A Novel Approach to Both the Enantiomers of Potent Glycosidase Inhibitor Isofagomine via PET-Promoted Cyclization of 1-[Benzyl(trimethylsilylmethyl)amino]-1,4,5-trideoxy-2,3-*O*-(1-methylethylidene)-*threo*-pent-4-ynitol

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Dedicated to Prof. H. E. Zimmerman on the occasion of his 75th birthday

Abstract: The cyclization of PET-generated α-trimethylsilylmethylamine radical cation to a tethered acetylene moiety has been exploited to solve the problem of the generation of an aminomethyl group next to a stereocenter in the synthesis of 1-*N*-iminosugar type glycosidase inhibitors. Its success is demonstrated by the synthesis of (+)- as well as (–)-isofagomine, an extremely potent β-glucosidase inhibitor of the 1-*N*-iminosugar class.

Keywords: photoinduced electron transfer (PET), α-trimethylsilylmethylamine radical cation, glycosidase inhibitors, 1-*N*-iminosugars, isofagomine

Analogues of carbohydrates in which one or more of the oxygen atoms have been substituted by a nitrogen are probably the best known inhibitors of glycosidases.[1] These alkaloids which are sugar mimics, are widespread in plants and microorganisms, and are suggested to bind to glycosidases by mimicking the shape and charge of the postulated oxocarbenium ion intermediate for the glycosidic bond cleavage reaction. Subsequent to the isolation of potent glycosidase inhibitors like nojirimycin (**1**), 1-deoxynojirimycin (**2**), swainsonine (**3**), casuarine (**4**) and a mild glycosidase inhibitor like fagomine (**5**), from natural sources, there has been a growing interest in the chemistry, biochemistry and pharmacology of these compounds.[2] Not only have these unique molecules proved to be a tool for studying the biological functions of oligosaccharides,[3] they have also been shown to possess a tremendous chemotherapeutic potential in the prevention of a variety of diseases like AIDS,[4] diabetes,[5] cancer[6] and viral infections like influenza.[7]

The unraveling of the mechanism of the glycosidases and identification of the positively charged flattened half chair oxocarbenium ion **6** as a transition state for the glycosidic bond cleavage reaction has led to extensive pioneering studies on the relationship between structure and inhibitory activity in glycosidase inhibitors.[8] Based on these studies, the last decade has seen a spurt in the activity of creative chemical design of a new class of sugar mimic inhibitors having a nitrogen atom at the anomeric position. The studies of Bols[9] and Ichikawa[10] have resulted in the design of potent glycosidase inhibitors like isofagomine (**7**)[11] (D-Glucose type 1-*N*-iminosugar), **8**[10] (D-Glucouronic acid type), **9**[10] (D- Galactose type), **10**[10,12] (L- Fucose type) and **11**.[10] Isofagomine (**7**,) in particular, has been found to be the most potent inhibitor of β-glucosidase from sweet almond ($K_i = 0.11$ μm),[11] a value which is almost 440 times lower than that of **2**. Although considerable attention[9a,10,13] has been directed to develop a synthetic approach for the 1-*N*-iminosugar type glycosidase inhibitors, the synthesis of these functionalized piperidines has not been easy due to difficulty involved in the generation of the aminomethyl group next to a stereocenter.

A couple of years ago, we undertook a program related with the design, synthesis and evaluation of new glycosidase inhibitors of the 1-*N*-iminosugar class and thought that it would be better to first address the problem of the construction of the aminomethyl group. In this context, we were encouraged to consider the evaluation of a methodology developed in our group[14] for the construction of amines of the type **15** by the cyclization of the photoin-

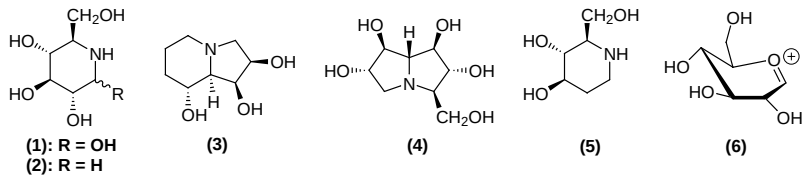

Figure 1 Structures of some potent glycosidase inhibitors isolated

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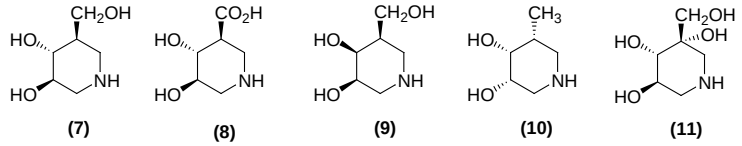


