Carbohydrate Research 343 (2008) 2215–2220

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: http://www.elsevier.com/locate/carres

Synthesis of pyrrolizidine alkaloids via 1,3-dipolar cycloaddition involving cyclic nitrones and unsaturated lactones

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ARTICLE INFO

Article history:
Received 14 January 2008
Accepted 21 April 2008
Available online 27 April 2008

Keywords:
Nitrone
Necine bases
Iminosugars
1,3-Dipolar cycloaddition

ABSTRACT

The 1,3-dipolar cycloaddition of cyclic nitrone derived from tartaric acid and (*S*)-5-hydroxymethyl-2(5*H*)-furanone leads to a single adduct which was transformed into 2,6-dihydroxyhastanecine via reaction sequence involving reduction of the lactone moiety, glycolic cleavage of the terminal diol, and the N–O hydrogenolysis followed by the intramolecular alkylation of the nitrogen atom.

1. Introduction

A large number of structurally different polyhydroxylated alkaloids have been isolated from natural sources such as plants or microorganisms. An apparent common structural feature of this group is a nitrogen-containing four- (azetidine), five- (pyrrolidine), or six-membered (piperidine) ring, or related fused ring systems (pyrrolizidine, indolizidine, and quinolizidine) built up from the above monocycles, substituted with one or more hydroxyl groups.[1,2] The structural similarity of these compounds to monosaccharides, reflected in fact that they are also called iminosugars, results in an interesting biological activity as selective inhibitors of glycosidases. Consequently, the iminosugars show antibacterial, antiviral, antitumor, or antidiabetic activities.[3] For these reasons, the synthesis of the iminosugars and their analogues has attracted attention of many academic and pharmaceutical laboratories including our group.[3–6]

Recently, we have reported that the 1,3-dipolar cycloaddition of five-membered cyclic nitrones to the α,β-unsaturated δ-lactones provides an attractive entry to the pyrrolizidine and indolizidine iminosugars.[6] We found that the cycloadditions involving δ-lactones proceed exclusively in the *exo* mode, and therefore in many cases only a single product is formed. The corresponding transformations involving γ-lactones proceed with a lower diastereoselectivity, as compared with the cycloaddition to the six-membered ones due to the possible formation of *endo* adducts.[7] A single adduct is formed only in the case of the matching pair when the *endo* approach of reactants is hindered. Cycloadducts **4** and **5** readily available from the D-glycero lactone **1** and nitrones of L-(+)-tartaric acid **2** and D-(+)-malic acid **3**, respectively, are particularly attractive. In the present paper, we demonstrate that the adduct **4**, easily accessible from the relatively inexpensive substrates, is a convenient starting material for the synthesis of necine alkaloids **6**–**9** which have 1(*S*) and 7a(*S*) configuration. Both of these stereogenic centers cannot be easily epimerized, and therefore have to be established at the cycloaddition step (see Chart 1).

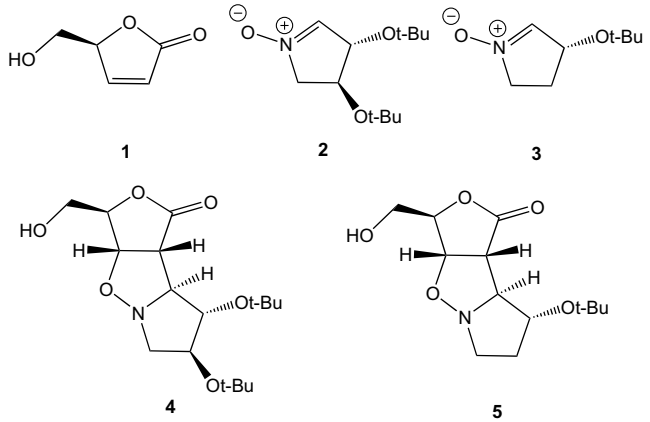

Chart 1.

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doi:10.1016/j.carres.2008.04.029

