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Asymmetric synthesis of (3*S*,4*R*,5*R*)-4,5-dihydroxy-3-methyl-2,3,4,5-tetrahydropyridazine: a formal synthesis of 1-azagulofagomine analogues

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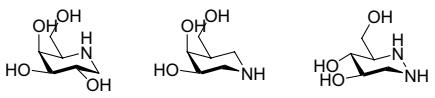
Abstract—The stereoselective synthesis of (3*S*,4*R*,5*R*)-4,5-dihydroxy-3-methyl-2,3,4,5-tetrahydropyridazine from [(*S*)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene is reported. The domino reaction of the 1-sulfinyldiene with 1,2,4-triazoline-3,5-dione (a hetero Diels–Alder, sulfoxide–sulfenate rearrangement, and sulfenate hydrolysis), *cis*-dihydroxylation of the resulting alkene and hydrazinolysis with elimination of a *N*-methylurazol residue are the key steps of the sequence.

1. Introduction

Polyhydroxylated heterocycles have become the subject of intensive studies over the last decade mainly due to their potential as biologically active compounds. Of particular interest are iminosugars, which may specifically inhibit glycosidases and therefore provide novel pharmaceutical lead compounds for new drugs.[1] Thus, galactostatin (Scheme 1) is a very potent α-galactosidase inhibitor but not as efficient as a β-galactosidase inhibitor,[2] whereas isofagomine[1a] and its stereoisomers[1e–g] (isogalactofagomine in Scheme 1) showed a reverse inhibitory profile. Hexahydropyridazines such as 1-azafagomine (Scheme 1),[1h,i] as well as its analogues of D-galactose,[3] L-fucose[4] or D-glucuronic acid[4] are also interesting 1-azasugar inhibitors, which are able to act simultaneously as efficient α- and β-glucosidases inhibitors.



Scheme 1.

The synthesis of enantiomerically pure polyhydroxylated pyridazines has been performed from naturally occurring chiral compounds (azafucofagomine[4] from D-ribose, azafagomine[1i] and azaglucuronofagomine[4] from L-xylose), which imposed some structural limitations. The chemoenzymatic synthesis of polyhydroxylated pyridazines has also been carried out by intermolecular Diels–Alder reaction of a racemic diene with Cookson's reagent (1-azafagomine,[5] 1-azagalactofagomine[3]) as the key step of the sequence. Only one report concerning the asymmetric synthesis of these compounds has been published.[6] It involves the use of 1-azafagomine as an enantiomerically pure chiral precursor in the synthesis of castanospermine. The limited number of procedures for synthesizing polyhydroxylated pyridazines confers special relevance to the search for new and versatile methods.

In connection with our research devoted to asymmetric Diels–Alder reactions mediated by sulfoxides, enantiomerically pure 1-sulfinyl-1,3-butadienes have proven to be efficient chiral dienes, mainly due to the almost complete stereoselectivity control of their Diels–Alder reactions. Moreover, the easy 2,3-sigmatropic rearrangement of the resulting adducts, which also takes place in an almost complete stereocontrolled manner, raises significantly the interest of these dienes.[7] Despite these advantages, their use in asymmetric synthesis is strongly limited by their rather low reactivity even with good

