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Synthesis of the New 7*S*-Aminolentiginosine and Derivatives

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Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday

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Abstract: The new 7*S*-aminolentiginosine has been synthesized by a diastereoselective 1,3-dipolar cycloaddition strategy starting from 3,4-dihydroxylated pyrroline *N*-oxides derived from L-tartaric acid in thirteen steps. The intermediate 7*S*-azidolentiginosine undergoes efficiently copper(I)-catalysed Huisgen cycloadditions to alkynes.

Keywords: azides; 1,3-dipolar cycloaddition; iminosugars; pyrroline *N*-oxides

Polyhydroxylated indolizidine alkaloids[1] such as (−)-swainsonine (**1**),[2] (+)-castanospermine (**2**),[3] and (+)-lentiginosine (**3**)[4] (Figure 1) have been attracting vast attention since their isolation owing to their resemblance with sugars and interest in their biological activities as a consequence. Their activity as glycosidase inhibitors suggests a potential role as therapeutic agents in many different pathologies such as viral infections, tumour metastasis, diabetes and genetic disorders.[5]

These attractive activities have stimulated much interest in the synthesis of unnatural analogues with the possibility of expanding their applications. Because of the growing interest in glycoconjugation,[6] we considered the possibility of synthesising polyhydroxylated indolizidines containing a functional group, like an amino group, which is amenable for further transformations such as, for example, the coupling with amino acids for the synthesis of peptide conjugates.

Lentiginosine, in spite of being the least hydroxylated compound of the series and the most recent to be studied, has shown a very promising and selective inhibitory activity against amyloglucosidase, higher than that of castanospermine (**2**).[7] This activity seems to depend on the peculiar *trans*-dihydroxy substitution of the 5-membered ring portion of the molecule, able to provide selective interactions with the enzyme cavity.[8] This finding suggests that a substitution on the six-membered ring should not hamper this favourable interaction and possibly furnish a handle to attach groups which could improve the interaction with the receptor. Preliminary computational studies[9] suggest that various substituents could be favourably accommodated in the enzyme cavity.

In this context we report here the successful stereoselective short synthesis of 7*S*-aminolentiginosine **4** (Scheme 1) applying the 1,3-dipolar cycloaddition strategy starting from a hydroxylated pyrroline *N*-oxide **5**.[10]

In the search of new R protecting groups on nitrone **5** to expand the potentiality of the strategy, the new (bis)benzoylated nitrone **11** was obtained in a very efficient way starting from L-tartaric acid (Scheme 2). Benzylimide **6** was obtained by heating the benzylammonium salt of tartaric acid in refluxing xylenes, with azeotropic removal of water, as recently

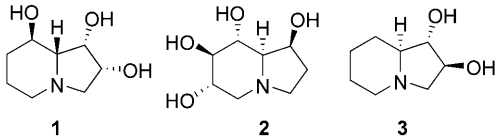

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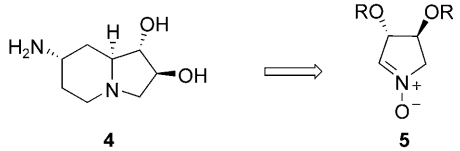
Figure 1. Polyhydroxylated indolizidine alkaloids.



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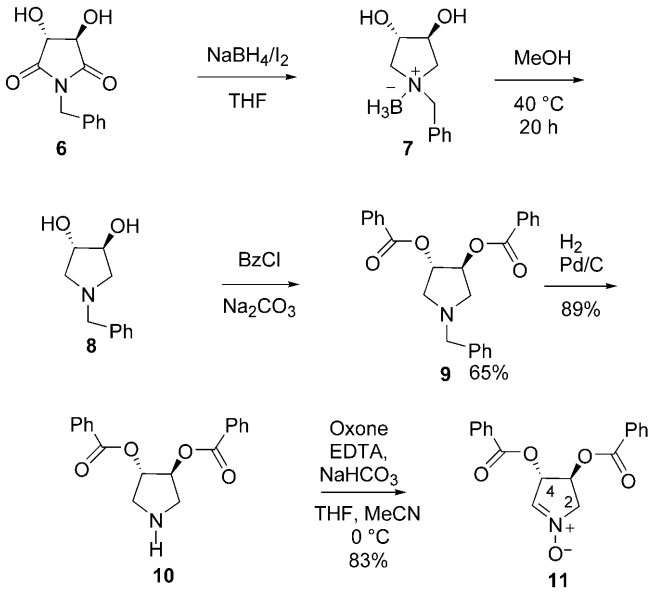
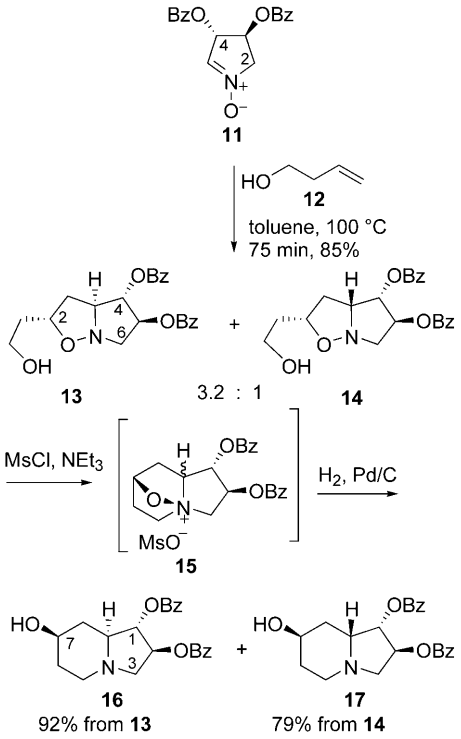
Scheme 1. Retrosynthesis of 7*S*-amino-lentiginosine.



