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Stereoselective Approach to Hydroxyindolizidines: Protection/Deprotection of the Nitrone Functionality via Cycloaddition/Retrocycloaddition

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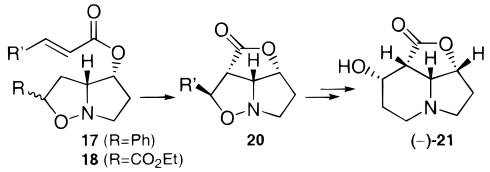
ABSTRACT



The enantiomerically pure indolizidine (–)-21 has been synthesized starting from L-malic acid. The key intermediate 20 has been assembled through an intramolecular 1,3-dipolar cycloaddition of a nitrone generated in situ by retrocycloaddition from isoxazolidine 17 or 18. The configuration of the new three stereocenters was set up with complete control in the cycloaddition step. The presented synthetic route provides a general and highly selective methodology toward indolizidines having the [1,8a]-cis configuration.

A large number of indolizidine alkaloids are present in nature.[1] These compounds show unique biological activities depending on the substitution pattern of the bicyclic ring system. Polyhydroxylated indolizidines,[1,2] like lentiginosine, swainsonine and castanospermine (Figure 1), are structural

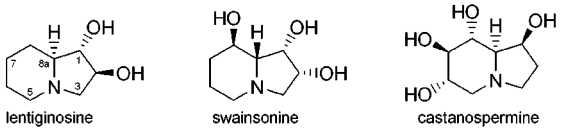


Figure 1.

analogues of carbohydrates and can competitively interact with glycosidases. The nature of the interaction between a particular enzyme and an iminosugar is determined by the number and the spatial position of hydroxy groups. The demand for new sugar analogues to study the key role of glycosidases in several biological processes[3] has prompted the search of new general and selective synthetic approaches to these substances.

The 1,3-dipolar cycloaddition of hydroxypyrroline *N*-oxides[4] followed by a suitable elaboration of the primary cycloadducts[5] has proved to be a practical strategy for the synthesis of lentiginosine[6] and of several hydroxyindolizine analogues.[4d,4g,6c] The trans reationship between C(1)-H and C(8a)-H of lentiginosine was achieved in the cycloaddition

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(2) (a) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497−534. (b) Vogel, P. *Chimica Oggi* **1992**, *10*, 9−15. (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199−210. (d) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*. 319−384. (e) Cossy, J.; Vogel, P. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publisher B. V., 1993; Vol. 12, pp 275−363.

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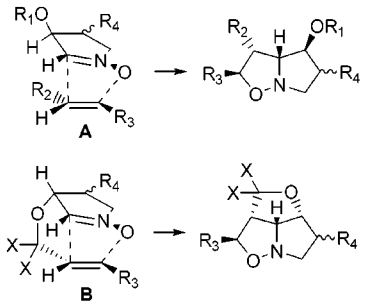
step as a result of the preferential attack of the dipolarophile anti to the C(3)-alkoxy substituent on the nitrone (**A**, Scheme 1).

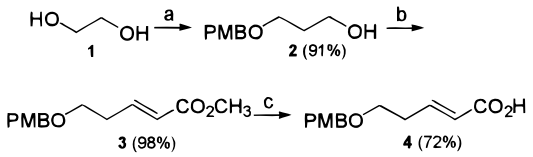
Scheme 1



The opposite facial selectivity could be selectively induced only by connecting the dipolarophile with the nitrone C(3)-substituent by an appropriate tether (**B**, Scheme 1). In a preliminary example, indeed, the intramolecular cycloaddition of 3-(allyloxy)-1-pyrrolin-*N*-oxide (**B**, X = R_3 = R_4 = H, Scheme 1) gave exclusively the expected endo-syn adduct.[4f] The resulting C(1)-H, C(8a)-H cis relative configuration would allow an entry to swainsonine and castanospermine analogues, if the linkage could be easily cleaved. An alkoxycarbonyl linker (**B**, X = O, Scheme 1) was then envisaged as a proper candidate. Therefore, the intramolecular version of the cycloaddition of 3-hydroxy-1-pyrroline *N*-oxide with 5-hydroxypent-2-enoate was studied and the results are reported in this communication.

The dipolarophile moiety, 5-(*p*-MeO-benzyloxy)-2-pentenoic acid (**4**) was obtained in good yield starting from 1,3-propanediol (**1**) (Scheme 2).

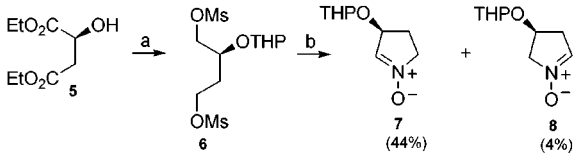
Scheme 2[a]



[a] Key:[7] (a) (i) *p*-anisaldehyde, *p*-TsOH cat., toluene, 110 °C; (ii) DIBAL, toluene 0°; (b) (i) $(COCl)_2$, DMSO, TEA, CH_2Cl_2 (Swern oxidation[8]); *(ii)* Trimethyl phosphonoacetate, K_2CO_3, H_2O; (c) NaOH 1 M, THF.

To connect the dipolarophile **4** to the nitrone moiety we considered to introduce **4** on a preformed nitrone deprotected at the C(3)-alkoxy substituent.[4f,g] To benefit from an easily removable group we synthesized the new THP protected pyrroline nitrone **7** in 44% overall yield through the well-established method[4f,g] starting from l-malic acid diethyl ester (**5**) (Scheme 3). The regioisomeric 5-pyrroline *N*-oxide **8** formed in 4% overall yield was easily separated by silica gel chromatography.

