 6H, 2Ac), 1.64 (m, 1H, H-5), 1.50 (m, 1H, H-5′), 1.18, 0.97 (2s, 18H, 2*t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 170.1, 135.6, 135.5, 133.1, 133.0, 129.8, 129.8, 127.8, 127.7, 76.4, 73.7, 71.7, 71.6, 71.4, 63.6, 63.4, 54.1, 45.6, 33.5, 28.1, 27.0, 20.8, 20.4, 19.5. HRMS (ESI) *m*/*z* calcd. for $C_{33}H_{48}NO_7Si$: 598.31946 $[M + H]^+$; found: 598.3195.

(1a*S*,2*S*,6a*S*,6b*S*,7*S*)-2-(*tert*-Butyldiphenylsiloxymethyl)-7-*tert*-butoxy-4,4-dimethyl-3,5-dioxa-pyrrolidino[1,2-*b*]-isoxazolidino[4,5]cycloheptane (19)

Compound **15** (0.051 g, 0.1 mmol) was dissolved in 2,2-dimethoxypropane (25 mL), treated with a catalytic amount

of *p*-TsOH, and kept under reflux for 1 h. Subsequently, the solution was cooled, neutralized with triethylamine, and evaporated. The residue was purified by chromatography affording **19** (0.048 g) in 87% yield. $[\alpha]_D$ +4.3° (*c* 1.3, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6) δ: 7.81 (m, 4H, Ph), 7.20 (m, 6H, Ph), 4.43 (bd, 1H, *J* = 4.6 Hz, H-1a), 4.35 (t, 1H, *J* = 6.9, 7.2 Hz, H-2), 4.23 (t, 1H, *J* = 11.8, 12.3 Hz, H-6), 4.12 (dd, 1H, *J* = 6.9, 9.9 Hz, C*H*HOTBDPS), 4.07 (dd, 1H, *J* = 7.2, 9.9 Hz, CH*H*OTBDPS), 3.57 (dt, 1H, *J* = 6.5, 5.2, 5.2 Hz, H-7), 3.42 (dd, 1H, *J* = 4.9, 11.8 Hz, H-6′), 3.17 (m, 1H, H-9), 3.07 (m, 1H, H-9′), 3.00 (d, 1H, *J* = 6.5 Hz, H-6b), 2.89 (dt, 1H, *J* = 12.3, 4.6, 4.9 Hz, H-6a), 1.56 (m, 1H, H-8), 1.47 (m, 1H, H-8′), 1.36, 1.33 (2s, 6H, $C(CH_3)_2$), 1.20, 0.96 (2s, 18H, 2*t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.6, 133.5, 129.6, 127.7, 101.5, 77.0, 74.2, 70.9, 70.1, 69.5, 64.0, 61.1, 54.4, 47.3, 33.9, 28.3, 26.8, 24.8, 23.9, 19.1. HRMS (ESI) *m*/*z* calcd. for $C_{32}H_{48}NO_5Si$: 554.32963 $[M + H]^+$; found: 554.3314.

(1a*S*,2*S*,6a*S*,6b*S*,7*S*)-7-*tert*-Butoxy-4,4-dimethyl-3,5-dioxa-2-hydroxymethylpyrrolidino[1,2-*b*]isoxazolidino-[4,5]cycloheptane (20)

Compound **19** (0.11 g, 0.2 mmol) was dissolved in THF (20 mL), treated with tetrabutylammonium fluoride (0.26 g, 1 mmol), and left overnight. Subsequently, the solvent was evaporated and the mixture was partially purified on a silica gel column to afford alcohol **20** (0.059 g, 94%). $[\alpha]_D$ +39.5° (*c* 0.7, CH_2Cl_2). IR (film, cm^{-1}): 3417. ^{1}H NMR (500 MHz, C_6D_6) δ: 4.17 (t, 1H, *J* = 11.8, 12.2 Hz, H-6), 4.12 (dd, 1H, *J* = 4.3, 8.6 Hz, H-2), 4.04 (d, 1H, *J* = 4.8 Hz, H-1a), 3.94 (dd, 1H, *J* = 8.6, 11.2 Hz, C*H*HOH), 3.62 (dd, 1H, *J* = 4.3, 11.2 Hz, CH*H*OH), 3.53 (q, 1H, H-7), 3.37 (dd, 1H, *J* = 5.1, 11.8 Hz, H-6′), 3.07 (m, 1H, H-9), 3.03 (m, 1H, H-9′), 2.94 (d, 1H, *J* = 6.7 Hz, H-6b), 2.84 (ddd, 1H, *J* = 4.8, 5.1, 12.2 Hz, H-6a), 1.50 (m, 1H, H-8), 1.44 (m, 1H, H-8′), 1.34, 1.32 (2s, 6H, $C(CH_3)_2$), 0.90 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, C_6D_6) δ: 101.4, 78.4, 73.3, 71.4, 70.9, 69.3, 64.0, 61.6, 54.3, 48.5, 33.8, 27.9, 25.0, 24.2. HRMS (ESI) *m*/*z* calcd. for $C_{16}H_{29}NO_5Na$: 338.1938 $[M + Na]^+$; found: 338.1952.