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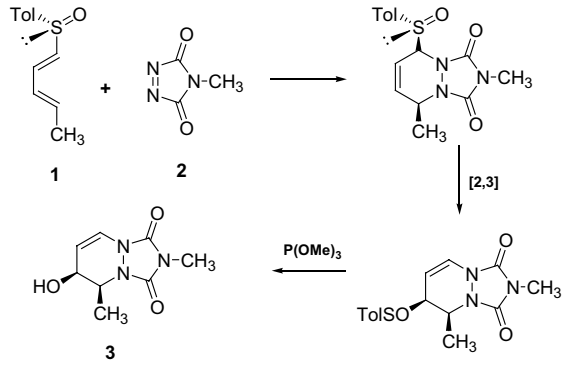
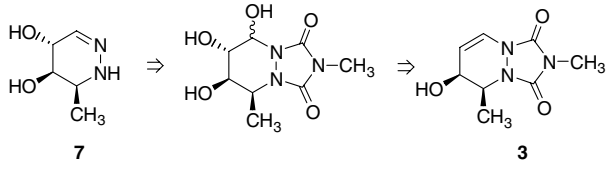
dienophiles.[8] Our group has recently found that reactions of these dienes with heterodienophiles, such as benzyl nitrosoformate, evolved under very mild conditions while retaining complete control of the stereoselectivity, allowing us access to L-ribitol derivatives in enantiomerically pure forms.[9] Analogously, their reactions with 4-methyl-1,2,4-triazoline-3,5-dione,[10] in the presence of $P(OMe)_3$ as a thiophilic agent, efficiently gave triazolocarbinol **3**, through a highly diastereoselective tandem hetero Diels–Alder cycloaddition/[2,3]-sigmatropic rearrangement/sulfenate trapping (Scheme 2).



Scheme 2.

As the relative configuration of the two stereogenic centres present in compound **3** is identical to that of the 1-azagulofagomine at C-3 and C-4, we focused our attention on the use of this adduct as a starting material for synthesizing enantiomerically pure polyhydroxypyridazines, according to the retrosynthetic sequence shown in Scheme 3, which involves the stereoselective dihydroxylation of the double bond and the elimination of the *N*-methylurazol group.

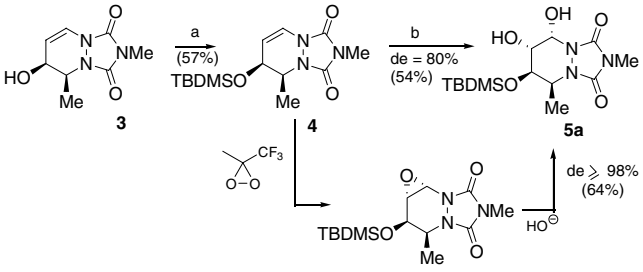


Scheme 3.

Herein we report the chemical transformation of triazolocarbinol **3** into (3*S*,4*R*,5*R*)-4,5-dihydroxy-3-methyl-2,3,4,5-tetrahydropyridazine, **7**, which can be used as a precursor for different 4,5-dihydroxyhexahydropyridazines via reduction methods[11] or by introducing different groups at C-3 while taking advantage of the reactivity of the iminic double bond. Moreover the residues at C-6 (Me in compound **7**) could also be chosen by electing the proper starting sulfinyldiene.[12]

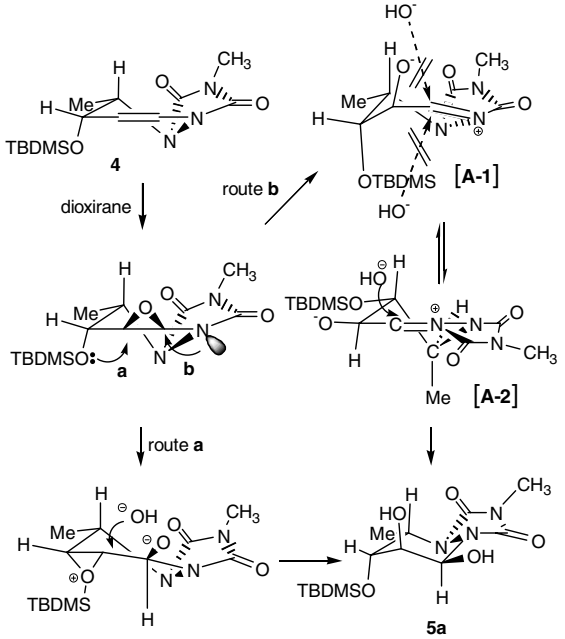
2. Results and discussion

As the two hydroxy groups on compound **7** adopt a *trans* arrangement, alkenol **3** was initially converted into its TBDMS derivative **4** (Scheme 4), thus avoiding a possible anchimeric assistance of the OH in the favoured approach of the oxidant. This was done by reaction of **3** with *tert*-butyldimethylsilyl chloride[13] (rt, 18 h, 42% isolated yield). The use of *tert*-butyldimethylsilyl triflate[14] allowed us to improve the yield (rt, 2 h, 57% isolated yield).



