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Note

Synthesis of polyhydroxyindolizidines from 5,6-dihydro-2*H*-pyran-2-one

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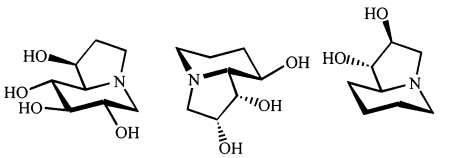
Abstract

(1a*R*,5a*R*,5b*S*,6*S*,7*S*)-6,7-Di-*tert*-butoxy-5-oxo-pyrrolidino[1,2-*b*]isoxazolidino[4,5-*c*]tetrahydropyran (**8**) prepared by (1,3)-dipolar cycloaddition of the cyclic nitrone **6** derived from tartaric acid to 5,6-dihydro-2*H*-pyran-2-one (**7**) was transformed into indolizidine **11** via a sequence of reactions involving methanolysis of the lactone ring, intramolecular alkylation of the nitrogen atom promoted by a carbontetrabromide–triphenylphosphine mixture and hydrogenolysis of the N–O bond. Decarboxylation of **11** provided known 7-hydroxylentiginosine derivative **14**, whereas oxidative decarboxylation gave indolizidine **15** structurally related to castanospermine.

Keywords: 1,3-Dipolar cycloaddition; (3*S*)-*tert*-Butoxy-1-pyrroline *N*-oxide; 7-Hydroxylentiginosine

Owing to a wide range of biological applications, iminosugars such as castanospermine (**1**),[1] swainsonine (**2**)[2] and lentiginosine (**3**)[3] become attractive synthetic targets for many laboratories (Scheme 1).[4]

It has been shown that (1,3)-dipolar cycloaddition of cyclic nitrones **4**–**6**[5] derived from tartaric acid to olefins offers a particularly attractive entry to indolizidines such as lentiginosine (**3**) and its derivatives.[4,6]



castanospermine (**1**) swainsonine (**2**) lentiginosine (**3**)

Scheme 1.

Recently we have reported on highly effective cycloaddition of the nitrone **6** to 5,6-dihydro-2*H*-pyran-2-one (**7**).[7] The reaction proceeds exclusively via the exo approach of the dipole to the *re*–*re* side of the lactone to afford adduct **8** in 91% yield (Scheme 2).

The strategy of the indolizidine synthesis via nitrones **4**–**6** has been reported by Brandi's[6c] and Wightman's[6d] groups. As substrates, 3-buten-1-ol[6c] and benzyl 3-butenoate[6d] have been used, respectively. The high effectiveness of (1,3)-dipolar cycloaddition of **6** to **7**, higher than those reported previously[6c,6d], prompted us to examine transformation of the adduct **8** into selected indolizidines (Scheme 2).

The lactone ring in **8** can be easily opened in methanol in the presence of anhydrous K_2CO_3 to afford hydroxyester **9** in 53% yield whereas unreacted **8** (34%) was recovered.

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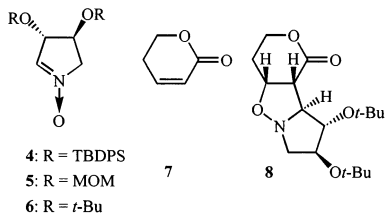
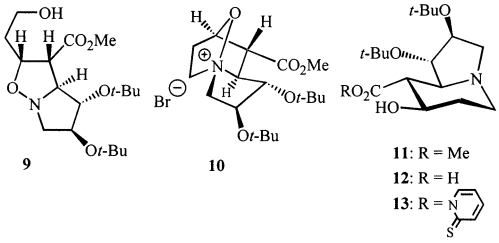
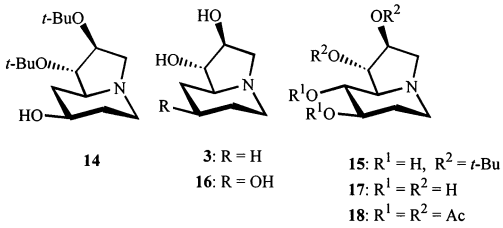


Scheme 2.



Scheme 3.



Scheme 4.