Scheme 2. Synthesis of (3*S*,4*S*)-4-(benzoyloxy)-1-oxido-3,4-dihydro-2*H*-pyrrol-3-yl benzoate (**11**).



Scheme 3. Synthesis of the indolizidine core.

reported by Rosenberg et al.[11] *N*-Benzyldihydroxypyrrolidine **8** was obtained by reduction of the *in situ* generated borane through a slight modification of Rosenberg's procedure. In particular, **6** was treated with $NaBH_4$ and I_2 at 0 °C and then heated at the reflux temperature for 6 h to reach a full conversion. After destroying the excess of borane with MeOH at room temperature, the pyrrolidine-borane adduct **7** was at first washed with water to remove NaI salt, then treated with MeOH at 40 °C to achieve, after benzoylation, **9** in 65% overall yield respect to **6**. In our hand, the reductive work-up procedure under neutral conditions resulted to be much more efficient and reproducible than the acidic one previously used,[11] especially for large-scale preparations.

The key oxidation of the C_2 symmetrical pyrrolidine **10** was attempted by several methods, such as SeO_2/H_2O_2,[12] and MTO/H_2O_2,[13] which were not satisfying for the reaction yields, or *N*-sulfonyloxaziridine,[14] not practical in large-scale syntheses for the cost and atom economy. It was found that oxone, recently employed by Font and co-workers to oxidize prolinol,[15] gave a very good yield (83%) also in the case of oxidation of **10** to nitrone **11** with a reaction very simple and convenient.

The cycloaddition of **11** to butenol **12** (Scheme 3), carried out in toluene at 100 °C for 75 min, gave two main cycloadducts **13** and **14**, besides a third one in traces, in 85% overall yield. The ratio of the two main cycloadducts **13** and **14**, 3.2:1, is somewhat lower than that obtained by the cycloaddition of *t*-Bu-protected nitrone to **12** (5:1), but similar to that obtained with TBDMS-protected nitrone.[16,12b] Also microwave conditions, at different temperatures and solvents, were tested, but no improvement of yield, selectivity, and reaction times was observed.

The minor diastereoisomer **14** derives from an *exo-syn* approach of the dipolarophile to the C-4 BzO substituent of the nitrone, less favoured than the common *exo-anti* approach[7] (Figure 2). The *exo* approach is highly favoured, because of the encumbering effect of the BzO C-3 group in an *endo* approach. Evidence for the assignment derives from proton NMR coupling constants of the bridgehead proton 3a-H with the vicinal 4-H, 3.1 Hz in **13** compared to 6.7 Hz in **14**, diagnostic for a *trans* and a *cis* relationship, respectively. The low diastereoselectivity can be ascribed to the relative flatness of the benzoyl group exerting a lower steric hindrance compared to *t*-Bu group.

