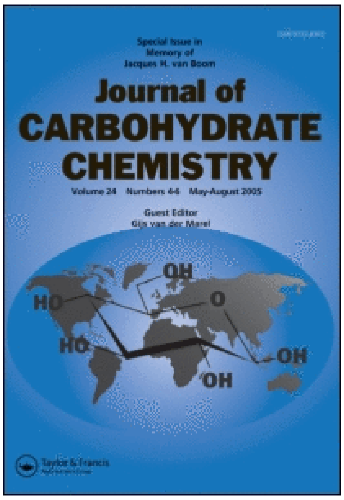


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of 2,3-Dihydroxy-1-Epilupinine

Konrad Paśniczek[a]; Margarita Jurczak[a]; Jolanta Solecka[b]; Zofia Urbańczyk-Lipkowska[a]; Marek Chmielewski[a]
[a] Institute of Organic Chemistry of the Polish Academy of Sciences, Warsaw, Poland [b] National Institute of Hygiene, Warsaw, Poland

To cite this Article Paśniczek, Konrad , Jurczak, Margarita , Solecka, Jolanta , Urbańczyk-Lipkowska, Zofia and Chmielewski, Marek(2007) 'Synthesis of 2,3-Dihydroxy-1-Epilupinine', Journal of Carbohydrate Chemistry, 26: 3, 195 — 211
To link to this Article: DOI: 10.1080/07328300701351540
URL: http://dx.doi.org/10.1080/07328300701351540

Journal of Carbohydrate Chemistry, 26:195–211, 2007

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300701351540

Synthesis of 2,3-Dihydroxy-1-Epilupinine

Konrad Paśniczek and Margarita Jurczak

Institute of Organic Chemistry of the Polish Academy of Sciences, Warsaw, Poland

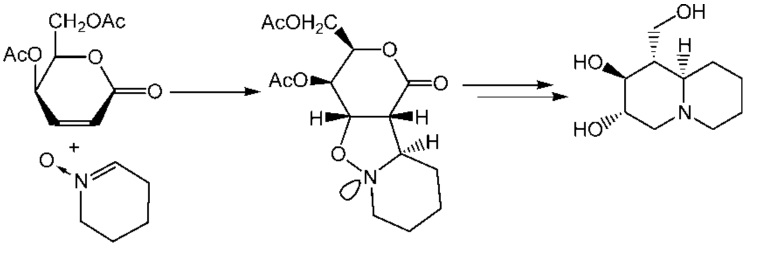
Jolanta Solecka

National Institute of Hygiene, Warsaw, Poland

Zofia Urbańczyk-Lipkowska and Marek Chmielewski

Institute of Organic Chemistry of the Polish Academy of Sciences, Warsaw, Poland

The 1,3-dipolar cycloaddition of unsaturated D-*threo*-hexaldonolactone **3** and a six-membered cyclic nitrone **11** led to a single adduct **15**, which could be transformed into (1*S*, 2*S*, 3*S*, 9a*S*)-2,3-dihydroxy-1-hydroxymethyl-quinolizidine **28** related to epilupinine via a reaction sequence involving rearrangement of the six-membered lactone ring into a 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.



Keywords Iminosugars, Nitrones, Aldono-1,5-lactone, 1,3-Dipolar cycloaddition

INTRODUCTION

Recently, we have reported that the cycloaddition of 2,3-unsaturated aldono-1,5-lactones **1–3** and the five-membered cyclic nitrones **4–6** proceeded

Received January 19, 2007; accepted March 20, 2007.
Address correspondence to Marek Chmielewski, Institute of Organic Chemistry of the Polish Academy of Sciences, 01-224 Warsaw, Poland. E-mail: chmiel@icho.edu.pl

exclusively in the *exo* mode to provide in many cases a sole product.[1–3] In particular, reaction between **3** and **5** afforded only one cycloadduct **7** as a result of the *anti* addition to both the acetoxymethyl- and the 4-acetoxy-group of the lactone (Chart 1).[3] The application of Brandi's methodology[4] to cycloadduct **7** offers a convenient approach to the indolizidine alkaloids. This has been demonstrated by the synthesis of 8-homocastanospermine (**8**)[5] and 1-homoaustraline (**9**) (Chart 1).[6] Both reported syntheses 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 fully defined configuration at all stereogenic centers, which corresponded well with those existing in both natural compounds, castanospermine[7] and australine.[8] Surprisingly, iminosugars **8** and **9** showed only a trace inhibition of α-glucosidase activity and no inhibition of β-glucosidase.[5,6] Both synthesized compounds have a hydroxymethyl group at the position adjacent to the bridgehead carbon atom in the place of the hydroxyl group. Such substituted pyrrolizidines,[9] indolizidines,[10] and quinolizidines[11] exist in nature, or have been obtained by the total synthesis.[12]

It was of interest to apply the same methodology to the synthesis of polyhydroxylated quinolizidines. It should, however, be pointed out that such compounds, except lupinine (**10**),[11] have not been found in nature. Polyhydroxylated quinolizidines,[13] particularly related to castanospermine, have been synthesized in order to find active glycosidase inhibitors.[14]

RESULTS AND DISCUSSION

Six-membered ring nitrone **11** (Chart 1) was obtained following the known procedure[15]; the dipole is not stable and has to be obtained directly before the use for the cycloaddition. The nitrone **11** was subjected to 1,3-dipolar

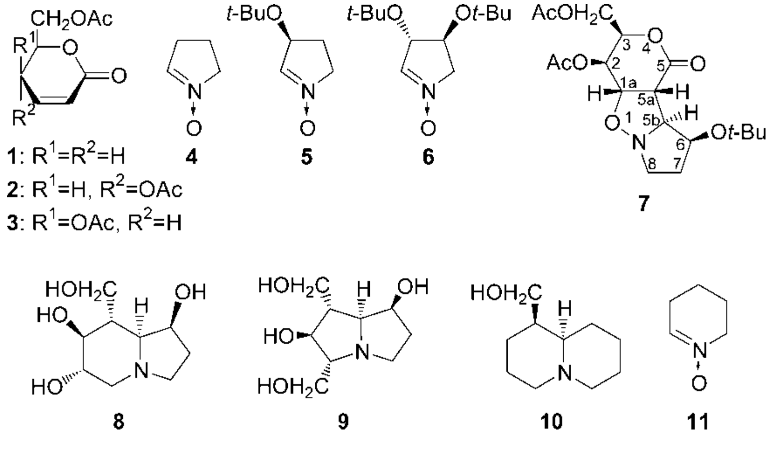


Chart 1:

cycloaddition with lactones **1–3**. Reaction between **1** and **11** provided a single adduct **12** as the result of *anti-exo* approach of reactants. The ^{1}H NMR spectrum of **12** at rt displayed lines characteristic of definite single nitrogen invertomers **12a** and **12b** in a ratio of about 2:1, respectively. Assignments were made on the basis of chemical shifts of H-5b protons, 2.24 ppm (*syn* to the free electron pair) for **12a** and 3.62 ppm (*anti*) for **12b**. In toluene-d_8 at 100°C, owing to the fast inversion process the ^{1}H NMR spectrum of adduct **12** displayed a presence of average signals only, but with substantial line broadening (Chart 2).

Reaction between **2** and **11** provided two adducts **13** and **14** in the ratio of about 3:2, respectively; the *anti-exo* approach to the terminal acetoxymethyl group dominated. Both adducts **13** and **14** at rt existed as two nitrogen invertomers in a ratio of 1.8:1 for **13a**/**13b** and 3:1 for **14a**/**14b**. As it was made before, the configuration at the nitrogen atom in both pairs of invertomers was assigned on the basis of the chemical shift of H-5b carbon atoms; upfield shifts testified the *syn* location of the proton and the free electron pair. Configuration of adducts **13** and **14** were assigned on the basis of coupling constants (toluene-d_8, 110°C) $J_{1a,2} = 3.7$ Hz for **13** (axial-psedoeqatorial) and 7.5 Hz (axial-pseudoaxial) for **14** (Chart 2).

Lactone **3** and nitrone **11** gave only one adduct **15** as the result of the *exo-anti* approach to both substituents in the dipolarophile. As with the others adducts, compound **15** at rt displayed the presence of two invertomers **15a**/**15b** in a ratio of about 1.25:1 (Chart 2). The major conformer has *syn* location of the H-5b proton and the free electron pair.

