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Stereoselective synthesis of a new trihydroxyindolizidine lactone

Federica Pisaneschi, Michela Piacenti, Franca M. Cordero and Alberto Brandi*

Dipartimento di Chimica Organica ''Ugo Schiff'', Università degli Studi di Firenze, via della Lastruccia 13, I-50019 Sesto F.no (FI), Italy

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Abstract—A general approach to 1,6,7-trihydroxyindolizidin-8-carboxylates is illustrated through the synthesis of a γ-lactone in an enantiopure form in seven steps starting from (3*S*)-3-*t*-butyloxy-1-pyrroline *N*-oxide and the acetonide of (2*E*,4*S*)-4,5-dihydroxy-2-pentenoic acid derived from (*S*)-malic acid and mannitol, respectively. The process was completely stereoselective and allowed the total control of the relative and absolute configuration of the five contiguous stereocentres of the product.

1. Introduction

Natural polyhydroxyindolizidines, such as (+)-castanospermine, (+)-lentiginosine and (−)-swainsonine (Fig. 1), display interesting biological activity as glycosidase inhibitors.[1,2] These alkaloids, which have a nitrogen atom in the ring decorated with several hydroxyl functionalities, mimic the structure of monosaccharides, although they display a less obvious structural relationship with them. For example, (+)-castanospermine can be regarded as a bicyclic derivative of 1-deoxynojirimycin (DNJ), with an ethylene bridge between the hydroxymethyl group and the ring nitrogen. For these reasons, they can compete with the natural substrates of these enzymes and have enormous therapeutic potential in many diseases, such as viral infection, cancer and diabetes.

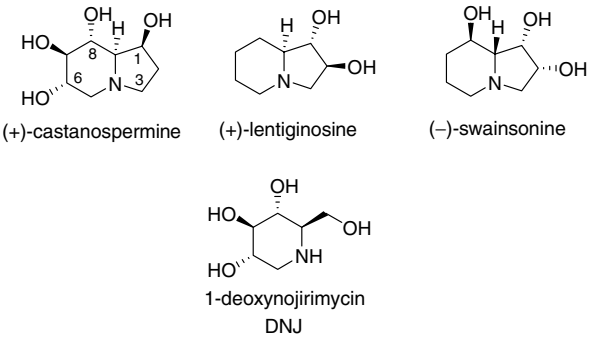

Figure 1. Naturally occurring glycosidase inhibitors.

Our group has been involved in providing a general access to natural and unnatural iminosugars through a cycloaddition strategy using enantiopure mono- and dihydroxylated pyrroline-*N*-oxides[3–7] as providers of the pyrrolidine component of the molecule and of diastereofacial control in the cycloaddition step, that is, in the establishment of various stereogenic centres of the final compound.[8–15] The use of an intramolecular process[15] expands the utility of the methodology, allowing the synthesis of indolizidine derivatives having a [1,8*a*]-*cis*-relationship as in castanospermine.

Herein, we report the application of the intramolecular 1,3-dipolar cycloaddition of an enantiopure monohydroxylated pyrroline-*N*-oxide to the stereoselective synthesis of γ-lactone of the (1*S*,6*R*,7*S*,8*S*,8a*S*)-1,6,7-trihydroxyindolizidin-8-carboxylic acid.

2. Results and discussion

The synthesis of indolizidine structures **1** containing the highest possible number of hydroxyl groups in the six-membered ring and a carboxylic group suitably linking the iminosugar to aglycone moieties (or easily reducible to hydroxymethyl group[15]) was planned starting from ketone **2**. The introduction of hydroxyl functionalities could be achieved via the carbonyl group of lactone **2**, which in turn, could be prepared by a two-step intramolecular 1,3-dipolar cycloaddition/thermal rearrangement

* Corresponding author. Tel.: +39 055 4573485; fax: +39 055 4573572; e-mail: alberto.brandi@unifi.it