Cycloadducts **13** and **14** could be only partially separated by chromatography on silica gel, unlike the *tert*-butyl-protected adducts. Therefore, it was more convenient to carry out the next step on the isomeric

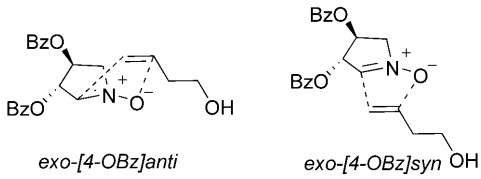


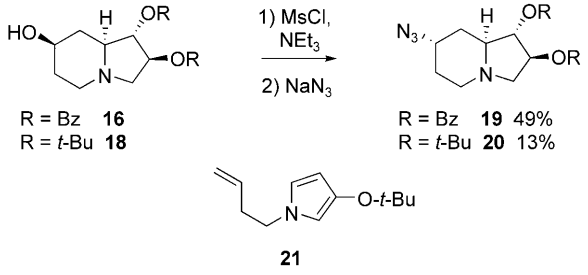
Figure 2. Preferred transition state trajectories of the cycloaddition to 1-buten-4-ol (**12**).

mixture as the corresponding diastereomeric indolizidines **16** and **17** were easily separable (Scheme 3). Mesylation of the mixture of isoxazolidine alcohols **13** and **14** produces the inner salts **15** which are not isolated, but immediately reduced by H_2 on Pd/C to indolizidines **16** and **17** in 92% and 79% yield, from **13** and **14** respectively, after chromatographic separation.

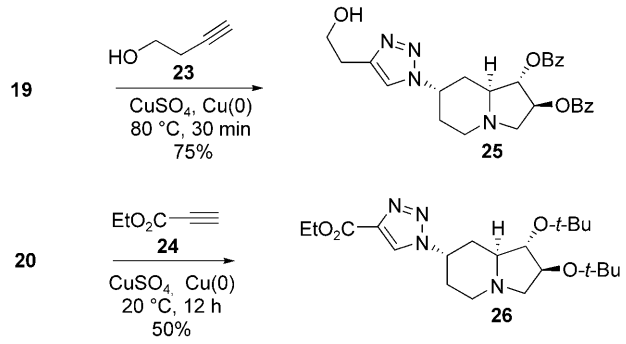
To introduce the amino group on C-7 of indolizidine **16** we chose the strategy of mesylation of the free 7-OH and nucleophilic substitution of the mesylate with NaN_3.[17] The reaction was performed also on the 1,2-(bis)-*t*-Bu protected indolizidinetriol **18**.[18] The reaction of the mesylate of **18** with NaN_3 in DMF at 80 °C for 2.5 h gave a mixture of two products (Scheme 4).

Besides the expected azide **20** obtained in poor 13% yield, a new product **21** was obtained in 21% yield to which the fragmented and pyrrole aromatized structure **21** was assigned on the basis of NMR and mass spectrometry data. The product **21** must derive from a Grob's fragmentation-type process,[19] followed by monodeprotection and elimination/aromatization of the pyrrole ring. A similar Grob's-type fragmentation of a tosylated isoxazolidine, in a different reducing context, was previously observed in our group.[16] Changing the conditions of temperature and reaction times did not affect much the results. The finding should be ascribed to the lability of the *t*-Bu protecting group in connection with the sulfonate protection of the 7-OH during the azide substitution. The problem, in fact, is not observed with the benzoylated indolizidine **16**. This gives the expected azide **19** in good 49% yield by reaction of the mesylate with NaN_3 in DMF at 80 °C for 22 h.

The reduction of the azide **19** with Raney Ni, and hydrolysis of benzoates by treatment of **22** with Ambersep in MeOH, affords, then, 7*S*-aminolentiginosine



Scheme 4. Synthesis of azides **19** and **20**.



Scheme 6. Cu(I)-catalysed Huisgen's cycloaddition.

4 in six steps from cycloadduct **13** and 19% overall yield (Scheme 5).

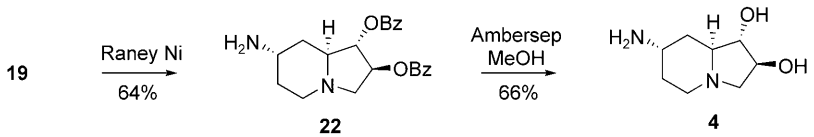
The formation of the intermediate azides allows another approach for conjugating the indolizidine moiety to other substrates, by running Huisgen's cycloaddition to alkynes. The Cu(I)-catalysed version[20,21] of the cycloaddition confers a high chemo- and regioselectivity to the process. To study the feasibility of it two examples of the addition of azide **19** to butyn-4-ol **23**, and azide **20** to ethyl propiolate **24**, were carried out (Scheme 6).

The cycloaddition of **19** to azide **23** occurs smoothly at 80 °C using microwaves as the heating device and affords good yield (75%) of the triazole **25**. The reaction of the more reactive propiolate **20** with *t*-Bu-protected azide **20** occurs at room temperature, more convenient for the lability of the dipolarophile, giving triazole **26** in 50% yield.