Adduct **15** was deacetylated with sodium methoxide in methanol and gave compound **16**. The reaction proceeded with the rearrangement of the

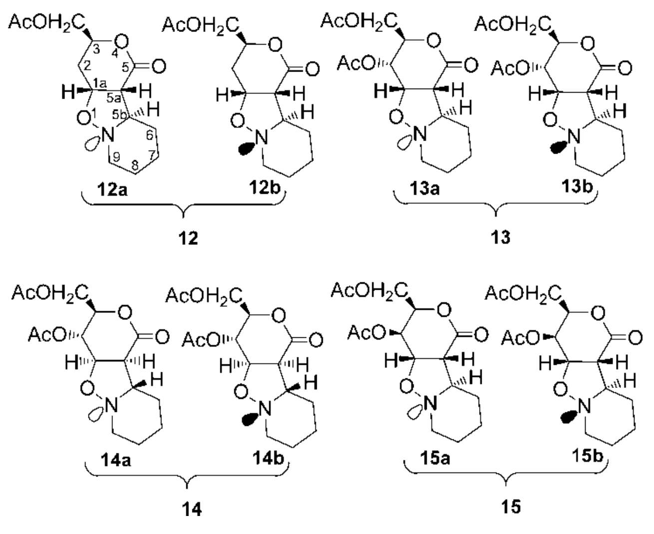
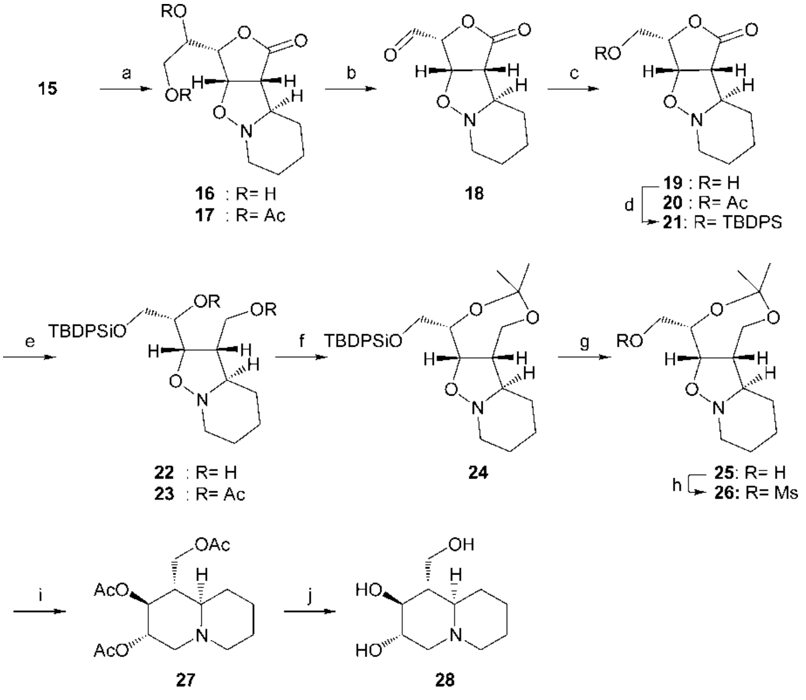


Chart 2:

six-membered lactone ring into a five-membered one. The glycolic cleavage of the terminal diol group in **16** with $NaIO_4$ followed by the reduction of the aldehyde group with sodium triacetoxyborohydride gave compound **19** in 83% yield (Sch. 1). The structure of **19** was proved by X-ray crystallography (Fig. 1).

Subsequently, the hydroxymethyl group was protected as a *t*-butyldiphenylsilyl derivative **21** and the lactone was reduced with sodium borohydride to give diol **22**. Both hydroxyl groups in **22** were masked by the formation of isopropylidene moiety (**24**). The desilylation of **24** with tetrabutylammonium fluoride led to the alcohol **25.** Introduction of the seven-membered ring to the piperidino[1,2-b]izoxazolidine fragment caused substantial broadening of signals in ^{1}H NMR spectra of compounds **24** and **25** due to the slow inversion process at the nitrogen atom. Therefore, the structure determinations of both compounds were made on the basis of assignments made for the final products of the synthesis, **27** and **28**.

Due to the low stability of isopropylidene fragment and the tendency of the terminal mesyloxymethyl group to undergo intramolecular alkylation of the nitrogen atom, the next three steps were performed with only partial purification of intermediary products. The alcohol **25** was mesylated to afford **26**, the



Scheme 1: (a) Na_2CO_3, MeOH; (b) $NaIO_4$, MeOH, H_2O; (c) $NaBH(OAc)_3$, CH_2Cl_2; (d) TBDPSCl, imidazole, CH_2Cl_2; (e) $LiBH_4$, THF; (f) 2,2-dimethoxypropane, TsOH; (g) *n*-Bu_4NF, THF; (h) MsCl, TEA, CH_2Cl_2; (i) 80% AcOH; H_2, Pd/C, K_2CO_3, AcOEt, MeOH; Ac_2O, TEA, DMAP, CH_2Cl_2; (j) 1.3% NH_3 in MeOH.

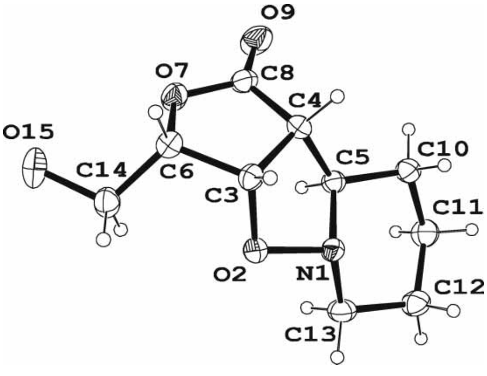


Figure 1: X-ray structure of compound **19** with crystallographical numbering scheme.

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 (quinolizidine **28**) was acetylated and characterized as the triacetate **27**. The complete deacetylation of **27** with ammonia in methanol furnished the (1*S*, 2*S*, 3*S*, 9a*S*)-2,3-dihydroxy-1-hydroxymethyl-quinolizidine **28**.

Compound **28** was tested on bovine kidney α-L-fucosidase, bovine liver β-D-galactosidase, bovine liver β-D-glucuronidase, rice α-D-glucosidase, almond β-D-glucosidase, and jack bean α-D-mannosidase inhibition. Under procedures described previously,[16–20] quinolizidine **28** did not show activity against any of the tested enzymes.

In summary, we have reported the simple synthesis of 2,3-dihydroxy-epilupinine **28** in which a proper selection of readily available components of the 1,3-dipolar cycloaddition controlled the absolute stereochemistry at all four stereogenic centers present in the target molecule. The inferences drawn from previous work allowed us to predict the stereochemical pathway of the 1,3-dipolar cycloaddition of six-membered-ring nitrone **11** and sugar unsaturated δ-lactone **3**. Consequently, only one diastereomer **15** with a fully defined configuration at all stereogenic centers was obtained and was used for the synthesis of title quinolizidine.

EXPERIMENTAL

^{1}H 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 from GmbH and HPLC-MS were recorded with Mariner and API 356 detectors. Column chromatography was performed with E. Merck Kiesel Gel (230–400 mesh).

Adduct **7** was obtained according to the known procedure.[3] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center, Cambridge, UK, as a supplementary publication: **19** (CCDC 634033).

(1a*R*, 3*S*, 5a*R*, 5b*R*)-3-Acetoxymethyl-piperidino(1,2-*b*)-tetrahydropyrano(3,4-*d*)isoxazol-5(*3H*)-one (12)