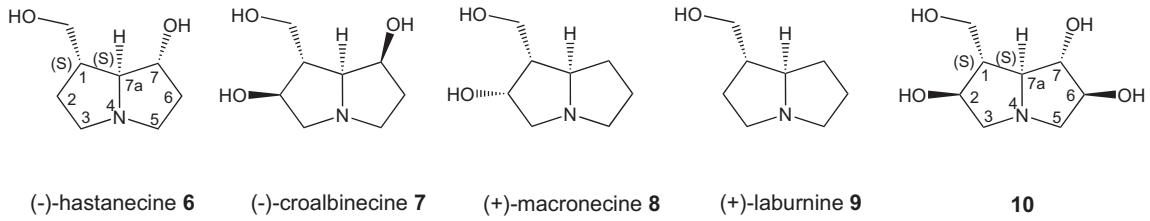


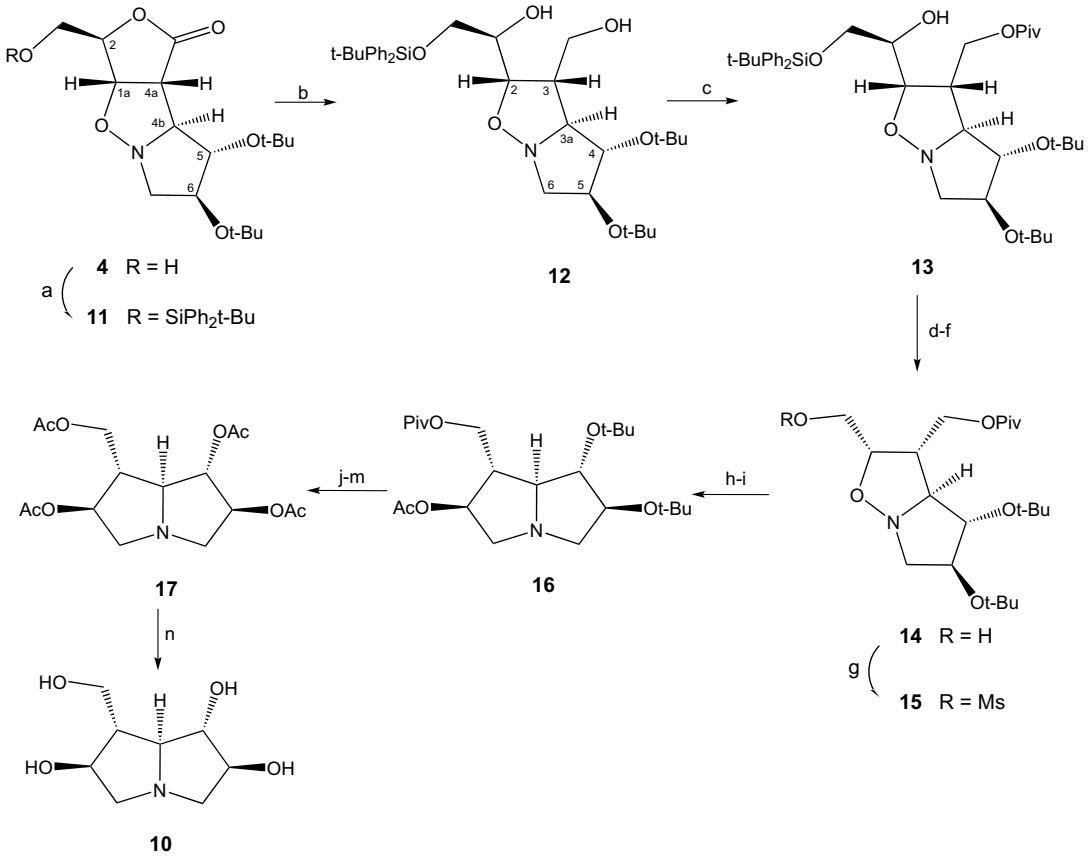
Chart 2.

The present paper describes the synthesis of dihydroxy-hastanecine **10** from adduct **4**. In comparison with the parent compound **6**, the pyrrolizidine **10** bears two additional hydroxy groups at the C-2 and C-6 carbon atoms. All secondary hydroxyls in **10**, however, can be easily removed and/or configurations of the adjacent carbon atoms can be inverted. Therefore, the adduct **4** can be treated as an entry not only to hydroxypyrrolizidine **10**, but also to other necine bases of several alkaloids such as (−)-hastanecine (**6**),[8] (−)-croalbinecine (**7**),[8b,9] (+)-macronecine (**8**),[10] and (+)-laburnine (**9**).[11] All these compounds display a variety of interesting biological activities[8–11] (see Chart 2).

2. Results and discussion

The synthesis of **10** is depicted in Scheme 1. The free hydroxy group in **4** was protected with *t*-$BuPh_2Si$ yielding **11**. Subsequently, the lactone moiety was reduced with BH_3–Me_2S complex to give diol **12**. The same reduction performed with $LiAlH_4$ led to desilylation of the substrate. The primary hydroxyl group in **12** was then selectively protected with pivaloyl chloride to give **13**. In turn, the compound **13** was subjected to the sequence of three reactions involving desilylation with tetrabutylammonium fluoride and $NaIO_4$-mediated diol cleavage followed by the reduction of aldehyde with $NaBH_4$ affording alcohol **14**. After mesylation of the hydroxy group followed by the hydrogenolysis of the N–O bond, the intramolecular N-alkylation afforded the pyrrolizidine **16**. The deprotection–acetylation sequence (pivaloyl protection was removed by the $LiAlH_4$ reduction and *t*-butyl protecting groups were removed by treatment with trifluoroacetic acid) provided peracetylated derivative **17** of target compound. The structure and configuration of **17** was confirmed by X-ray structure analysis (Fig. 1).[12] The final deprotection was performed by the treatment of **17** with 1% solution of ammonia in methanol to afford pyrrolizidine **10**.

Since the hydroxymethyl group stemming from lactone **1** was removed at the later stage of the synthesis of **10**, one could con-



Scheme 1. Reagents and conditions: (a) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, −15 °C to rt; (b) BH_3–Me_2S, THF, rt; (c) PivCl, DMAP, CH_2Cl_2, −15 °C to rt; (d) TBAF, THF, rt; (e) $NaIO_4$, MeOH, rt; (f) $NaBH_4$, MeOH, rt; (g) MsCl, Et_3N, CH_2Cl_2, −15 °C to rt; (h) H_2, 10% Pd/C, EtOAc–MeOH (4:1), rt; (i) Ac_2O, Et_3N, rt; (j) $LiAlH_4$, Et_2O, rt; (k) Ac_2O, Et_3N, rt; (l) CF_3COOH, rt; (m) Ac_2O, Et_3N, rt; (n) 1% NH_3 in MeOH, rt.