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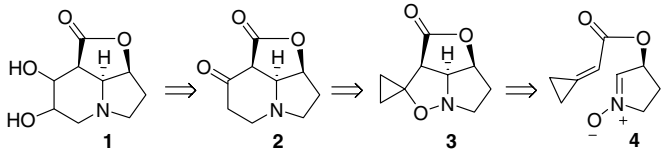
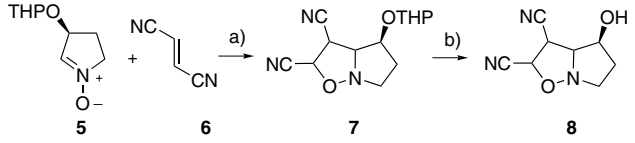


Scheme 1.

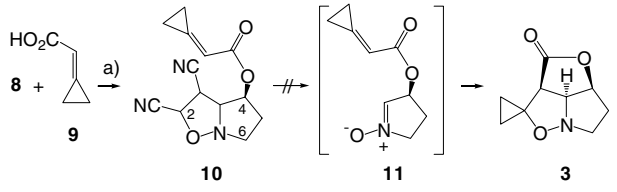
(DC–TR) sequence[16,17] starting from nitrone **4** (Scheme 1).

Monohydroxylated cyclic nitrone **5**, derived from L-malic acid and protected at the OH functionality as a tetrahydropyranyl (THP) ether, was chosen as the starting material. In a previous paper,[15] we reported that the OH-deprotected nitrone was not configurationally stable and thus it was necessary to protect the 1,3-dipole function before coupling a dipolarophile with the hydroxy moiety. The protection was achieved by means of a 1,3-dipolar cycloaddition with a dipolarophile, which was subsequently removed by a thermally induced cycloreversion. Fumaronitrile **6** proved to be the best protecting dipolarophile. Nitrone **5** was added to fumaronitrile **6** to give isoxazolidine **7** as a mixture of three (not separated) isomers in a very good yield (86%). The THP group was then removed and the configurationally stable alcohol **8** (Scheme 2) esterified with the desired dipolarophile.



Scheme 2. Reagents and conditions: (a) CH_2Cl_2, rt, overnight (86%); (b) Amberlyst 15, MeOH, 55 °C (97%).[15]

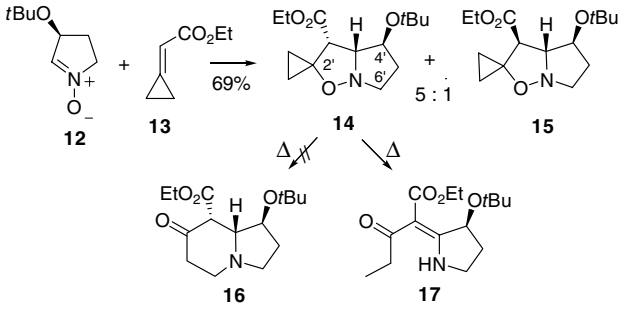
Cyclopropylideneacetic acid **9**, synthesized according to known procedures,[18,19] was utilized as dipolarophile and then introduced on alcohol **8** by esterification mediated by chlorotriazine, to give **10** in 55% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) 2-chloro-4,6-dimethoxy-1,3,5-triazine, NMM, THF (55%).

Unfortunately, any attempt to run the retrocycloaddition/deprotection and further the intramolecular DC–TR process failed, probably due to the instability of the methylenecyclopropane moiety under the reaction conditions (refluxing toluene).

To verify the possibility of obtaining [1,8a]-*trans*-indolizidinone **16** from a cyclopropylidene acetate, the intermolecular variant[20–22] of the process was also studied. The cycloaddition of the nitrone **12** with ethyl cyclopropylideneacetate **13**[18,19] gave two diastereomeric cycloadducts **14** and **15**, derived, respectively, from *anti-endo* and *anti-exo* approaches, in 5:1 ratio and good yield (69%) (Scheme 4).



Scheme 4.