Lactone **1** (34 mg, 0.2 mmol) and nitrone **11** (30 mg, 0.3 mmol) were dissolved in dry toluene (2 mL), and kept at rt for 3 days. The progress of reaction was monitored using TLC. Subsequently, the solvent was evaporated and the product was purified by chromatography using hexane/AcOEt 1:2 v/v as an eluent to afford **12** (37 mg, 68%). $[\alpha]_D$ mixture of invertomers +15.9 (*c* 0.7, CH_2Cl_2); IR (film, $CHCl_3$): υ 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) taken for the mixture δ: major component: 4.77 (dddd, 1H, $J = 1.7$, 3.5, 5.5, 11.6 Hz, H-3), 4.46 (ddd, 1H, $J = 1.4$, 3.7, 8.3 Hz, H-1a), 4.25 (dd, 1H, $J = 3.5$, 12.1 Hz, C*H*HOAc), 4.20 (dd, 1H, $J = 5.5$, 12.1 Hz, CH*H*OAc), 3.46 (m, 1H, H-9), 3.15 (dd, 1H, $J = 8.3$, 10.3 Hz, H-5a), 2.48 (m, 1H, H-9′), 2.24 (ddd, 1H, $J = 2.3$, 10.3, 11.0 Hz, H-5b), 2.16 (m, 1H, H-6), 2.09 (s, 3H, OAc), 2.00 (ddd, 1H, $J = 1.4$, 1.7, 15.4 Hz, H-2), 1.87 (ddd, 1H, $J = 3.7$, 11.6, 15.4 Hz, H-2′), 1.85–1.72 (m, 2H, H-7,8), 1.66 (m, 1H, H-8′), 1.52 (m, 1H, H-6′), 1.22 (m, 1H, H-7′); minor component: 4.85 (m, 1H, H-1a), 4.77 (m, 1H, H-3), 4.26–4.18 (m, 2H, CH_2OAc), 3.62 (m, 1H, H-5b), 3.40 (m, 1H, H-5a), 3.16 (m, 1H, H-9), 2.57 (m, 1H, H-9′), 2.09 (m, 1H, H-6), 2.08 (s, 3H, OAc), 2.00–1.92 (m, 3H, H-2,2′,6′), 1.78 (m, 1H, H-8), 1.59 (m, 1H, H-7), 1.56 (m, 1H, H-8′), 1.38 (m, 1H, H-7′); ^1H NMR (500 MHz, toluene-d_8, 100°C) δ: 4.49 (m, 1H, H-3), 4.07 (m, 1H, H-1a), 3.95 (dd, 1H, $J = 5.6$, 11.9 Hz, C*H*HOAc), 3.89 (dd, 1H, $J = 4.1$, 11.9 Hz, CH*H*OAc), 3.05 (m, 1H, H-5a), 2.84 (t, 1H, $J = 8.9$ Hz, H-9), 2.40 (m, 1H, H-9′), 1.90 (m, 1H, H-2), 1.68 (s, 3H, OAc), 1.56 (m, 1H, H-5b), 1.46–1.20 (m, 6H, H-2′,6, 6′, 7, 8, 8′), 0.95 (m, 1H, H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: major component 170.5, 169.3, 72.8, 71.3, 70.7, 65.0, 55.0, 51.6, 28.9, 28.8, 24.4, 23.3, 20.7; minor component 170.5, 169.7, 72.7, 72.2, 65.6, 65.0, 50.0, 47.5, 29.6, 24.2, 23.7, 20.7, 18.1; MSHR (ESI) m/z $[M + H]^+$, calcd. for $C_{13}H_{20}NO_5$: 270.1336. Found: 270.1334.

(1a*S*, 2*S*, 3*R*, 5a*R*, 5b*R*)-2-Acetoxy-3-acetoxymethyl-piperidino(1,2-*b*)-tetrahydropyrano(3,4-*d*)isoxazol-5(*3H*)-one (13) and (1a*R*, 2*S*, 3*R*, 5a*S*, 5b*S*)-2-Acetoxy-3-acetoxymethyl-piperidino(1,2-*b*)-tetrahydropyrano(3,4-*d*) isoxazol-5(*3H*)-one (14)

Lactone **2** (46 mg, 0.2 mmol) and nitrone **11** (30 mg, 0.3 mmol) were dissolved in dry toluene (3 mL) and left at rt for 3 days. The progress of reaction was monitored by TLC. Subsequently, the solvent was evaporated and the products were separated by chromatography using hexane/AcOEt 1:1 v/v as an eluent to afford **13** (31 mg, 47%) and **14** (21 mg, 32%).

13: m.p. 109.5–110.5°C; $[\alpha]_D$ mixture of invertomers +120.2 (c 1.2, CH_2Cl_2); IR (film $CHCl_3$): v 1745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) taken for the mixture of invertomers δ: major component **13a**, 5.23 (dd, 1H, J = 3.7, 9.5 Hz, H-2), 4.94 (ddd, 1H, J = 2.2, 3.9, 9.5 Hz, H-3), 4.54 (dd, 1H, J = 3.7, 8.5 Hz, H-1a), 4.37 (dd, 1H, J = 3.9, 12.6 Hz, C*H*HOAc), 4.27 (dd, 1H, J = 2.2, 12.6 Hz, CH*H*OAc), 3.52 (m, 1H, H-9), 3.26 (dd, 1H, J = 8.5, 10.0 Hz, H-5a), 2.54 (m, 1H, H-9′), 2.32 (ddd, 1H, J = 2.3, 10.0, 11.2 Hz, H-5b), 2.22 (m, 1H, H-6), 2.14, 2.08 (2s, 6H, 2 × OAc), 1.85 (m, 1H, H-8), 1.66 (m, 1H, H-8′), 1.56–1.45 (m, 2H, H-6′,7), 1.23 (m, 1H, H-7′); minor component **13b**, 5.16 (dd, 1H, J = 3.2, 9.8 Hz, H-2), 5.01 (ddd, 1H, J = 2.1, 3.0, 9.8 Hz, H-3), 4.84 (dd, 1H, J = 3.2, 8.4 Hz, H-1a), 4.38 (dd, 1H, J = 3.0, 12.6 Hz, C*H*HOAc), 4.28 (dd, 1H, J = 2.1, 12.6 Hz, CH*H*OAc), 3.66 (m, 1H, H-5b), 3.42 (dd, 1H, J = 6.8, 8.4 Hz, H-5a), 3.10 (m, 1H, H-9), 2.84 (m, 1H, H-9′), 2.14, 2.08 (2s, 6H, 2 × OAc), 1.94–1.73 (m, 4H, H-6,7,7′,8), 1.58–1.42 (m, 2H, H-6′,8′); ^{1}H NMR (500 MHz, toluene-d_8 100°C) δ: 5.02 (dd, 1H, J = 3.7, 9.3 Hz, H-2), 4.70 (ddd, 1H, J = 2.7, 4.3, 9.3 Hz, H-3), 4.36 (dd, 1H, J = 3.7, 8.3 Hz, H-1a), 4.21 (dd, 1H, J = 4.3, 12.4 Hz, C*H*HOAc), 4.04 (dd, 1H, J = 2.7, 12.4 Hz, CH*H*OAc), 3.04 (m, 1H, H-9), 2.80 (t, 1H, 8.3 Hz, H-5a), 2.46 (m, 1H, H-9′), 1.78 (m, 1H, H-5b), 1.72 (2s, 6H, 2 × OAc), 1.48–1.24 (m, 5H, H-6, 6′, 7, 8, 8′), 0.97 (m, 1H, H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) taken for the mixture of invertomers δ: major component, 170.4, 169.4, 167.6, 73.0, 71.2, 71.1, 66.2, 61.4, 55.1, 52.3, 28.9, 24.4, 23.2, 20.7, 20.6; minor component, 170.4, 169.7, 168.5, 72.8, 71.4, 66.8, 66.1, 61.4, 50.3, 50.2, 24.5, 22.0, 20.8, 20.6, 19.6; MSHR (ESI) m/z $[M+H]^+$, calcd. for $C_{15}H_{22}NO_7$: 328.13908. Found: 328.13965.

14: $[\alpha]_D$ mixture of invertomers +33.5 (c 0.5, CH_2Cl_2); IR (film, $CHCl_3$): v 1746 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) taken for the mixture of invertomers δ: major component, 5.19 (dd, 1H, J = 7.7, 9.0 Hz, H-2), 4.48 (ddd, 1H, J = 2.0, 5.0, 9.0 Hz, H-3), 4.42 (dd, 1H, J = 5.0, 12.4 Hz, C*H*HOAc), 4.35 (dd, 1H, J = 7.7, 9.7 Hz, H-1a), 4.22 (dd, 1H, J = 2.0, 12.4 Hz, CH*H*OAc), 3.46 (m, 1H, H-9), 3.25 (dd, 1H, J = 9.7, 9.8 Hz, H-5a), 2.56 (m, 1H, H-9′), 2.46 (ddd, 1H, J = 2.0, 9.8, 10.9 Hz, H-5b), 2.38 (m, 1H, H-6), 2.12, 2.08 (2s, 6H, 2 × OAc), 1.86–1.74 (m, 2H, H-7,8), 1.64 (m, 1H, H-8′), 1.51 (m, 1H, H-6′), 1.30 (m, 1H, H-7′); minor component, 5.21 (m, 1H, H-2), 4.59 (m, 1H, H-3), 4.48 (m, 1H, H-1a), 4.42 (m, 1H, C*H*HOAc), 4.25 (m, 1H, CH*H*OAc), 3.75 (m, 1H, H-5b), 3.35 (m, 1H, H-5a), 3.10 (m, 1H, H-9), 2.95 (m, 1H, H-9′), 2.12, 2.08 (2s, 6H, 2 × OAc), 2.00–1.20 (m, 6H, H-6,6′,7,7′,8,8′); ^{1}H NMR (500 MHz, toluene-d_8 100°C) δ: 5.16 (dd, 1H, J = 7.5, 9.1 Hz, H-2), 4.30

(dd, 1H, $J = 5.1, 12.4$ Hz, C*H*HOAc), 4.07 (dd, 1H, $J = 7.5, 9.5$ Hz, H-1a), 4.01 (dd, 1H, $J = 2.8, 12.4$ Hz, CH*H*OAc), 3.92 (ddd, 1H, $J = 2.8, 5.1, 9.1$ Hz, H-3), 3.14 (m, 1H, H-9), 2.67 (dd, 1H, $J = 8.1, 9.5$ Hz, H-5a), 2.42 (m, 1H, H-9′), 1.75, 1.68 (2s, 6H, 2 × OAc), 1.70 (m, 1H, H-5b), 1.50–1.25 (m, 5H, H-6, 6′, 7, 8, 8′), 1.03 (m, 1H, H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: major component, 170.5, 169.1, 169.1, 75.5, 74.9, 70.0, 67.6, 61.0, 55.1, 50.3, 29.6, 24.6, 23.3, 20.8, 20.7; MSHR (EI) m/z $M^{+\bullet}$, calcd. for $C_{15}H_{21}NO_7$: 327.13180. Found: 327.13167.

