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Synthesis of Lentiginosine by Stereoselective Chiral Nitrone Cycloaddition and Thermal Rearrangement of Strained Spiroisoxazolidine

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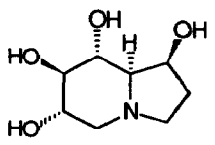
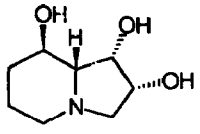
***Abstract**: The total synthesis of Lentiginosine (3) is reported. The strategy is based on the 1,3-dipolar cycloaddition of a TBDPS protected 3,4-dihydroxypyrroline N-oxide to methylenecyclopropane followed by the thermal rearrangement of the resulting spirocyclopropaneisoxazolidine to give the functionalised indolizidine skeleton. The compound shows an $[\alpha]_D$ value identical, but opposite in sign, with that reported for the natural isomer which has been assigned the same absolute configuration.*

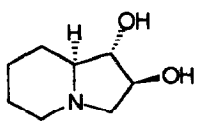
The thermal rearrangement of 5-spirocyclopropane isoxazolidines has recently revealed a practicable and versatile method for the regio- and stereoselective synthesis of indolizidine skeletons.[1] Since the substrates incorporating the cyclopropyl ring can be obtained by 1,3-dipolar cycloaddition of nitrones to methylenecyclopropanes, the judicious choice of the partner nitrone for the cycloaddition allows the application of the methodology to different class of ring systems and natural products. Our group[2] and others[3] recently proposed a convenient synthesis of chiral protected 3,4-dihydroxypyrroline N-oxides, derived from tartaric acid, that we envision as excellent candidates for the synthesis of polyhydroxylated indolizidines by using our methodology. These polyhydroxylated indolizidines (as castanospermine 1, swainsonine 2 and their analogues)[4] have already demonstrated their importance as specific inhibitors of glycosidases[5] and, some of them, as anti-HIV agents.[6]



Castanospermine (1)



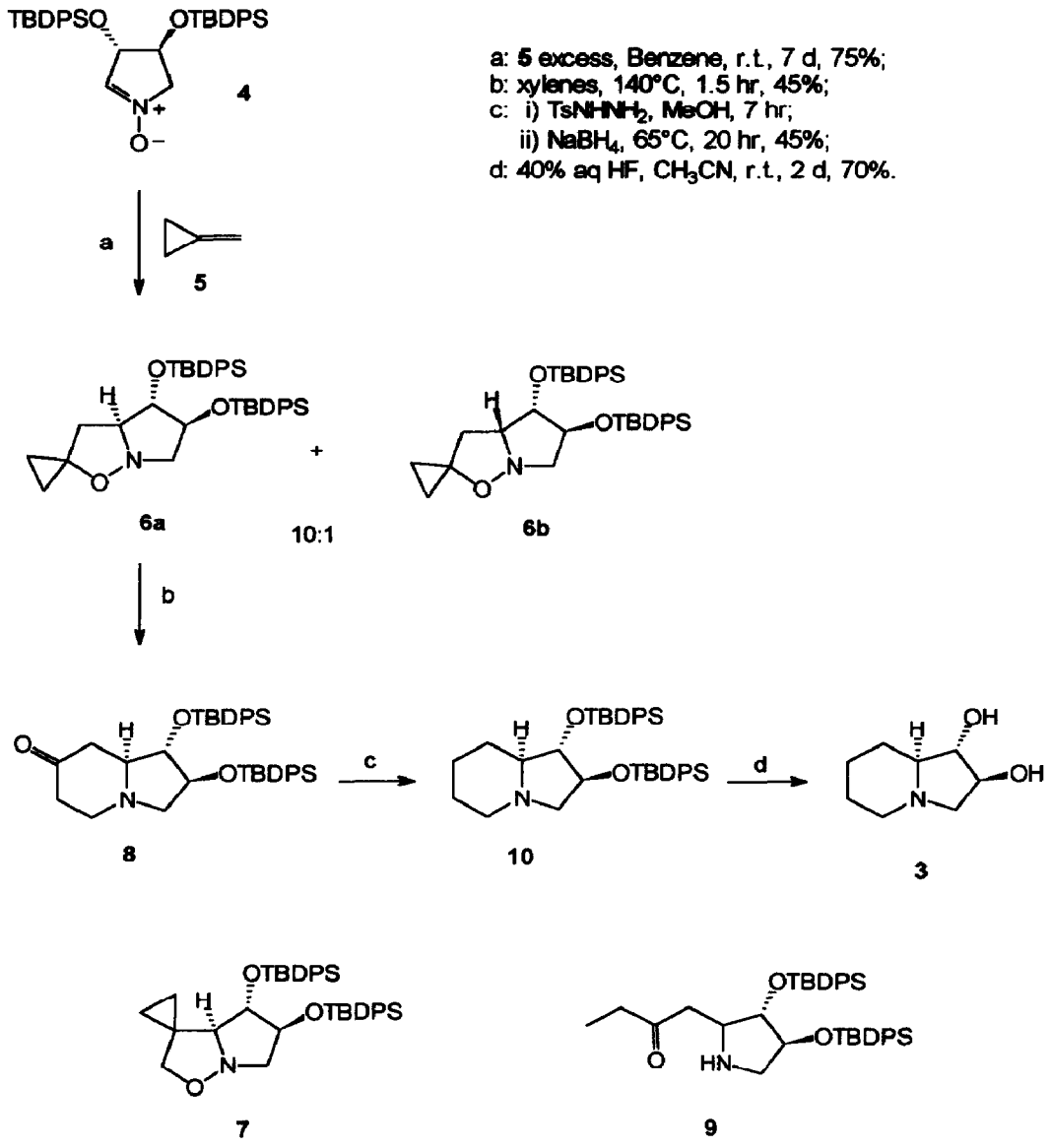
Swainsonine (2)