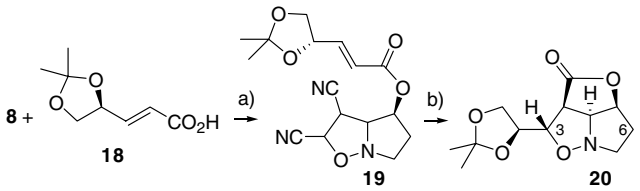
By refluxing **14** in xylenes, a complex reaction mixture was obtained from which only traces of enaminone **17**, a product of rearrangement with 1,5-H shift,[17] was recovered after purification. Indolizidinone **16** was not even detected in the reaction mixture.

To reach our goal, it was clear that a different strategy, starting from the same nitrone, should be used. Another logical option was to install the hydroxyl functionality already in the dipolarophile. The protected enantiomerically pure *E*-dihydroxypentenoic acid **18** was suitable as it could be synthesized in a straightforward way starting from mannitol.[23,†]

Esterification of alcohol **8** with **18** gave isoxazolidine **19** in 65% yield. Esters **19**, when refluxed in xylenes for 10 min, lost fumaronitrile by cycloreversion and spontaneously underwent intramolecular cycloaddition to exclusively give tricyclic cycloadduct **20** in 84% yield (Scheme 5).

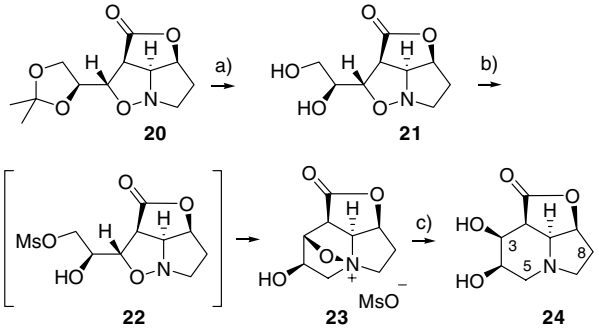
After hydrolysis of the acetonide, diol **21** was mesylated. Using 1 equiv of mesylchloride and performing the reaction at 0 °C, the primary alcohol was selectively mesylated in the presence of the secondary. Mesylate **22** could not be isolated as the isoxazolidine nitrogen atom spontaneously underwent an intramolecular nucleophilic displacement. Salt **23** was directly subjected to catalytic hydrogenation to give indolizidine lactone **24**

† The free acid is obtained in 83% yield from the ethyl ester by treating the ester with NaOH 1 M in THF at rt followed by neutralization with acid.



Scheme 5. Reagents and conditions: (a) DMAP/DMAP.TFA cat., DIC, CH_2Cl_2, rt, 4 d (65%); (b) xylenes, reflux, 10 min (84%).

after treatment with a strongly basic ionic-exchange resin. Finally, purification by chromatography on silica gel afforded pure **24** in 31% overall yield from **21** and with complete control of the five stereogenic centres (Scheme 6).



Scheme 6. Reagents and conditions: (a) (i) TFA, CH_2Cl_2, 0 °C then rt, 2 h; (ii) CH_3CN, DIPEA (99%); (b) MsCl, pyridine, 0 °C, 3 h; (c) (i) Pd/C, H_2 (1 atm), MeOH, rt, overnight; (ii) Ambersep 900 OH, MeOH (31%).

3. Conclusion

The synthesis of the indolizidine lactone **24** presented herein has many interesting aspects. The high stereoselectivity allowed us to run seven steps (starting from nitrone **5** and dipolarophile **18**) without any formation of diastereomeric by-products and, therefore, without any need for separation. The method allowed complete control of the absolute configuration of five contiguous stereogenic centres in these molecules with many stereogenic carbons. The choice of the appropriate configuration of the starting malic acid, and the *E*- or *Z*-configuration of the dipolarophile, and moreover, the intra- or intermolecular version of the cycloaddition is able to give rise to a whole family of stereodifferentiated polyhydroxyindolizidine carboxylic acid derivatives. Finally, compound **24**, is a suitable precursor for the linkage of the iminosugar structure to different substrates using the carboxyl tether. Research along this line is currently in progress in our laboratories.