(1a*S*,2*S*,6a*S*,6b*S*,7*S*)-7-*tert*-Butoxy-4,4-dimethyl-3,5-dioxa-2-mesyloxymethylpyrrolidino[1,2-*b*]isoxazolidino-[4,5]cycloheptane (21)

Alcohol **20** (0.063 g, 0.2 mmol) was dissolved in dry dichloromethane (20 mL), treated with triethylamine (0.040 g, 0.4 mmol), and 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 (15 mL) and water (15 mL), dried and evaporated to get crude **21** (0.0755 g, 96%). $[\alpha]_D$ –2.0° (*c* 0.45, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6) δ: 4.35 (dd, 1H, *J* = 8.8, 10.5 Hz, C*H*HOMs), 4.22 (ddd, 1H, *J* = 1.0, 3.8, 8.8 Hz, H-2), 4.09 (t, 1H, *J* = 11.8, 12.3 Hz, H-6), 4.08 (dd, 1H, *J* = 3.9, 10.5 Hz, CH*H*OMs), 3.93 (d, 1H, *J* = 4.9 Hz, H-1a), 3.54 (q, 1H, H-7), 3.33 (dd, 1H, *J* = 5.3, 11.8 Hz, H-6′), 3.05 (m, 1H, H-9), 3.00 (m, 1H, H-9′), 2.91 (d, 1H, *J* = 6.7 Hz, H-6b), 2.82 (ddd, 1H, *J* = 4.9, 5.3, 12.3 Hz, H-6a), 2.19 (s, 3H, Ms), 1.49 (m, 2H, H-8,8′), 1.31, 1.27 (2s, 6H, $C(CH_3)_2$), 1.06 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, C_6D_6) δ: 101.8, 77.9, 73.6, 71.6, 71.0, 69.6, 68.4, 61.7, 54.5, 48.5, 36.4, 34.0, 28.1, 25.0, 24.1. HRMS (ESI) *m*/*z* calcd. for $C_{17}H_{32}NO_7S$: 394.1894 $[M + H]^+$; found: 394.1913.

(1*S*,6*S*,7*S*,8*S*,9*S*)-6,7-Diacetoxy-8-acetoxymethyl-1-*tert*-butoxyindolizidine (23)

Compound **21** (0.04 g, 0.1 mmol) was dissolved in 80% acetic acid (15 mL) and kept at room temperature for 1 h. Subsequently, the solvent was evaporated, the residue was dissolved in methanol (20 mL) and treated with a catalytic amount of 10% Degussa Pd/C under hydrogen. After 24 h, the catalyst was filtered and the solvent was evaporated. The residue was dissolved in triethylamine (10 mL) and treated with acetic anhydride (10 mL) and DMAP (2 mg). After 2 h, the solvents were evaporated and a crude product was purified on a silicagel column using hexane – ethyl acetate (1:1 *v*/*v*) as the eluent to afford **23** (0.021 g, 55%). $[\alpha]_D$ +103° (*c* 0.1, $CHCl_3$). IR (film, cm^{-1}): 1746, 1231. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.14 (t, 1H, *J* = 9.6, 10.5 Hz, H-7), 5.08 (dt, 1H, *J* = 5.0, 9.6, 10.0 Hz, H-6), 4.21 (dd, 1H, *J* = 2.7, 11.7 Hz, C*H*HOAc), 4.15 (ddd, 1H, *J* = 2.1, 5.3, 6.8 Hz, H-1), 4.12 (dd, 1H, *J* = 2.6, 11.7 Hz, CH*H*OAc), 3.35 (dd, 1H, *J* = 5.0, 10.3 Hz, H-5), 3.12 (dt, 1H, *J* = 1.6, 8.8, 9.0 Hz, H-3), 2.33 (m, 1H, H-8), 2.29 (dd, 1H, *J* = 5.3, 10.8 Hz, H-8a), 2.16 (dddd, 1H, *J* = 1.5, 6.8, 8.8, 13.4 Hz, H-2), 2.07, 2.05, 1.99 (3s, 9H, 3Ac), 2.04 (m, 1H, H-3′), 1.95 (m, 1H, H-5′), 1.90 (dddd, 1H, *J* = 2.0, 9.0, 9.1, 13.3 Hz, H-2′), 1.20 (s, 9H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.0, 170.5, 170.1, 74.1, 72.3, 71.9, 70.2, 66.8, 59.8, 53.7, 52.7, 38.3, 35.1, 28.8, 20.89, 20.85, 20.85. HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{32}NO_7$: 386.2173 $[M + H]^+$; found: 386.2189.

