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Variable and Stereoselective Synthesis of Azasugar Analogues by a Ruthenium-Catalyzed Ring Rearrangement

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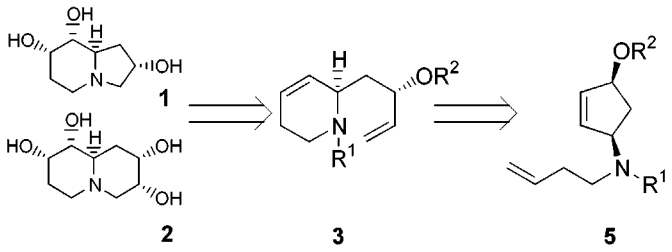
ABSTRACT



A novel ruthenium-catalyzed ring opening/ring closing tandem metathesis reaction with a catalytic transfer of stereocenters from a ring to an olefinic chain is described. This ring rearrangement serves as the key step in the stereoselective synthesis of the new azasugar analogues 1 and 2.

During the past few years, ring closing metathesis (RCM) has become a useful method in the synthesis of numerous carbo- and heterocycles,[1] mainly utilizing Grubbs' ruthenium catalyst [Ru].[2] This method has also been increasingly applied as a key step in the synthesis of important natural products.[3] The ruthenium-catalyzed ring opening metathesis (ROM) has only rarely been used, with the principal exception of polymerizations (ROMP),[4] for the conversion of strained cyclic olefins into monomeric products. For example, ROM has successfully been combined with a highly selective cross metathesis (CM) using an acyclic olefin to avoid polymerization.[5] A combination of ROM and RCM by using suitably substituted cyclic olefins is possible as well. Strained cyclic olefins bearing an alkene side chain rearrange due to the loss of ring strain.[6] Such ring rearrangement reactions can also be combined with a final CM step.[6a] The ROM of relatively unstrained cyclic olefins such as cyclopentene and cyclohexene derivatives proceeds with reactants bearing two olefinic substituents in combination with a double RCM.[7] The driving force of these tandem reactions

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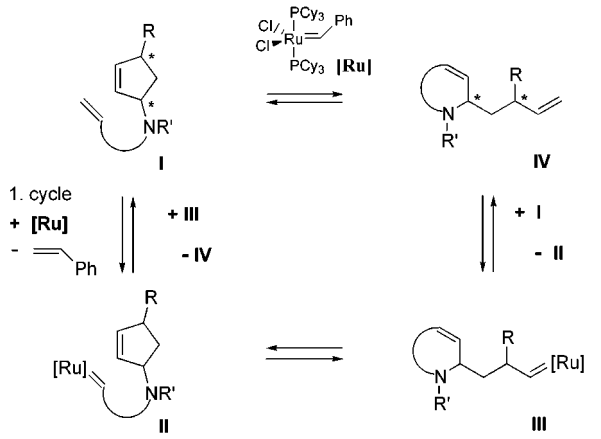
is the entropy gain in the formation of a volatile olefin, which is usually ethylene.

Herein we would like to report a ruthenium-catalyzed ring rearrangement of chiral cyclopentene derivatives of type **I** and the application of this concept to the synthesis of new indolizidine and quinolizidine azasugar analogues.

As depicted in Scheme 1, we assume that the most accessible terminal double bond reacts initially with the

Scheme 1



catalyst to form the ruthenium−carbene complex **II**. The intramolecular formation of a metallacyclobutane with the endocyclic double bond in **II** followed by [2 + 2]-cycloreversion forms carbene complex **III**. This process is faster than the reaction of **I** with **II**, which would lead to dimerization products, and these were not observed.