In conclusion, a short straightforward synthesis of the new 7*S*-aminolentiginosine is achieved as a new tool for the conjugation of this iminosugar with other biomolecules. The coupling could be carried out by "click chemistry" by using the intermediate azide, as it is shown in two examples. The triazole ring has, by itself, some biomimetic character.[22] Finally, 7*S*-aminolentiginosine is a non-natural example of an amino-substituted sugar mimic,[23] for which a likely glycosidase inhibitor activity can be foreseen.

Experimental Section

For experimental details and spectral data for all new compounds, see the Supporting Information.



Scheme 5. Synthesis of 7*S*-aminolentiginosine.

(3*S*,4*S*)-4-(Benzoyloxy)-1-oxido-3,4-dihydro-2*H*-pyrrol-3-yl Benzoate (11)

AcOH (4.34 mL) was added to a suspension of **9** (3.06 g, 7.6 mmol) in MeOH (50 mL) and THF (9 mL) at 0 °C. Then, a catalytic amount of 10% Pd/C (500 mg) was added and the mixture was stirred under a H_2 atmosphere (1 atm) overnight at room temperature. The mixture was filtered through a short pad of Celite and concentrated under reduced pressure. The obtained white solid was dissolved in AcOEt (60 mL) and washed with a saturated aqueous Na_2CO_3 solution (45 mL). The aqueous solution was extracted with AcOEt (2×30 mL). The combined organic phases were washed with H_2O, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude *(3S,4S)-4-(benzoyloxy)pyrrolidinyl benzoate* (**10**)[19] as a pale yellow oil (yield: 2.115 g, 89%), which was directly oxidized.

$NaHCO_3$ (2.85 g, 33.95 mmol) was added to a stirred solution of the crude amine **10** (2.115 g, *ca.* 6.8 mmol) in a 4 :1 mixture of CH_3CN-THF (12.5 mL) and aqueous Na_2EDTA (0.01 M, 9.5 mL). The mixture was then cooled in an ice bath and Oxone® (4.4 g, 7.15 mmol) was added portionwise over 3 h. The mixture was stirred at 0 °C for 45 min and then diluted with EtOAc (35 mL) and H_2O (37 mL). The two phases were separated and the aqueous solution was extracted with EtOAc (2×25 mL). The combined organic phases were washed with H_2O (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude pyrroline-*N*-oxide **11** (yield: 1.831 g, 83%) as a white solid, that can be used in the next step without further purification. A sample purified by chromatography on silica gel (eluent: petroleum ether/EtOAc, 2:1) afforded analytically pure **11**. R_f = 0.38; m. p. 155–158 °C (with decomposition); $[\alpha]_D^{25}$: = +220.53 (*c* 0.525, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.10–8.00 (m, 4H, Ph), 7.65–7.57 (m, 2H, Ph), 7.50–7.43 (m, 4H, Ph), 7.17–7.15 (m, 1H, 5-H), 6.11–6.09 (m, 1H, 4-H), 5.74 (dm, *J* = 6.3, 1H, 3-H), 4.73 (dddd, *J* = 15.7, 6.3, 2.1, 1.2 Hz, 1H, 2-H_a), 4.07 (dddd, *J* = 15.7, 2.1, 1.2, 0.7 Hz, 2-H_b); ^{13}C NMR (50 MHz): δ = 165.4 (s, CO), 165.3 (s, CO), 133.9 (d, Ph), 133.8 (d, Ph), 130.3 (d, C-2), 129.8 (d, 4C, Ph), 128.6 (d, 4C, Ph), 128.4 (s, Ph), 128.3 (s, Ph), 78.2 (d, C-3), 72.3 (d, C-4), 67.2 (t, C-5); IR ($CDCl_3$): ν = 1725, 1579, 1452, 1317, 1263, 1105 cm^{-1}; MS (EI): *m/z* (%) = 325 (1, M^+), 203 (10), 105 (100), 82 (11), 77 (30); anal. calcd. for $C_{18}H_{15}NO_5$ (325.31): C 66.46, H 4.65 , N 4.31; found C 66.32, H 4.36, N 4.25.