The terminal hydroxy group in **9**, similar to the Brandi's[6c] approach, may be used for intramolecular alkylation of the nitrogen atom. An attempt to introduce a bromine atom of the hydroxy group using the carbontetrabromide–triphenylphosphine procedure gave a tricyclic ammonium salt **10** which, without isolation, was subjected to hydrogenolysis of the N–O bond to yield indolizidine **11** (Scheme 3).

Compound **11** has at C-1, -2, -7 and -8a carbon atoms configurations of known 7-hydroxylentiginosine **16**.[6c,8] The additional methoxycarbonyl function at C-8 can be removed by decarboxylation, or oxidatively decarboxylated in order to introduce a new hydroxy group.

We investigated several classical decarboxylation conditions of free acid **12**.[9] Due to the presence of the hydroxy group in the β-position, significant decomposition of the substrate was noticed. The best result was obtained by application of Barton's *N*-hydroxy-thiopyrolidinone methodology.[10] Free acid **12**, readily available by saponification of **11** with lithium hydroxide, was transformed into ester **13** which in situ was decarboxylated under argon using *t*-butylmercaptan to afford **14** in 64% yield. The use of tributyltin hydride as a free radical promotor in the same reaction gave a worse result. Compound **14** has been transformed in the past by Brandi's group into lentiginosine **3**[6c] by deoxygenation at C-7 and deprotection of *t*-butyl ethers or into 7-hydroxylentiginosine **16**[6c,8] by deprotection of *t*-butyl ethers (Scheme 4).

Decarboxylation of compound **13** with *t*-butylmerkaptan, performed in the presence of air, led to the introduction of a hydroxy function to the C-8 carbon atom in 40% yield. Owing to sterical preferences, formation of compound **15** proceeds with retention of configuration at C-8. Compound **15** deprotected with trifluoroacetic acid provides indolizidine **17** which was characterized as tetraacetate **18** (Scheme 4).

In summary, we reported a formal, highly stereoselective approach to lentiginosine **3**, and to 7-hydroxylentiginosine **16**. We described also the synthesis of indolizidine **17** which is a structural isomer of castanospermine **1**.

1. Experimental

^{1}H NMR spectra were recorded on a Brucker DRX 500 Avance Spectrometer. IR spectra were obtained on an FT-IR-1600 Perkin–Elmer spectrophotometer. Rotations were measured with a JASCO P 3010 digital polarimeter. Mass spectra were determined with AMD 604 Inectra GmbH and PerSeptive Biosystems Mariner spectrometers. Column chromatography was performed on E. Merck Silica Gel 230–400 mesh.

Nitrone **6** was obtained by the known procedure.[5a] Synthesis of **8** has been described earlier.[7]

*(2*R,*3*R,*3a*S,*4*S,*5*S*)-4,5-Bis*-tert-*butoxy-2-(2′-hydroxyethyl)-3-methoxycarbonyl-hexahydropyrrolo[1,2-*b*]isoxazole* (**9**).—A solution of lactone **8** (0.68 g, 2.08 mmol) in dry MeOH (20 mL) was treated with anhyd K_2CO_3 (0.14 g, 1.04 mmol) at rt and stirred. The progress

of the reaction was monitored by TLC. When ca. 2/3 of the substrate was converted into **9** (2 h), the mixture was diluted with CH_2Cl_2 (100 mL) and filtered through Celite. Subsequently the filtrate was washed with 1 M aq $NaHSO_4$ (15 mL) and brine, dried and concentrated. Chromatographical purification afforded methyl ester **9** (0.4 g, 53% yield) and recovered lactone **8** (0.23 g, 34%). Compound **9**: colorless oil; $[\alpha]_D$ +86.9° (*c* 1.0, $CHCl_3$); IR (film): 3441, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.60 (dt, 1 H, H-2), 3.91 (dd, 1 H, $J_{3,3a}$ 5.7, $J_{3a,4}$ 3.1 Hz, H-3a), 3.89 (m, 1 H, H-5), 3.83 (bt, 1 H, H-4), 3.79–3.72 (m, 1 H, H-2′a,2′b), 3.73 (s, 3 H, OCH_3), 3.52 (dd, 1 H, $J_{2,3}$ 7.3 Hz, H-3), 3.50 (dd, 1 H, $J_{5,6a}$ 5.4, $J_{6a,6b}$ 11.9 Hz, H-6a), 2.95 (dd, 1 H, $J_{5,6b}$ 5.7 Hz, H-6b); ^{13}C NMR ($CDCl_3$): δ 171.42, 80.96, 76.83, 76.61, 74.21, 74.05, 73.43, 60.75, 60.40, 56.23, 51.99, 32.25, 28.55, 28.39; EI/HR MS: *m*/*z*: 382.2210, $[M+Na]^+$; Calcd for $C_{18}H_{33}NNaO_6$: 382.2200.

