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A new nitrone from C_2 symmetric piperidine for the synthesis of hydroxylated indolizidinone

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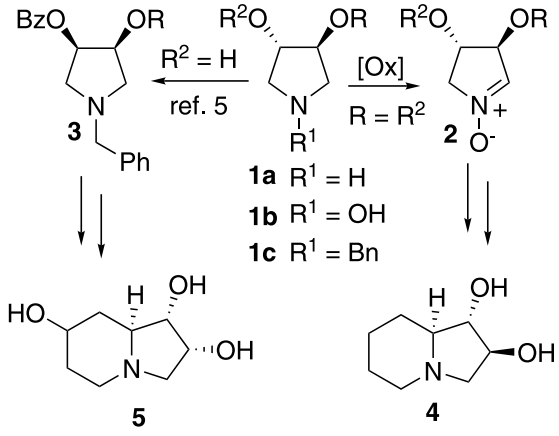
Abstract—The oxidation of a C_2 symmetric piperidine, obtained through a ring enlargement process of the enantiopure protected (4*R*)-hydroxy-(2*S*)-hydroxymethyl pyrrolidine, is reported. Oxidation with *C*-phenyl-*N*-phenylsulfonyloxaziridine afforded the corresponding nitrone that is too unstable for isolation and which reacted in situ with dimethyl maleate. The major adduct was transformed to the corresponding protected dihydroxyindolizidinone. © 2002 Elsevier Science Ltd. All rights reserved.

Polyhydroxyindolizidines are valuable biologically active molecules that can function as glycosidase inhibitors.[1] 1,3-Dipolar cycloadditions are convenient methods that afford various examples of optically active polyhydroxyindolizidines[2] starting from enantiopure mono- and dialkoxy five-membered ring nitrones derived from compounds of the 'chiral pool'.[3] Lentiginosine (**4**), the most powerful indolizidine inhibitor of amyloglycosidase, was synthesized from nitrone **2** (Scheme 1).[4] The key step of the synthesis was the oxidation of pyrrolidine **1a**, or *N*-hydroxy derivative **1b**, both derived from natural tartaric acid, to the corresponding nitrone **2**. Furthermore, indolizidine **5** was synthesized from **1c** by applying a Mitsunobu reaction to the monoprotected derivative of **1c**, which produced the desymmetrized *meso* form of the (3*S*,4*R*) 3,4-dihydroxypyrrolidine **3**.[5] The recent development, by one of our groups, of a straightforward synthesis of enantiopure substituted 3-hydroxypiperidines from enantiopure 2-hydroxymethylpyrrolidines[6] allowed us to study the 1,3-dipolar cycloaddition of substituted piperidine nitrones to activated olefins and to compare the results with those obtained with substituted pyrrolidine nitrones. Furthermore, the use of enantiopure six-membered alkoxynitrones will be an alternative synthetic pathway to synthesize indolizidine derivatives with a strict control of the relative and absolute stereochemistry of the substituents on the six-membered ring of the indolizidines.[7] In this communication we would like to report the oxidation of an enantiopure C_2 3,5-disilyloxypiperidine **9**, the subsequent cycloaddition reaction of the corresponding nitrone with dimethyl maleate **12** and the transformation of the major cycloadduct to the corresponding indolizidinone.

When compound **6**, synthesized from the commercially available (4*R*)-hydroxy-(2*S*)-hydroxymethylpyrrolidine, was treated with trifluoroacetic anhydride and then with triethylamine and then with NaOH, the substi-



Scheme 1.

Keywords: C_2 symmetry; 1,3-dipolar cycloaddition; nitrone; indolizidinone.