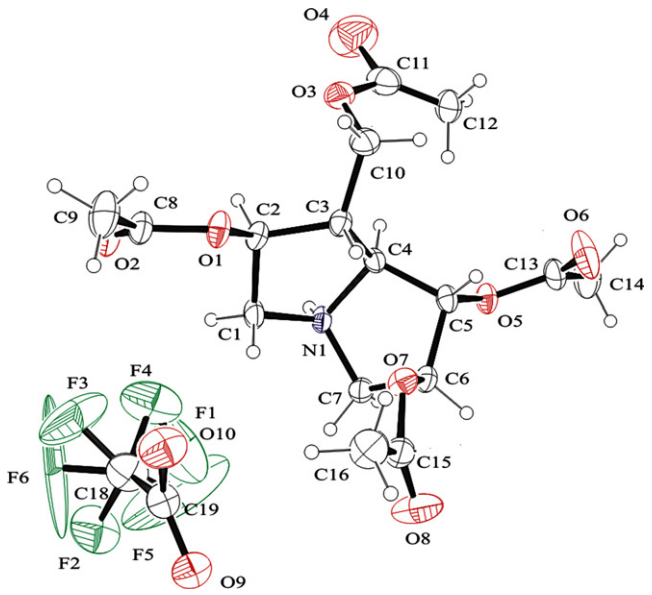


Figure 1. ORTEP drawing of X-ray structure of **17** (salt with CF_3COOH).[12]

sider the use of a non-chiral furanone **18** as the component of the 1,3-cycloaddition with nitrone **2**. In such a case, the preferred approach of reactants should be *exo* and *anti* to the 3-*Ot*-Bu of the nitrone, and the resulting configuration at C-1a and C-4a of both adducts should be the same. It has been reported, however, that the cycloaddition of **18** and **2** leads to the mixture of two *exo* adducts **19** and **20** (Scheme 2) in a ratio of about 9:1.[7] Moreover, the reduction of lactone **19** gave diol **21** with two difficult to discriminate primary hydroxyl groups. Silylation of **21** with equimolar amount of *t*-$BuPh_2SiCl$, or its acylation with equimolar amount of PivCl led in both cases to the mixture of substrate **21**, double-substituted compound **22** (**23**) and two mono-substituted **24** and **25** (**26** and **27**), which could not be easily separated into pure regioisomers (Scheme 2). The ratio of products **22**:**24**:**25** amounted to 4:1.5:1 (HPLC), respectively, whereas that of **23**:**26**:**27** amounted to 5:1.5:1 (HPLC). The assignment of gross structure of compounds **24**–**27** was based on HRMS spectra. The low stereoselectivity of the **21** monoprotection practically precludes the use of the adduct **19** as the substrate for the synthesis leading to **10**, as well as to **6**–**9**.

Compound **10** 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,[13–16] compound **10** displayed only low activity against the α-D-glucosidase, 37% in concentration 7.26 mM.

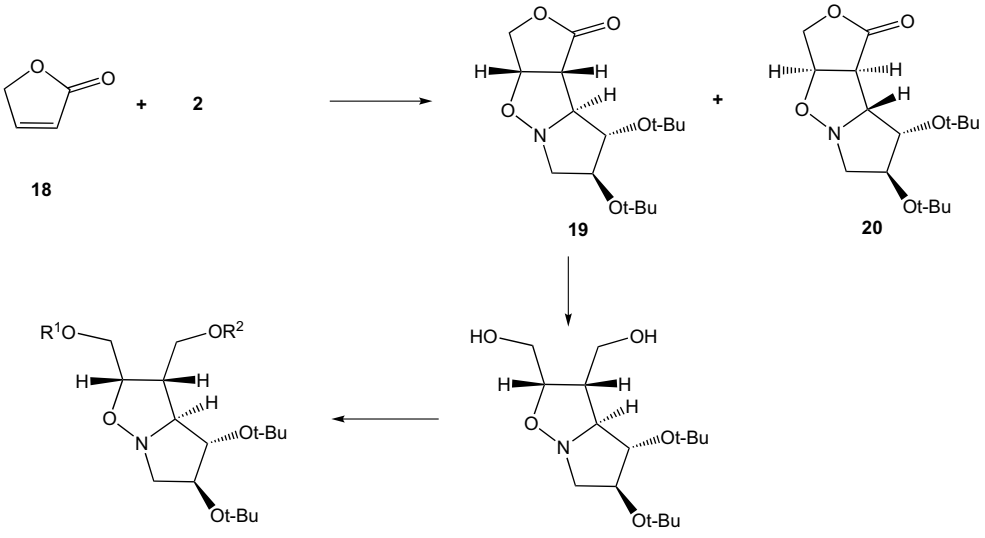
3. Experimental

3.1. General methods

Melting points were determined using Köfler hot-stage apparatus with microscope and were uncorrected. Proton and carbon NMR spectra were recorded on a Bruker DRX 500 Avance Spectrometer at 500 MHz and 125 MHz, respectively, using deuterated solvents and TMS as an internal standard. Chemical shifts are reported as δ values in ppm and coupling constants are in Hertz. Infrared spectra were obtained on an FT-IR-1600 Perkin–Elmer spectrophotometer. The optical rotations were measured with a JASCO J-1020 digital polarimeter. High resolution mass spectra were recorded on ESI-TOF Mariner spectrometer (Perspective Biosystem). X-ray analyses were performed on Nonius MACH3 difractometer.