Figure 2 Structures of some potent glycosidase inhibitors synthesised

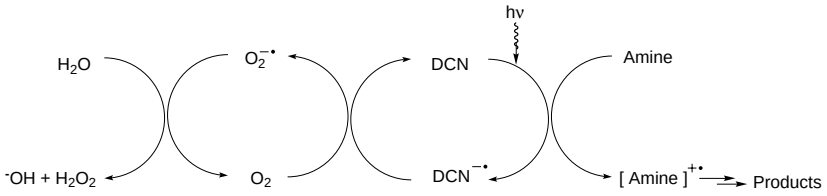


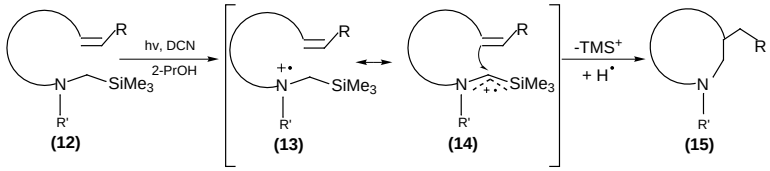
Figure 3 1,4-Dicyanonaphthalene as the light harvesting electron acceptor

duced electron transfer (PET) generated α-trimethylsilylmethylamine radical cation **14** to a tethered π-functionality. The photosystem employed to generate the reactive intermediate **14** utilized 1,4-dicyanonaphthalene (DCN) as the light harvesting electron acceptor as shown in Figure 3. The concept used in such cyclizations (Scheme 1) involved a three centered amine radical cationic species **14** as reactive intermediate where the radical cation is delocalized between nitrogen and silicon atom due to the vertical overlap of the filled C–Si orbital and the half vacant nitrogen orbital.[15]

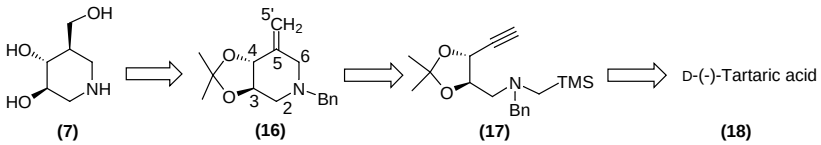
This reactive intermediate was designed to eliminate the assistance of the lone pair of the nitrogen to the α-amino radical in order to facilitate its cyclization to the tethered π-functionality. It may be pertinent to mention here that the attempt to cyclize a free α-amino radical with tethered olefins is known to have failed owing to its reduced radicaloid character,[16] a direct consequence of the nitrogen lone pair interference.

Drawing consequences from the above conceptual design, we envisaged a precursor of the type **16** for the synthesis of most of the 1-*N*-iminosugar type glycosidase inhibitors. It was assumed that by having the correct stereochemistry at C-3 and C-4 and by carrying out simple organic transformations at the C-5–C-5' centre, one can have a general route to access this class of inhibitors. With these premises, we evaluated a retro-synthetic route for the synthesis of isofagomine (**7**) as outlined in Scheme 2 and report herein the full details[17] of the success of our strategy by synthesizing both enantiomers of isofagomine.

