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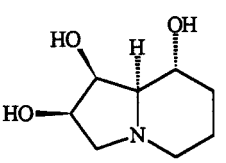
Stereoselective cycloaddition reactions of carbohydrate derivatives

Pál Herczegh*, Imre Kovács, Gyöngyi Erdősi, Tamás Varga, Attila Agócs, László Szilágyi[a], Ferenc Sztaricskai, Amaya Berecibar[b], Gabor Lukacs[b], Alain Olesker[b]

Research Group of Chemistry of Antibiotics of the Hungarian Academy of Sciences, H-4010 Debrecen, Hungary
[a]*Institute of Organic Chemistry, L. Kossuth University, H-4010 Debrecen, Hungary*
[b]*Institut de Chimie des Substances Naturelles, C.N.R.S.,F-91198 Gif-sur-Yvette, France*

Abstract: Structural analogs of swainsonine and castanospermine have been synthesized using [4+2] cycloadditions of chiral azomethines with Danishefsky diene. Similar hydroxyindolizidines were prepared by [3+2] dipolar cycloadditions of sugar derived cyclic nitrones with methyl acrylate. Stereoselectivity of [2+2] photocycloadditions of uridine derivatives was also studied.

Swainsonine[1] (**1**) and castanospermine[2] (**2**) belong to the large family of naturally occurring compounds classified as alkaloids or antibiotics as they are produced either by plants or microorganisms. These substances can be characterized as polyhydroxylated, five- or six membered, nitrogen-containing heterocycles or annelated bicyclics as indolizidines and quinolizidines. Another common feature shared by nojirimicin, galactostatine, fagomine, nectrisine, alexine, nagstatine, and **1** and **2** is that all of them resemble pyranose or furanose sugars: they are sugar mimics and inhibitors of glycosidase enzymes. As a consequence, aza sugar analogs frequently have many interesting biological properties. Swainsonine and castanospermine show antimetastatic, antitumor, immunoregulatory, antiviral activities[3]. Therefore, much effort has been devoted in recent years to the chemical synthesis of **1** and **2** and their structural analogs[3,4]. As part of our synthetic studies concerning cycloaddition reactions of carbohydrate derivatives we have elaborated two methods for the construction of polyhydroxyindolizidines and quinolizidines.



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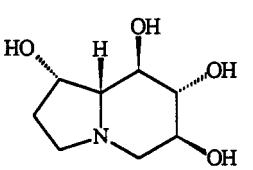
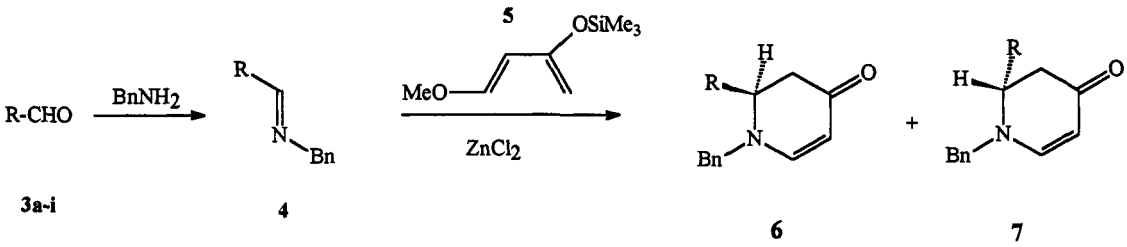


2

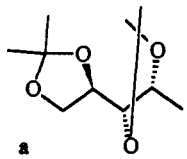
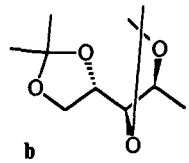
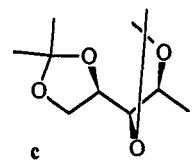
The [4+2] hetero-Diels-Alder route[5,6]

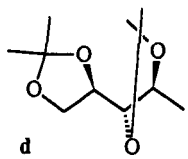
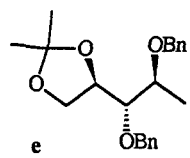
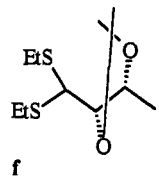
The key step of this methodology was a [4+2] cycloaddition or cyclocondensation reaction of a chiral azomethine under Lewis acid catalysis[7]. The Schiff bases were obtained *in situ* from aldehydes prepared from sugars by single procedures (Fig. 1).