*(1*S,*2*S,*7*R,*8*R,*8a*S*)-1,2-Bis*-tert-*butoxy-7-hydroxy-8-methoxycarbonyl-indolizidine* (**11**). —Compound **9** (0.30 g, 0.84 mmol) in dry pyridine (8 mL) was treated with triphenylphosphine (0.44 g, 1.67 mmol) and carbon tetrabromide (0.29 g, 0.87 mmol). The mixture was stirred at rt until disappearance of the substrate (3 h), then evaporated to dryness, dissolved in MeOH (10 mL) and shaken under hydrogen (70 psi) for 2 h in the presence of $Pd(OH)_2$–C. Subsequently the suspension was filtered and concentrated. The crude product was purified by chromatography to give **11** (0.21 g, 72%); colorless oil; $[\alpha]_D$ +22.2° (*c* 1.0, $CHCl_3$); IR (film): 3443, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.91 (dt, 1 H, $J_{1,2}$ 3.0, $J_{2,3}$ 2.7, $J_{2,3'}$ 6.9 Hz, H-2), 3.85 (dd, 1 H, $J_{1,8a}$ 4.8 Hz, H-1), 3.81 (m, 1 H, H-7), 3.74 (s, 3 H, OCH_3), 2.95 (ddd, 1 H, $J_{5,6}$ 2.4, $J_{5,6'}$ 4.2, $J_{5,5'}$ 12.3 Hz, H-5), 2.90 (dd, 1 H, $J_{3,3'}$ 9.9 Hz, H-3), 2.69 (dd, 1 H, H-3′), 2.49–2.43 (m, 2 H, H-8,8a), 2.34 (dd, 1 H, $J_{5',6}$ 2.9, $J_{5',6'}$ 12.5 Hz, H-5′), 1.83 (m, 1 H, H-6), 1.68 (dt, 1 H, $J_{6',7}$ 11.7, $J_{6,6'}$ 12.5 Hz, H-6′), 1.19, 1.18 (2s, 18 H, 2 *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 173.26, 83.22, 78.32, 74.23, 73.81, 72.01, 66.68, 58.56, 52.63, 51.58, 48.47, 31.02, 28.94, 28.83; ESI/HR MS: *m*/*z*: 366.2258, $[M+Na]^+$; Calcd for $C_{18}H_{33}NNaO_5$: 366.2251.

*(1*S,*2*S,*7*R,*8*R,*8a*S*)-1,2-Bis*-tert-*butoxy-8-carboxy-7-hydroxy-indolizidine* (**12**).—To a stirred solution of ester **11** (0.18 g, 0.53 mmol) in a mixture 3:1 THF–water (5 mL) was added LiOH (0.33 g, 0.8 mmol). The resulting reaction mixture was stirred at rt for 24 h. Subsequently the solution was diluted with mixture 1:1 THF–MeOH (15 mL), filtered with Florisil while free carboxylic acid was liberated, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography to afford **12** (0.15 g, 89%); colorless oil; $[\alpha]_D$ +38.0° (*c* 1.0, $CHCl_3$); IR (film): 3348, 1596 cm^{-1}; ^1H NMR (Py-d_5): δ 4.45–4.30 (bm, 2 H, H-1,H-7), 4.06 (dt, 1 H, H-2), 3.02 (dd, 1 H, $J_{2,3}$ 3.1, $J_{3,3'}$ 9.8 Hz, H-3), 3.02–2.93 (bm, 2 H, H-8,8a), 2.89 (t, 1 H, $J_{2,3'}$ 9.6 Hz, H-3′), 2.80 (bs, 1 H, H-5), 2.49 (bt, 1 H, H-5′), 1.98 (bm, 1 H, H-6), 1.91 (m, 1 H, H-6′), 1.32, 1.18 (2s, 18 H, 2 *t*-Bu). ESI/HR MS: *m*/*z*: 330.2278, $[M+H]^+$; Calcd for $C_{17}H_{32}NO_5$: 330.2275.