(1a*S*, 2*R*, 3*R*, 5a*R*, 5b*R*)-2-Acetoxy-3-acetoxymethyl-piperidino(1,2-*b*)-tetrahydropyrano(3,4-*d*)isoxazol-5(*3H*)-one (15)

Lactone **3** (91 mg, 0.4 mmol) and nitrone **11** (59 mg, 0.6 mmol) were dissolved in dry toluene (4 mL) and left and rt for 72 h and then it was refluxed for 2 h. The progress of reaction was monitored using TLC. Subsequently, the solvent was evaporated and the product was purified by chromatography using hexane/AcOEt 1:1 v/v as an eluent to afford **15** (112 mg, 86%). m.p. 115–117°C; $[\alpha]_D$ mixture of invertomers +17.6 (c 1.1, CH_2Cl_2); IR (film, CH_2Cl_2): υ 1746 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) taken for the mixture of invertomers δ: major component, 5.13 (m, 1H, H-2), 4.91 (m, 1H, H-3), 4.24 (m, 1H, H-1a), 4.23 (d, 2H, CH_2OAc), 3.50 (m, 1H, H-9), 3.22 (dd, 1H, $J = 8.7$, 10.0 Hz, H-5a), 2.50 (m, 1H, H-9′), 2.26 (ddd, 1H, $J = 2.2$, 10.0, 11.2 Hz, H-5b), 2.17–1.30 (m, 6H, H-6,6′,7,7′,8,8′), 2.12, 2.10 (2s, 6H, 2 × OAc); minor component, 5.13 (m, 1H, H-2), 4.91 (m, 1H, H-3), 4.60 (dd, 1H, $J = 2.2$, 8.6 Hz, H-1a), 4.23 (d, 2H, CH_2OAc), 3.60 (ddd, 1H, $J = 4.1$, 4.1, 8.5 Hz, H-5b), 3.42 (dd, 1H, $J = 8.5$, 8.6 Hz, H-5a), 3.15 (m, 1H, H-9), 2.63 (m, 1H, H-9′), 2.17–1.30 (m, 6H, H-6, 6′, 7, 7′, 8, 8′), 2.12, 2.08 (2s, 6H, 2 × OAc); ^{13}C NMR (125 MHz, $CDCl_3$) taken for the mixture δ: major component, 170.2, 169.1, 168.5, 73.8, 73.5, 70.5, 65.8, 61.9, 55.1, 50.6, 28.7, 24.3, 23.2, 20.6, 20.6; minor component, 170.2, 169.3, 167.9, 74.3, 73.4, 65.7, 64.8, 61.9, 50.2, 47.2, 24.4, 22.9, 20.6, 20.6, 18.7; MSHR (ESI) m/z $[M + Na]^+$, calcd. for $C_{15}H_{21}NO_7Na$: 350.1207. Found: 350.1210.

(1a*S*, 2*R*, 4a*R*, 4b*R*, 1′*R*)-2-(1′,2′-Dihydroxyethyl)-piperidino(1,2-b)-tetrahydrofuro(3,4-d)isoxazol-4(*3H*)-one (16)

Cycloadduct **15** (327 mg, 1.0 mmol) dissolved in MeOH (60 mL) was treated with sodium carbonate (106 mg, 1.0 mmol) and stirred at rt for 40 min; the progress of reaction was monitored by TLC. Subsequently, the reaction mixture was neutralized with amberlit IR-1200 [H^+] resin, diluted with methylene chloride (70 mL), filtered, and evaporated. The residue was purified by chromatography using hexane/AcOEt 1:4 v/v as an eluent to afford compound **16** (221 mg; 91%). m.p. 136–138°C; $[\alpha]_D$–28.2 (*c* 0.15, CH_2Cl_2); IR (film, CH_2Cl_2): υ 3388, 1751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 4.97 (dd, 1H, $J = 6.6$, 8.1 Hz, H-1a), 4.70 (dd, 1H, $J = 2.8$, 6.6 Hz, H-2), 4.17 (ddd, 1H, $J = 2.8$, 5.4, 6.1 Hz, CHOH), 3.80 (dd, 1H, $J = 6.1$, 11.0 Hz, C*H*HOH), 3.73 (dd, 1H, $J = 5.4$, 11.0 Hz, CH*H*OH), 3.67 (dd, 1H, $J = 4.9$, 11.2 Hz, H-4b), 3.46 (m, 1H, H-8), 3.23 (d, 1H, $J = 8.1$ Hz, H-4a), 3.00 (ddd, 1H, $J = 3.4$, 12.6, 15.6 Hz, H-8′), 1.78 (dddd, 1H, $J = 2.0$, 3.5, 3.8, 12.6 Hz, H-6), 1.73 (tt, 1H, $J = 3.8$, 12.6 Hz, H-7), 1.63 (m, 1H, H-5), 1.55 (dddd, 1H, $J = 3.5$, 11.2, 12.6, 13.1 Hz, H-5′), 1.44 (tt, 1H, $J = 3.3$, 12.6 Hz, H-6′), 1.35 (m, 1H, H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 82.9, 76.3, 69.4, 63.9, 63.6, 54.9, 49.9, 25.7, 22.3, 18.7; MSHR (ESI) *m/z* $[M + Na]^+$, calcd. for $C_{11}H_{17}NO_5Na$: 266.0999. Found: 266.0989.

(1a*S*, 2*R*, 4a*R*, 4b*R*, 1′*R*)-2-(1′,2′-Diacetoxyethyl)-piperidino[1,2-b]-tetrahydrofuro[3,4-d]isoxazol-4(*3H*)-one (17)

Diol **16** (12 mg, 0.05 mmol) dissolved in triethylamine (2 mL) was treated with acetic anhydride (2 mL) and DMAP (0.01 mmol), and left for 30 min. After a standard workup the crude product was purified by chromatography using hexane/AcOEt 2:1 v/v as an eluent to afford **17** (14 mg, 87%). $[\alpha]_D$ −21.6 (*c* 0.48, CH_2Cl_2); IR (film CH_2Cl_2): υ 1771, 1745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.45 (dd, 1H, $J = 2.6$, 8.3 Hz, H-9), 4.86 (dd, 1H, $J = 5.4$, 6.4 Hz, H-1a), 4.65 (dd, 1H, $J = 5.4$, 8.3 Hz, H-2), 4.50 (d, 1H, $J = 12.3$ Hz, H-10), 4.40 (dd, 1H, $J = 2.6$, 12.3 Hz, H-10′), 3.60 (dd, 1H, $J = 3.7$, 9.8 Hz, H-4b), 3.38 (dd, 1H, $J = 14.9$ Hz, H-8), 3.26 (d, 1H, $J = 6.4$, Hz, H-4a), 2.10, 2.09 (2s, 6H, 2 × OAc), 1.80–1.20 (m, 6H, H-5, 5′, 6, 6′, 7, 7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 170.5, 169.8, 80.9, 74.7, 70.1, 63.5, 62.8, 55.3, 50.0, 25.0, 22.2, 20.9, 20.7, 18.9; MSHR (ESI) *m/z* $[M + Na]^+$, calcd. for $C_{15}H_{21}NO_7Na$: 350.1210. Found: 350.1204.