(1*S*,6*S*,7*S*,8*S*,9*S*)-8-Acetoxymethyl-1,6,7-triacetoxy-indolizidine (24)

Compound **23** (0.02 g, 0.052 mmol) was dissolved in trifluoroacetic acid (5 mL) and stirred for 2 h. Subsequently, the solvent was carefully evaporated and the residue was dissolved in triethylamine (1 mL) and treated with acetic anhydride (1 mL) and DMAP (1 mg). After 1 h, the mixture was evaporated and the residue purified by chromatography using hexane – ethyl acetate (1:1 *v*/*v*) as the eluent to afford **24** (0.012 g, 62%). $[\alpha]_D$ +64.5° (*c* 0.18, $CHCl_3$). IR (film, cm^{-1}): 1745. ^{1}H NMR (500 MHz, C_6D_6) δ: 5.28 (dt, 1H, *J* = 5.1, 9.6, 10.0 Hz, H-6), 5.20 (dd, 1H, *J* = 9.6, 10.8 Hz, H-7), 5.12 (ddd, 1H, *J* = 1.3, 4.6, 7.2 Hz, H-1), 4.30 (dd, 1H, *J* = 4.8, 11.8 Hz, C*H*HOAc), 3.97 (dd, 1H, *J* = 3.1, 11.8 Hz, CH*H*OAc), 3.11 (dd, 1H, *J* = 5.1, 10.3 Hz, H-5), 2.63 (m, 1H, H-3), 2.36 (m, 1H, *J* = 3.1, 4.8, 10.4, 10.8 Hz, H-8), 1.92 (m, 1H, H-2), 1.77, 1.75, 1.70, 1.66 (4s, 12H, 4Ac), 1.74–1.70 (m, 2H, H-5′, H-8a), 1.60 (m, 1H, H-2′), 1.54 (m, 1H, H-3′). ^{13}C NMR (125 MHz, C_6D_6) δ: 169.9, 169.9, 169.7, 169.5, 73.2, 72.5, 71.9, 66.6, 61.0, 53.4, 51.6, 39.3, 32.6, 20.5, 20.42, 20.38, 20.36. HRMS (ESI) *m*/*z*, calcd. for $C_{17}H_{25}NO_8Na$: 394.1472 $[M + Na]^+$; found: 394.1486.

(1*S*,6*S*,7*S*,8*S*,9*S*)-8-Hydroxymethyl-1,6,7-trihydroxy-indolizidine (8-homocastanospermine, 13)

Compound **23** (0.013 g, 0.035 mmol) was dissolved in 1.3% of ammonia in methanol (5 mL) and left for 24 h at room temperature. Subsequently, the solvent was evaporated