4. Experimental

4.1. General

All the reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were appropriately dried before use. NMR spectra were recorded in $CDCl_3$ and the data are reported in (ppm) from TMS. Multiplicity of the ^{13}C NMR was determined by means of APT. In mass spectra, relative percentages are shown in brackets. R_f values refer to TLC on 0.25 mm silica gel plates.

4.2. (4*S*)-2,3-Dicyanohexahydropyrrolo[1,2-*b*]isoxazol-4-yl cyclopropylideneacetate 10

N-Methylmorpholine (NMM; 235 μL, 2.14 mmol) was added dropwise to a solution of cyclopropylideneacetic acid **9** (63 mg, 0.65 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (136 mg, 0.78 mmol) in dry THF (1.5 mL). The mixture was stirred at rt for 1.5 h, then a solution of isoxazolidines **8** (58 mg, 0.32 mmol) in dry THF (2.5 mL) was added. The mixture was stirred overnight. The solvent was removed under reduced pressure and the recovered solid dissolved in CH_2Cl_2. The organic layer was washed with a saturated solution of $NaHCO_3$ and with a saturated solution of $NaHSO_4$, then dried over Na_2SO_4, filtered and concentrated. Purification of the crude residue by chromatography on silica gel (petroleum ether/AcOEt, 6:1) afforded esters **10** (46 mg, 55%) as a white solid. ^1H NMR (200 MHz, major isomer): δ 6.23 (m, 1H, O_2CCH=), 5.34 (m, 1H, 4-H), 5.10 (s, 1H, 2-H), 4.13 (m, 2H, 3-H, 3a-H), 3.73–3.60 (m, 1H, 6-H_a), 3.48–3.29 (m, 1H, 6-H_b), 2.56–2.37 (m, 1H, 5-H_a), 2.15–2.04 (m, 1H, 5-H_b), 1.52–1.20 (m, 4H, =CCH_2CH_2).

4.3. Ethyl (3′*R*,3a′*R*,4′*S*)- and (3′*S*,3a′*R*,4′*S*)-4′-*tert*-butoxytetrahydro-3′*H*-spiro[cyclopropane-1,2′-pyrrolo[1,2-*b*]isoxazole]-3′-carboxylate 14 and 15

Ethyl cyclopropylideneacetate **13** (106 mg, 0.84 mmol) was added to a solution of nitrone **12** (100 mg, 0.64 mmol) in toluene (0.64 mL). The mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the crude product purified on silica gel (petroleum ether/AcOEt, 5:1). The diastereoisomers **14** (104 mg) and **15** (20 mg) were obtained in a 5:1 ratio (overall yield: 69%). Compound **14**: $R_f = 0.22$ (pentane/AcOEt, 4:1); $[\alpha]_D^{23} = +55.2$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz): δ 4.28–4.11 (m, 1H, 4′-H), 4.18 (q, $J = 6.9$ Hz, 2H, CH_2CH_3), 4.03 (dd, $J = 9.2$, 2.6 Hz, 1H, 3a′-H), 3.44 (d, $J = 9.5$ Hz, 1H, 3′-H), 3.38–3.18 (m, 2H, 6′-H), 2.35–2.17 (m, 1H, 5′-H_a), 1.78–1.65 (m, 1H, 5′-H_b), 1.30 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.15 (s, 9H, *t*-Bu), 1.12–0.82 (m, 4H, C-2CH_2CH_2C-2); ^{13}C NMR (50 MHz): δ 170.9 (s, CO), 77.4 (d, C-4′), 73.8 (s, CMe_3), 73.6 (d, C-3a′), 64.2 (s, C-2′), 60.7 (t, CH_2CH_3), 55.0 (t, C-6′), 53.8 (d, C-3′), 34.2 (t, C-5′), 28.3 (q, CMe_3), 14.2 (t, CH_2CH_3), 12.7, 7.5 (t, C-2CH_2CH_2C-2); IR ($CDCl_3$): ν 2977, 1740, 1363, 1174 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 283 (1) [M^+], 226 (18), 209 (11), 180 (14), 170 (60), 152 (13), 57 (100). Elemental analysis calcd for $C_{15}H_{25}NO_4$ (283.36): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.10; H, 9.00; N, 5.26.