(1a*S*, 2*R*, 4a*R*, 4b*R*)-2-Formyl-piperidino[1,2-b]-tetrahydrofuro[3,4-d]isoxazol-4(*3H*)-one (18)

Compound **16** (243 mg, 1.0 mmol) was dissolved in methanol/water 6:1 (20 mL). Upon stirring at rt, sodium metaperiodide (428 mg, 2.0 mmol) was added. The stirring was continued for 3 h. Subsequently, the mixture was filtered, evaporated, and passed through a silica gel using CH_2Cl_2:methanol

95:5 v/v to afford partially purified product (80%). A small sample of **18** was purified by chromatography using CH_2Cl_2/methanol 4:1 v/v as an eluent. $[\alpha]_D$ +18.6 (*c* 0.8, CH_2Cl_2); IR (film): υ 3374, 1770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 9.55 (d, 1H, $J = 1.7$ Hz, CHO), 5.14 (dd, 1H, $J = 7.1$, 7.6 Hz, H-1a), 4.78 (dd, 1H, $J = 1.7$, 7.1 Hz, H-2), 3.65 (dd, 1H, $J = 6.7$, 9.4 Hz, H-4b), 3.35 (m, 1H, H-8), 3.15 (d, 1H, $J = 7.6$ Hz, H-4a), 2.93 (m, 1H, H-8′), 1.78 (m, 1H, H-6), 1.71 (m, 1H, H-7), 1.58 (m, 2H, H-5,5′), 1.43 (m, 1H, H-6′), 1.30 (m, 1H, H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.8, 176.1, 84.5, 76.6, 64.8, 53.8, 49.5, 25.4, 22.5, 18.9; MSHR (ESI) *m/z* $[M + MeOH + Na]^+$, calcd. for $C_{11}H_{17}NO_5Na$: 266.0999. Found: 266.0998; MSHR (ESI) *m/z* $[M + EtOH + Na]^+$, calcd. for $C_{12}H_{19}NO_5Na$: 280.1155. Found: 280.1155.

(1a*S*, 2*S*, 4a*R*, 4b*R*)-2-Hydroxymethyl-piperidino(1,2-b)-tetrahydrofuro(3,4-d)isoxazol-4(*3H*)-one (19)

Aldehyde **18** (169 mg, 0.8 mmol) was dissolved in dry CH_2Cl_2 (45 mL) and treated with 2 equiv. $NaBH(OAc)_3$. The mixture was stirred for 5 h at rt. After disappearance of the substrate (TLC), it was filtered through Celite and evaporated. The crude product was purified by chromatography using hexane/AcOEt 1:2 v/v as an eluent to afford **19** (130 mg, 76%). m.p. 101–103°C; $[\alpha]_D$ −2.8 (*c* 0.2, CH_2Cl_2); IR (film $CHCl_3$): υ 3417, 1767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 4.94 (dd, 1H, $J = 6.3$, 8.0 Hz, H-1a), 4.68 (ddd, 1H, $J = 4.1$, 5.2, 6.3 Hz, H-2), 4.04 (dd, 1H, $J = 4.1$, 12.2 Hz, C*H*HOH), 3.97 (dd, 1H, $J = 5.2$, 12.2 Hz, CH*H*OH), 3.65 (dd, 1H, $J = 4.8$, 10.6 Hz, H-4b), 3.43 (m, 1H, H-8), 3.23 (d, 1H, $J = 8.0$ Hz, H-4a), 3.00 (ddd, 1H, $J = 3.5$, 11.7, 15.3 Hz, H-8′), 1.80–1.70 (m, 2H, H-6,7), 1.63–1.50 (m, 2H, H-5,5′), 1.45 (m, 1H, H-6′), 1.34 (m, 1H, H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 82.9, 76.1, 63.7, 60.3, 54.9, 49.9, 25.4, 22.3, 18.9; MSHR (ESI) *m/z* $[M + Na]^+$, calcd. for $C_{10}H_{15}NO_4Na$: 236.0893. Found: 236.0888.

(1a*S*, 2*S*, 4a*R*, 4b*R*)-2-Acetoxymethyl-piperidino(1,2-b)-tetrahydrofuro(3,4-d)isoxazol-4(*3H*)-one (20)

Compound **20** was obtained according to the procedure described for **17** (97%). m.p. 108–111°C; $[\alpha]_D$ −31.1 (*c* 0.7, CH_2Cl_2); IR (film CH_2Cl_2): υ 1766, 1739 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ: 4.59 (dd, 1H, $J = 3.6$, 12.2 Hz, C*H*HOAc), 4.42 (dd, 1H, $J = 8.4$, 12.2 Hz, CH*H*OAc), 4.25 (ddd, 1H, $J = 3.6$, 5.7, 8.4 Hz, H-2), 3.99 (dd, 1H, $J = 5.7$, 7.3 Hz, H-1a), 3.31 (dd, 1H, $J = 4.4$, 11.0 Hz, H-4b), 3.10 (br d, 1H, $J = 15.0$ Hz, H-8), 2.47 (ddd, 1H, $J = 3.3$, 12.5, 15.0 Hz, H-8′), 2.38 (d, 1H, $J = 7.3$ Hz, H-4a), 1.68 (s, 3H, OAc), 1.45 (m, 1H, H-7), 1.28 (m, 1H, H-6), 1.07–0.73 (m, 4H, H-5,5′,6′,7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.0, 170.7, 80.9, 75.0, 63.7, 62.5, 55.0, 49.9, 25.0, 22.3, 20.8, 18.9; MSHR (ESI) m/z $[M + Na]^+$, calcd. for $C_{12}H_{17}NO_5Na$: 278.0999. Found: 278.1008.

(1a*S*, 2*S*, 4a*R*, 4b*R*)-2-(*tert*-Butyldiphenylsiloxymethyl)-piperidino(1,2-b)-tetrahydrofuro(3,4-d)isoxazol-5(*3H*)-one (21)

Alcohol **19** (149 mg, 0.7 mmol) was dissolved in dry CH_2Cl_2 (60 mL) and treated with *tert*-butylodiphenylsililyl chloride (241 mg, 0.88 mmol) and imidazole (95 mg, 1.4 mmol). The mixture was left at rt for 24 h. Subsequently, the mixture was washed with water (30 mL), brine (30 mL), and water (30 mL). The organic layer was dried and evaporated. The crude product was purified by chromatography using hexane/AcOEt 5:1 v/v as an eluent to afford **21** (316 mg, 81%). $[\alpha]_D$ +5.1 (c 0.5, CH_2Cl_2); IR (film CH_2Cl_2): v 1773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.84 (dd, 1H, $J = 5.4$, 7.3 Hz, H-1a), 4.65 (ddd, 1H, $J = 5.4$, 5.6, 6.8 Hz, H-2), 4.05 (dd, 1H, $J = 5.6$, 11.0 Hz, C*H*HOSi), 4.01 (dd, 1H, $J = 6.8$, 11.0 Hz, CH*H*OSi), 3.53 (ddd, 1H, $J = 1.4$, 5.0, 9.9 Hz, H-4b), 3.25 (dd, 1H, $J = 1.4$, 7.3 Hz, H-4a), 3.20 (m, 1H, H-8), 2.88 (m, 1H, H-8′), 1.74–1.23 (4 m, 6H, H-5,5′,6,6′,7,7′), 1.06 (s, 9H, O*t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.5, 83.9, 75.2, 63.5, 61.6, 54.9, 49.9, 26.8, 25.0, 22.2, 19.2, 19.1; MSHR (ESI) m/z $[M + H]^+$, calcd. for $C_{26}H_{34}NO_4Si$: 452.22516. Found: 452.2264.

(2*S*, 1′*S*, 3*S*, 3a*S*)-2-(2′-*tert*-Butyldiphenylsiloxyethyl-1′-hydroxy)-3-(hydroxymethyl)-piperidino(1,2-b)dihydro-(*3H*)-isoxazole (22)

Lactone **21** (316 mg, 0.7 mmol) was dissolved in THF (70 mL), treated with $LiBH_4$ (31 mg, 1.4 mmol), and left for 12 h. Subsequently, unreacted borohydride was decomposed with water (0.5 mL). The mixture was filtered through Celite, evaporated, and purified by chromatography using CH_2Cl_2/methanol 95:5 v/v as an eluent to afford **22** (229 mg, 72 %). $[\alpha]_D$ +0.5 (c 0.2, MeOH); IR (film): v 3227 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.65 (d, 1H, $J = 9.8$ Hz, H-2), 3.92 (dd, 1H, $J = 3.2$, 12.0, Hz, C*H*HOH), 3.89 (dd, 1H, $J = 5.9$, 8.0 Hz, H-1′), 3.86 (dd, 1H, $J = 5.9$, 12.0 Hz, CH*H*OH), 3.76 (dd, 1H, $J = 4.9$, 12.5 Hz, H-3a), 3.73 (dd, 1H, $J = 5.9$, 10.1 Hz, C*H*HOTBDPS), 3.66 (dd, 1H, $J = 8.0$, 10.1 Hz, CH*H*OTBDPS), 3.48 (m, 1H, H-7), 3.01 (dddd, 1H, $J = 3.2$, 5.9, 9.8, 12.5 Hz, H-3), 2.92 (ddd, 1H, $J = 3.1$, 11.6, 13.7 Hz, H-7′), 2.29 (ddd, 1H, $J = 4.9$, 4.9, 13.7, 15.4 Hz, H-4), 2.12 (qt, 1H, $J = 3.8$, 13.7 Hz, H-6), 1.92 (m, 1H, H-4′), 1.71 (m, 1H, H-5), 1.65 (m, 1H, H-6′), 1.44 (qt, 1H, $J = 4.0$, 13.7 Hz, H-5′), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 77.5, 69.8, 67.8, 64.3, 58.6, 58.5, 45.7, 26.9, 24.1, 23.4, 19.2, 17.2; MSHR (ESI) m/z $[M + H]^+$, calcd. for $C_{26}H_{38}NO_4Si$: 456.2565. Found: 456.2574.