and the residue was purified by chromatography using methanol – ethyl acetate (1:1 *v*/*v*) as the eluent to afford **24** (5.8 mg, 82%). $[\alpha]_D$ +35.8° (*c* 0.55, CH_3OH). IR (KBr, cm^{-1}): 3380. ^1H NMR (500 MHz, CD_3OD) δ: 4.32 (m, 1H, H-1), 3.90 (dd, 1H, *J* = 2.2, 10.9 Hz, C*H*HOH), 3.76 (ddd, 1H, *J* = 2.3, 5.1, 10.8 Hz, CH*H*OH), 3.58 (ddd, 1H, *J* = 5.0, 8.8, 10.4 Hz, H-6), 3.26 (dd, 1H, *J* = 8.8, 10.1 Hz, H-7), 3.18 (dd, 1H, *J* = 5.0, 10.6 Hz, H-5), 3.08 (ddd, 1H, *J* = 2.0, 9.0, 9.1 Hz, H-3), 2.25 (dddd, 1H, *J* = 2.0, 5.5, 9.0, 13.9 Hz, H-2), 2.08 (ddd, 1H, *J* = 9.1, 9.1, 9.1 Hz, H-3′), 1.91 (dd, 1H, *J* = 10.2, 10.9 Hz, H-5′), 1.86 (m, 2H, H-8,8a), 1.75 (dddd, 1H, *J* = 1.7, 9.0, 9.1, 13.8 Hz, H-2′). ^{13}C NMR (125 MHz, CD_3OD) δ: 75.8, 73.2, 71.8, 71.6, 61.1, 58.0, 53.5, 43.9, 34.2. HRMS (ESI) *m*/*z* calcd. for $C_9H_{18}NO_4$: 204.1230 $[M + H]^+$; found: 204.1227.

Biological tests

The β-glucosidase activity of **13** was measured by the modification of the procedures described previously (10, 11). The reaction mixture consisted of 100 μL of 0.014 mol/L *p*-nitrophenyl β-D-glucopyranoside, 250 μL of 0.2 mol/L acetate buffer (pH 4.6), 50 μL of inhibitor solution (either water or methanol), and 100 μL of enzyme solution (3 μg/mL). After incubation for 15 min at 30 °C, the reaction was terminated by the addition of 1 mL of 2% sodium carbonate. The absorbance of liberated *p*-nitrophenol was measured at 405 nm.

The α-glucosidase activity of **13** was measured by modification of the procedures described previously (12, 13). The reaction mixture consisted of 25 μL of 0.0165 mol/L *p*-nitrophenyl α-D-glucopyranoside, 403 μL of 0.1 mol/L acetate buffer (pH 4.0), 50 μL of inhibitor solution (either water or methanol), and 22 μL of enzyme solution (10 times diluted). After incubation for 15 min at 37 °C, the reaction was terminated by the addition of 1 mL of 2% sodium carbonate. The absorbance of liberated *p*-nitrophenol was measured at 405 nm.