Scheme 4. Reagents and conditions: (a) TBDMSOTf/Et_3N; (b) OsO_4–NMO/acetone–H_2O.

cis-Dihydroxylation of *O*-silyl ether **4**, performed with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine N-oxide (NMO), afforded a 90:10 mixture of the two possible *cis*-diols, **5a** and **5b**. The major isomer **5a** was isolated pure in 46% yield and exhibited the *trans* arrangement between the OTBDMS and adjacent OH groups, as unequivocally established by ^1H NMR ($J_{4,5} = 9.3$ Hz). The stereochemical result can be explained by assuming that the approach of the reagent is to the less hindered face of the double bond,[15] in the presumably most stable conformation of compound **4** as shown in Scheme 5.



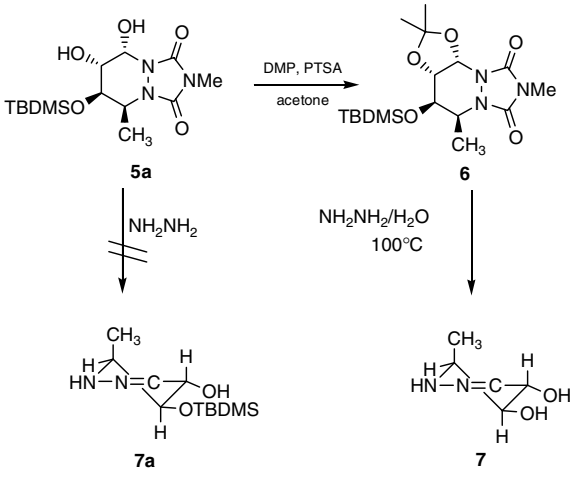
Scheme 5.

The use of (trifluoromethyl)methyldioxirane as an oxidizing agent allowed us to improve the stereoselectivity. Thus the reaction of **4** with this oxirane, generated in

situ,[16] in basic medium, afforded diol **5a** as the only diastereoisomer (de ⩾98%, according to ^{1}H RMN) in a 64% isolated yield. Since the reaction involved the initial formation of the epoxide followed by its opening under the basic conditions used, the formation of **5a** as the only diastereoisomer indicates that both steps, epoxidation and hydrolysis of the oxirane, are completely stereoselective.

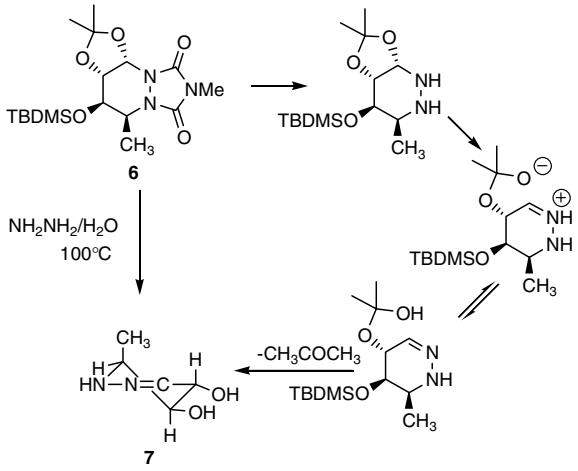
Steric grounds can be used to explain satisfactorily the exclusive approach of the dioxirane to the less hindered face of the double bond, which in turn would also be favoured from a electrostatic point of view due to the repulsion of the oxidizing reagent with the OTBDMS group (Scheme 5). In order to explain the unexpected exclusive formation of the *cis*-diol, it is necessary to assume that the oxirane opening must take place in a step prior to the attack of the nucleophile because a direct attack of the HO^- group to the epoxide would yield the *trans*-diol. The anchimeric assistance of the neighbouring *tert*-butyldimethylsilylether group, followed via the attack of the HO^- to the so generated intermediate (route **a**, Scheme 5) would explain the observed stereoselectivity (double inversion at the oxiranic carbon). A more reasonable explanation is based on the assumption that the opening of the epoxide takes place by the lone electron pair at the adjacent nitrogen yielding the iminio intermediate **A** (route **b**, Scheme 5), which in turn would be attacked by the nucleophile. Such attack must be governed by steric effects and thus would take place at the less hindered face of the C=N bond. As both faces of this bond are highly hindered in conformation **A-1**, the intermediate would adopt the conformation **A-2** prior to being attacked by the nucleophile on the opposite face to that occupied by the methyl group (see Scheme 5) yielding exclusively the *cis*-diol **5a**.