(1a*S*, 1′*S*, 2*S*, 2a*S*)-1a-(1′-Acetoxy-2′-*tert*-butylodiphenylsiloxyethyl)-3-acetoxymethyl-piperidino(1,2-b)dihydro-(*3H*)-isoxazole (23)

Compound **23** was obtained according procedure described for **17** (89%). $[\alpha]_D$ +2.1 (*c* 0.1, CH_2Cl_2); IR (film): *v* 1768, 1743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.24 (bt, 1H, H-1′), 4.47 (m, 1H, H-2), 4.11 (m, 2H, CH_2OAc), 3.75 (m, 2H, $CH_2OTBDPS$), 3.45 (m, 1H, H-7), 2.65 (m, 1H, H-3), 2.50 (m, 1H, H-7′), 2.05, 2.03 (2s, 6H, 2 × OAc), 2.04 (m, 1H, H-3a), 1.94 (m, 1H, H-4), 1.85–1.60 (m, 3H, H-5,6,6′), 1.45 (m, 1H, H-4′), 1.26 (m, 1H, H-5′), 1.04 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7, 169.9, 74.4, 71.4, 70.5, 62.5, 62.4, 55.1, 48.0, 29.0, 26.7, 24.7, 23.6, 21.2, 20.8, 19.2; MSHR (ESI) m/z $[M + Na]^+$, calcd. for $C_{30}H_{41}NO_8SiNa$: 540.2776. Found: 540.2768.

(1a*S*, 2*S*, 6a*S*, 6b*R*)-2-(*tert*-Butyldiphenylsiloxymethyl)-4,4-dimethyl-3,5-dioxa-piperidino(1,2-b)izoxazolidino(4,5-c)cycloheptane (24)

Compound **22** (228 mg, 0.5 mmol) was dissolved in 2,2-dimethoxypropane (50 mL) and treated with *p*-TsOH (5 mg). The mixture was refluxed for 1 h. Subsequently, it was cooled and treated with Et_3N (1 mL). After evaporation of solvents the mixture was purified by chromatography using hexane/AcOEt 3:1 v/v as an eluent to afford **24** (233 mg, 94%). $[\alpha]_D$ +13.2 (*c* 0.6, CH_2Cl_2); ^1H NMR (500 MHz, toluene-d_8, 100°C) δ: 4.19 (m,1H, H-1a), 4.17 (ddd, 1H, $J = 1.9$, 5.6, 7.3 Hz, H-2), 4.04 (dd, 1H, $J = 5.6$, 10.3 Hz, C*H*HOTBDPS), 4.01 (dd, 1H, $J = 7.3$, 10.3 Hz, CH*H*OTBDPS) 3.85 (dd, 1H, $J = 9.0$, 12.6 Hz, H-6), 3.52 (dd, 1H, $J = 5.0$, 12.6 Hz, H-6′), 3.26 (td, 1H, $J = 3.6$, 10.5 Hz, H-10), 2.56 (m, 1H, H-10′), 2.50 (ddd, 1H, $J = 3.1$, 10.5, 11.0 Hz, H-10′), 2.26 (m, 1H, H-6b), 2.16 (m, 1H, H-6a), 1.54 (m, 1H, H-9), 1.44 (m, 1H, H-8), 1.38 (2s, 6H, 2 × CH_3), 1.37–1.26 (m, 3H, H-7,7′9′), 1.16 (s, 9H, *t*-Bu); 1.05 (m, 1H, H-8′); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 101.8, 77.2, 72.3, 64.3, 61.5, 50.3, 31.9, 29.7, 29.4, 26.8, 26.8, 22.7, 19.2, 19.2, 14.1; MSHR (ESI) m/z $[M + H]^+$, calcd. for $C_{29}H_{42}NO_4Si$: 496.2878. Found: 496.2858.

(1a*S*, 2*S*, 6a*S*, 6b*R*)-4,4-Dimethyl-3,5-dioxa-2-hydroxymethyl-piperidino(1,2-b)izoxazolidino(4,5-c)cycloheptane (25)

Compound **24** (198 mg, 0.4 mmol) was dissolved in THF (30 mL) and treated with 5 equiv. tetrabutylammonium fluoride. After 24 h at rt, the mixture was filtered through celite and evaporated to afford partially purified **25** (83 mg, 91%), which was used for the next step. Small sample was purified by chromatography using methanol/AcOEt 5:95 v/v as an eluent to prove identity of compound **25**. $[\alpha]_D$ +2.1 (*c* 0.2, CH_2Cl_2); IR (film CH_2Cl_2): *υ* 3419 cm^{-1}; MSHR (ESI) *m/z* $[M+Na]^+$, calcd. for $C_{13}H_{23}NO_4Na$: 280.1519. Found: 280.1531.

(1a*S*, 2*S*, 6a*S*, 6b*R*)-4,4-Dimethyl-3,5-dioxa-2-mesyloxymethyl-piperidine(1,2-b)izoxazolidino(4,5-c) cycloheptane (26)

Alcohol **25** (68 mg, 0.3 mmol) dissolved in dry CH_2Cl_2 (20 mL) was treated with TEA (61 mg, 0.6 mmol) and cooled to −5°C. Subsequently, mesyl chloride (41 mg, 0.36 mmol) was added and the temperature was allowed to raise to rt. After 30 min the mixture was washed with brine (20 mL) and water (20 mL), dried, and evaporated to afford crude **26** (88 mg, 96%). Small sample was purified using hexane/AcOEt, 1:2 v/v as an eluent to prove identity of compound **26**. $[\alpha]_D$ −11.7 (*c* 0.2, CH_2Cl_2); MSHR (ESI) *m/z* $[M+H]^+$, calcd. for $C_{14}H_{26}NO_6S$: 336.1475. Found: 336.1491.

(1*S*, 2*S*, 3*S*, 9a*S*)-1-Acetoxymethyl-2,3-diacetoxy-quinolizidine (27)

Compound **26** (91 mg, 0.3 mmol) was dissolved in 80% acetic acid (30 mL) and the solution was refluxed for 10 min. Subsequently, solvents were evaporated and the residue, in order to remove traces of water, was twice treated with toluene (2 × 20 mL) and twice carefully evaporated. The oily residue was dissolved in AcOEt/methanol (4:1 v/v, 35 mL) and treated with anhydrous K_2CO_3 (41 mg) and 10% Pd/C (11 mg). The mixture was hydrogenated at rt for 24 h. Subsequently, the catalyst was filtered off and the solvents were evaporated. The residue was dissolved in TEA (10 mL) and treated with acetic anhydride (10 mL) and DMAP (0.03 mmol). After 4 h at rt, solvents were evaporated and the crude product was purified by chromatography using hexane/AcOEt 3:2 v/v as an eluent to afford **27** (72 mg, 73 %). $[\alpha]_D$ +0.8 (*c* 0.45, CH_2Cl_2); IR (film CH_2Cl_2): *υ* 1745 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 5.26 (dd, 1H, *J* = 9.6, 10.3 Hz, H-2), 5.22 (ddd, 1H, *J* = 4.8, 9.6, 10.0 Hz, H-3), 4.20 (dd, 1H, *J* = 2.8, 12.1 Hz, C*H*HOAc), 3.91 (dd, 1H, *J* = 2.4, 12.1 Hz, CH*H*OAc), 2.90 (dd, 1H, *J* = 4.8, 11.0 Hz, H-4), 2.48 (m, 1H, H-6), 1.94 (dd, 1H, *J* = 10.0, 11.0 Hz, H-4′), 1.80 (m, 1H, H-9a), 1.77, 1.75, 1.71 (3s, 9H, 3 × OAc), 1.70 (m, 1H, H-6′), 1.65 (m, 1H, H-9), 1.51 (dddd, 1H, *J* = 2.4, 2.8, 10.3, 10.5 Hz, H-1), 1.48 (m, 1H, H-8), 1.38 (m, 1H, H-7), 1.30 (m, 1H, H-7′), 0.95 (m, 1H, H-8′), 0.87 (m, 1H, H-9′); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 170.4, 170.1, 169.8, 71.8, 71.7, 60.8, 59.1, 57.7, 55.8, 45.8, 29.5, 25.5, 24.0, 20.5, 20.4, 20.3; MSHR (ESI) *m/z* $[M+H]^+$, calcd. For $C_{16}H_{26}NO_6$: 328.1754. Found: 328.1749.