Lentiginosine (3)

As a first example of our strategy[7] we report on the synthesis of the alkaloid Lentiginosine,[8] isolated from *Astragalus lentiginosus*, known as the least hydroxylated glycosidase inhibitor. Its absolute configuration was tentatively assigned as 3 by Molyneux, Elbein and coworkers[8] on the basis of biosynthetic considerations and suggested our L-tartaric acid derived nitrones as the appropriate precursors. Only another synthesis of the alkaloid 3 recently appeared, where the same chiral precursor was used employing a different strategy.[9]

Scheme 1



a: 5 excess, Benzene, r.t., 7 d, 75%;
b: xylenes, 140°C, 1.5 hr, 45%;
c: i) $TsNHNH_2$, MeOH, 7 hr;
ii) $NaBH_4$, 65°C, 20 hr, 45%;
d: 40% aq HF, CH_3CN, r.t., 2 d, 70%.

O,O'-*tert*-Butyldiphenylsilyl (TBDPS) protected nitrone 4[2b] reacted with methylenecyclopropane (5) at room temperature to give isoxazolidines **6a,b**[10] in 75% yield and 10:1 ratio. The cycloaddition resulted highly regioselective, because the regioisomer 7 is observed only in traces in the crude reaction mixture.[1,11] A high degree of stereoselectivity is also displayed by the nitrone, the desired diastereoisomer **6a** being predominantly obtained in the cycloaddition, as expected considering the stereoface differentiation given by the bulky TBDPSO group closer to the approaching dipolarophile.[2b] The structural assignment relies on the observation of a coupling constant of 2.5 Hz between the bridgehead proton and the vicinal HCOTBDPS in **6a** in accord with a cis relationship between the bridgehead proton and the adjacent TBDPSO group.

The isoxazolidine **6a** was heated in xylene at reflux to give quantitatively a clean thermal rearrangement. Unfortunately, only 45% of the indolizidinone **8**[10] was obtained from the rearrangement. The large production (55%) of the enaminone isomer 9[10] observed in this reaction can be ascribed to the steric hindrance of TBDPSO groups that hampers the coupling of the diradical intermediate.[1] Reduction of the ketone **8** via the tosylhydrazone gave the TBDPS protected Lentiginosine **10**[12] in 45% yield. Deprotection of **10** with 40% aqueous HF in acetonitrile[13] gave **3**[14] in 70% yield as an analytically pure material which solidified upon standing, identical by spectroscopical means with the natural Lentiginosine.[8a]