(1*S*,2*S*,7*S*,8a*S*)-7-Azido-2-(benzoyloxy)octahydro-1-indolizinyl Benzoate (19)

Methanesulfonyl chloride (MsCl, 0.327 mL, 4.24 mmol) was added dropwise to a solution of **16** (809 mg, 2.12 mmol) and triethylamine (1.462 mL, 10.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred under nitrogen at room temperature for 2 h and the resulting suspension was diluted with CH_2Cl_2 (9 mL) and H_2O (9 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (2× 9 mL). The collected organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced presure. The crude product was filtered through a short pad of silica gel (eluent: EtOAc/petroleum ether, 1:1) and evaporation of the solvent afforded *(1S,2S,7R,8aS)-1-(benzoyloxy)-7-[(methylsulfonyl)oxy]octahydro-2-indolizinyl benzoate* (yield: 848 mg, 87%) as a white solid, which was used in the next step without further purification.

A mixture of the mesylate (591 mg, 1.29 mmol) and NaN_3 (209 mg, 3.2 mmol) in DMF (3.1 mL) was heated to 80 °C for 22 h. The reaction mixture was diluted with EtOAc (8 mL) and H_2O (9 mL), the two phases were separated and the aqueous phase was extracted with EtOAc (9×8 mL). The collected organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: CH_2Cl_2) to afford azide **19** (yield: 296 mg, 56%) as a colorless oil. R_f = 0.34; $[\alpha]_D^{25}$: +109.70 (*c* 0.500, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.10–8.03 (m, 4H, Ph), 7.60–7.52 (m, 2H, Ph), 7.48–7.40 (m, 4H, Ph), 5.43–5.36 (m, 2H, 1-H, 2-H), 4.07–4.02 (m, 1H, 7-H), 3.19 (d, *J* = 11.2 Hz, 1H, 3-H_a), 2.95–2.86 (m, 2H, 3-H_b, 5-H_a), 2.55 (ddd, *J* = 11.1, 8.4, 2.4 Hz, 1H, 8a-H), 2.42 (dt, *J* = 3.0, 11.6 Hz, 1H, 5-H_b), 2.13 (dm, *J* = 13.6 Hz, 1H, 8-H_a), 1.98–1.77 (m, 3H, 6-H, 8-H_b); ^{13}C NMR (100 MHz): δ = 166.4 (s, C=O), 165.9 (s, C=O), 133.3 (d, Ph), 133.1 (d, Ph), 129.9 (d, 2C, Ph), 129.8 (d, 2C, Ph), 129.7 (s, Ph), 129.5 (s, Ph), 128.4 (d, 2C, Ph), 128.3 (d, 2C, Ph), 81.9 (d, C-1), 77.4 (d, C-2), 61.7 (d, C-8a), 59.5 (t, C-3), 55.5 (d, C-7), 47.3 (t, C-5), 33.2 (t, C-8), 28.6 (t, C-6); IR ($CDCl_3$): ν = 2930, 2815, 2098, 1718, 1602, 1451, 1276, 1112 cm^{-1}; HR-MS: *m/z* = 407.17102, calcd. for $C_{22}H_{23}N_4O_4$ $[M+H]^+$: 407.17138; anal. calcd. for $C_{22}H_{22}N_4O_4$ (406.4): C 65.01, H 5.46, N 13.78; found: C 64.70, H 5.08, N 13.55.

7*S*-Aminolentiginosine (4)

(1S,2S,7S,8aS)-7-Amino-2-(benzoyloxy)octahydro-1-indolizinyl benzoate (22): A water suspension of activated Raney-Ni was added dropwise to a solution of **19** (250 mg, 0.615 mmol) in MeOH (6 mL). The mixture was stirred at room temperature for 1 h, filtered through a short pad of Celite and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **22** (yield: 150 mg, 64%) as a pale yellow solid, that was directly deprotected without further purification. ^{1}H NMR (400 MHz): δ = 8.10–8.00 (m, 4H, Ph), 7.59–7.51 (m, 2H, Ph), 7.47–7.38 (m, 4H, Ph), 5.42 (br dd, *J* = 6.2, 3.0 Hz, 1H, 2-H), 5.26 (dd, *J* = 7.9, 3.0 Hz, 1H, 1-H), 3.56–3.51 (m, 1H, 7-H), 3.14 (br d, *J* = 11.2 Hz, 1H, 3-H_a), 3.03 (dd, *J* = 11.2, 6.7 Hz, 1H, 3-H_b), 2.89–2.76 (m, 2H, 5-H_a, 8a-H), 2.74–2.62 (m, 1H, 5-H_b), 2.28 (br d, *J* = 14.3 Hz, 1H, 8-H_a), 1.93–1.85 (m, 2H, 6-H), 1.85–1.74 (m, 1H, 8-H_b); ^{13}C NMR (50 MHz): δ = 166.0 (s, C=O), 165.6 (s, C=O), 133.2 (d, Ph), 133.1 (d, Ph), 129.7 (d, 4C, Ph), 129.4 (s, Ph), 129.3 (s, Ph), 128.3 (d, 2C, Ph), 128.2 (d, 2C, Ph), 82.1 (d, C-1), 77.2 (d, C-2), 60.3 (d, C-8a), 59.1 (t, C-3), 45.8 (t, C-5), 45.6 (d, C-7), 32.0 (t, C-8), 27.9 (t, C-6); HR-MS: *m/z* = 381.18190, calcd. for $C_{22}H_{25}N_2O_4$ $[M+H]^+$: 381.18088.