Thin layer chromatography (TLC) was performed on aluminum sheets Silica Gel 60 F_{254} (20 × 20 × 0.2) from Merck. Column chromatography was carried out using Merck silica gel 230–400 mesh. The TLC spots were visualized in UV (254 nm) and by treatment with alcoholic solution of ninhydrine.

All solvents were dried and purified applying standard techniques.[17] Cycloadduct **4** was prepared following our previous procedure.[7]



Scheme 2.

3.2. (1a*S*,2*R*,4a*R*,4b*S*,5*S*,6*S*)-5,6-Di-*tert*-butoxy-2-*tert*-butyldiphenylsilyloxymethyl-hexahydrofuro[3,4-*d*]pyrrolo-[1,2-*b*]isoxazol-1(3*H*)-one (11)

To a cooled (−15 °C) solution of 1.0 g (2.9 mmol) of the adduct **4** and 0.3 g (4.4 mmol) of imidazole in dichloromethane (50 mL), 0.9 mL (0.9 g, 3.2 mmol) of *t*-BuPh$_2$SiCl was added. The progress of reaction was monitored by TLC (hexane–ethyl acetate 2:1 v/v). After disappearance of substrate, reaction mixture was diluted with dichloromethane (50 mL), washed with water (2 × 25 mL), brine (25 mL), and dried over anhydrous Na_2SO_4. After removal of solvent residue was chromatographed on silica gel (hexane–ethyl acetate 9:1 then 4:1 v/v) affording 1.68 g (99%) of **11** as a colorless oil; $[\alpha]_D$ +48.1 (*c* 1.34, CH_2Cl_2); IR (film, CH_2Cl_2) *ν*: 1779, 1113 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) *δ*: 7.72–7.20 (10H, m, 2 × Ph), 4.75 (1H, d, *J* 6.2 Hz, H-1a), 4.24 (1H, dd, *J* 2.8, 1.9 Hz, H-2), 4.14 (1H, dd, *J* 2.7, 2.2 Hz, H-4b), 4.02 (1H, dd, *J* 4.2, 3.4 Hz, H-5), 3.82 (1H, ddd, *J* 5.8, 5.5, 4.2 Hz, H-6), 3.77 (1H, dd, *J* 6.2, 2.7 Hz, H-4a), 3.57 (1H, dd, *J* 11.5, 2.8 Hz, CH*H*OSi), 3.53 (1H, dd, *J* 12.1, 5.8 Hz, H-7), 3.23 (1H, dd, *J* 11.5, 1.9 Hz, C*H*HOSi), 2.97 (1H, dd, *J* 12.1, 5.5 Hz, H-7′), 1.18 (9H, s, *t*-Bu), 1.08 (9H, s, *t*-Bu), 1.00 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 176.3, 136.0, 135.8, 133.3, 132.4, 130.3, 130.2, 128.5, 128.35, 82.9, 82.1, 80.1, 76.9, 75.8, 74.3, 73.8, 64.2, 61.2, 55.9, 28.8, 28.4, 26.9, 19.3; HRMS (ESI): calcd for $C_{33}H_{48}NO_6Si$: 582.32676 [M+H$^+$], found: 582.3268.

3.3. (*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-((2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-di-*tert*-butoxy-3-(hydoxymethyl)hexahydropyrrolo[1,2-*b*]-isoxazol-2-yl)ethanol (12)

A 2 M solution of BH_3–Me_2S in THF (7 mL) was added to a solution of 1.68 g (2.9 mmol) of lactone **11** in 25 mL THF under argon. The progress of reaction was monitored by IR spectra. After consumption of the lactone, excess of borane was destroyed by addition of methanol (ca. 20 mL). Solvents were evaporated in vacuum and the residue was dissolved in 30 mL of 7 N ammonia solution in methanol and stirred overnight. Subsequently, solvent was removed under diminished pressure and the oil residue was purified on silica gel (hexane–ethyl acetate 1:1 v/v) affording 1.3 g (77%) of diol **12** as a colorless oil; $[\alpha]_D$ +25.0 (*c* 4.6, CH_2Cl_2); IR (film, CH_2Cl_2) *ν*: 3369, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$–D_2O) *δ*: 7.70–7.33 (10H, m, 2 × Ph), 4.24 (1H, dd, *J* 9.1, 6.3 Hz, H-2), 3.96 (1H, ddd, *J* 9.1, 6.5, 3.3 Hz, C*H*(OH)CH$_2$OSi), 3.93–3.86 (2H, m, C*H*HOH, C*H*HOSi), 3.86–3.81 (2H, m, H-4, H-5), 3.71 (1H, dd, *J* 10.4, 6.5 Hz, CH*H*OSi), 3.63 (1H, dd, *J* 11.6, 3.9 Hz, CH*H*OH), 3.43 (1H, dd, *J* 12.0, 5.6 Hz, H-6), 3.09 (1H, dd, *J* 4.2, 3.8 Hz, H-3a), 2.94 (1H, m, H-3), 2.82 (1H, dd, *J* 12.0, 6.0 Hz, H-6′), 1.19 (9H, s, *t*-Bu), 1.14 (9H, s, *t*-Bu), 1.07 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 135.9, 133.8, 130.0, 128.3, 82.2, 77.6, 77.1, 74.1, 73.8, 73.4, 70.1, 66.7, 62.0, 61.2, 28.9, 28.4, 27.1, 19.6; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{51}NO_6SiNa$: 608.3378 [M+Na$^+$], found: 608.3380.

