SYNTHESIS OF TETRAHYDROXYLATED INDOLIZIDINES

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Introduction

Polyhydroxylated indolizidines belong to a diverse group of iminosugar alkaloids - carbohydrate analogs having endocyclic oxygen replaced by a nitrogen atom. The ongoing interest in these derivatives is due to their potent inhibitory activity against glycosidases, attributed to the carbohydrate-mimicking structure. Glycosidases are enzymes catalyzing the hydrolysis of the glycosidic bond of carbohydrates and glycoconjugates, which is a common process in nature. They participate in a number of biologically important processes, including post-translational protein processing, lysosomal catabolism of glycoconjugates, or digestive processes.[1] Their regulation by specific inhibitors has potential in the treatment of various diseases. Interest in iminosugars is therefore understandable and was reflected in many reported syntheses. Polyhydroxylated indolizidines exhibit a wide range of biological effects, including anticancer, antiviral, antimetastatic, antiproliferative, or immunomodulatory activity. The most eminent representatives of this group are (-)-swainsonine (**1**), (+)-castanospermine (**2**), and (+)-lentiginosine (**3**).[2]

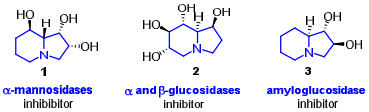


Figure 1: Representatives of polyhydroxylated indolizidines.

Synthesis of tetrahydroxylated spiroindolizidines

Implementation of spirocyclic system

Recently, we have reported the synthesis of polyhydroxylated spiro-annelated tetrahydrofurodolizidines.[3] The key intermediate of the synthesis **6** was prepared in seven steps from cheap and bioavailable starting materials: 2-furaldehyde **4** and L-glutamic acid **5**.[4] Considering acidic protons on the carbonyl α-position of 5-membered lactam, we realized we can implement spirocyclic system by suitable alkylation. Thus, the conditions to achieve mono-alkylation of lactam **6** were initially experienced (Table 1). The alkylation with methyl iodide (entry 1) afforded the corresponding 9-methyl substituted lactam **7** as a mixture of isomers **7a** and **7b** with dr 1:1**.** When reaction was carried with benzyl bromide and allyl bromide (entries 2-3), corresponding isomers **5a** and **6a** were formed with excellent diastereoselectivity (*dr* = 12/1). We assume that in both cases, the steric effects influence the stereochemical course of mono-alkylation from the less hindered convex face of the lactam **6**.

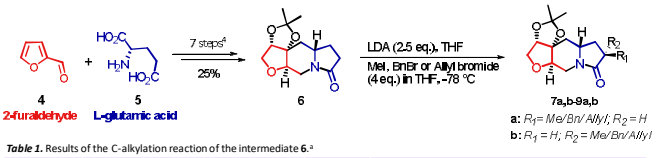


Table 1. Results of the C-alkylation reaction of the intermediate **6**.[a]

Entry	Product	R	*dr*[b] a:b	Yield (%)[c]		
				a+b	a	b
1	7	methyl	1:1	87	39	NI[d]
2	8	benzyl	12:1	87	40	NI[d]
3	9	allyl	12:1	89	82	6

[a] Reactions were performed in dry solvent **[b]** *dr* was determined from NMR. **[c]** Isolated yields. **[d]** Not isolated.

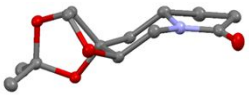
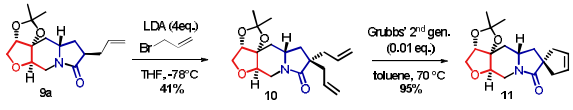


Figure 1. Stick plot of protected diol **6** (hydrogen atoms were omitted for clarity). Steric effects influence the stereochemical course of mono-alkylation from the less hindered convex face of the enolate form obtained from lactam **6** (entry 2-3).

Spiro-cyclopentene ring installation on furoindolizidine's core was achieved using alkene ring-closing metathesis (RCM) as a key step of the synthesis (Scheme 1). To prepare required bis-allyl derivative **10**, second allylation was carried out under the same conditions as the first one (using 4 eq. of LDA) and afforded **10** in moderate isolated yield (41%). Following RCM in the presence of 2nd generation Grubbs' catalyst provided spirocyclopentane **11** in 95% yield.



Scheme 1 : Preparation of spirocyclopentane **11**.

Dihydroxylation of spirocycloalkene

In the next step, the stereoselectivity of dihydroxylation of **11** was studied (Table 2). The stereochemistry of products was assigned based on comprehensive NMR studies. Reaction with a catalytic amount of osmium tetroxide, using NMO as a re-oxidant afforded a mixture of diastereomeric diols **12a** and **12b** in 1:2 ratio (entry 1). The preference for **12b** is interesting since its formation involves the attack of a double bond from the sterically more hindered face. These results suggest that osmium tetraoxide is delivered to the double bond intramolecularly through the complexation with the oxygen of the amide group. (Figure 2.)