(1*S*, 2*S*, 3*S*, 9a*S*)-2,3-Dihydroxy-1-hydroxymethyl-quinolizidine (28)

Compound **27** (33 mg, 0.1 mmol) was dissolved in 1.3% solution of ammonia in methanol (10 mL) and left at rt for 24 h. Subsequently, solvents were evaporated and the product was purified by chromatography using methanol/ CH_2Cl_2 4:1 v/v as an eluent to afford **28** (17 mg, 87%). $[\alpha]_D$ +3.5 (*c* 0.7, MeOH); IR (film): υ 3307 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ: 3.98 (dd, 1H, $J = 2.5$, 11.4 Hz, C*H*HOH), 3.77 (dd, 1H, $J = 3.3$, 11.4 Hz, CH*H*OH), 3.60 (ddd, 1H, $J = 4.8$, 8.9, 10.8 Hz, H-3), 3.42 (dd, 1H, $J = 8.9$, 10.7 Hz, H-2), 2.92 (dd, 1H, $J = 4.8$, 11.2 Hz, H-4), 2.93 (m, 1H, H-6), 2.16 (m, 1H, H-6′), 2.10 (m, 1H, H-9), 2.06 (dd, 1H, $J = 10.8$, 11.2 Hz, H-4′), 2.02 (dt, 1H, $J = 2.6$, 10.6 Hz, H-9a), 1.85 (m, 1H, H-8), 1.71 (m, 1H, H-7), 1.65 (m, 1H, H-7′), 1.37 (m, 1H, H-8′), 1.28 (dddd, 1H, $J = 2.5$, 3.3, 10.6, 10.7 Hz, H-1), 1.20 (m, 1H, H-9′); ^{13}C NMR (125 MHz, CD_3OD) δ: 74.5, 72.6, 62.7, 62.0, 58.5, 57.4, 30.2, 26.1, 24.9; MSHR (ESI) m/z $[M+H]^+$, calcd. for $C_{10}H_{20}NO_3$: 202.1447. Found: 202.1447.

MEASUREMENTS OF ENZYME INHIBITION

The following hydrolases were used: α-L-glucosidase from rice (type V, 63.43 U/mg, 1.34 mg/mL, Sigma); β-D-glucosidase from almonds (25.8 U/mg, 95.4% protein, Sigma); α-D-mannosidase from jack bean (6.2 mg prot./mL, 22 U/mg, Sigma); α-L-fucosidase from bovine kidney (28.0 U/mg, 0.55 mg prot./mL, Sigma); β-D-galactosidase from bovine liver (0.148 U/mg, Sigma) solution (0.562 U/mL); and β-D-glucuronidase from bovine liver (2630 U/mg, Sigma) solution (4909 U/mL). These enzymes were assayed with appropriate p-nitrophenyl glycoside substrates (phenolphthalein β-glucuronide for β-glucuronidase), which were also purchased from Sigma. Hydrolase activities were measured by modification of the procedures described previously.[15–19]

ACKNOWLEDGEMENTS

This work was supported by the Ministry of Science and Information Grant # 3 T09A 025 28.

REFERENCES

[1] Jurczak, M.; Rabiczko, J.; Socha, D.; Chmielewski, M.; Cardona, F.; Goti, A.; Brandi, A. Diastereoselection in 1,3-dipolar cycloadditions of a chiral cyclic nitrone to α,β-unsaturated δ-lactones. Tetrahedron Asymm. **2000**, *11*, 2015–2022.

[2] Socha, D.; Jurczak, M.; Frelek, J.; Klimek, A.; Rabiczko, J.; Urbańczyk-Lipkowska, Z.; Suwińska, K.; Chmielewski, M.; Cardona, F.; Goti, A.; Brandi, A.

1,3-Dipolar cycloaddition of a nitrone derived from (*S*)-malic acid to α,β-unsaturated δ-lactones. Tetrahedron Asymm. **2001**, *12*, 3163–3172.

[3] Paśniczek, K.; Socha, D.; Jurczak, M.; Frelek, J.; Suszczyńska, A.; Urbańczyk-Lipkowska, Z.; Chmielewski, M. Double asymmetric induction in 1,3-dipolar cycloaddition of nitrones to 2,3-unsaturated sugar 1,5-lactones. J. Carbohydr. Chem. **2003**, *22*, 613–629.

[4] (a) Goti, A.; Fedi, V.; Nannelli, L.; De Sarlo, F.; Brandi, A. Cycloaddition of an enantiopure cyclic nitrone to maleate: straightforward synthesis of the necine base (−)-hastanecine. Synlett. **1997**, 577–579; (b) Goti, A.; Cardona, F.; Brandi, A. Improved syntheses of (+)-lentiginosine and (1*S*, 2*S*, 7*R*, 8a*S*)-trihydroxyoctahydroindolizine by butenol cycloaddition to enantiopure protected dihydroxy pyrroline *N*-oxides. Synlett. **1996**, 761–763; (c) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. Straightforward access to enantiomerically pure, highly functionalized pyrrolizidines by cycloaddition of maleic acid esters to pyrroline *N*-oxides derived from tartaric, malic and aspartic acids − synthesis of (−)-hastanecine, 7-*epi*-croalbinecine and (−)-croalbinecine. Eur. J. Org. Chem. **2000**, 3633–3645; (d) Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F.M.; Brandi, A. Total synthesis of (−)-rosmarinecine by intramolecular cycloaddition of (*S*)-malic acid derived pyrroline *N*-oxide. Org. Lett. **2001** *3*, 1367–1369; (e) McCaig, A.E.; Meldrum, K.P.; Wightman, R.H. Synthesis of trihydroxylated pyrrolizidines and indolizidines using cycloaddition reactions of functionalized cyclic nitrones, and the synthesis of (+)- and (−)-lentiginosine. Tetrahedron **1998**, *54*, 9429–9446.

[5] Paśniczek, K.; Socha, D.; Jurczak, M.; Solecka, J.; Chmielewski, M. Synthesis of 8-homocastanospermine. Can. J. Chem. **2006**, *84*, 534–539.

[6] Socha, D.; Paśniczek, K.; Jurczak, M.; Solecka, J.; Chmielewski, M. Synthesis of 1-homoaustraline. Carbohydr. Res. **2006**, *341*, 2005–2011.

[7] (a) Hohenschutz, L.D.; Bell, E.A.; Jewess, P.J.; Lewerothy, D.P.; Pryce, R.J.; Arnold, E.; Clardy, J. Castanospermine, a 1,6,7,8-tetrahydroxyoctahydroindolizine alkaloid, from seeds of *Castanospermum australe*. Phytochemistry **1981**, *20*, 811–814; (b) Pastuszak, I.; Molyneux, R.J.; James, L.F.; Elbein, A.D. Lentiginosine, a dihydroxyindolizidine alkaloid that inhibits amyloglucosidase. Biochemistry **1990**, *26*, 1886–1891.

[8] (a) Tropea, J.E.; Molyneux, R.J.; Kaushal, G.P.; Pan, Y.T.; Mitchell, M.; Elbein, A.D. Australine, a pyrrolizidine alkaloid that inhibits amyloglucosidase and glycoprotein processing. Biochemistry **1989**, *28*, 2027–2034; (b) Molyneux, R.J.; Benson, M.; Wong, R.Y.; Tropea, J.E.; Elbein, A.D. Australine, a novel pyrrolizidine alkaloid glucosidase inhibitor from *Castanospermum australe*. J. Nat. Prod. **1988**, *51*, 1198–1206.

[9] (a) Mattocks, A.R. Ed.; *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, 1986; (b) Hartman, T.; Witte, L. *Alkaloids: Chemical & Biological Perspectives*; Pelletier, S.W., Ed.; Oxford: Pergamon, 1995; *9*, 155–233; (c) Liddell, J.R. Pyrrolizidine alkaloids. Nat. Prod. Rep. **1998**, *15*, 363–370; (d) Robins, D.J. The pyrrolizidine alkaloids. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G.W., Eds.; Springer-Verlag: Wien, 1982; 41, 115–203; (e) Mead, E.W.; Looker, M.; Gardner, D.R.; Stermitz, F.R. Pyrrolizidine alkaloids of *Liatris punctata* and its root parasite, *Castilleja integra*. Phytochemistry **1992**, *31*, 3255–3257.

[10] (a) Denmark, S.E.; Thorarensen, A. Tandem [4 + 2]/[3 + 2] cycloadditions of nitroalkenes. Chem. Rev. **1996**, *96*, 137–166; (b) Michael, P.J. Indolizidine and quinolizidine alkaloids. Nat. Prod. Rep. **1999**, *16*, 675–696; (c) Michael, P.J.

Indolizidine and quinolizidine alkaloids. Nat. Prod. Rep. **2002**, *19*, 719–741; (d) Michael, P.J. Indolizidine and quinolizidine alkaloids. Nat. Prod. Rep. **2005**, *22*, 603–626.