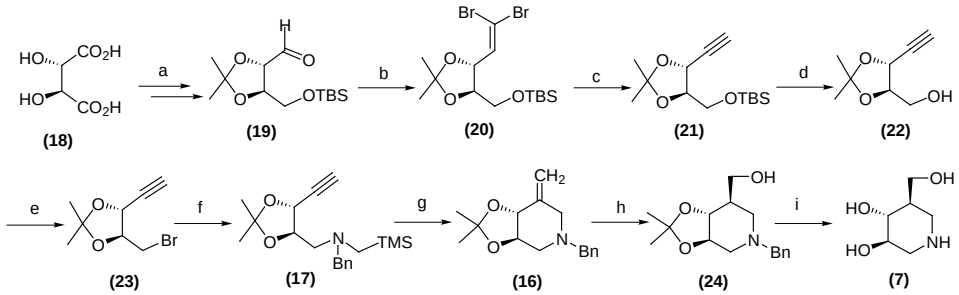
The synthesis of **16** commenced by utilizing D-(–)-tartaric acid as the starting material as shown in Scheme 3. The aldehyde **19**, prepared in over 80% yield by following the reported procedure,[18] was converted to the acetylene **21** utilizing Corey's protocol.[19] Compound **21** was further transformed to the corresponding bromo derivative **23** involving simple organic transformations.[20] Refluxing a mixture of **23** and $PhCH_2NHCH_2TMS$[21] in dry acetonitrile in the presence of anhydrous K_2CO_3 and a small amount of TBAI (tetrabutyl ammonium iodide) afforded **17** in fairly good yield. In the absence of TBAI, the reaction took an extraordinarily long time to complete and longer refluxing hours led to the formation of many side prod-



Scheme 1



Scheme 2



Scheme 3 *Reagents and Conditions*: (a) Ref. 18, 80% yield from tartaric acid; (b) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 2 h, 65%; (c) BuLi, THF, –78 °C, 1 h, 90%; (d) TBAF, THF, 0 °C to r.t., 4 h, 85%; (e) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to r.t., 1 h, 80%; (f) $PhCH_2NHCH_2TMS$, K_2CO_3, TBAI, MeCN, reflux, 96 h, 65%; (g) hν, DCN, 2-PrOH, 90 min, 60%; (h) 9-BBN, THF, 0 °C to r.t., 20 h, then NaOH, H_2O_2, 0 °C to r.t., 4 h, 45%; (i) (i) HCl, MeOH, r.t., 1 h, then NH_4OH, ~100%; (ii) $Pd(OH)_2$ on C, H_2, 75 psi, EtOH, 10 h, 95%

ucts. The coupling of **23** with $PhCH_2NHCH_2TMS$ could be accelerated using a cesium carbonate–TBAI (cat) mixture, however, the yields did not exceed beyond 60%. An alternative route to **17** via nucleophilic displacement of the mesylate of the alcohol **22** was also attempted but the reaction never proceeded to completion and the recovery of the mesylate proved difficult due to its high polarity.

PET-initiated cyclization of **17**, carried out by irradiating a dilute solution of **17** and 1,4-dicyanonaphthalene in propan-2-ol (500 mL) in a pyrex vessel using a 450 W Hanovia medium pressure lamp as the light source, led to an efficient formation of **16**. Hydroboration of **16** with 9-BBN (9-borabicyclo[3.3.1]nonane) proceeded preferentially from the α- face to yield **24** in which the *trans* diaxial relationship of H-4 with H-3 and H-5 was supported by the observed high coupling constants (J = 10.7 and 8.9 Hz). The hydroboration selectivity from the α- face could be explained either by considering the steric hindrance exerted by H-4 and H-6 to the bulky 9-BBN or the preferential low energy equatorial orientation of the bulky bicyclic boron in the four membered transition state.

Removal of the acetonide moiety from **24** followed by *N*-debenzylation gave isofagomine (**7**) as a free base ($[\alpha]_D^{20}$ +16.2 (c = 0.32, EtOH)). The spectral data of **7** was in good agreement with that reported for its hydrochloride salt. The structure of **7** was also confirmed by converting it to its corresponding hydrochloride salt and comparing its optical rotation ($[\alpha]_D^{20}$ +20.7 (c = 0.4, EtOH)) with the reported value[11] ($[\alpha]_D$ +19.6 (c = 0.85, EtOH)). In the similar manner, (–)-isofagomine (**28**) was also synthesized starting from L-(+)-tartaric acid as shown in the Scheme 4.