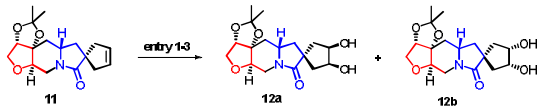


Table 2. Results of dihydroxylation of ***11***.

entry	reagent	reaction time [h]	*dr* (12a:12b)	Yield [%][e] (12a:12b)
1	OsO_4 (cat.)[a]	12	1:2[c]	22:41
2	AD-mix α[b]	12	>99:1[d]	93
3	AD-mix β[b]	12	>99:1[d]	90

[a] Reaction was carried out with osmium tetroxide (0.02 eq.) and NMO (1 eq.) in a mixture of acetone/H_2O (10/1) at rt. **[b]** Reactions with AD-mix were performed in tBuOH/water (3:1) in the presence of methanesulfonamide (1eq.) at rt. **[c]** *dr* was determined based on isolated yields. **[d]** *dr* was determined from NMR of crude. **[e]** Isolated yields after separation.

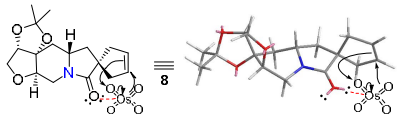
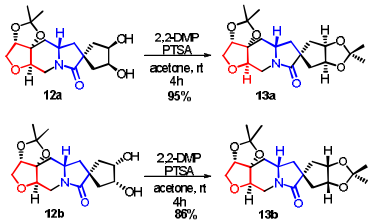


Figure 2

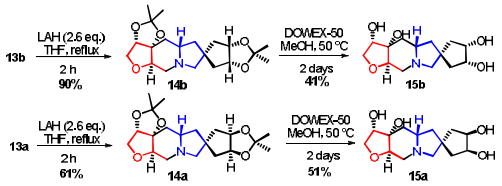
Further, we performed asymmetric dihydroxylation to enhance diastereoselectivity of dihydroxylation (entry 2-3). Unexpectedly, both reagents afforded the same diastereomer **12a**. Presumably, the diastereoselectivity is in this case a reflection of ligand size, not its asymmetry, and bulky Sharpless ligands can access a double bond of **11** only from the less hindered upper side.

In this manner, both diastereomers can be prepared with modest to excellent diastereoselectivity and employed in the rest of the synthesis separately. Diols **12a** and **12b** (Scheme 2) were protected separately afterwards by reaction with 2,2-dimethoxypropane to afford diacetonides **13a** and **13b** in a very good yield (> 86%) in both cases.



Scheme 2 *: Protection of diols with 2,2-DMP to obtain diacetonides **13a,b***

Last two steps of the synthesis included reduction of the lactam carbonyl functional group of diacetonide **13b** to afford **14b** (90% yield) followed by the deprotection of dihydroxyl groups using the DOWEX acidic resin to obtain the expected spiro-tetrahydroxyindolizidine **15b**. The same procedure was applied on the diacetonide **13a** to afford another spiro-tetrahydroxyindolizidine diastereomer **15a** in 31% yield in two steps (Scheme 3).



Scheme 3 *:Synthesis of tetrahydroxy spiro-cyclopentane furoindolizidines **15a** and **15b** from acetonides **13a** and **13b***

Conclusion

In summary, acetonid **6** obtained from biosourced *L*-Glutamic acid (*L*-GA) was used as an advanced building-block to prepare optically pure, in few steps affordable spiro[cyclopentane-indolizidine]-tetraol diastereomers **15a,b** as a new oxacarba-spiroindolizidine framework. The sequential approach used for the construction of tetracyclic spiro-compounds' core consists α-carbonyl alkylation followed by alkene ring-closing metathesis as the key step. Chiral oxacarba-spiroindolizidine tetraols were obtained by the sequence of steps consisting of alkene *cis*-dihydroxylation, diol protection and lactam carbonyl reduction followed ultimately by acetonide deprotection.

References

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2. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J., *Tetrahedron Asymmetry* **2000,** *11* (8), 1645-1680
3. Fraňová, P.; Marchalín, Š.; Šafář, P.; Cvečko, M.; Moncol, J.; Žídeková, I.; Othman, M.; Daïch,A. *New J. Chem.* **2021,** *45*, 15956-15967.
4. Šafář, P.; Marchalín, Š.; Cvečko, M.; Moncol, J.; Dujnič, V.; Šoral, M.; Daïch, A. Org. Biomol. Chem. **2020**, *18*, 6384-6393.

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