3.4. (2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-2-((*R*)-2′-*tert*-butyldiphenylsilyloxy-1′-hydroxyethyl)-3-pivaloyloxymethyl-hexahydropyrrolo[1,2-*b*]isoxazol (13)

The PivCl (0.3 mL, 0.30 g, 2.5 mmol) was added to cooled (0 °C) solution of diol **12** (1.3 g, 2.2 mmol) and DMAP (0.54 g, 4.4 mmol) in CH_2Cl_2 (30 mL). The progress of reaction was controlled by TLC (hexane–ethyl acetate 4:1 v/v). Subsequently, the post-reaction mixture was diluted with dichloromethane (20 mL), washed with sodium carbonate (30 mL), water (30 mL), brine (30 mL), and then organic layer was dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified on silica gel (hexane–ethyl acetate 9:1→4:1 v/v) affording 1.19 g of **13** (80%); colorless oil; $[\alpha]_D$ −4.1 (*c* 1.5, CH_2Cl_2); IR (film, CH_2Cl_2) *ν*: 1730 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) *δ*: 7.90–7.10 (10H, m, 2 × Ph), 4.70 (1H, dd, *J* 11.1, 5.2 Hz, C*H*HOPiv), 4.42 (1H, dd, *J* 11.1, 7.9 Hz, CH*H*OPiv), 4.31 (1H, dd, *J* 9.0, 5.5 Hz, H-2), 4.06 (1H, dd, *J* 10.2, 3.0 Hz, C*H*HOSi), 3.98 (1H, ddd, *J* 9.0, 6.3, 3.0 Hz, C*H*(OH)-CH$_2$OSi), 3.88 (1H, dd, *J* 10.2, 6.3 Hz, CH*H*OSi), 3.82–3.75 (2H, m, H-4, H-5), 3.68 (1H, m, H-3a), 3.52 (1H, dd, *J* 11.6, 5.0 Hz, H-6), 3.09–3.03 (1H, dddd, *J* 7.9, 5.5, 5.2, 2.0 Hz, H-3), 2.97 (1H, dd, *J* 11.6, 6.0 Hz, H-6′), 2.67 (1H, br s, OH), 1.22 (9H, s, *t*-Bu), 1.14 (9H, s, *t*-Bu), 1.13 (9H, s, *t*-Bu), 0.97 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 177.8, 135.9, 130.1, 128.1, 81.9, 76.5, 76.4, 73.8, 73.4, 73.1, 69.7, 67.1, 63.3, 61.5, 48.9, 38.8, 29.2, 28.5, 27.4, 27.1, 19.5; HRMS (ESI) *m*/*z* calcd for $C_{38}H_{59}NO_7SiNa$: 692.3924 [M+Na$^+$], found: 692.3924.

3.5. (2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-2-hydroxymethyl-3-pivaloyloxymethyl-hexahydropyrrolo[1,2-*b*]isoxazol (14)

A solution of 0.50 g (0.75 mmol) of **13** and TBAF (0.26 g, 0.83 mmol) in THF (25 mL) was stirred under argon atmosphere. The progress of reaction was monitored by TLC (hexane–ethyl acetate 4:1 v/v). After disappearance of the substrate, solvent was evaporated and the residue was dissolved in methanol (20 mL), treated with $NaIO_4$ (0.32 g, 1.5 mmol), and stirred at room temperature for 1 h (TLC, CH_2Cl_2–MeOH 9:1 v/v). Subsequently, the reaction mixture was filtered and the solution was treated with $NaBH_4$ (29 mg, 0.75 mmol). The progress of the reaction was monitored by TLC (hexane–ethyl acetate 1:1 v/v). The mixture was then acidified by 5% HCl aq and then neutralized with triethylamine. Solvents were evaporated in vacuo. The oily residue was purified on silica gel (hexane–ethyl acetate 1:1 v/v) to afford 0.25 g (83%) of **14**; colorless oil; $[\alpha]_D$ +72.6 (*c* 0.85, CH_2Cl_2); IR (film, CH_2Cl_2) *ν*: 3256, 1728 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) *δ*: 4.35 (2H, m, CH_2OPiv), 4.24 (1H, m, H-2), 3.85 (2H, m, H-4, H-5), 3.78 (2H, m, CH_2OH), 3.56 (1H, m, H-6), 3.50 (1H, m, H-3a), 3.20 (1H, br s, OH), 3.08 (1H, m, H-6′), 2.92 (1H, m, H-3), 1.15 (9H, s, *t*-Bu), 1.14 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 177.5, 81.7, 78.9, 77.9, 74.1, 73.9, 73.6, 63.1, 61.8, 61.7, 48.5, 38.7, 28.9, 28.5, 27.3; HRMS (ESI): calcd for $C_{21}H_{39}NO_6Na$: 424.2670 [M+Na$^+$], found: 424.2671.