Compound **15**: $R_f = 0.18$ (petroleum ether/AcOEt, 5:1); $[\alpha]_D^{23} = +115.0$ (*c* 0.4, $CHCl_3$); ^1H NMR (200 MHz): δ 4.17 (dd, $J = 7.0$, 2.2 Hz, 1H, 4′-H), 4.23–4.02 (m, 3H,

3a′-H, CH_2CH_3), 3.36–3.26 (m, 2H, 6′-H), 3.16 (d, $J = 4.4$ Hz, 1H, 3′-H), 2.32–2.14 (m, 1H, 5′-H_a), 1.78–1.64 (m, 1H, 5′-H_b), 1.26 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.17 (s, 9H, *t*-Bu), 1.09–0.66 (m, 4H, C-2CH_2CH_2C-2); ^{13}C NMR (50 MHz): δ 170.0 (s, CO), 77.1 (d, C-4′), 73.8 (s, CMe_3), 73.1 (d, C-3a′), 63.9 (s, C-2′), 61.1 (t, CH_2CH_3), 56.0 (d, C-3′), 55.1 (t, C-6′), 33.0 (t, C-5′), 28.4 (q, CMe_3), 14.2 (q, CH_2CH_3), 9.6–8.2 (t, C-2CH_2CH_2C-2); IR ($CDCl_3$): ν 2977, 1745, 1363, 1261, 1179 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 283 (2) [M$^+$], 238 (3), 226 (23), 210 (7), 180 (11), 170 (20), 154 (16), 124 (38), 96 (46), 57 (100). Elemental analysis calcd for $C_{15}H_{25}NO_4$ (283.36): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.39; H, 9.08; N, 5.30.

4.4. (4*S*)-2,3-Dicyanohexahydropyrrolo[1,2-*b*]isoxazol-4-yl (2*E*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenoate 19

A solution of dimethylaminopyridine (DMAP; 102 mg, 0.83 mmol) and trifluoroacetic acid (TFA; 31 μL, 0.4 mmol) in dry CH_2Cl_2 (4.1 mL) was added to a solution of acid **18** (710 mg, 4.13 mmol) in dry CH_2Cl_2 (24 mL). The resulting mixture was added to isoxazolidine **8** (341.5 mg, 1.91 mmol) dissolved in dry CH_2Cl_2 (12 mL). Diisopropylcarbodiimide (DIC; 600 μL, 4.1 mmol) was added dropwise at rt and the reaction mixture stirred at rt for 4 days and then the solvent was removed at reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/AcOEt, 4:1) to afford **19** (415 mg, 65%) as a colourless oil. $R_f = 0.21$ (petroleum ether/AcOEt, 4:1); ^{1}H NMR (200 MHz): δ 6.95 (dd, $J = 15.2$, 5.3 Hz, 1H, $O_2CCH{=}CH$), 6.12 (dd, $J = 15.7$, 1.3 Hz, 1H, $O_2CCH{=}CH$), 5.35 (m, 1H, 4-H), 5.08 (s, 1H, 2-H), 4.69 (m, 1H, ═CHCHO), 4.26–4.07 (m, 2H, 3-H, CHHO), 4.02 (dd, $J = 8.9$, 2.4 Hz, 1H, 3a-H), 3.74–3.60 (m, 2H, 6-H_a, CHHO), 3.46–3.29 (m, 1H, 6-H_b), 2.59–2.39 (m, 1H, 5-H_a), 2.15–2.05 (m, 1H, 5-H_b), 1.46 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); ^{13}C NMR (50 MHz): δ 165.5 (s, CO), 146.7 (d, $O_2CCH{=}CH$), 120.8 (d, $O_2CCH{=}CH$), 115.5 (s, CN), 115.3 (s, CN), 110.2 (s, CMe_3), 78.0, 74.6, 72.3, 68.3 (d, C-2, C-3a, C-4, ═CHCHO), 68.5 (t, CH_2O), 55.0 (t, C-6), 43.0 (d, C-3), 30.5 (t, C-5), 26.3 (q, CH_3), 25.5 (q, CH_3); IR ($CDCl_3$): ν 2990, 2936, 2256, 1723, 1661, 1374, 1259, 1064 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 333 (0.06) [M$^+$], 318 (10), 276 (5), 240 (5), 161 (56), 97 (79), 84 (100), 77 (56).

