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Synthesis of 1-homoaustraline

Dariusz Socha,[a] Konrad Paśniczek,[a] Margarita Jurczak,[a] Jolanta Solecka[b] and Marek Chmielewski[a,*]

[a]*Institute of Organic Chemistry of the Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*
[b]*National Institute of Hygiene, 00-791 Warsaw, Poland*

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Dedicated to Professor Janusz Jurczak on the occassion of his 65th birthday

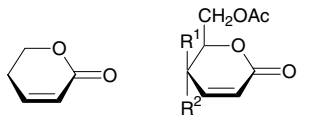
Abstract—The 1,3-dipolar cycloaddition of a five-membered cyclic nitrone derived from malic acid and unsaturated D-*threo*-hexono-lactone leads to a single adduct, which was transformed into 1-homoaustraline *via* a reaction sequence involving rearrangement of the six-membered lactone ring into the five-membered one, removal of the terminal carbon atom from the sugar chain, reduction of the lactone fragment into triol, protection of primary hydroxy groups, mesylation of the secondary one, cleavage of the N–O bond, and the intramolecular alkylation of the nitrogen atom.

Keywords: Iminosugars; Homoaustraline; Nitrones; Aldono-1,5-lactone; 1,3-Dipolar cycloaddition; Glucosidases

1. Introduction

Recently, we have reported on the cycloaddition of 2,3-unsaturated δ-lactones **1**–**3** and the five-membered cyclic nitrones **4** or **5**, which proceeds exclusively in the exo mode and results in a high preference for the anti addition to both the acetoxymethyl group of the lactone and the 3-*tert*-butoxy group of the nitrone.[1–3] In the case of mismatched pairs (syn either to acetoxymethyl or to 3-*tert*-butoxy group), the 4-*O*-acetyl group of the lactone assumes a decisive role in the control of the stereochemical outcome of the cycloaddition. This stereochemical preferences leads, in many cases, to formation of a single adduct or at least a high preponderance of a single adduct.[3] Particularly attractive are the exclusive formation of adducts **6** and **7** from the nitrone **4** and the D-*threo* 4-*O*-acetyl-lactone **2** and D-*erythro* 4-*O*-acetyl-lactone **3**, respectively.[3]

We have shown that application of the known methodology[4] to cycloadduct **8** offers a convenient approach to the indolizidine alkaloids. This has been demonstrated by the synthesis of 7-hydroxy-lentiginosine (**9**) and the formal synthesis of lentiginosine (**10**).[5] The straightforward access to adducts **6** and **7** enables



1 **2**: R^1 = OAc, R^2 = H; **3**: R^1 = H, R^2 = OAc **4** **5**

* Corresponding author. Tel.: +48 22 631 87 88; fax: +48 22 632 66 81; e-mail: chmiel@icho.edu.pl

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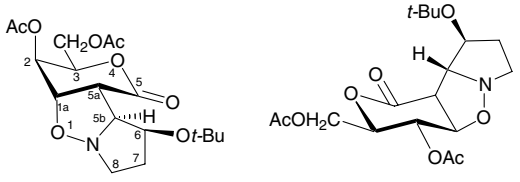
convenient entry to the corresponding pyrrolizidines and indolizidines with an (*R*) or (*S*) configuration at the bridgehead carbon atom.[6]



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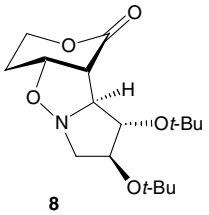

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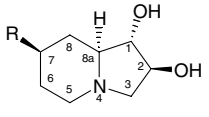
Both components of the cycloaddition, the nitrone and the unsaturated lactone, carry over their own substituents (such as protected hydroxyl groups) with their original configurations, whereas the configuration at C-1a, C-5a, and C-5b of the cycloadduct is established during the reaction. Adduct **6** is particularly interesting because it has anti located *tert*-butoxy group and the bridgehead proton H-5b,[3] which corresponds to an anti rearrangement of OH-1 and H-8a in indolizidines, or OH-1 and H-7a in pyrrolizidines. Such a geometry, found in many indolizidines and pyrrolizidines, for example, castanospermine (**11**),[6d] swainsonine (**12**),[7] or australine (**13**),[8] cannot be achieved by the cycloaddition of simple olefins to the nitrone **4** or by its alkylation with nucleophiles since this direction of approach is highly hindered by the unfavorable steric interactions. In order to force the syn approach of the dipolarophile to the substituent at C-3 of the nitrone Brandi's group[9] performed 1,3-dipolar cycloaddition as an intramolecular process. In the case of cycloaddition of the nitrone **4** to the lactone **2**, syn approach of **2** to the *tert*-butoxy group was coerced by substituents in the lactone.

2. Results and discussion

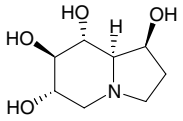
Recently we have shown that the adduct **6** with identical configurations at C-1a, 2, 5a, 5b, and 6 carbon atoms, which is the same as in castanospermine (**11**) at C-7, 6, 8, 8a, and C-1 atoms, can be easily transformed into the iminosugars related to **11**, especially into 8-homocastanospermine (**14**).[10] The same adduct **6** opens also an easy access to australine **13**[8] and related compounds *via* intramolecular alkylation of the nitrogen atom by the activated C-2 carbon atom. It should be stressed that the configuration at C-2 of the adduct **6** undergoes inversion during the nitrogen alkylation step, consequently leading to the correct configuration at C-3 of australine-related compounds. The present paper describes the synthesis of a derivative of australine in which the 1-hydroxy group was replaced by the hydroxymethyl substituent (1-homoaustraline; **15**). Synthesis of a number of 7-hydroxymethyl-indolizidines using intramolecular 1,3-dipolar cycloaddition has been reported recently by the Brandi's group.[9b]

Aldehydo-lactone **16**, the substrate for the synthesis, was obtained from adduct **6** following a earlier reported two-step procedure,[10] which involves rearrangement of the six-membered lactone ring into the five-membered one by deacetylation of **6** followed by glycolic cleavage of the terminal diol group. Subsequently, the aldehydo-lactone **16** was reduced to the triol **17** and both primary hydroxy groups were protected with *tert*-butyldiphenylsilyl ethers to afford **19**. The remaining secondary hydroxy group was mesylated to give compound **21** (Scheme 1).

Hydrogenolysis of the N–O bond over Pd/C caused prompt intramolecular alkylation of the nitrogen atom, which proceeded with inversion of configuration at the carbon atom bearing the mesyloxy group to afford **22**, which was characterized as the acetate **23**. The configuration of **23** was confirmed by ^{1}H NMR spectroscopy. The coupling constants $J_{1,2}$ and $J_{2,3}$ (both 8.2 Hz) confirmed the axial position of H-1, H-2, and H-3 protons. NOEs measurements showed a spin–spin interaction between H-1 (δ 2.59 ppm) and H-3 (δ 2.90 ppm) protons.



9: R=OH
10: R=H



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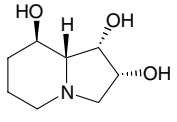

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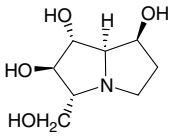

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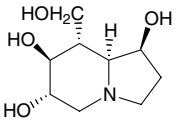

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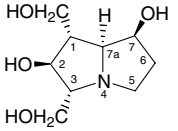

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