3.6. (2*S*,3*S*,3a*S*,4*S*,5*S*)-4,5-Di-*tert*-butoxy-2-mesyloxymethyl-3-pivaloyloxymethyl-hexahydropyrrolo[1,2-*b*]isoxazol (15)

A mesyl chloride (72 μL, 0.11 g, 0.93 mmol) was added to a cooled solution of alcohol **14** (0.25 g, 0.62 mmol) and Et_3N (0.26 mL, 0.19 g, 1.86 mmol) in CH_2Cl_2 (5 mL). The progress of reaction was controlled by TLC (hexane–ethyl acetate 1:1 v/v). After dilution with dichloromethane (20 mL), the post-reaction mixture was washed with water (2 × 10 mL), brine (10 mL), and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified on silica gel (hexane–ethyl acetate 1:1 v/v) affording 0.27 mg (92%) of mesylate **15**; colorless oil; $[\alpha]_D$ +84.2 (*c* 0.11, CH_2Cl_2); IR (film, CH_2Cl_2) *ν*: 1730 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) *δ*: 4.38–4.28 (3H, m, H-2, CH_2OMs), 4.02 (1H, dd, *J* 11.7, 5.5 Hz, C*H*HOPiv), 3.96 (1H, dd, *J* 11.4, 7.7 Hz, CH*H*OPiv), 3.77 (1H, ddd, *J* 5.4, 5.1, 3.6 Hz, H-5), 3.73 (1H, dd, *J* 3.6, 3.3 Hz, H-4), 3.49 (1H, dd, *J* 12.4, 5.4 Hz, H-6), 3.37 (1H, dd, *J* 4.6, 3.3 Hz, H-3a), 3.02 (1H, dd, *J* 12.4, 5.1 Hz, H-6′), 2.72 (1H, dddd, *J* 7.7, 6.3, 5.5, 4.6 Hz, H-3), 2.39 (3H, s, Ms), 1.15 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu), 0.99 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 177.4, 82.0, 77.7, 75.8, 74.0, 73.9, 73.7, 67.9, 62.0, 61.9, 48.7, 37.0, 28.8, 28.4, 27.2; HRMS (ESI): calcd for $C_{22}H_{41}NO_8NaS$: 502.2445 [M+Na$^+$], found: 502.2470.

3.7. (1*S*,2*S*,6*S*,7*S*,7a*S*)-2-Acetoxy-6,7-di-*tert*-butoxy-1-(pivaloyloxymethyl)hexahydro-pyrrolizine (16)

A solution of mesylate **15** (0.27 g, 0.57 mmol) in AcOEt–MeOH (4:1 v/v, 10 mL) was hydrogenated over 10% Pd on charcoal (25 mg) under atmospheric pressure. Reaction was monitored by TLC (hexane–ethyl acetate 1:1 v/v). Subsequently, the post-reaction mixture was filtered through Celite and concentrated in vacuo. Residue was dissolved in Et_3N (3 mL) and 0.5 mL of Ac_2O was added. After 30 min of stirring at room temperature reaction mixture was concentrated and product was isolated on a silica gel column (hexane–ethyl acetate 2:1 v/v) to afford 0.22 g (89%) of **16** as a colorless oil; $[\alpha]_D$ −2.1 (*c* 4.8, CH_2Cl_2); IR (film, CH_2Cl_2) *v*: 1732 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 5.31 (1H, ddd, *J* 5.7, 5.4, 4.7 Hz, H-6), 4.30 (1H, dd, *J* 11.5, 4.8 Hz, C*H*HOPiv), 4.08 (1H, dd, *J* 11.5, 6.4 Hz, CH*H*OPiv), 4.00–3.92 (1H, m, H-1, H-2), 3.50 (1H, dd, *J* 11.4, 5.7 Hz, H-5), 3.38–3.32 (2H, m, H-3, H-7a), 2.93 (1H, dd, *J* 11.4, 4.7 Hz, H-5′), 2.77 (1H, m, H-7), 2.72 (1H, dd, *J* 10.4, 5.7 Hz, H-3′), 1.61 (3H, s, C*H*$_3$C=O), 1.20 (9H, s, *t*-Bu), 1.16 (9H, s, *t*-Bu), 1.04 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 177.7, 169.6, 81.4, 79.1, 77.5, 73.8, 73.5, 70.7, 63.4, 59.7, 58.7, 48.2, 38.9, 29.0, 28.5, 27.3, 20.5; HRMS (ESI): calcd for $C_{23}H_{42}NO_6$: 428.3007 [M+H$^+$], found: 428.3027.

3.8. (1*S*,2*S*,6*S*,7*S*,7a*S*)-2,6,7-Triacetoxy-1-acetoxymethyl-hexahydropyrrolizine (17)