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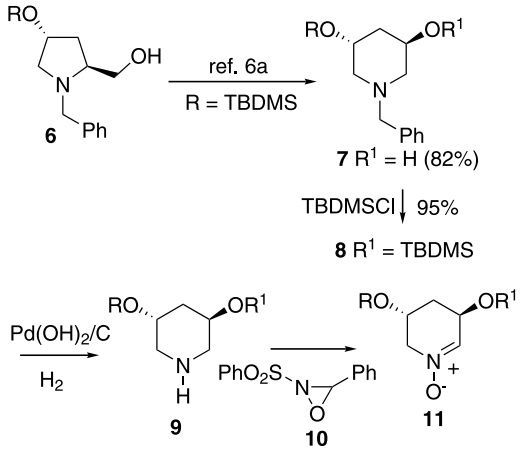
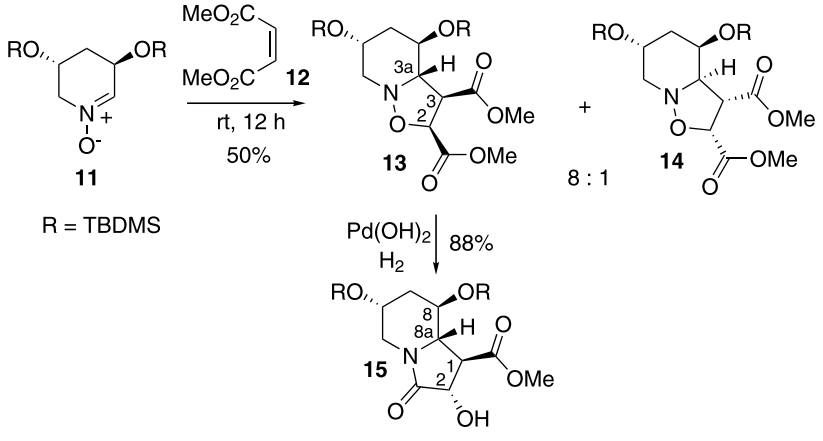
tuted piperidine **7** was isolated in 82% yield. The obtained piperidine **7** was then transformed to the C_2 symmetric piperidine **8** in 95% yield by protecting the free hydroxyl group with TBDMSCl (Et_3N, DMAP, CH_2Cl_2) (Scheme 2). Reductive debenzylation of **8** afforded the secondary amine **9** but its transformation to the corresponding nitrone **11**, proved to be troublesome. The usual oxidative reagents such as SeO_2,[8] Na_2WO_4[9] and H_2O_2 afforded only complex mixture of compounds. This is a first marked difference between C_2 symmetric piperidine **9** and C_2 symmetric pyrrolidine **1a**, as this latter compound was smoothly oxidized to **2** in good yield.[5] Nevertheless, this behavior is not peculiar to substituted piperidines, since pyrrolidines derived from **3** could not be oxidized with these reagents. Finally, a good conversion of **9** to **11** was obtained by using *C*-phenyl-*N*-phenylsulfonyloxaziridine (**10**)[10] as piperidine **9** was transformed in quantitative yield to nitrone **11**.[11] Nitrone **11** was extremely unstable and unsuitable for isolation in appreciable chemical purity and yield. It is worthy of note that its instability is common to other members of this group and in general six-membered ring nitrones are known to form dimers.[12] Furthermore, this nitrone represents an example of a small group of enantiopure alkoxy substituted six-membered ring nitrones, often



Scheme 2.

obtained from sugars.[13,7] Due to its instability, nitrone **11** was used in situ directly for 1,3-dipolar cycloaddition reactions. Reactions with non-activated dipolarophiles such as allyl alcohol or 3-buten-1-ol as well as simple acrylates afforded only complex mixtures of which the expected adducts were only a minor part and could not be isolated. The use of a reactive dipolarophile such as dimethyl maleate (**12**) afforded two diastereoisomeric adducts **13** and **14** in an 8:1 ratio (similar to that obtained with five-membered nitrones)[3c] in acceptable yield (50%) (Scheme 3). ^1H and ^{13}C NMR spectra showed broad signals presumably due to slow nitrogen interconversion. Heating at 100°C (d_6-DMSO) caused sharpening of the signals.[13c] The structure derived from an *exo* approach of the reagents was assigned to both compounds **13** and **14**, on the basis of their ^1H NMR spectra and by comparison with the ^1H NMR spectra of the adducts derived from cycloaddition of unsubstituted six-membered ring nitrone with dimethyl maleate (**12**).[14] The major isomer **13** showed the same pattern for H3 and H2 (H3: 3.54 ppm, t, $J=9.9$ Hz; H2: 4.80 ppm, d, $J=9.9$ Hz) as the major isomer obtained from the non-substituted piperidine nitrone (H3: 3.41 ppm, t, $J=10.0$ Hz; H_2: 4.74 ppm, d, $J=10.0$ Hz).[14] The presence of the same pattern for the minor isomer **14** (H3: 3.68 ppm, t, $J=9.0$ Hz; H2: 4.79 ppm, d, $J=9.0$ Hz) led us to assign the same relative stereochemistry to H3a, H3, and H2. The cycloaddition indicates that nitrone **11**, is more selective with respect to the corresponding five-membered ring nitrone **2**, which gave a mixture of three products with dimethyl maleate in a ratio 13:1.4:1.[3c] As in the case of nitrone **11** the products derived from an *endo* approach were not isolated, it seems that the axial orientation of the 5-alkoxy substituent hampers the *endo* approach of the reacting maleate due to severe steric interaction (Fig. 1).