Several reports concerning the elimination of the *N*-methylurazol group from compounds exhibiting a similar structure to that of the *cis*-diol **5a** by reaction with hydrazine have been published.[15,16a,17] However when **5a** was treated with this reagent under the reported conditions, we could not obtain the desired product **7a** (Scheme 6) but instead a complex mixture of reaction.



Scheme 6.

Therefore we decided to protect the free hydroxyl groups before elimination of the *N*-methylurazol one. Thus, the treatment of diol **5a** with DMP in PTSA gave rise to its acetonide **6** (0 °C, 35 h, 75% isolated yield), which was then isolated pure by flash column chromatography. Hydrazinolysis of **6** in neat NH_2NH_2/H_2O at 100 °C led to the 4,5-dihydroxy-3-methyl-2,3,4,5-tetrahydropyridazine **7** in a quantitative yield (Scheme 6). This compound would be obtained as a result of several subsequent reactions: *N*-methylurazol elimination by hydrazine; opening of the acetonide ring with nitrogen's assistance; proton's interchange and finally elimination of the acetone from the resulting hemiacetal to afford the hydrazone derivative **7** (Scheme 7).



Scheme 7.

3. Conclusion

In summary, 4,5-dihydroxy-3-methyl-2,3,4,5-tetrahydropyridazine **7** has been prepared in 25% overall yield according to a short five steps sequence starting from [(*S*)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene **1** with an asymmetric hetero Diels–Alder reaction, dihydroxylation of the adduct and final hydrazinolysis as the key steps. This procedure constitutes a new and versatile approach to the asymmetric synthesis of polyhydroxypyridazines that could be used in the synthesis of analogues of 1-azagulofagomine and its derivatives. These reactions are other examples that show the usefulness of the sulfinyl group as a versatile chiral inductor that can be used to achieve an efficient control of the stereoselectivity and simultaneously provide further functionalization of the molecule.

4. Experimental

4.1. General

Dry solvents and liquid reagents were distilled under argon just prior to use: THF and diethyl ether were

distilled from sodium and benzophenone ketyl; DIA was dried over sodium hydroxide and distilled over calcium hydride; CH_2Cl_2 was dried over P_2O_5 and stored over molecular sieves. All reaction vessels were flame dried and flushed with argon. TLC was performed on glass plates coated with silica gel G (Merck), spots being developed either with sulfuric acid in ethanol (10%) or with phosphomolybdic acid in ethanol. Silica gel Merck 60 (230–400 mesh) was used for flash chromatography. Optical rotations were measured with a 141 Perkin–Elmer polarimeter. Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined in a Gallenkamp MFB-595. ^{1}H NMR (300 MHz, $CDCl_3$ or D_2O) and ^{13}C NMR (75.5 MHz $CDCl_3$ or D_2O) spectra were performed with a Bruker AC-300 spectrometer. Chemical shifts are given in ppm (δ), relative to $SiMe_4$ as the internal reference; signal multiplicities are quoted as s, singlet; d, doublet; dd, double doublet; ddd, doubled double doublet; dq, double quartet; t, triplet; q, quartet; and m, multiplet. *J*-values are given in hertz. Mass spectra were recorded by the direct insertion technique by electronic impact (EI) at 70 eV or FAB using a VG AutoSpec spectrometer.