Scheme 3[a]

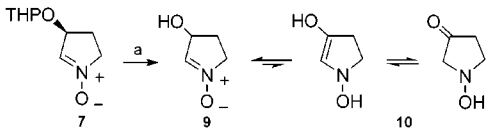


[a] Key: (i) 2*H*-dihydropyran, Amberlyst 15, pentane, rt; (ii) $LiAlH_4$, diethyl ether, reflux temperature; (iii) MsCl, TEA, CH_2Cl_2, 0 °C; (b) (i) NH_2OH HCl, TEA, reflux temperature; (ii) HgO, CH_2Cl_2, 0 °C → rt.

The pyrroline *N*-oxide **9**, disappointingly, lost enantiomeric purity in the deprotection step. Albeit the THP protecting group could be removed in very mild conditions, the best being Amberlyst 15 in methanol, the nitrone **9** (Scheme 3) was obtained always in low yield accompanied by partial or total racemization as indicated by variation of specific rotation. Purification by silica gel chromatography or recrystallization also caused racemization of **9**.[9]

The lack of configurational stability of **9** can tentatively be explained with the occurrence of a fast, not detectable by NMR, nitrone−hydroxyenamine tautomerism[11] (Scheme 4).

Scheme 4[a]



a:[10] Amberlyst 15, CH_3OH, 40 °C

To overcome the problem of partial racemization, it appeared opportune to seek a protection of the nitrone

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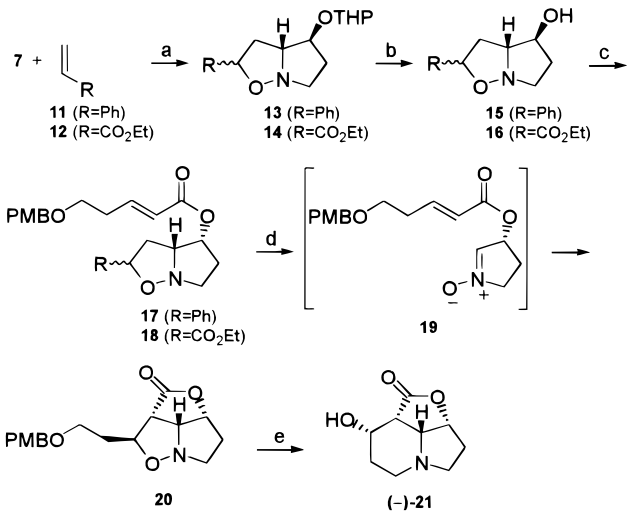
(8) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(9) In previous reports (see ref 3f,g) the deprotection of a TIPS or TBDMS protected 3-hydroxy-1-pyrroline *N*-oxide was erroneously reported as giving enantiopure **9**.

functionality which would allow the safe introduction of the dipolarophile moiety. To our knowledge, only two methods have been proposed to protect a nitrone functionality: an addition of HCN[12] or a reversible cycloaddition reaction.[13] However, only occasional examples of the latter procedure have been reported in synthetic sequences.[14]

Styrene (**11**) and ethyl acrylate (**12**) were used as masking dipolarophiles (Scheme 5). The corresponding cycloadducts

Scheme 5



[a] Key: R = Ph: toluene, 80 °C, 10 h, 79%; R = CO_2Et: CH_2Cl_2, rt, 70%; (b) Amberlyst 15, CH_3OH, 40 °C, **15**: 90% yield (77% conversion); **16**: 53%; (c) R = Ph: **4**, PPh_3 (polystyrene supported), DEAD, CH_2Cl_2, 59%; R = CO_2Et: **4**, PPh_3, DEAD, THF, 82% (50% conversion); (d) R = Ph: *o*-dichlorobenzene, 190 °C, 64 h, 62%; R = CO_2Et: *o*-dichlorobenzene, 150 °C, 3 h, 74%; (e) (i) TFA, CH_2Cl_2, rt; (ii) MsCl, TEA, CH_2Cl_2, 0 °C; H_2, Pd−C, CH_3OH.

13 and **14** from nitrone **7** were obtained in high yields as mixtures of diastereoisomers. No separation of diastereomeric pairs was necessary at this step, as both diastereoisomers could undergo deprotection followed by introduction of the dipolarophile. Deprotection with Amberlyst 15 gave isoxazolidines **15** and **16** without epimerization at C-4. The introduction of the dipolarophile was achieved through a Mitsunobu reaction[15] of the free acid **4**. The inversion of configuration afforded the more valuable final products with the configuration deriving from D-malic acid.[16]

Isoxazolidines **17** and **18** were then heated in a high boiling solvent in order to induce retrocycloaddition-intramolecular cycloaddition (Scheme 5). Phenyl substituted isoxazolidines **17** required a higher temperature (190 °C) than the ethoxycarbonyl ones **18** (150 °C). In both cases the intermediate nitrone **19** was not observed and the isoxazolidine **20** was the only product recovered in good yields (Scheme 5). Of course, compound **20** was the same product deriving from the two different isoxazolidine mixtures **17** and **18**, and showed the same specific rotation ($[\alpha]_D^{19} = -17.9$ (c = 0.547, $CHCl_3$)), which is a further confirmation of the high stereoselectivity of the process.

Preliminary studies have already demonstrated the utility of cycloadduct **20** as precursor of hydroxyindolizidines. In fact, deprotection of the methoxybenzyl ether in **20** followed by mesylation and hydrogenolysis[17] afforded indolizidine **21** (Scheme 5). It is worth underlining the versatility of this approach. A simple esterification, instead of a Mitsunobu reaction, would lead, at the end, to the enantiomer of indolizidine **21**.

Optimization of the whole process, as well as the application of the same strategy to the synthesis of other related compounds, including natural products, is now in progress in our laboratories.

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Supporting Information Available: Experimental procedures and spectral and analytical data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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