4.5. (2a*S*,3*S*,6a*S*,6b*S*)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]hexahydro-2*H*-1,4-dioxa-4a-azacyclopenta-[*cd*]pentalen-2-one 20

A solution of ester **19** (41 mg, 0.12 mmol) in xylenes (11 mL) was refluxed for 10 min. The mixture was purified by chromatography on silica gel (first petroleum ether to remove the high boiling solvent, then petroleum ether/AcOEt, 1:1). The tricyclic isoxazolidine **20** (26.1 mg, 84%) was obtained as white solid. $R_f = 0.22$ (petroleum ether/AcOEt, 1:1); $[\alpha]_D^{25} = +27.8$ (*c* 1.28, $CHCl_3$); ^{1}H NMR (200 MHz): δ 5.47 (m, 1H, 6a-H), 4.41–4.22 (m, 3H, 3-H, 6b-H, CHO), 4.11 (dd, $J = 8.9$, 5.7 Hz, 1H, CHHO), 3.94 (dd, $J = 8.9$, 4.0 Hz, 1H, CHHO), 3.71 (dd, $J = 8.8$, 1.8 Hz, 1H, 2a-H), 3.47–3.34 (m, 1H, 5-H_a), 3.17–3.02 (m, 1H, 5-H_b), 2.33–2.23 (m, 2H, 6-H), 1.49 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (50 MHz): δ 176.8 (s, CO), 110.1 (s, OCO), 84.1, 82.8, 74.6, 70.7 (d, C-6a, C-6b, C-3, CHO), 66.9 (t, CH_2O), 53.3 (t, C-5), 51.5 (d, C-2a), 32.1 (t, C-6), 26.9 (q, CH_3), 25.0 (q, CH_3); IR ($CDCl_3$): ν 2990, 2929, 1773, 1374, 1185, 1073, 1053 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 255 (4) [M$^+$], 240 (19), 226 (4), 180 (6), 168 (9), 152 (13), 134 (46), 105 (89), 84 (100); Elemental analysis calcd for $C_{12}H_{17}NO_5$ (255.27): C, 55.68; H, 6.77; N, 5.41. Found: C, 56.45; H, 6.71; N, 5.73.

4.6. (2a*S*,3*S*,6a*S*,6b*S*)-3-[(1*S*)-1,2-Dihydroxyethyl]hexahydro-2*H*-1,4-dioxa-4a-azacyclopenta[*cd*]pentalen-2-one 21