The stereostructure of product **7a** was determined by X-ray crystallography and the configuration of the other cycloadducts were deduced from their CD-spectra. All of the cyclocondensations resulted in 6,1'-*threo* products with high diastereoselectivity due to the chelate stabilization of a conformation of azomethines by zinc chloride (Fig. 2).



3a-i

R	 **a**	 **b**	 **c**
Solvent	THF; dioxane	THF	dioxane
Ratio of diast. **6**/**7**	06/94; 17/83	94/06	67/33
Yield (%)	79; 79	80	65

R	 **d**	 **e**	 **f**
Solvent	THF	THF; MeCN	dioxane
Ratio of diast. **6**/**7**	90/10	65/35; 95/05	14/86
Yield (%)	61	62; 76	77

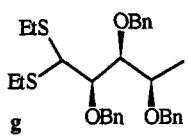
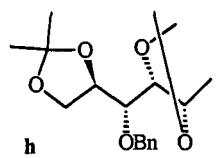
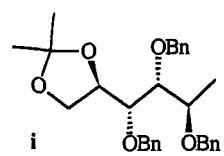
R	 **g**	 **h**	 **i**
Solvent	THF	THF	THF
Ratio of diast. **6**/**7**	20/80	92/08	0/100
Yield (%)	65	72	86

Figure 1.

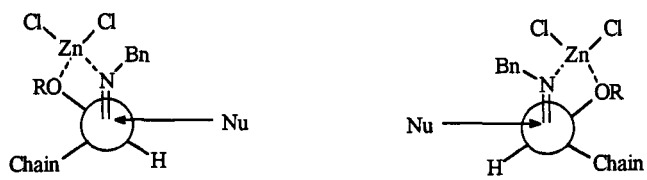


Figure 2.

The keto group of piperidones could be reduced stereoselectively with the concomitant saturation of the CC double bond. After hydrolytic removal of the terminal dioxolane protection of the side chains, glycol cleavage and subsequent intramolecular reductive amination of the intermediate aldehyde led to indolizidines and quinolizidines **12-18**. This reaction sequence is demonstrated on an example in Fig. 3.

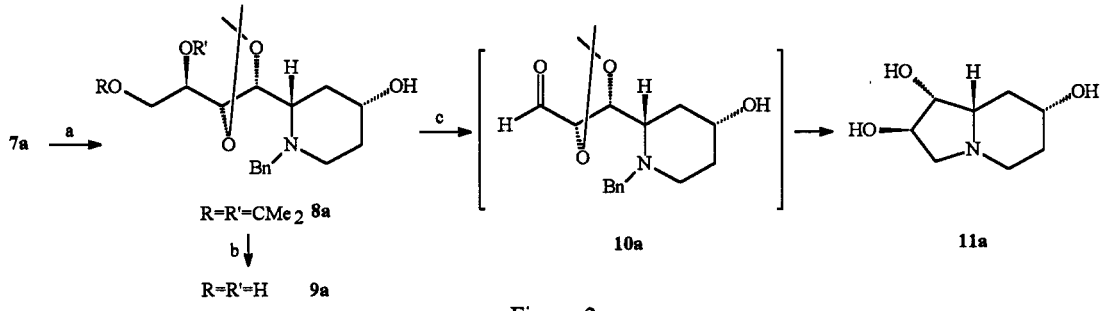


Figure 3.

Using this methodology the following swainsonine and castanospermine analogs have been synthesized.

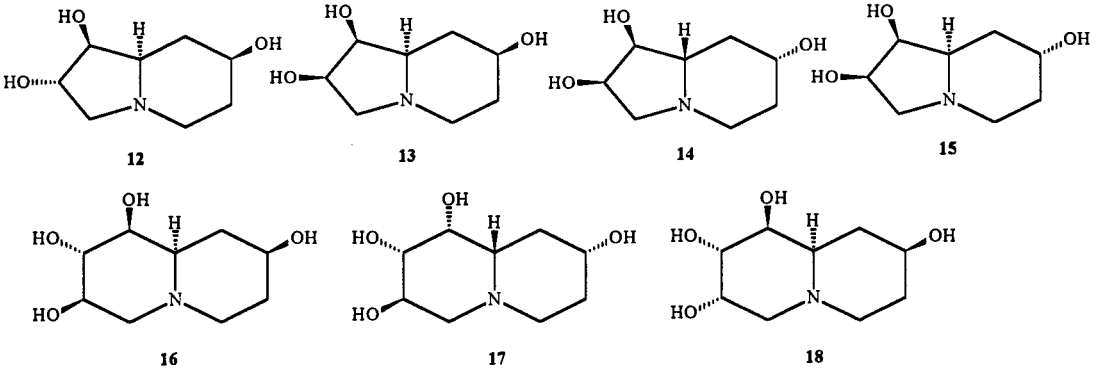


Figure 4.