4.2. Hydroxyl group protection of (4*S*,5*S*)-5,8-dimethyl-4-hydroxy-1,6,8-triazobicyclo-[4,3,0]non-2-en-7,9-dione, 3

Method A: To a solution of **3** (530 mg, 2.69 mmol) in dry CH_2Cl_2 (5 mL), DMF (1.8 mL) and imidazole (366 mg, 5.38 mmol) were added. After 10 min stirring at room temperature, *tert*-butyldimethylsilyl chloride (837 mg, 5.58 mmol) was added. The reaction mixture was stirred at the same temperature for 18 h. The resulting solution was hydrolyzed with water (5 mL) and the aqueous phase extracted with Et_2O (4×4 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (Et_2O/ hexane, 2:1), to obtain a lonely pure product identified as:

(4S,5S)-5,8-Dimethyl-4-tert-butyldimethylsilyloxy-1,6,8-triazobicyclo[4,3,0]non-2-en-7,9-dione, **4**, (350 mg, 1.13 mmol, 42%): white solid; mp 58–59 °C; $[\alpha]_D^{20}$ +182 (*c* 0.31, acetone); $R_f = 0.61$ (Et_2O/hexane, 2:1); ^{1}H NMR ($CDCl_3$): 0.12 (s, 3H, CH_3–Si), 0.13 (s, 3H, CH_3–Si), 0.91 (s, 9H, $(CH_3)_3$–C–Si), 1.14 (d, 3H, $J_{Me,5} = 6.6$, CH_3–C_5), 3.11 (s, 3H, CH_3–N), 4.42 (ddc, 1H, $J_{5,Me} = 6.6$, $J_{5,4} = 6.0$, $J_{5,3} = 0.7$, H–C_5), 4.68 (ddd, 1H, $J_{4,5} = 6.0$, $J_{4,3} = 1.4$, $J_{4,2} = 2.1$, H-C4), 4.92 (ddd,1H, $J_{3,2} = 8.3$, $J_{3,4} = 1.4$, $J_{3,5} = 0.7$, H-C3), 6.75 (dd, 1H, $J_{2,4} = 2.1$, $J_{2,3} = 8.3$, H–C_2); ^{13}C NMR ($CDCl_3$): −4.9, −4.8 (CH_3–Si), 10.8 (CH_3–C5), 18.0 ($(CH_3)_3$–C), 25.2 (CH_3–N), 25.6 ($(CH_3)_3$–C), 51.0 and 64.9 (C4, C5), 108.0 and 116.0 (C2, C3) and 139.0, 147.2 (C=O); HRMS exact mass: 311.166080, calculated mass: 311.166520.

Method B: To a solution of **3** (100 mg, 0.51 mmol) in dry CH_2Cl_2 (18 mL), under argon atmosphere, at 0 °C, triethylamine (0.12 mL, $d = 0.726$, 0.87 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.18 mL, $d = 1.151$, 0.77 mmol) were added. The reaction mixture was stirred for 2 h at the same temperature and then hydrolyzed with ice (8 mL). The aqueous phase was washed with Et_2O (3×3 mL), the combined organic layers dried over with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (Et_2O/hexane, 2:1), to obtain the pure 4-*tert*-butyldimethylsilyloxy derivative **4** (89 mg, 0.28 mmol, 57%).