All reagents were used as supplied. All reactions involving hygroscopic reagents were carried out under argon using oven dried glassware. CH_2Cl_2 and MeCN were distilled from CaH_2 under argon and stored over molecular sieves. THF was distilled from sodium–benzophenone ketyl prior to use. Reactions were followed either by TLC or by gas chromatography. Optical rotations were obtained using JASCO 181 digital polarimeter using Na light. ^1H and ^{13}C NMR were run on Bruker AC-200, MSL-300 instruments. IR spectra were recorded on a Perkin Elmer FT-IR model 1620. Mass spectra (EI, 70eV) were obtained on a Finnigan-Mat 1020C instrument. GC/MS was performed on a Shimadzu QP 5000 GC/MS coupled to Shimadzu 17A GC using a DB1 column. GC analysis was performed on a Perkin Elmer 8700 GC using a SGE BP1 column. Melting points were determined on a Thermonik Campbell melting point apparatus. Column chromatography was performed using 100–200 mesh silica gel obtained from SRL India Ltd.

1,1-Dibromo-5-[(*tert*-butyldimethylsilyl)oxy]-1,2-dideoxy-3,4-*O*-(1-methylethylidene)-D-*threo*-pent-1-ene (20)

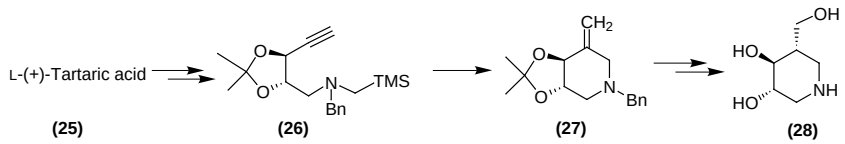
To a stirred solution of CBr_4 (1.21 g, 3.65 mmol) and Ph_3P (1.91 g, 7.3 mmol) in anhyd CH_2Cl_2 (15 mL) was added a solution of the aldehyde **19** (500 mg, 1.82 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and to it was added a large excess of hexane to precipitate the Ph_3PO. The resulting mixture was quickly passed through a short pad of silica gel. The solvent was removed under reduced pressure and the residue was column chromatographed (silica gel, hexane–EtOAc, 24:1) to afford pure **20** as a colorless liquid (508 mg, 65%); $[\alpha]_D^{20}$ +7.2 (c = 0.44, $CHCl_3$). L-isomer: $[\alpha]_D^{20}$ –8.0 (c = 0.9, $CHCl_3$).

^1H NMR (200 MHz, $CDCl_3$): δ = 6.50 (d, J = 8.8 Hz, 1 H), 4.65 (dd, J = 8.8, 7.3 Hz, 1 H), 3.80 (m, 3 H), 1.40 (s, 6 H), 0.90 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.1, 109.7, 93.5, 80.6, 77.9, 62.3, 26.8, 25.7, 18.1, –5.4.

IR (neat): ν = 1625, 1461, 1371, 1217 cm^{-1}.

MS: *m/z* (%) = 415 (M^+ – 15, 1), 343 (1), 315 (39), 285 (6), 256 (5), 200 (11), 137 (45), 73 (86), 57 (100).



Scheme 4

5-[(*tert*-Butyldimethylsilyl)oxy]-1,2-dideoxy-3,4-*O*-(1-methylethylidene)-D-*threo*-pent-1-yne (21)

To a solution of **20** (600 mg, 1.39 mmol) in anhyd THF (4 mL) was added a 2 M hexane solution of BuLi (3.5 mL, 7 mmol) at –78 °C over a period of 5 min. The reaction mixture was stirred at –78 °C for 1 h and was quickly brought up to 0 °C. Thereupon it was quenched by rapid addition of a large excess of water (15 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4). The solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 19:1) to afford **21** as a colorless oil (340 mg, 90%); $[\alpha]_D^{20}$ +11.1 (*c* = 0.97, $CHCl_3$). L-isomer: $[\alpha]_D^{20}$ –10.7 (*c* = 1.18, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.60 (dd, *J* = 7.4, 1.9 Hz, 1 H), 4.15 (m, 1 H), 3.80 (d, *J* = 4.4 Hz, 2 H), 2.55 (d, *J* = 1.9 Hz, 1 H), 1.45 (s, 3 H), 1.50 (s, 3 H), 0.90 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.4, 82.0, 81.1, 74.1, 66.8, 61.8, 26.7, 26.0, 25.6, 18.1, –5.6.