The [3+2] dipolar cycloaddition method

A second approach is based on the generation of cyclic nitrones by intramolecular conjugate addition of unsaturated oximes reported first by Grigg et al.[10] as a 1,3-azaprotio cyclotransfer reaction. The chiral aldehyde **21** was synthesized from D-xylose using a Wittig chain elongation of the intermediate pentodialdose derivative **19** the reaction of which with hydroxylamine afforded a diastereoisomeric mixture of cyclic nitrones **22** directly[9]. The latter was allowed to react with methyl acrylate as a dipolarophile. The 1,3-dipolar cycloaddition reaction proceeded with good stereoselectivity: two diastereoisomers were formed in a 3:1 ratio and the major isomer crystallized out from the reaction mixture. Three new chiral centers are generated in the reaction sequence **21-23** . Therefore, formation of two diastereomers instead of the possible eight represents a high selectivity (Fig. 5).

The isoxazolidine ring of **23** was subsequently transformed into a pyrrolidine ring by reduction of the N-O bond followed by lactamization. Reduction of the amide carbonyl and hydrolytic and hydrogenolytic removal of the protective groups led to the **27** acetic acid analog of castanospermine.

Another isomeric pentodialdose mercaptal, the L-arabino derivative **29** prepared from D-galactose in four steps[12] was also used as starting compound[11].In this case the cyclic nitrone **31** obtained from the unsaturated oxo compound **30** was reacted with allyl-trityl ether as a dipolarophile. A mixture of two stereoisomers in a ratio of 95:5 was formed. As in the case of **22** the cycloaddition of **31** is charaterized by *exo* orientation of the dipolarophile and the sterochemistry of the adducts was also directed by the bulky benzyloxy and methoxycarbonylmethyl substituents in positions 3 and 6 of the nitrones.

The trityl protective group of **32** was removed by acid hydrolysis followed by methanesulfonylation of the hydroxyl group (**33**). Catalytic hydrogenolysis of **33** resulted the reduction of the N-O bond, intramolecular alkylation of the piperidine NH and removal of O-benzyl groups. The ester group was removed by hydrolysis to give the indolizidine derivative **34**.