*(1*S,*2*S,*7*R,*8a*S*)-1,2-Bis*-tert-*butoxy-7-hydroxy-indolizidine* (**14**).—A solution of acid **12** (40 mg, 0.12 mmol) in MeCN (4 mL) was treated with *N*-hydroxy-pyridin-2-thione (18 mg, 0.14 mmol), DCC (29 mg, 0.14 mmol) and DMAP (17 mg, 0.14 mmol) and stirred at 50 °C under an Ar atmosphere. After disappearance of the substrate (about 2 h) the reaction mixture was subjected to reduction by *tert*-butylthiol. To the reaction mixture was added *tert*-butylthiol (40 μL, 0.36 mmol) and the mixture was stirred for 1 h at 50 °C under an Ar atmosphere. Subsequently, it was evaporated to dryness. The crude product was purified by chromatography to give **14** (22 mg, 64% yield); mp = 117–119 °C, lit.[8] 118–119 °C; $[\alpha]_D$ +49.7° (*c* 0.45, $CHCl_3$), lit.[8] $[\alpha]_D$ +53.0° (*c* 1.05, $CHCl_3$); IR (film): 3391 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.84 (ddd, 1 H, $J_{1,2}$ 4.0, $J_{2,3}$ 1.7, $J_{2,3'}$ 7.2 Hz, H-2), 3.67 (dd, 1 H, $J_{1,8a}$ 8.5 Hz, H-1), 3.59 (m, 1 H, H-7), 2.93 (m, 1 H, H-5), 2.90 (dd, 1 H, $J_{3,3'}$ 10.0 Hz, H-3), 2.43 (dd, 1 H, H-3′), 2.19 (m, 1 H, H-8), 1.97 (m, 1 H, H-5′), 1.87 (m, 1 H, H-6), 1.82 (m, 1 H, H-8a), 1.61 (m, 1 H, H-6′), 1.28 (bq, 1 H, H-8); ^{13}C NMR ($CDCl_3$): δ 83.24, 77.97, 73.85, 73.68, 69.82, 65.40, 61.16, 50.57, 37.97, 34.26, 29.25, 28.71; ESI/HR MS: *m*/*z*: 286.2382, $[M+H]^+$; Calcd for $C_{16}H_{32}NO_3$: 286.2395.