IR (neat): ν = 3300, 1460, 1380, 1260, 1220 cm^{-1}.

MS: *m/z* (%) = 255 (M^+ – 15, 8), 213 (2), 197 (3), 155 (100), 125 (66), 73 (44).

1,2-Dideoxy-3,4-*O*-(1-methylethylidene)-D-*threo*-pent-1-ynitol (22)

To a solution of **21** (700 mg, 2.59 mmol) in anhyd THF (3 mL), was added a 1 M solution of TBAF in THF (3.10 mL) at 0 °C. The reaction mixture was stirred at r.t. for about 4 h and to this was added water (3 mL) followed by EtOAc (7 mL) and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture upon column chromatography (silica gel, $CHCl_3$–EtOAc, 9:1) afforded pure **22** as a colorless liquid (345 mg, 85%); $[\alpha]_D^{20}$ +6.9 (*c* = 2.13, MeOH). L-isomer: $[\alpha]_D^{20}$ –7.3 (*c* = 2.0, MeOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.60 (dd, *J* = 7.9, 1.9 Hz, 1 H), 4.20 (m, 1 H), 3.94 (dd, *J* = 12.3, 3.0 Hz, 1 H), 3.68 (dd, *J* = 12.3, 3.2 Hz, 1 H), 2.55 (d, *J* = 1.9 Hz, 1 H), 1.80 (br s, 1 H), 1.50 (s, 3 H), 1.45 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 110.6, 82.0, 80.7, 74.6, 66.2, 60.7, 26.6, 25.8.

IR ($CHCl_3$): ν = 3446, 3290, 1460, 1379, 1215 cm^{-1}.

MS: *m/z* (%) = 141 (M^+ – 15, 64), 124 (11), 96 (47), 80 (31), 52 (100).

(4*S*, 5*R*)-4-(Bromomethyl)-5-ethynyl-2,2-dimethyl-1,3-dioxolane (23)

To a stirred solution of CBr_4 (1.50 g, 4.54 mmol) and **22** (590 mg, 3.78 mmol) in anhyd CH_2Cl_2 (12 mL) at 0 °C, was added Ph_3P (1.488 g, 5.67 mmol) in small portions. The resultant dark red solution was stirred at r.t. for 1 h. Large excess of hexane was added to the mixture and the contents were quickly filtered through a pad of silica gel. The solvent was removed in vacuo. The compound was pure enough (660 mg, 80%, crude yield) and was used as such for the next step. For spectral purposes, **23** was purified completely by a quick flash column chromatography (silica gel, hexane–EtOAc, 94:6).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.58 (dd, *J* = 6.4, 2.4 Hz, 1 H), 4.33 (m, 1 H), 3.50 (m, 2 H), 2.59 (d, *J* = 2.4 Hz, 1 H), 1.50 (s, 3 H), 1.45 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 111.6, 80.7, 77.3, 75.0, 69.2, 31.1, 27.0, 26.3.

IR (neat): ν = 3310, 1400, 695 cm^{-1}.

GC/MS: *m/z* = 205, 203 (both M^+ – 15), 145, 143, 96.

1-[Benzyl(trimethylsilylmethyl)amino]-1,4,5-trideoxy-2,3-*O*-(1-methylethylidene)-D-*threo*-pent-4-ynitol (17)