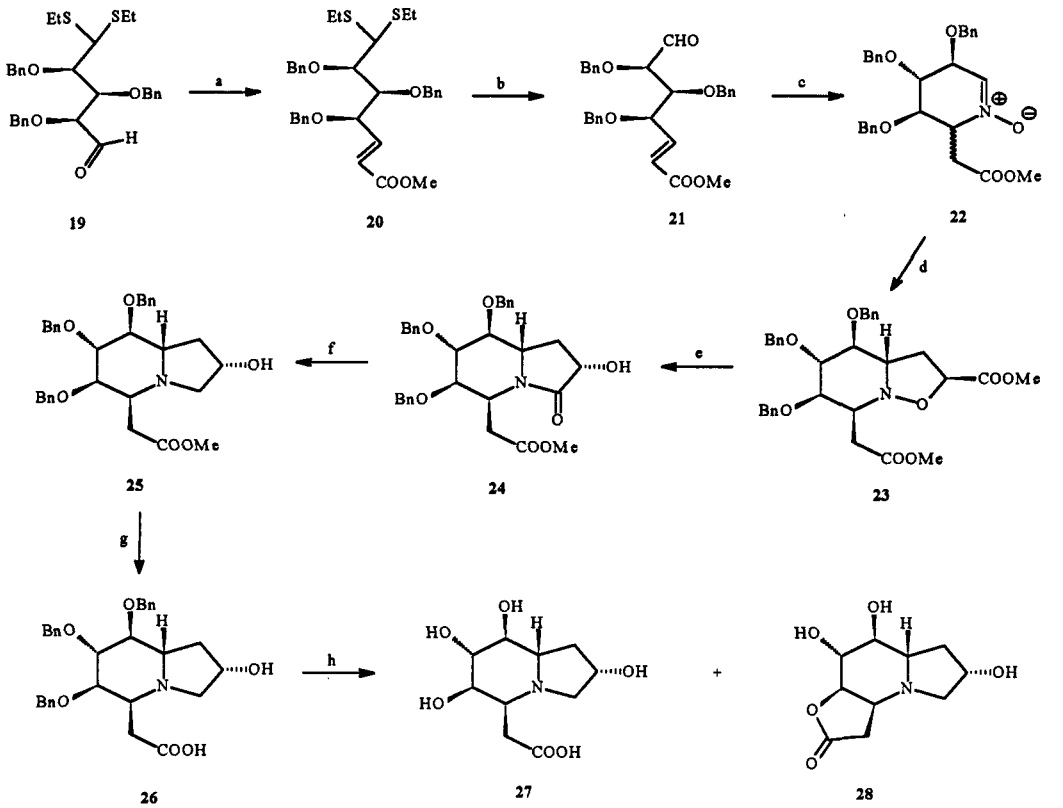


Figure 5.
(a) Ph_3PCHCO_2Me; (b) $HgCl_2$, $CdCO_3$; (c) H_2NOH; (d) methyl acrylate; (e) Zn, AcOH; (f) Me_2SBH_3; (g) $Ba(OH)_2$; (h) H_2, Pd(C)

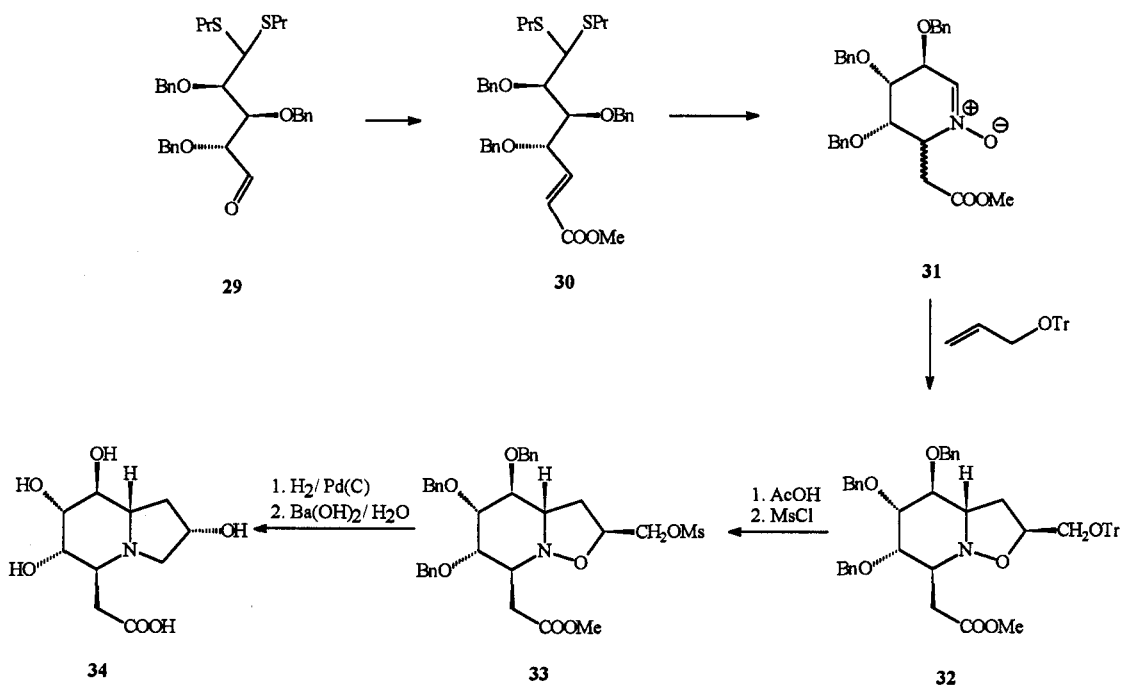


Figure 6.