The catalytic cycle is completed by the reaction of **III** with another molecule of **I** by methylene transfer yielding product **IV** and re-forming the ruthenium carbene complex **II**. In principle, dimerization would be possible too but was not observed in the presence of ethylene. Since all steps in this tandem process are reversible, the yield of **IV** strongly depends on the different thermodynamic stabilities of substrate **I** and product **IV**.[8]

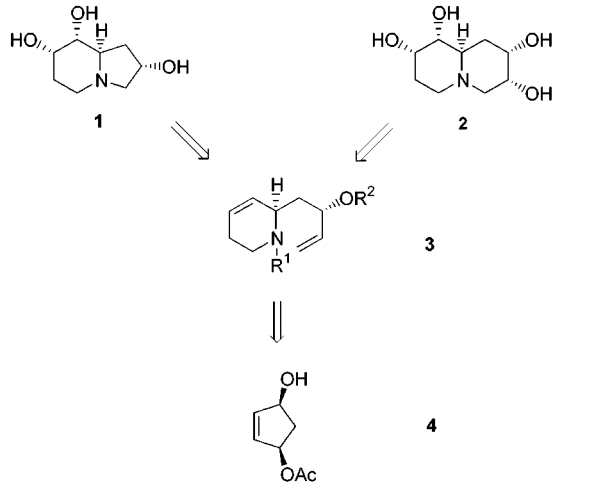
This concept of ring rearrangement opens flexible access toward heterocycles of defined configuration originating from readily available enantiomerically pure carbocycles. In this rearrangement reaction a catalytic transfer of stereocenters from a cyclic core into a side chain takes place.

Heterocyclic structures such as piperidines, indolizidines, or quinolizidines form the skeleton of many pharmaceuticals and natural products.[9] Polyhydroxylated indolizidine alkaloids and their ring-expanded analogues have attracted remarkable attention due to their ability to inhibit glycohydrolases resulting in potential antibacterial, antiviral, antimetastatic, or antidiabetes activity.[10,11] Most of these active compounds are naturally occurring alkaloids, isolated from plants and microorganisms, and have been targets of many total syntheses.[10,12] However, unnatural analogues are interesting targets as well and may be useful in obtaining a better understanding of mechanisms of action and may aid in the design of even more potent inhibitors.

To the best of our knowledge, indolizidines and quinolizidines with the substitution patterns of **1** or **2**, respectively, are unknown and were therefore chosen for our synthesis. Our efforts were focused on the creation of a flexible and stereocontrolled access to these classes of compounds by applying the methodology presented above.

Both heterocycles can be obtained by diastereoselective dihydroxylation and appropriate cyclization from the key intermediate **3**, which can be derived from the (1*R*,3*S*)-(+)-*cis*-4-cyclopentene-1,3-diol 1-acetate **4** via the described ring rearrangement (Scheme 2). The synthetic route to the

Scheme 2



enantiomerically pure polyhydroxylated indolizidines and quinolizidines **1** and **2** should allow for variation of the configuration of the stereocenters by small modifications of the synthetic pathway.

Compound **4** is readily prepared in high enantiomeric purity (>99% ee) by enzymatic hydrolysis of the *meso*-diacetate.[13] Several enantiomerically pure metathesis precur-

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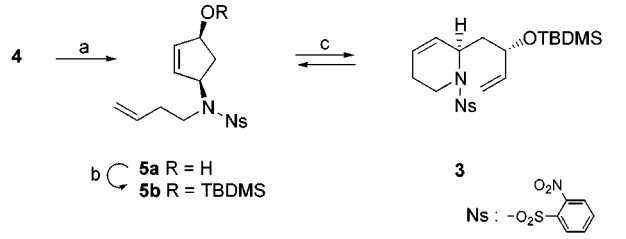
sors of type **I** can be synthesized from **4**. The *cis*-cyclopentene derivative **5a** was obtained by Pd^0-catalyzed allylation of *N*-nosylbutenylamine with **4** (Scheme 3).[14]

Scheme 3[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, *N*-nosylbutenylamine, DMF, rt to 40 °C (80%); (b) TBDMSCl, imidazole, DMF, rt (98%); (c) 1 mol % [Ru], CH_2Cl_2, rt (95%).