(1S,2S,7S,8aS)-7-Aminooctahydro-1,2-indolizinediol (4): Ambersep 900-OH was added to a solution of crude **22** (128 mg, 0.33 mol) in MeOH (5 mL) and the mixture was maintained at room temperature for 2 h under gentle magnetic stirring. The reaction mixture was filtered through cotton wool and concentrated under reduced pressure to give **4** (yield: 38 mg, 0.22 mmol, 66%). $[\alpha]_D^{24}$: −16.666 (*c* 0.27, MeOH); ^{1}H NMR (CD_3OD, 400 MHz): δ = 3.97 (ddd, *J* =

7.2, 3.5, 1.5 Hz, 1H, 2-H), 3.60 (dd, $J=8.4$, 3.5 Hz, 1H, 1-H), 3.29–3.24 (m, 1H, 7-H), 2.85 (dd, $J=10.6$, 1.5 Hz, 1H, 3-H_a), 2.76 (ddd, $J=11.4$, 4.7, 2.6 Hz, 1H, 5-H_a), 2.63 (dd, $J=10.6$, 7.2 Hz, 1H, 3-H_b), 2.37 (dt, $J=2.9$, 12.4 Hz, 1H, 5-H_b), 2.18 (ddd, $J=11.6$, 8.4, 2.7 Hz, 1H, 8a-H), 1.92 (dq, $J=13.3$, 2.4 Hz, 1H, 8-H_a), 1.84 (br dt, $J=4.4$, 13.1 Hz, 1H, 6-H_a), 1.63–1.54 (m, 2H, 6-H_b, 8-H_b); ^{13}C NMR (CD_3OD, 100 MHz): $\delta=85.1$ (d, C-1), 77.8 (d, C-2), 64.1 (d, C-8a), 62.6 (t, C-3), 48.2 (t, C-5), 45.2 (d, C-7), 35.9 (t, C-8), 32.2 (t, C-6); HR-MS: $m/z=173.1290$, calcd. for $C_8H_{17}N_2O_2$ $[M+H]^+$: 173.1294.

(1*S*,2*S*,7*R*,8a*S*)-2-(Benzoyloxy)-7-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]octahydro-1-indolizinyl Benzoate (25)