A mixture of **23** (550 mg, 2.51 mmol), $PhCH_2NHCH_2TMS$ (970 mg, 5 mmol), anhyd K_2CO_3 (1.73 g, 12.55 mmol) and TBAI (50 mg, 0.13 mmol) in anhyd MeCN (12 mL) was refluxed under argon for about 96 h. The mixture was filtered and the filtrate concentrated. The dark orange residue was column chromatographed (silica gel, hexane–EtOAc, 19:1) to afford pure **17** as a colorless liquid (540 mg, 65%); $[\alpha]_D^{20}$ +1.2 (*c* = 21.2, $CHCl_3$). L-isomer **26**: $[\alpha]_D^{20}$ –0.7 (*c* = 11.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 4.39 (dd, *J* = 7.1, 2.0 Hz, 1 H), 4.25 (m, 1 H), 3.72 (d, *J* = 13.7 Hz, 1 H), 3.49 (d, *J* = 13.7 Hz, 1 H), 2.67 (dd, *J* = 13.1, 5.3 Hz, 1 H), 2.57 (dd, *J* = 13.1, 5.3 Hz, 1 H), 2.50 (d, *J* = 2.0 Hz, 1 H), 2.16 (d, *J* = 14.7 Hz, 1 H), 2.02 (d, *J* = 14.7 Hz, 1 H), 1.47 (s, 3 H), 1.37 (s, 3 H), 0.05 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.6, 128.8, 128.0, 126.7, 110.2, 81.6, 80.7, 74.1, 68.8, 62.8, 58.4, 47.2, 26.9, 25.9, –1.3.

IR (neat): ν = 3310, 760, 720 cm^{-1}.

MS: *m/z* (%) = 331 (M^+, 8), 258 (10), 206 (100), 91 (80), 73 (19).

(3a*R*,7a*R*)-5-Benzyl-2,2-dimethyl-7-methylenehexahydro[1,3]dioxolo[4,5-*c*]pyridine (16)

A solution containing **17** (960 mg, 2.9 mmol) and 1,4-dicyanonaphthalene (160 mg, 0.9 mmol) in propan-2-ol (500 mL) was irradiated in an open vessel using a 450 W Hanovia medium pressure mercury vapor lamp as the light source. The lamp was immersed in a Pyrex water-jacketed immersion well so as to allow only wavelengths greater than 280 nm to pass through. After about 90 min of irradiation, the consumption of the starting material was found to be almost complete and the irradiation was discontinued. The solvent was removed under reduced pressure and the residue was column chromatographed (silica gel, hexane–acetone, 20:1) to afford the cyclized product **16** as a white crystalline solid (450 mg, 60%); mp (uncorrected) 94–96° C; $[\alpha]_D^{20}$ –50.9 (*c* = 1.9, $CHCl_3$). For the corresponding (3a*S*,7a*S*) isomer **27**: $[\alpha]_D^{20}$ = +49.2 (*c* = 0.7, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 5.05 (d, *J* = 1.0 Hz, 1 H), 4.90 (d, *J* = 1.0 Hz, 1 H), 3.80 (m, 1 H), 3.73 (d, *J* = 13.2 Hz, 1 H), 3.65 (d, *J* = 13.2 Hz, 1 H), 3.57 (m, 1 H), 3.33 (m, 2 H), 2.80 (d, *J* = 12.7 Hz, 1 H), 2.37 (t, *J* = 10.3 Hz, 1 H), 1.45 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.4, 137.7, 128.8, 128.2, 127.1, 110.9, 105.1, 81.7, 77.5, 61.5, 57.1, 54.5, 26.8, 26.6.

IR ($CHCl_3$): ν = 1674, 769, 669 cm^{-1}.

MS: *m/z* (%) = 259 (M^+, 5), 201 (67), 91 (100).

[(3a*R*,7*R*,7a*R*)-5-Benzyl-2,2-dimethylhexahydro[1,3]dioxolo-[4,5-*c*]pyridin-7-yl]methanol (24)