The specific optical rotation of our compound ($[\alpha]_D$ = +3.2°, c 0.27 in MeOH) resulted identical in value, but opposite in sign, with that reported for the natural compound which was assigned, however, the same absolute configuration.[8a] A similar controversial result was obtained by the Japanese researchers[9] who found an $[\alpha]_D$ = +0.19° for **3**, and imputed the positive value to the presence of a diastereomeric impurity. Misfitting of these results with the data reported by Molyneux and Elbein is apparent.[8a] Our straightforward synthesis of **3** is stereoselective, only one step being involved in the formation of the new stereogenic centre with high stereocontrol, while the stereocentres deriving from the starting tartaric acid, apparently, are unaffected during the process. The results of the Japanese group is of very little help in clarifying the matter, since the $[\alpha]_D$ value is positive, but very close to zero. Moreover, the optical rotation of the claimed diastereomeric impurity is not reported.[9] From all these data, we can conclude that either the sign of the optical rotation[15] or the absolute configuration of natural Lentiginosine was not correctly assigned.

Further studies are underway in our laboratory to synthesise (–)-Lentiginosine from D-tartaric acid and, possibly, to compare both enantiomers with the natural Lentiginosine.

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12. **10:** $[\alpha]_D^{25}$ = +11.8° (c 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.77-7.62 (m, 8 H), 7.50-7.25 (m, 12 H), 4.33 (m, 1 H), 4.06 (dd, J = 8, 3 Hz, 1 H), 2.73-2.60 (m, 2 H), 2.03 (dd, J = 10.3, 6.6 Hz, 1 H), 1.92-1.25 (m, 8 H), 1.03 (s, 9 H), 0.96 (s, 9 H). ^{13}C NMR ($CDCl_3$): (aromatic signals not reported) δ 87.1 d, 80.0 d, 69.9 d, 60.9 t, 52.7 t, 28.4 t, 27.0 q, 26.8 q, 24.7 t, 24.1 t, 19.3 s, 19.1 s. MS: m/z (rel. int.) 633 ($M^{\cdot+}$, 2), 556 (17), 378 (16), 259 (10), 199 (49), 183 (13), 135 (30), 122 (13), 97 (100). Anal. Calcd for $C_{40}H_{51}NO_2Si_2$: C, 75.78; H, 8.11; N, 2.21. Found C, 76.09; H, 8.37; N, 2.13.
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14. **(1*S*, 2*S*, 8a*S*)-1,2-Dihydroxyindolizidine (3):** R_f (eluant CH_2Cl_2:MeOH:30% aq NH_3 41:8:1) = 0.3; upon standing crystallizes as a white solid, mp 106-107 °C (previously reported as a colorless liquid, ref. 8a and 9). $[\alpha]_D^{25}$ = +3.2°, $[\alpha]_{546}$ = +2.0°, $[\alpha]_{435}$ = -0.7°, $[\alpha]_{405}$ = -2.5° (c 0.27, MeOH).[15] ^1H NMR (D_2O): δ 4.02 (ddd, J = 7.3, 4.0, 1.8 Hz, 1 H), 3.62 (dd, J = 8.8, 4.0 Hz, 1 H), 2.98 (broad d, J = 11.2 Hz, 1 H), 2.88 (dd, J = 11.3, 1.8 Hz, 1 H), 2.76 (dd, J = 11.3, 7.3 Hz, 1 H), 2.22 (dd, J = 11.2, 2.9 Hz, 1 H), 2.20-2.10 (m, 1H), 1.95-1.10 (m, 6 H). ^{13}C NMR (D_2O): δ 84.9 d, 78.0 d, 71.5 d, 62.7 t, 55.4 t, 29.8 t, 26.3 t, 25.4 t. MS: m/z (rel. int.) 157 ($M^{\cdot+}$, 22), 140 (10), 97 (100), 84 (29), 69 (37). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found C, 60.99; H, 9.63; N, 8.66.
15. Authors in ref. 8a claimed the presence of impurities in the isolated natural compound which, considering the low absolute [α] value, could be responsible of the observed difference. On the other hand, the values of [α] measured at different wavelenght,[14] showed as in ref. 8a a counterclockwise trend of the optical rotation on decreasing the wavelenght.

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