In a microwave reaction tube were added a mixture of azide **19** (60 mg, 0.148 mmol) and 97% pure 3-butyn-1-ol (**23**, 0.013 mL, 0178 mmol) in a 1:1 mixture of water and *t*-BuOH (0.6 mL), copper powder (4 mg, 0.06 mmol) and copper sulfate (16 mg. 0.1 mmol). The mixture was stirred for 30 min at 80 °C, using an irradiation power of 100 W. Then, other two portions of **23** (0.013 mL) were added and the mixture was heated at 80 °C for 30 min after each addition. The reaction mixture was concentrated under reduced pressure, then diluted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography on silica gel (eluent: EtOAc/MeOH, 14:1) to afford analytically pure triazole **25** (yield: 53 mg, 75%). $R_f=0.26$; $[\alpha]_D^{22}$: +115.39 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta=$ 8.10–8.06 (m, 2H, Ph), 8.04–8.01 (m, 2H, Ph), 7.59–7.54 (m, 2H, Ph), 7.46–7.41 (m, 5H, Ph, triazole), 5.46–5.39 (m, 2H, 1-H, 2-H), 4.80–4.74 (m, 1H, 7-H), 3.99–3.92 (m, 2H, CH_2OH), 3.22 (d, $J=11.2$ Hz, 1H, 3-H_a), 3.01 (ddd, $J=11.3$, 4.7, 2.4 Hz, 1H, 5-H_a), 2.96 (dd, $J=11.2$, 6.7 Hz, 1H, 3-H_b), 2.94 (t, $J=5.7$ Hz, 2H, CH_2CH$_2$OH), 2.75–2.67 (m, 2H, 8-H_a, 8a-H), 2.63 (dt, $J=2.9$, 11.8 Hz, 1H, 5-H_b), 2.57 (br s, 1H, OH), 2.43–2.27 (m, 2H, 6-H), 2.22 (ddd, $J=14.5$, 11.8, 4.4 Hz, 1H, 8-H_b); ^{13}C NMR (100 MHz): $\delta=166.3$ (s, C=O), 166.0 (s, C=O), 145.4 (s, triazole), 133.3 (d, Ph), 133.2 (d, Ph), 129.8 (d, 4C; Ph), 129.6 (s, Ph), 129.3 (s, Ph), 128.4 (d, 2C, Ph), 128.3 (d, 2C, Ph), 121.0 (d, triazole), 82.1 (d, C-1), 77.4 (d, C-2), 61.6 (t, *C*H_2OH), 61.5 (d, C-8a), 59.3 (t, C-3), 53.8 (d, C-7), 47.6 (t, C-5), 33.5 (t, C-8), 29.2 (t, C-6), 28.6 (t, *C*H_2CH$_2$OH); IR ($CDCl_3$): $\nu=3627$, 3456 br, 2957, 2836, 1718, 1603, 1451, 1280, 1113 cm^{-1}; HR-MS: $m/z=477.21325$, calcd. for $C_{26}H_{29}N_5O_4$ $[M+H]^+$: 477.21325; anal. calcd. for $C_{26}H_{28}N_4O_5$ H_2O (494.5): C 63.15, H 6.11, N 11.33; found: C 63.37, H 6.01, N 11.25.

(1*S*,2*S*,7*S*,8a*S*)-7-Azido-1,2-di-*tert*-butoxyoctahydroindolizine (20)

Cold freshly distilled MsCl (0.3 mL, 3.87 mmol) was added dropwise to a solution of 2-[(2*S*,3a*S*,4*S*,5*S*)-4,5-di-*tert*-butoxyhexahydropyrrolo[1,2-*b*]isoxazol-2-yl]ethanol (1.6 g, 3.52 mmol) and NEt_3 (0.69 mL, 4.93 mmol) in CH_2Cl_2 (distilled over P_2O_5, 16.4 mL) at 0 °C under N_2. The mixture was stirred for 1 h at 0 °C, and concentrated under reduced pressure. The residue was diluted with THF (9 mL) and reconcentrated for two times. The residue was dissolved in MeOH (42 mL), treated with a catalytic amount of 10% Pd/C (187 mg) and reacted under H_2 atmosphere (1 Atm) overnight. The reaction mixture was filtered through a short pad of Celite and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (7 mL) and washed with a saturated aqueous $NaHCO_3$ solution (7 mL). The aqueous solution was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases washed with H_2O (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude *(1S,2S,7R,8aS)-1,2-di-tert-butoxyoctahydro-7-indolizinol* (**18**; yield: 970 mg, 96%) as a yellow waxy solid, which was used in the next step without further purification.

Methanesulfonyl chloride (0.52 mL, 6.73 mmol) was added dropwise to a solution of **18** (960 mg, 3.36 mmol) and triethylamine (2.34 mL, 16.8 mmol) in CH_2Cl_2 (4.8 mL) at 0 °C. The mixture was stirred under nitrogen at room temperature for 2 h and the resulting suspension was diluted with CH_2Cl_2 (15 mL) and H_2O (15 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (2×15 mL). The collected organic phases were washed with brine (3×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude *(1S,2S,7R,8aS)-1,2-di-tert-butoxyoctahydro-7-indolizinyl methanesulfonate* (yield: 1.2 g, 98%) was obtained as an orange oil and was used in the next step without further purification.