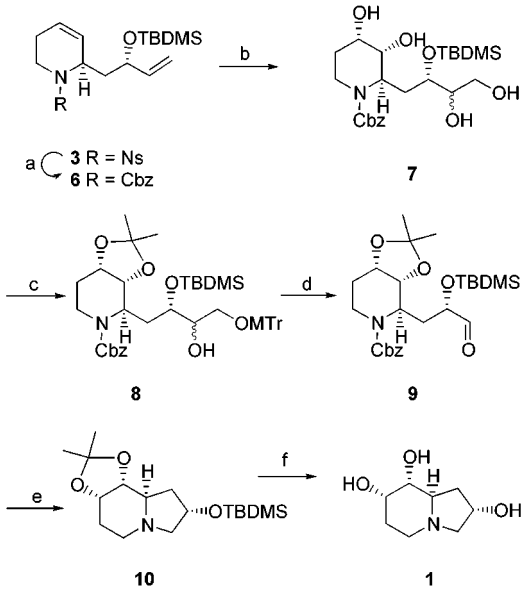
Investigations in our group have shown that introduction of the bulky TBDMS-protecting group, to give **5b**, has a favorable effect on the equilibrium of the ring rearrangement. Whereas a 1:2-mixture (as judged by ^1H NMR) of starting material and rearranged product was obtained from **5a**, the rearrangement of **5b** with only 1 mol % of [Ru] in CH_2Cl_2 resulted in the formation of a single product, **3**, as determined by NMR spectroscopy after approximately 24 h. We suppose that a bulky protecting group causes differences in the relative thermodynamic stabilities of substrate and product. According to Hoveyda,[8a] ethylene (an amount of approximately the solvent volume) was added via syringe to the solution to accelerate the rearrangement reaction and to avoid the formation of dimerization byproducts.

After filtration through silica, the unsaturated piperidine **3**, which serves as the key intermediate in the synthesis of both heterocycles **1** and **2**, was obtained in a virtually quantitative yield.

The indolizidine azasugar **1** was prepared as shown in Scheme 4. Deprotection of **3** followed by Cbz protection in one pot yielded **6**.

In the next step, both double bonds in **6** were dihydroxylated by employing a catalytic amount of OsO_4 and 2.5 equiv of NMO to yield **7**.[15] As expected, the endocyclic double bond was exclusively attacked from the α-side, whereas the stereoselection at the side chain was rather low, resulting in the formation of two diastereomers. However, the configuration of the acyclic, secondary hydroxyl group was not important in the synthesis. To differentiate between the endocyclic and acyclic diol, in the subsequent synthesis steps, the primary alcohol in **7** was selectively protected with the sterically demanding 4-methoxytrityl group by employing

Scheme 4[a]



[a] Reagents and conditions: (a) (i) K_2CO_3, PhSH, DMF, 45 °C, (ii) CbzCl, rt (82%); (b) OsO_4, 2.5 equiv of NMO, acetone/H_2O 1/1, 0 °C to rt (50% de); (c) (i) 4-MTrCl, Et_3N, CH_2Cl_2, rt, (ii) $(MeO)_2CMe_2$, PPTS, rt (90% over three steps); (d) $NaIO_4$, HCOOH/Et_2O 1/1, 0 °C to rt (60%); (e) Pd/C, H_2, methanol, rt (93%); (f) AcOH, rf (50%) (MTrCl, 4-methoxytrityl chloride; NMO, *N*-methylmorpholine *N*-oxide).

1.5 equiv of 4-methoxytrityl chloride, which was carefully added over a period of 48 h.[16] The remaining endocyclic diol was then ketalized[17] in dimethoxypropane over 78 h to give the orthogonally protected piperidine derivative **8**, which was isolated in 90% yield over three steps.