[2+2] Photochemical cycloadditions of uridine derivatives

Starting a synthetic program covering saturated pyrimidine nucleoside analogs we decided to study some photocycloadditions of uridine derivatives. The [2+2] photoadditions of uracil[13] and uridine[14,15] with alkenes have been studied. For biological studies we aimed to prepare dihydroorotidine analogs, therefore we attempted to react **35** with acrylate esters under photochemical conditions.

When a solution of **35** and methyl acrylate was irradiated using a mercury lamp and a Pyrex filter, four isomers of **37a** were formed in equal amount[16]. Three new chiral centers were generated in this reaction but, for steric reasons, only cis annelated products can be assumed. Thus, for **36a** no diastereoselectivity could be observed. When chiral acrylates such as (+)menthyl and and (-)menthyl esters **36b** and **36c** were used the stereoselectivity could be improved. Photoaddition of **36b** resulted in only two diastereomers in 1:1 ratio while irradiation of **35** and **36c** yielded a 2:1 mixture of isomers.

Usually stereoselectivity of intramolecular reactions exceeds the selectivity of the intermolecular variants. Indeed, in our case, irradiating **38** only one diastereoisomer was formed. Compound **39** is a cyclobutane analog of dihydroorotidine. Its chemical transformations and study of further intramolecular cycloadditions of pyrimidine nucleosides are in progress.

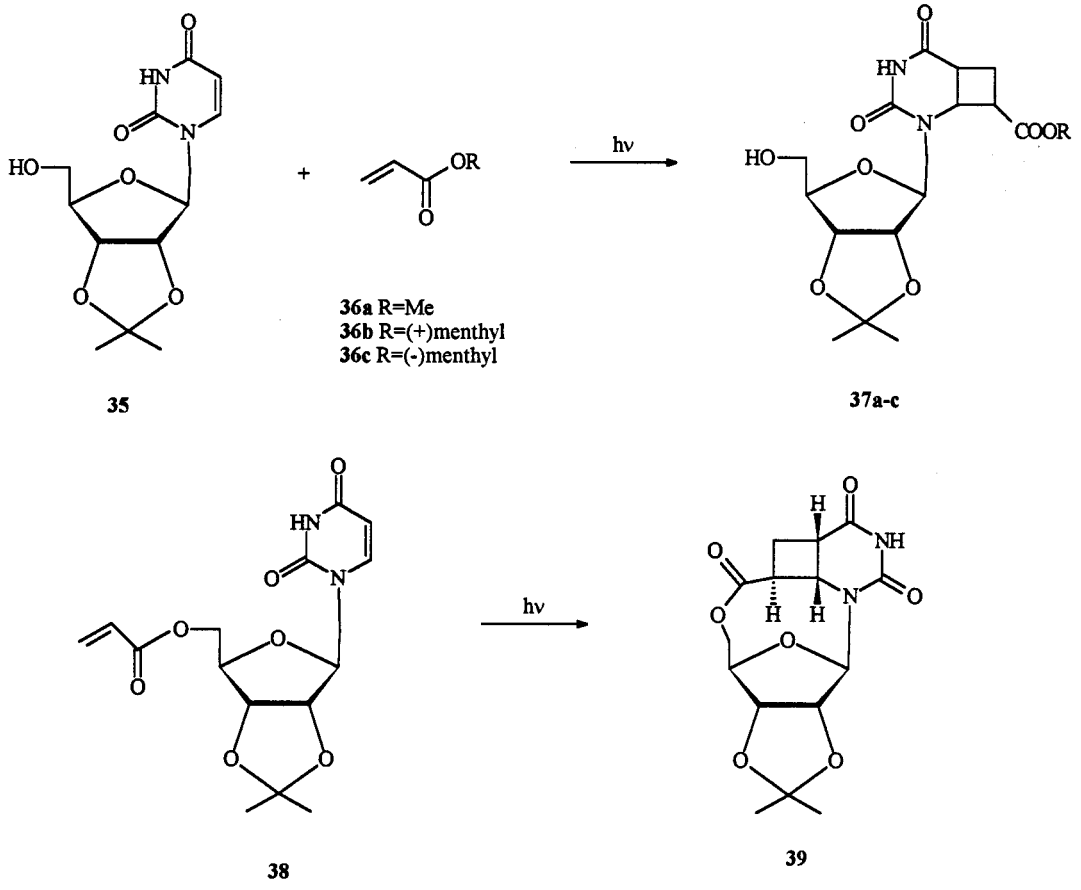


Figure 7.

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