A mixture of the mesylate (1.2 g, 3.3 mmol) and NaN_3 (429 mg, 6.6 mmol) in DMF (7.9 mL) was heated at 40 °C for 4 h and then at 80 °C for 2.5 h. The reaction mixture was diluted with H_2O (25 mL) and extracted with petroleum ether (3×30 mL). The collected organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc, initially 19:1 then 4:1) to afford *(1S,2S,7S,8aS)-7-azido-1,2-ditert-butoxyoctahydroindolizine* (**20**; yield: 129 mg, 0.42 mmol, 13%) as a pale yellow waxy solid and compound **21** (yield: 138 mg, 0.7 mmol, 21%) as a brown oil. Data for **20**: $R_f=0.11$ (eluent: petroleum ether/EtOAc, 8:2); ^{1}H NMR (400 MHz): $\delta=3.99$ (quintet, $J=$ 3.0 Hz, 1H, 7-H), 3.81 (ddd, $J=7.0$, 4.0, 1.6 Hz, 1H, 2-H), 3.60 (dd, $J=8.5$, 3.9 Hz, 1H, 1-H), 2.89 (ddd, $J=10.1$, 1.4 Hz, 1H, 3-H_a), 2.75 (ddd, $J=11.1$, 4.6, 2.2 Hz, 1H, 5-H_a), 2.49 (dd, $J=10.1$, 7.1 Hz, 1H, 3-H_b), 2.22 (dt, $J=2.9$, 11.8 Hz, 1H, 5-H_b), 2.11–1.97 (m, 2H, 8-H_a, 8a-H), 1.87 (dddd, $J=14.1$, 12.4, 4.6, 3.4 Hz, 1H, 6-H_a), 1.73 (d quintet, $J=14.1$, 2.5 Hz, 1H, 6-H_b), 1.59–1.46 (m, 1H, 8-H_b), 1.19 (s, 9H, *t*-Bu), 1.17 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz): $\delta=83.4$ (d, C-1); 76.8 (d, C-2), 73.7 (s, *t*-Bu), 73.6 (s, *t*-Bu), 61.7 (t, C-3), 61.0 (d, C-8a), 55.9 (d, C-7), 47.9 (t, C-5), 32.7 (t, C-8), 29.3 (q, 3C, *t*-Bu), 28.8 (q, 3C, *t*-Bu), 28.7 (t, C-6); HR-MS: $m/z=311.24415$, calcd. for $C_{16}H_{31}N_4O_2$ $[M+H]^+$: 311.24415.

Ethyl 1-[(1*S*,2*S*,7*S*,8a*S*)-1,2-Di-*tert*-butoxyoctahydro-7-indolizinyl]-1*H*-1,2,3-triazole-4-carboxylate (26)

Copper podwer (3.6 mg, 0.06 mmol) and copper sulfate (28.3 mg. 0.177 mmol) were added to a mixture of azide **20** (70 mg, 0.22 mmol) and ethyl propiolate (**24**, 0.039 mL, 0.38 mmol) in a 1:1 mixture of water and *t*-BuOH (1 mL) cooled at 0 °C. The reaction mixture was stirred at room temperature overnight then concentrated, diluted with CH_2Cl_2, dried over Na_2SO_4, filtered, concentrated. The

crude product was purified by chromatography on silica gel (eluent: initially petroleum ether/EtOAc, 4:1, then EtOAc/MeOH, 10:1) to afford **26** (yield: 52 mg, 50%) as a pale yellow solid. $R_f = 0.16$ (EtOAc); ^{1}H NMR (400 MHz): $\delta =$ 8.18 (s, 1H, triazole), 4.91–4.86 (m, 1H, 7-H), 4.43 (q, $J =$ 7.1 Hz, 2H, CH_2CH_3), 3.80 (ddd, $J = 7.0$, 3.9, 1.5 Hz, 1H, 2-H), 3.66 (dd, $J = 7.7$, 3.9 Hz, 1H, 1-H), 2.96–2.88 (m, 2H, 3-H_a, 5-H_a) 2.60–2.54 (m, 1H, 8-H_a), 2.48 (dd, $J = 10.2$, 7.0 Hz, 1H, 3-H_b), 2.46–2.40 (m, 1H, 6-H_a), 2.35–2.22 (m, 2H, 5-H_b, 6-H_b), 2.02–1.91 (m, 2H, 8-H_b, 8a-H), 1.42 (t, $J = 7.1$ Hz; 3H, CH_2CH_3); 1.20 (s, 9H, *t*-Bu), 1.17 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz): $\delta = 160.7$ (s, CO), 139.7 (s, triazole), 126.6 (d, triazole), 83.6 (d, C-1); 76.7 (d, C-2), 74.0 (s, *t*-Bu), 73.9 (s, *t*-Bu), 61.7 (t, C-3), 61.3 (t, OCH_2), 60.8 (d, C-8a), 54.8 (d, C-7), 48.0 (t, C-5), 33.2 (t, C-8), 29.3 (q, 3C, *t*-Bu), 28.8 (q, 3C, *t*-Bu), 28.6 (t, C-6), 14.5 (dq, CH_3); HR-MS: $m/z =$ 409.28182, calcd. for $C_{21}H_{37}N_4O_4$ $[M+H]^+$: 409.28093.

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