Trifluoroacetic acid (TFA; 0.6 mL) was added dropwise to a solution of **20** (36.9 mg, 0.14 mmol) in CH_2Cl_2 (6.4 mL) at 0 °C. The mixture was warmed up to rt and stirred for 2 h. The solvent was removed under reduced pressure to give the trifluoroacetate salt of **21**, which was stirred in acetonitrile in the presence of *N*,*N*-diisopropylethylamine (DIPEA) overnight. The solvent was removed under reduced pressure and the crude product purified by chromatography on silica gel (AcOEt/MeOH, 40:5) to give **22** (29.8 mg, 99%) as a deliquescent white solid. $R_f = 0.16$ (AcOEt/MeOH, 40:5); $[\alpha]_D^{20} = +28.4$ (*c* 0.4, MeOH); ^{1}H NMR (200 MHz): δ 5.11 (dt, $J = 5.9$, 4.0 Hz, 1H, 7a-H), 4.43 (dd, $J = 6.2$, 2.9 Hz, 1H, 7b-H), 4.35 (dd, $J = 6.2$, 2.9 Hz, 1H, 3-H), 3.77 (dd, $J = 8.8$, 2.9 Hz, 1H, 2a-H), 3.66 (td, $J = 6.2$, 3.3 Hz, 1H, CHOH), 3.66–3.55 (m, 1H, CHHOH), 3.46 (dd, $J = 11.9$, 6.0 Hz, 1H, CHHOH), 3.10 (m, 2H, 6-H), 2.18–2.05 (m, 2H, 5-H); ^{13}C NMR (50 MHz): δ 179.3 (s, CO), 83.3, 82.5 (d, C-7a, C-3), 70.0, 69.8 (d, C-7b, CHOH), 61.5 (t, CH_2OH), 51.4 (t, C-6), 51.0 (d, C-2a), 30.2 (t, C-7); IR ($CDCl_3$): ν 3633, 2928, 1771, 1361, 1186, 1053 cm^{-1}; MS (70 eV, EI): *m*/*z* (%) 215 (30) [M$^+$], 198 (6), 196 (7), 184 (17), 179 (5), 153 (18), 124 (7), 86 (71), 83 (100).

4.7. (2a*S*,3*S*,4*R*,8a*S*,8b*S*)-3,4-Dihydroxyoctahydro-2*H*-furo[4,3,2-*hi*]indolizin-2-one 24

Cold methanesulfonylchloride (MsCl; 14.4 μL, 0.17 mmol) was added dropwise to a solution of diol **21** (40.1 mg, 0.17 mmol) in dry pyridine (3 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and then the solvent evaporated under reduced pressure. The solid was dissolved in MeOH (3 mL) and a catalytic amount of Pd/C added. The mixture was stirred overnight under a hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH, treated with Ambersep 900 OH, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to yield **24** (10.5 mg, 31%) as a colourless oil. $R_f = 0.12$ (CH_2Cl_2/MeOH, 10:1); $[\alpha]_D^{20} = +5.6$ (*c* 0.16, MeOH); ^{1}H NMR (200 MHz): δ 5.06 (t,

$J = 4.4$ Hz, 1H, 8a-H), 4.06–3.98 (m, 2H, 3-H, 4-H), 3.92–3.84 (m, 1H, 8b-H), 3.53 (ddd, $J = 10.4$, 8.6, 5.5 Hz, 1H, 7-H_a), 3.34 (dd, $J = 14.8$, 2.7 Hz, 1H, 5-H_a), 3.02 (td, $J = 7.9$, 1.5 Hz, 1H, 7-H_b), 2.89–2.78 (m, 2H, 2a-H, 5-H_b), 2.22 (dd, $J = 13.7$, 5.3 Hz, 1H, 8-H_a), 2.07–1.86 (m, 1H, 8-H_b); ^{13}C NMR (50 MHz): δ 173.6 (s, C-2), 85.5, 71.0, 70.2, 61.4 (d, C-3, C-4, C-8a, C-8b), 52.7 (t, C-7), 50.6 (t, C-5); 40.6 (d, C-2a), 32.4 (t, C-8); IR ($CDCl_3$): ν 3468, 2921, 1747, 1438, 1348, 1180, 1059 cm^{-1}; MS (70 eV, EI): m/z (%): 199 (27) [M^+], 197 (23), 171 (5), 107 (35), 97 (100), 84 (85). Elemental analysis calcd for $C_9H_{13}NO_4$ (199.20): C, 54.26; H, 6.58; N, 7.03. Found: C, 53.96; H, 6.18; N, 6.71.

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