To a 1 M solution of $LiAlH_4$ (0.76 mL) in Et_2O (20 mL) compound **16** (0.22 g, 0.51 mmol) in Et_2O (10 mL) was added. After disappearance of the substrate (TLC), 100 μL of saturated solution of Na_2SO_4 was added and the mixture was stirred in ultrasound bath for 5 min. After filtration through Celite and evaporation of the solvent, the residue was dissolved in Et_3N (2 mL) and treated with Ac_2O (0.3 mL). After 45 min solvents were removed under diminished pressure and the residue was purified on a silica gel column (hexane–ethyl acetate 1:2 v/v). Subsequently, the product was dissolved in CF_3COOH (5 mL) and stirred overnight. After evaporation of the solvent the residue was acetylated with Ac_2O (0.3 mL) in Et_3N (2 mL). The solvents were then removed under diminished pressure and the crude product was purified on silica gel (hexane–ethyl acetate 1:3 v/v) to afford 0.12 g (68%) of **17**; mp of salt with CF_3COOH: 146–147 °C (benzene–CH_2Cl_2 2:1 v/v); For free amine: colorless oil; $[\alpha]_D$: +2.1 (*c* 0.6, CH_2Cl_2); IR (film, CH_2Cl_2) *v*: 1739, 1230 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 5.36 (1H, m, H-2), 5.30 (1H, m, H-1), 5.12 (1H, m, H-6), 4.28 (1H, dd, *J* 11.3, 5.5 Hz, C*H*HOAc), 4.15 (1H, dd, *J* 11.3, 6.1 Hz, CH*H*OAc), 3.37 (1H, dd, *J* 11.7, 5.7 Hz, H-3), 3.32 (1H, dd, *J* 11.0, 6.0 Hz, H-5), 3.24 (1H, m, H-7a), 2.78 (1H, dd, *J* 11.7, 4.9 Hz, H-3′), 2.70 (1H, dd, *J* 11.0, 5.5 Hz, H-5′), 2.64 (1H, m, H-7), 1.70 (3H, s, C*H*$_3$C=O), 1.59 (3H, s, C*H*$_3$C=O), 1.58 (3H, s, C*H*$_3$C=O), 1.57 (3H, s, C*H*$_3$C=O); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 170.0, 169.8, 169.5, 169.2, 81.5, 79.0, 76.8, 71.4, 63.4, 58.6, 57.1, 48.6, 20.37, 20.30, 20.27, 20.25; HRMS (ESI): calcd for $C_{16}H_{23}NO_8Na$: 380.1316 [M+Na$^+$], found: 380.1331.

3.9. (1*S*,2*S*,6*S*,7*S*,7a*S*)-2,6,7-Trihydroxy-7-(hydroxymethyl)hexahydropyrrolizine (10)

The 58 mg (0.16 mmol) of **17** was dissolved in 15 mL of 1% solution of NH_3 in methanol and stirred at room temperature for 17 hr under argon atmosphere. Then the solvent was removed and residue was purified on Florisil (ethyl acetate–methanol 1:1, then methanol) affording 28 mg (93%) of compound **1** as a colorless oil; $[\alpha]_D$ −3.6 (*c* 0.5, MeOH); IR (film, CH_2Cl_2) *v*: 3357, 3194 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) *δ*: 4.12–4.01 (3H, m, H-1, H-2, H-6), 3.69 (1H, dd, *J* 10.9, 5.5 Hz, C*H*HOH), 3.58 (1H, dd, *J* 10.9, 6.6 Hz, CH*H*OH), 3.27–3.15 (2H, m, H-3, H-5), 3.09 (1H, dd, *J* 7.5, 4.2 Hz, H-7a), 2.88–2.81 (2H, m, H-3′, H-5′), 2.24 (1H, m, H-7); ^{13}C NMR (125 MHz, CD_3OD) *δ*: 82.8, 79.7, 74.9, 73.7, 63.1, 62.9, 60.5, 54.3; HRMS (ESI): calcd for $C_8H_{16}NO_4$: 190.1074 [M+H$^+$], found: 190.1066.

3.10. (2*S*,3*S*,3a*S*,4*S*,5*S*)-2,3-Bis(hydroxymethyl)-4,5-di-*tert*-butoxy-hexahydropyrrolo[1,2-*b*]isoxazol (21)

A 2 M solution of BH_3–Me_2S in THF (2 mL) was added to a solution of 100 mg (0.319 mmol) of lactone **19** in 10 mL THF under argon. The progress of reaction was monitored by IR spectra. After consumption of the lactone, the excess of borane was destroyed by addition of methanol (ca. 20 mL). Solvents were evaporated in vacuum and the residue was dissolved in 30 mL of 7 N ammonia solution in methanol and stirred overnight. Subsequently solvent was removed under diminished pressure and the oil residue was purified on silica gel (CH_2Cl_2–MeOH 30:1 v/v) affording 76 mg (75%) of diol **21** as a colorless oil; $[\alpha]_D$ +32.0 (*c* 3.0, CH_2Cl_2); IR (film, CH_2Cl_2) *v*: 3341, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$-D_2O) *δ*: 4.55 (1H, ddd, *J* 5.7, 5.5, 4.5 Hz, H-2), 4.12–4.00 (2H, m, H-5, C^{3}C*H*HOH), 3.96 (1H, dd, *J* 12.6, 5.5 Hz, C^{2}C*H*HOH), 3.92–3.82 (3H, C^{2}CH*H*OH, H-4, H-6), 3.70 (1H, dd, *J* 11.2, 5.0 Hz, C^{3}CH*H*OH), 3.60 (1H, dd, *J* 4.9, 3.1 Hz, H-3a), 3.26 (1H, dd, *J* 12.2, 7.1 Hz, H-6′), 2.95–2.85 (1H, m, H-3), 1.21 (9H, s, *t*-Bu), 1.19 (1H, s, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 81.3, 81.0, 80.9, 68.6, 60.7, 59.4, 51.0, 28.7, 28.3; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{32}NO_5$: 318.2280 [M+H$^+$], found: 318.2277.