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References

1. M. Jurczak, J. Rabiczko, D. Socha, M. Chmielewski, F. Cardona, A. Goti, and A. Brandi. Tetrahedron: Asymmetry, **11**, 2015 (2000).
2. D. Socha, M. Jurczak, J. Frelek, A. Klimek, J. Rabiczko, Z. Urbańczyk-Lipkowska, K. Suwińska, M. Chmielewski, F. Cardona, A. Goti, and A. Brandi. Tetrahedron: Asymmetry, **12**, 3163 (2001).
3. K. Paśniczek, D. Socha, M. Jurczak, J. Frelek, A. Suszczyńska, Z. Urbańczyk-Lipkowska, and M. Chmielewski. J. Carbohydr. Chem. **22**, 613 (2003).
4. (*a*) A. Goti, V. Fedi, L. Nannelli, F. De Sarlo, and A. Brandi. Synlett, 577 (1997); (*b*) A. Goti, F. Cardona, and A. Brandi. Synlett, 761 (1996). (*c*) A. Goti, S. Cicchi, M. Cacciarini, F. Cardona, V. Fedi, and A. Brandi. Eur. J. Org. Chem. 3633 (2000); (*d*) A. Goti, M. Cacciarini, F. Cardona, F.M. Cordero, and A. Brandi. Org. Lett. **3**, 1367 (2001); (*e*) A. Goti, S. Cicchi, V. Fedi, L. Nannelli, and A. Brandi. J. Org. Chem. **62**, 3119 (1997); (*f*) A. Goti, M. Cacciarini, F. Cardona, F.M. Cordero, and A. Brandi. Org. Lett. **3**, 1367 (2001); (*g*) F. Pisaneschi, C.D. Monica, F.M. Cordero, and A. Brandi. Tetrahedron Lett. **43**, 5711 (2002); (*h*) A.E. McCaig, K.P. Meldrum, R.H. Wightman. Tetrahedron, **54**, 9429 (1998); (*i*) A.B. Holmes, B. Bourdin, I. Collins, E.C. Davison, A.J. Rudge, T.C. Stork, and J. Warner. Pure Appl. Chem. **69**, 531 (1997); (*j*) S.E. Denmark and A. Thorarensen. J. Am. Chem. Soc. **119**, 125 (1997); (*k*) S.E. Denmark and A.R. Hurd. J. Org. Chem. **65**, 2875 (2000); (*l*) S.E. Denmark and J.J. Cottell. J. Org. Chem. **66**, 4276 (2001); (*m*) J. Tufariello. Acc. Chem. Res. **12**, 396 (1979).
5. D. Socha, M. Jurczak, and M. Chmielewski. Carbohydr. Res. **336**, 315 (2001), and refs. cited therein.
6. (*a*) G.W.J. Fleet, L.E. Fellows, and B. Winchester. *In* Bioactive compounds from plants. *Edited by* P.J. Chadwick and J. March. Wiley and Sons, Chichester, UK. 1990. p. 112; (*b*) N. Asano, R.J. Nash, R.J. Molyneux, and G.W.J. Fleet. Tetrahedron: Asymmetry, **11**, 1645 (2000); (*c*) Y. Chapleur (*Editor*). Carbohydrate mimics. Wiley-VCH, Weinheim. 1998; (*d*) A.E. Stütz. Iminosugars as glycosidase inhibitors. Wiley-VCh, Weinheim. 1999; (*e*) O.R. Martin and Ph. Compain (*Editors*). Curr. Top. Med. Chem. **3**(5), (2003), and refs. cited therein; (*f*) A. El Nemr. Tetrahedron, **56**, 8579 (2000); (*g*) F.-X. Felpin and J. Lebreton. Eur. J. Org. Chem. 3693 (2003); (*h*) J. Cossy and P. Vogel. *In* Studies in natural products chemistry. *Edited by* Atta-ur-Rahman. Elsevier, Amsterdam. 1993. p. 275; (*i*) P. Herczegh, I. Kovacs, and F. Sztaricskai. Recent progress in chemical synthesis of antibiotics. *Edited by* G. Lukacs and M. Ohno. Springer-Verlag, Berlin. 1993. p. 751; (*j*) L. Cipolla, B. La Ferla, and F. Nicotra. Curr. Top. Med. Chem. **3**, 485 (2003).
7. (*a*) L.D. Hohenschutz, E.A. Bell, P.J. Jewess, D.P. Lewerothy, R.J. Pryce, E. Arnold, and J. Chardy. Phytochemistry, **20**, 811 (1981); (*b*) I. Pastuszak, R.J. Molyneux, L.F. James, and A.D. Elbien. Biochemistry, **29**, 1886 (1990).
8. (*a*) B.L. Reinhart, K.M. Robinson, A.J. Payne, M.E. Wheatley, J.L. Fisher, P.S. Liu, and W. Chang. Life Sci. **41**, 2325 (1987); (*b*) E. Truscheit, W. Frommer, L. Junge, L. Müller, D.D. Schmidt, and W. Wingender. Angew. Chem. Int. Ed. Engl. **20**, 744 (1981); (*c*) R. Pili, J. Chang, R.A. Partis, R.A. Mueller, F.J. Chrest, and A. Passaniti. Cancer Lett. **55**, 2995 (1995); (*d*) M.A. Spearman, B.C. Ballon, J.M. Gerrard, A.H. Greenberg, and J.A. Wright. Cancer Lett. **60**, 185 (1991); (*e*) E.J. Nichols, R. Manger, S. Hakomori, A. Herscovies, and L.R. Rohrschneider. Mol. Cell. Biol. **5**, 3467 (1985); (*f*) R.M. Ruprecht, S. Mullaney, J. Anderson, R. Bronson, and J. Acquired Immune Defic. Syndr. **2**, 149 (1989).
9. F.M. Cordero, F. Pisaneschi, M. Gensini, A. Goti, and A. Brandi. Eur. J. Org. Chem. 1941 (2002).
10. T. Niva, S. Inouye, T. Tsuruoka, Y. Koaze, and T. Niida. Agr. Biol. Chem. **34**, 966 (1970).
11. T. Tsuruoka, H. Fukuyasu, M. Ishii, T. Usui, S. Shibahara, and S. Inouye. J. Antibiot. **49**, 155 (1996).
12. G. Legler. Adv. Carbohydr. Chem. Biochem. **48**, 319 (1990).
13. H.U. Bergmeyer (*Editor*). Methods of enzymatic analysis. 3rd ed. 1984. p. 152.