The 4-methoxytrityl protecting group of **8** was selectively removed under mild acidic conditions.[18] Without workup, the resulting free exocyclic diol was successfully cleaved by addition of sodium periodate to give aldehyde **9** (60% yield over two steps), which was considered an optimal precursor for the closure of the second ring. Reductive amination with Pd/C and H_2 under atmospheric pressure yielded indolizidine **10**. Complete deprotection in refluxing concentrated acetic acid gave the novel compound (2*S*,7*S*,8*R*,-8a*R*)-octahydroindolizine-2,7,8-triol **1** in an overall yield of 13% over 11 steps.

A small variation of the synthetic route described above, starting with key intermediate **3**, also allows for the short and stereoselective synthesis of polyhydroxylated quinolizidines. First, **3** was deprotected to give alcohol **11** (Scheme 5) to serve as chelating compound in the next step. Dihydroxylation of the terminal double bond in **11** with

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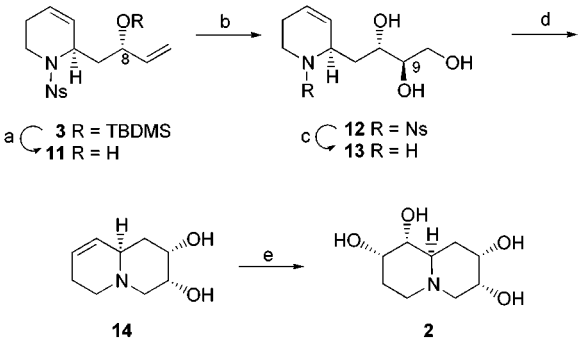
Scheme 5[a]



[a] Reagents and conditions: (a) TBAF, THF, rt (96%); (b) OsO_4, 1 equiv of NMO, acetone/H_2O 1/1 0 °C to rt (60%) 70% de; (c) K_2CO_3, PhSH, DMF, 40 °C (90%); (d) PPh_3, DEAD, pyridine, 0 °C (53%); (e) OsO_4, 1.5 equiv of NMO, acetone/H_2O 1/1 0 °C to rt (81%) > 95% de (DEAD, diethyl azadicarboxylate).

catalytic amounts of OsO_4 and 1 equiv of NMO resulted in chemoselective formation of the triol **12**, which was isolated in 60% yield with a diastereomeric ratio of 85:15. Complete separation of the diastereomers was difficult at this stage and was therefore performed after the cyclization step where the configuration of the hydroxyl groups at C8 and C9 of the major diastereomer were also assigned to the structure given for quinolizidine **14** by NOED measurement.

Compound **12** was deprotected and subjected to several cyclization conditions. The best results were achieved by a Mitsunobu reaction[19] in pyridine at 0 °C to give **14** in 53% yield. At this stage, the separation of diastereomers resulting from the dihydroxylation reaction was easily carried out by column chromatography. The double bond in **14** enables several possibilities for further functionalizations. C*is*-dihydroxylation with OsO_4 and NMO yielded (1*R*,2*S*,7*R*,8*S*,-9a*R*)-octahydroquinolizidine-1,2,7,8-tetrol **2** as a single diastereomer (determined by ^{1}H NMR) in an overall yield of 13% (eight steps).

In summary, we present a highly efficient ring opening/ring closing tandem metathesis process and the application of this method to the syntheses of the new azasugar analogues **1** and **2**. Starting from readily available enantiomerically pure substrates, the intramolecular ring rearrangement concept opens up flexible access toward substituted heterocycles with defined stereochemistry transferring chirality from a metathesis precursor into its products. Applications of this approach to other members of the indolizidine or quinolizidine family of alkaloids by simple modification of the routes described above can be foreseen. Several studies on this subject are currently being performed in our group.

Acknowledgment. A NaFöG scholarship (Berlin) for U.V. is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterizations for compounds **1**−**3** and **5**−**17** (^{1}H NMR, ^{13}C NMR, IR, HRMS; EA for **3**, **5**, **6**, **9**, **13**, **14**). This material is available free of charge via the Internet at http://pubs.acs.org.

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