[11] (a) Saito, K.; Murakoshi, I. Chemistry, biochemistry and chemotaxonomy of lupine alkaloids in the Leguminosae. In *Studies in Natural Products Chemistry. Structure and Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1995; 15, 519–549; (b) Michael, J.P. In. *The Alkaloids. Chemistry and Biology*; Cordell, G.A., Ed.; Academic Press: New York, 2001; *55*, 91–258; (c) Howard, A.S.; Michael, J.P. In. *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1986; *28*, 183–308; (d) Aslanov, K.A.; Kushmuradov, Y.K.; Sadykov, A.S. Lupine alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: London, 1987; *31*, 117–192; (e) Wang, H.H.; Cheng, J.T. Antitrichomonal activity of matrine, an active substance from Sophora flavescens. Phytother. Res. **1994**, *8*, 70–73; (f) Wang, G.L.; Zhang, S.S.; Li, Z.H.; Liu, S.F. Relation of effects of matrine on rat vasa deferens to activation of calcium channels. Acta Pharmacol. Sin. **1994**, *15*, 279–281; (g) Hu, Z.L.; Zhang, J.P.; Qian, D.H.; Lin, W.; Xie, W.F.; Zhang, X.R.; Chen, W.Z. Effects of matrine on mouse splenocyte proliferation and release of interleukin-1 and -6 from peritoneal macrophages in vitro. Acta Pharmacol. Sin. **1996**, *17*, 259–261.

[12] (a) Iwashita, T.; Kusumi, T.; Kakisawa, H. Syntheses of isoretronecanol and lupinine. J. Org. Chem. **1982**, *47*, 230–233; (b) Hua, D.H.; Miao, S.W.; Bravo, A.A.; Takemo, D.J. Asymmetric total synthesis of (−)-lupinine and (+)-epi-lupinine via α-sulfinyl ketimine stereocontrolled reduction of β-sulfinyl enamines. Synthesis ***1991***, 970–974; (c) Wanner, M.J.; Koomen, G.J. Oxidative deamination of tetrahydroanabasine with *o*-quinones: an easy entry to lupinine, sparteine, and anabasine. J. Org. Chem. **1996**, *61*, 5581–5586; (d) Chang, M.-Y.; Tai, H.-M.; Lin, C.-H.; Chang, N.-C. Synthesis of lupinine. Heterocycles **2005**, *65*, 395–402.

[13] (a) Bernotas, R.C.; Ganem, B. Efficient preparation of enantiomerically pure cyclic aminoalditols, total synthesis of 1-deoxynojirimycin and 1-deoxymannojirimycyn. Tetrahedron Lett. **1985**, *26*, 1123–1126; (b) Gradnig, G.; Berger, A. Grassberger, V.; Stütz, A.E.; Legler, G. First synthesis of (1*R*, 2*R*, 3*S*, 9*S*, 9a*R*)-1,2,3,9-tetrahydroxy-quinolizidine, a novel isosteric homologue of the glucosidase inhibitor castanospermine. Tetrahedron Lett. **1991**, *32*, 4889–4892; (c) Liu, P.S.; Rogers, R.S.; Kang, M.S.; Sunkara, P.S. Synthesis of polyhydroxylated indolizidine and quinolizidine compounds-potent inhibitors of α-glucosidase I. Tetrahedron Lett. **1991**, *32*, 5853–5856; (d) Rassu, G.; Casiraghi, G.; Pinna, L.; Spanu, P.; Cornia, F.U.-M.; Zanardi, F. Efficient total syntheses of (1*R*, 2*R*, 3*R*, 9*R*, 9a*R*)-1,2,3,9-tetrahydroxyquinolizidine and its enantiomer. Tetrahedron **1993**, *49*, 6627–6636; (e) Pearson, W.H.; Hembre, E.J. Synthesis of novel polyhydroxylated quinolizidines: Ring expanded analogs of glycosidase inhibitory indolizidines. Tetrahedron Lett. **1993**, *34*, 8221–8224; (f) Pearson, W.H.; Hembre, E.J. Synthesis of tetrahydroxyquinolizidines: ring-expanded analogs of the mannosidase inhibitor swainsonine. J. Org. Chem. **1996**, *61*, 5537–5545; (g) Herczegh, P.; Kovács, I.; Sztaricskai, F.; Berecibar, A.; Riche, C. Cycloaddition reactions of carbohydrate derivatives. Part VI. Quinolizidine analogs of castanospermine. Tetrahedron **1995**, *51*, 2969–2978; (h) Pandit, U.K.; Overkleeft, H.S.; Borer, B.C.; Bieräugel, H. Synthesis mediated by ring-closing metathesis - applications in the synthesis of azasugars and alkaloids. Eur. J. Org. Chem. **1999**, 959–968.

[14] (a) Fleet, G.W.J.; Fellows, L.E.; Winchester, B. Plagiarizing plants: aminosugars as a class of glycosidase inhibitors. In *Bioactive Compounds from Plants*; Chadwick, P.J., March, J., Eds.; Wiley & Sons: Chichester, 1990, 112–125; (b) Asano, N.; Nash, R.J.; Molyneux, R.J.; Fleet, G.W.J. Sugar-mimic glycosidase inhibitors: natural occurrence, biological activity and prospects for therapeutic

application. Tetrahedron Asymm. **2000**, *11*, 1645–1680; (c) Chapleur, Y. Ed.; *Carbohydrate Mimics*; Wiley-VCH: Weinheim, 1998; (d) Stütz, A.E. Ed.; *Iminosugars as Glycosidase Inhibitors*; Wiley-VCH: Weinheim, 1999; (e) Martin, O.R.; Compain, Ph. Ed.; Design, synthesis and biological evaluation of iminosugar-based glycosyltransferase inhibitors. In *Curr. Top. Med. Chem*; 2003; 3, 541–560 (f) El Nemr, A. Synthetic methods for the stereoisomers of Swainsonine and its analogues. Tetrahedron **2000**, *56*, 8579–8629; (g) Felpin, F.-X.; Lebreton, J. Recent advances in the total synthesis of piperidine and pyrrolidine natural alkaloids with ring-closing metathesis as a key step. Eur. J. Org. Chem. **2003**, 3693–3712; (h) Cossy, J.; Vogel, P. Hydroxylated indolizidines and their synthesis. In *Studies in Natural Products Chemistry. Stereoselestive Synthesis (Part H)* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993 *12*, 275–364; (i) Herczegh, P.; Kovacs, I.; Sztaricskai, F. Chemistry of biologically important hydroxylated indolizidines: synthesis of swainsonine, castanospermine and slaframine. In *Recent Progress in Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ohno, M., Eds. Springer-Verlag: Berlin 1993, 751–828; (j) Felpin, F.-X.; Lebreton, J. Recent advances in the total synthesis of piperidine and pyrrolidine natural alkaloids with ring-closing metathesis as a key step. Eur. J. Org. Chem. **2003**, 3693–3712; (k) Cipolla, L. La Ferla, B.; Nicotra, F. General methods for iminosugar synthesis. Curr. Top. Med. Chem. **2003**, *3*, 485–511.

[15] Cordero, F.M.; Mechetti, F.; De Sarlo, F.; Brandi, A. New synthesis of (methoxycarbonyl)-indolizidin-7-one and -quinolizidin-2-one: an access to β-amino acids with indolizidine and quinolizidine backbone. Gazz. Chim. Ital. **1997**, *127*, 25–30.

[16] Tsuruoka, T.; Fukuyasu, H.; Ishii, M.; Usui, T.; Shibahara, S.; Inouye, S. Inhibition of mouse tumor metastasis with Nojirimycin-related compounds. J. Antibiot. **1996**, *49*, 155–161.

[17] Legler, G. Glycoside hydrolases: mechanistic information from studies with reversible and irreversible inhibitors. Adv. Carbohydr. Chem. Biochem. **1990**, *48*, 319–384.

[18] (a) Rauscher, E. Colorimetric method assay. In *Meth. Enzym. Anal.* 3rd Edn.; Bergmeyer, H.U., Ed.; Verlag Chemie: Weinheim, 1984; 4, 157–160.; (b) Faber, Ch. N; Glew, R. H. α-D-Mannosidase. In *Meth. Enzym. Anal.* 3rd Edn.; Bergmeyer, H.U., Eds.; Verlag Chemie: Weinheim, 1984; 4230–240.

[19] Li, Y.-T. Studies on the glycosidases in jack bean meal. I. Isolation and properties of α-mannosidase. J. Biol. Chem. **1967**, *242*, 5474–5480.

[20] Saul, R.; Chambers, J.P.; Molyneux, R.J.; Elbein, A.D. Castanospermine, a tetrahydroxylated alkaloid that inhibits β-glucosidase and β-glucocerebrosidase. Arch. Biochem. Biophys. **1983**, *221*, 593–597.