*(1*S,*2*S,*7*R,*8*R,*8a*S*) - 1,2 - Bis* - tert - *butoxy-7,8-dihydroxy-indolizidine* (**15**).—A solution of acid **12** (40 mg, 0.12 mmol) in MeCN (4 mL) was treated with *N*-hydroxy-pyridin-2-thione (18 mg, 0.14 mmol), DCC (29 mg, 0.14 mmol) and DMAP (17 mg, 0.14 mmol) and stirred at 50 °C. After disappearance of the substrate (about 2 h) the reaction mixture was subjected to reduction by *tert*-butylthiol. To the reaction mixture was added *tert*-butylthiol (40 μL, 0.36 mmol) and the mixture was stirred for 1 h at 50 °C. Subsequently it was evaporated to dryness. The crude product was purified by chromatography to give **15** (14 mg, 39% yield); mp = 133–135 °C, $[\alpha]_D$ + 29.0° (*c* 0.5, $CHCl_3$); IR (film): 3411 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.01 (dd, 1 H, $J_{1,2}$ 3.9, $J_{1,8a}$ 7.9 Hz, H-1), 3.89 (ddd, 1 H, $J_{2,3}$ 2.1, $J_{2,3'}$ 7.0 Hz, H-2), 3.50 (t, 1 H, $J_{7,8}$ 8.4, $J_{8,8a}$ 8.9 Hz, H-8), 3.42 (ddd, 1 H, $J_{7,6}$ 4.8, $J_{7,6'}$ 11.2 Hz, H-7), 2.96 (dd, 1 H, $J_{3,3'}$ 10.0 Hz, H-3), 2.87 (m, 1 H, H-5), 2.74 (bs, 1 H, H-8a), 2.54 (dd, 1 H, H-3′), 2.09 (bt, 1 H, H-5′), 1.87 (m, 1 H, H-6), 1.70 (tdd, 1 H, $J_{5,6'}$ 4.5, $J_{3',6'}$ 12.5, $J_{6,6'}$ 12.5 Hz, H-6′), 1.29, 1.19 (2s, 18 H, 2 *t*-Bu); ESI/HR MS: *m*/*z*: 324.2104, $[M + Na]^+$; Calcd for $C_{16}H_{31}NNaO_4$: 324.21457. Acetate: colorless oil; $[\alpha]_D$ + 3.5° (*c* 0.3, $CHCl_3$); IR (film): 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.14 (t, 1 H, $J_{7,8}$ 9.4, $J_{8,8a}$ 9.9 Hz, H-8), 4.80 (dt, 1 H, $J_{7,6}$ 6.8, $J_{7,6'}$ 9.8 Hz, H-7), 3.92 (ddd, 1 H, $J_{1,2}$ 2.1, $J_{2,3}$ 3.2, $J_{2,3'}$ 6.5 Hz, H-2), 3.83 (dd, 1 H, $J_{1,8a}$ 4.1 Hz, H-1), 2.92 (m, 1 H, H-5), 2.88 (dd, 1 H, $J_{3,3'}$ 9.6 Hz, H-3), 2.80 (dd, 1 H, H-3′), 2.51 (m, 1 H, H-5′), 2.49 (dd, 1 H, H-8a′), 2.03, 2.01 (2s, 6 H, 2 Ac), 1.90–1.79 (m, 2 H, H-6,6′), 1.182, 1.180 (2s, 18 H, 2 *t*-Bu); ESI/HR MS: *m*/*z*: 386.2527, $[M + H]^+$; Calcd for $C_{20}H_{36}NO_6$: 386.2537.

*(1*S,*2*S,*7*R,*8*R,*8a*S*) 1,2,7,8-Tetraacetoxy-indolizidine* (**18**).—A solution of indolizidine **15** (7 mg, 0.022 mmol) in trifluoroacetic acid (1 mL) was left at rt for 24 h. Subsequently the acid was removed under diminished pressure and the crude product was acetylated with 1:1 Ac_2O–pyridine mixture in the presence of a catalytic amount of DMAP. Subsequently the mixture was evaporated and the residue was purified by chromatography to give **18** (5.5 mg, 66%); colorless syrup; $[\alpha]_D$ + 14.3° (*c* 0.5, $CHCl_3$); IR (film): 1747, 1236 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.17 (dd, 1 H, $J_{1,2}$ 2.2, $J_{1,8a}$ 7.1 Hz, H-1), 5.08 (t, 1 H, $J_{7,8}$ 9.4, $J_{8,8a}$ 9.6 Hz, H-8), 5.02 (ddd, 1 H, $J_{2,3}$ 1.0, $J_{2,3'}$ 6.3 Hz, H-2), 4.80 (ddd, 1 H, $J_{6,7}$ 5.3, $J_{6',7}$ 11.5 Hz, H-7), 3.02 (bd, 1 H, H-3), 2.99 (ddd, 1 H, $J_{5,6}$ 2.4, $J_{5,6'}$ 4.7, $J_{5,5'}$ 11.5 Hz, H-5), 2.75 (dd, 1 H, $J_{3,3'}$ 11.0 Hz, H-3′), 2.30 (dd, 1 H, H-8a), 2.22 (ddd, 1 H, $J_{5',6}$ 2.8, $J_{5',6'}$ 12.5 Hz, H-5′), 2.06 (m, 1 H, H-6), 1.81 (m, 1 H, $J_{6,6'}$ 11.5 Hz, H-6′), 2.09, 2.03, 2.02, 1.98 (4s, 12 H, 4 Ac); ESI/HR MS: *m*/*z*: 380.1307, $[M + Na]^+$; Calcd for $C_{16}H_{23}NNaO_8$: 380.1316.

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