4.3. Asymmetric dihydroxylation of (4*S*,5*S*)-5,8-dimethyl-4-*tert*-butyldimethylsilyloxy-1,6,8-triazobicyclo-[4,3,0]-non-2-en-7,9-dione, 4, with OsO_4

To a solution of **4** (87 mg, 0.28 mmol) in acetone/water (1.6:1.7 mL), at 0 °C, *N*-methylmorpholine N-oxide (42 mg, 0.31 mmol) and OsO_4 (40 μL, 4% in water, $d = 1.04$, 6×10^{-4} mmol) were added. The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 30 additional hours. It was then treated with Na_2SO_3 (40 mg, 0.32 mmol), being stirred for 30 min. After that, the solvent was removed and the residue is diluted in CH_2Cl_2, with vigourous stirring. The resulting suspension was filtered through a thick pad of Celite and concentrated. The residue was a mixture of both *cis*-diols in a 90:10 ratio (de = 80%); after column chromatography (acetone/CH_2Cl_2, 1:7) the major *cis*-diol **5a** was isolated pure.

(2S,3S,4R,5S)-2,3-Dihydroxy-5,8-dimethyl-4-tert-butyldimethylsilyloxy-1,6,8-triazobicyclo[4,3,0]nonan-7,9-dione, **5a**, (42 mg, 0.13 mmol, 46%): syrup; $[\alpha]_D^{20}$ −3.4 (*c* 0.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 0.13 (s, 3H, CH_3–Si), 0.15 (s, 3H, CH_3–Si), 0.92 (s, 9H, $(CH_3)_3$–C–Si), 1.17 (d, 3H, $J_{Me,5} = 6.7$, CH_3–C5), 3.05 (s, 3H, CH_3–N), 3.80 (dd, 1H, $J_{3,2} = 3.9$, $J_{3,4} = 9.3$, H-C3), 4.09 (dd, 1H, $J_{4,3} = 9.3$, $J_{4,5} = 5.7$, H-C4), 4.31 (dc, 1H, $J_{5,Me} = 6.7$, $J_{5,4} = 5.7$, H-C5), 5.68 (d, 1H, $J_{2,3} = 3.9$, H-C2); ^{13}C NMR ($CDCl_3$): −4.8, −4.6 (CH_3–Si), 9.7 (CH_3–C5), 18.0 ($(CH_3)_3$–C–Si), 25.3 (CH_3–N), 25.7 ($(CH_3)_3$–C–Si), 52.7, 68.7, 69.1, 75.8 (C2, C3, C4, C5) and 152.0, 154.0 (C=O); HRMS exact mass: 345.172240, calculated mass: 345.172000.

4.4. Reaction of (4*S*,5*S*)-5,8-dimethyl-4-*tert*-butyl-dimethylsilyloxy-1,6,8-triazobicyclo[4,3,0]non-2-en-7,9-dione 4, with trifluoromethylmethyldioxirane

To a solution of **4** (202 mg, 0.65 mmol) in CH_3CN/H_2O (3:2, 14 mL), at 0 °C, 1,1,1-trifluoroacetone (1 mL) and $NaHCO_3$ (665 mg) were added. Oxone (3.15 g) was added in portions (20 min). The mixture was stirred at 0 °C for 1 h, then filtered, the acetonitrile removed under reduced pressure and the aqueous solution was extracted with CH_2Cl_2 (6×2 mL) and AcOEt (8×2 mL), successively. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. A lonely pure product identified as diol **5a** (144 mg, 0.41 mmol, 64%) was obtained.

4.5. Acetonation of (2*S*,3*S*,4*R*,5*S*)-2,3-dihydroxy-5,8-dimethyl-4-*tert*-butyldimethylsilyloxy-1,6,8-triazo-bicyclo-[4,3,0]nonan-7,9-dione, 5a

To a solution of diol **5a** (44 mg, 0.13 mmol) in acetone (1 mL) at 0 °C, 2,2-dimethoxypropane (1.6 mL,

$d = 0.849$ g/mL, 12.6 mmol) and PTSA were added. The mixture was stirred at room temperature for 12 h and then the solution hydrolyzed by the addition of a saturated aqueous solution of $NaHCO_3$ (2 mL) and extracted with AcOEt (3×3 mL) and CH_2Cl_2 (3×3 mL), successively. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure and the residue purified by column chromatography (Et_2O/hexane, 1.5:1) to give compound **6** (37 mg, 0.093 mmol, 75%) as a yellow syrup.