The major diastereoisomer **13**[15] was finally transformed to the corresponding indolizidinone **15**[16] by reductive cleavage of the N–O bond (Scheme 3). The ^1H and ^{13}C NMR spectra of compound **15** and NOE experiments confirmed the structural assignment. NOE experiments showed a *cis* relationship between protons H8–H1 and



Scheme 3.

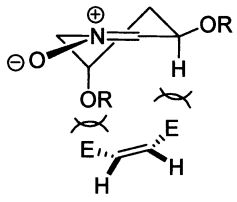


Figure 1. Disfavored *endo–anti* approach of the reagents.

protons H8a–H2 in accordance with structure **15** (Scheme 3). Hydrogen H1 (2.83 ppm) showed two coupling constants of 6.6 Hz with the vicinal hydrogens and the bridgehead hydrogen atom H8a (3.52 ppm) showed two coupling constants with vicinal hydrogens of 8.7 and 6.6 Hz. This compound represents a new example of polyhydroxyindolizidinones constructed through a 1,3-dipolar cycloaddition of an enantiopure six-membered ring nitrone. The limited stability of nitrone **11** hampered a more extensive use with non-activated dipolarophiles. Nevertheless, the synthetic process that starts from a C_2 symmetric piperidine can be considered as an alternative synthesis of indolizidinones bearing a precise substitution pattern on the six-membered ring.

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11. **11**: ^{1}H NMR ($CDCl_3$): δ 7.08 (m, 1H), 4.63 (m, 1H), 4.34 (m, 1H), 3.86 (dd, 1H, $J=14.5$, 1.5 Hz), 3.60 (dd, 1H, $J=14.5$, 4.0 Hz), 2.00 (m, 1H), 1.75 (ddd, 1H, $J=12.8$, 7.3, 2.6 Hz), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 128.9 (d), 64.9 (d), 63.9 (d), 36.7 (t), 29.8 (t), 25.8 (q), 18.1 (s), −4.72 (q); MS (m/z): 359 [M^+], 342, 286, 210, 197, 147, 128, 73.
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15. **13**: $[\alpha]_D^{20}=+10$ (c 0.38, $CHCl_3$); mp = 77–79°C; ^{1}H NMR ($CDCl_3$): δ 4.80 (d, $J=9.9$ Hz, 1H), 4.28 (m, 2H), 3.68 (s, 3H), 3.63 (s, 3H), 3.54 (t, $J=9.9$ Hz, 1H), 2.93 (m, 2H), 1.92 (m, 1H), 1.66 (m, 2H), 0.89 (s, 9H), 0.87 (s, 9H), 0.09 (s, 6H), 0.074 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 170.6 (s), 168.8 (s), 76.7 (d), 67.89 (d), 65.9 (d), 59.7 (d), 53.8 (d), 52.2 (q), 52.00 (q), 41.0 (t), 29.5 (t), 25.7 (q), 25.5 (q), 18.0 (s), 17.7 (s), −5.0 (q), −5.1 (q). MS (m/z) 503 [M^+], 446, 284, 210, 73. $C_{23}H_{45}Si_2NO_7$ required C, 54.84; H, 9.00; N, 2.78. Found: C, 54.59; H, 9.09; N, 2.95.
16. **15**: $[\alpha]_D^{20}=-52$ (c 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.46 (d, $J=6.6$ Hz, 1H), 4.12 (m, 1H), 3.92 (bd, $J=11.8$ Hz), 3.78 (m, 1H), 3.76 (s, 3H), 3.52 (dd, $J=8.7$, 6.6 Hz, 1H), 2.83 (t, $J=6.6$ Hz, 1H), 2.77 (bd, $J=11.8$ Hz, 1H), 2.08 (m, 1H), 1.56 (m, 1H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 172.9 (s), 171.7 (s), 74.1 (d), 70.0 (d), 65.5 (d), 62.0 (d), 52.5 (d), 51.6 (q), 46.4 (t), 41.2 (t), 25.7 (q), 18.0 (s), 17.8 (s), −4.83 (q), −4.87 (q); $C_{22}H_{43}Si_2NO_6$ required C, 55.78; H, 9.16; N, 2.96. Found: C, 55.93; H, 9.06; N, 3.10.