To a stirred solution of **16** (130 mg, 0.5 mmol) in THF (4 mL), was added dropwise a 0.5 M THF solution of 9-BBN (10 mL, 5 mmol). The resulting mixture was stirred at r.t. for about 20 h. To this was added successively water (2 mL), 1 N NaOH solution (1.5 mL) and 30% solution of H_2O_2 (1.5 mL) at 0 °C. The mixture was stirred at r.t. for 4 h and extracted with EtOAc (3 × 5 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue upon chromatographic purification (silica gel, hexane–EtOAc, 3:2) yielded **24** as a gummy mass (63 mg, 45%); $[\alpha]_D^{20}$ +14.8 (*c* = 0.5, MeOH). For its enantiomer, the (3a*S*,7*S*,7a*S*) isomer: $[\alpha]_D^{20}$ –14.0 (*c* = 1.7, MeOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 3.70 (dd, *J* = 10.3, 3.9 Hz, 1 H), 3.65 (m, 4 H), 3.24 (dd, *J* = 9.3, 3.9 Hz, 1 H), 3.15 (dd, *J* = 10.7, 8.9 Hz, 1 H), 2.95 (dd, *J* = 11.3, 3.9 Hz, 1 H), 2.18 (m, 2 H), 1.95 (m, 1 H), 1.45 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.0, 128.2, 127.3, 110.9, 82.1, 77.3, 63.5, 61.9, 54.3, 53.4, 41.5, 26.7.

GC/MS: *m/z* = 277 (M^+), 262, 216, 201, 186, 158, 132, 120, 91.

(3*R*,4*R*,5*R*)-5-(Hydroxymethyl)piperidine-3,4-diol (Isofagomine 7)

To a stirred solution of the alcohol **24** (20 mg, 0.07 mmol) in distilled MeOH (1 mL) was added concd HCl (0.1 mL) at 0 °C. The reaction mixture was allowed to stir at r.t. for over an hour and was basified by the addition of a slight excess of NH_4OH solution. The solvent was removed under reduced pressure and the residue was allowed to stand overnight in anhyd $CHCl_3$ (2 mL). The residue was washed again with $CHCl_3$ (1 mL) and the combined organic portion was concentrated and the residue was purified by flash column chromatography (silica gel, $CHCl_3$–MeOH, 20:1) to give pure *N*-benzylisofagomine as a thick gum (17 mg, ~100%); $[\alpha]_D^{20}$ +12.6 (*c* = 0.39, EtOH). For the corresponding (3*S*,4*S*,5*S*) isomer: $[\alpha]_D^{20}$ –13.2 (*c* = 1.1, EtOH).

^{1}H NMR (200 MHz, D_2O): δ = 7.30 (m, 5 H), 3.73 (dd, *J* = 11.3, 3.4 Hz, 1 H), 3.55 (m, 4 H), 3.15 (dd, *J* = 10.2, 9.3 Hz, 1 H), 2.95 (m, 2 H), 1.95 (m, 2 H), 1.70 (m, 1 H).

^{13}C NMR (75 MHz, D_2O): δ = 128.9, 127.1, 126.5, 72.4, 69.8, 60.0, 59.4, 55.5, 52.4, 41.3.

A solution of *N*-benzylisofagomine (16 mg, 0.06 mmol) in EtOH was hydrogenated (75 psi, r.t.) in the presence of $Pd(OH)_2$ on charcoal (20%) (2 mg) for about 10 h. The mixture was passed through a pad of Celite and the solvent was evaporated off to yield **7** as a semi-solid (9.4 mg, 95%); $[\alpha]_D^{20}$ +16.2 (*c* = 0.32, EtOH). Hydrochloride salt of **7**: $[\alpha]_D^{20}$ +20.7 (*c* = 0.4, EtOH) (Lit[11] $[\alpha]_D^{20}$ +19.6 (*c* = 0.85, EtOH)). For (–)-isofagomine (**28**): $[\alpha]_D^{20}$ –15.7 (*c* = 0.19, EtOH). For (–)-isofagomine hydrochloride $[\alpha]_D^{20}$ –20.2 (*c* = 0.31, EtOH).

^{1}H NMR (300 MHz, D_2O): δ = 3.76 (dd, *J* = 11.4, 3.3 Hz, 1 H), 3.59 (dd, *J* = 11.5, 6.7 Hz, 1 H), 3.48 (m, 1 H), 3.27 (dd, *J* = 10.6, 8.8 Hz, 1 H), 3.12 (m, 2 H), 2.43 (m, 2 H), 1.70 (m, 1 H).

^{13}C NMR (75 MHz, D_2O): δ = 70.2, 68.4, 57.1, 45.9, 42.9, 41.0.

MS: *m/z* (%) = 147 (M^+, 44), 129 (42), 112 (62), 98 (100).

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