3.11. Monoprotection of diol 21

3.11.1. Method A

To a cooled (−15 °C) solution of 18 mg (57 μmol) of the diol **21** and 7.8 mg (114 μmol) of imidazole in dichloromethane (2 mL), 16 μL (17 mg, 62 μmol) of *t*-BuPh_2SiCl was added. After disappearance of the substrate, reaction mixture was diluted with dichloromethane (5 mL), washed with water (2 mL), brine (2 mL), and dried over anhydrous Na_2SO_4. The ratio of products **22**:**26**:**27** amounted to 4:1.5:1, respectively (HPLC). After column chromatography on a silica gel column (hexane–ethyl acetate 4:1 v/v), 13.5 mg (24%) of **22** and a mixture of **24** and **25** (4 mg; 19%; characterized by MS only) were isolated.

3.11.2. (2*S*,3*S*,3a*S*,4*S*,5*S*)-2,3-Bis(*tert*-butyldiphenylsilyloxymethyl)-4,5-di-*tert*-butoxy-hexahydropyrrolo[1,2-*b*]-isoxazol (22)

$[\alpha]_D$ +7.7 (*c* 2.0, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) *δ*: 7.81–7.20 (20H, 4 × Ph), 4.41 (1H, m, H-2), 4.24 (1H, d, *J* 6.7 Hz, H-3a), 4.21–4.12 (2H, H-5, C^{3}C*H*HOSi), 4.06–3.96 (3H, H-6, C^{2}C*H*HOSi, C^{3}CH*H*O-Si), 3.92 (1H, dd, *J* 11.6, 5.0 Hz, C^{2}CH*H*OSi), 3.68 (1H, t, *J* 6.7, 6.7 Hz, H-4), 3.12 (1H, dd, *J* 11.6, 9.1 Hz, H-6′), 2.73 (1H, m, H-3), 1.15 (9H, s, *t*-Bu), 1.14 (9H, s, *t*-Bu), 1.10 (9H, s, *t*-Bu), 0.99 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: without aromatic signals, 81.2, 80.9, 79.3, 74.7, 74.3, 67.8, 51.3, 29.3, 28.3, 27.1, 27.0, 19.2; HRMS (ESI) *m*/*z* calcd for $C_{48}H_{68}NO_5Si_2$: 794.4636 [M+H$^+$], found: 794.4632. A mixture of **24** and **25** HRMS (ESI) *m*/*z* calcd for $C_{32}H_{49}NO_5SiNa$: 578.3278 [M+Na$^+$], found: 578.3274.

3.11.3. Method B

To a cooled (0 °C) solution of diol **21** (13.5 mg; 43 μmol) and 4.6 mg (38 μmol) of DMAP in dichloromethane (2 mL), PivCl (5.3 μL, 5.2 mg, 45 μmol) was added. The progress of reaction was monitored by TLC (hexane–ethyl acetate 1:1 v/v). After disappearance of substrate, reaction mixture was diluted with dichloromethane (5 mL), washed with sat. Na_2CO_3 (1 mL), brine (1 mL), and dried over anhydrous Na_2SO_4. The ratio of products **23**:**26**:**27** amounted to 5:1.5:1 (HPLC). After column chromatography on

silica gel (hexane–ethyl acetate 1:2 v/v), 8 mg (26%) of **23** and a mixture **26** and **27** (3 mg, 18%, characterized by MS only) were isolated.

3.11.4. (2*S*,3*S*,3a*S*,4*S*,5*S*)-2,3-Bis(pivaloyloxymethyl)-4,5-di-*tert*-butoxy-hexahydropyrrolo[1,2-*b*]isoxazol (23)

$[\alpha]_D$ +37.8 (*c* 0.95, CH_2Cl_2); IR (film) *ν*: 1730 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) *δ*: 4.54 (1H, dd, *J* 11.6, 3.5 Hz, C^2CHHOPiv), 4.46 (1H, ddd, *J* 7.6, 6.3, 3.5 Hz, H-2), 4.27 (1H, dd, *J* 11.6, 7.6 Hz, C^2CH*H*OPiv), 4.22–4.12 (2H, C^3CH_2OPiv), 3.85–3.78 (2H, m, H-4, H-5), 3.60 (1H, dd, *J* 11.9, 5.1 Hz, H-6), 3.50 (1H, dd, *J* 3.9, 3.7 Hz, H-3a), 3.06 (1H, dd, *J* 11.9, 5.0 Hz, H-6′), 2.82–2.73 (1H, m, *J* 7.2, 6.3, 6.3, 3.9 Hz, H-3), 1.23 (9H, s, *t*-Bu), 1.19 (9H, s, *t*-Bu), 1.14 (9H, s, *t*-Bu), 1.01 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 177.4, 177.3, 81.8, 77.0, 75.2 73.6, 73.4, 73.3, 62.5, 62.4, 61.6, 58.7, 48.7, 38.6, 38.5, 28.7, 28.2, 27.0, 26.9; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{47}NO_7Na$: 508.3244 [M+Na^+], found: 508.3249. A mixture of **26** and **27** HRMS (ESI) *m*/*z* calcd for $C_{21}H_{39}NO_6Na$: 424.2675 [M+Na^+], found: 424.2676.

Acknowledgment

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

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