(2S,3S,4R,5S)-5,8-Dimethyl-2,3-O-isopropyliden-4-tert-butyldimethylsilyloxy-1,6,8-triazobicyclo-[4,3,0]nonan-7,9-dione, **6**: $[\alpha]_D^{20}$ −83.3 (*c* 1.10, $CHCl_3$); $R_f = 0.38$ (Et_2O/hexane, 2:1); ^{1}H NMR ($CDCl_3$): 0.11 (s, 3H, CH_3–Si), 0.14 (s, 3H, CH_3–Si), 0.90 (s, 9H, $(CH_3)_3$–Si), 1.28 (d, 3H, $J_{5,Me} = 6.7$, CH_3–C5), 1.41 and 1.47 (2s, each 3H, $C(CH_3)_2$), 3.08 (s, 3H, CH_3–N), 4.03 (dd, 1H, $J_{4,3} = 5.6$, $J_{4,5} = 4.9$, H-C4), 4.22 (dc, 1H, $J_{5,Me} = 6.7$, $J_{5,4} = 4.9$, H-C5), 4.23 (dd, 1H, $J_{3,4} = 5.6$, $J_{3,2} = 5.9$, H-C3), 5.91 (d, 1H, $J_{2,3} = 5.9$, H-C2); ^{13}C RMN ($CDCl_3$): −5.0, −4.6 (CH_3–Si), 11.3 (CH_3–C5), 17.9 (($CH_3)_3$–C), 25.2 (CH_3–N), 25.6 (($CH_3)_3$–C), 26.6, 27.5 ($C(CH_3)_2$), 51.7, 70.2, 74.1, 80.1 (C2, C3, C4, C5), 110.7 ($C(CH_3)_2$), 152.0, 153.0 (C=O); HRMS exact mass: 386.212000, calculated mass: 386.211125.

4.6. Hydrazinolysis of (2*S*,3*S*,4*R*,5*S*)-5,8-dimethyl-2,3-*O*-isopropyliden-4-*tert*-butyldimethylsilyloxy-1,6,8-triazobicyclo-[4,3,0]nonan-7,9-dione, 6

Compound **6** (14 mg, $3{,}6\times10^{-2}$ mmol) was dissolved in hydrazine hydrate (3 mL). The obtained solution was heated under reflux for 18 h and then concentrated in vacuo. The residue was dissolved in methanol and purified by SCX column chromatography, using a NH_3/methanol (7 M) mixture as eluent, to give compound **7** (5 mg, 0.035 mmol, quantitative).

(3S,4R,5R)-4,5-Dihydroxy-3-methyltetrahydropyridazine, **7**: $[\alpha]_D^{20}$ +145 (*c* 0.2, $CHCl_3$); ^{1}H NMR (D_2O): 1.14 (d, 3H, $J_{Me,3} = 6.7$, CH_3–C3), 3.11 (dc, 1H, $J_{3,Me} = 6.7$, $J_{3,4} = 3.3$, H-C3), 3.69 (ddd, 1H, $J_{4,6} = 1.8$, $J_{4,5} = 2.9$, $J_{4,3} = 3.3$, H-C4), 3.80 (dd, 1H, $J_{5,6} = 2.8$, $J_{5,4} = 2.9$, H-C5), 6.76 (dd, 1H, $J_{6,5} = 2.8$, $J_{6,4} = 1.8$, H-C6). ^{13}C RMN (D_2O): 13.3 (CH_3–C3), 47.5 (C3), 64.0 and 69.3 (C4 and C5) 137.8 (C6); HRMS for $C_5H_9\ DN_2O_2$: exact mass: 131.081040, calculated mass: 131.080504.

Acknowledgements

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References and notes

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