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Synthesis of hydroxylated hexahydropyrrolo[2,1-*b*]thiazoles

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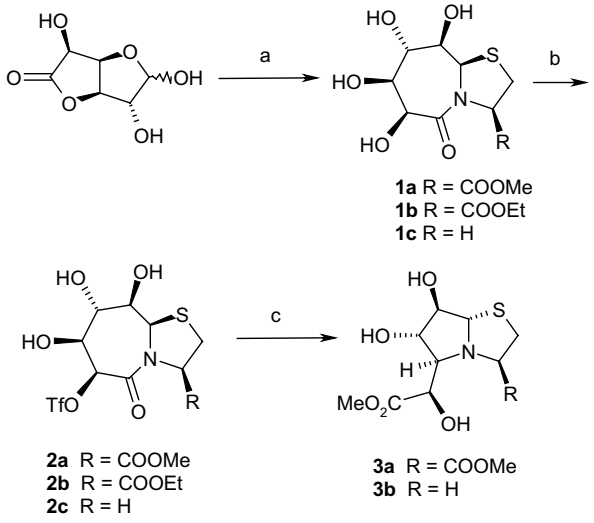
Abstract—An unexpected ring contraction of 7,5-fused bicyclic thiazolidinelactams yields hexahydropyrrolo[2,1-*b*]thiazoles in a single synthetic step. Three stereocentres are inverted along the highly stereoselective reaction path. The title compounds are further transformed into thio-analogues of polyhydroxylated pyrrolizidine alkaloids.

Polyhydroxylated pyrrolizidine alkaloids are effective glycosidase inhibitors isolated from a wide variety of plants[1] and some of them show anticancer[2] or antiviral[3] activities. One powerful synthetic approach to polyhydroxylated pyrrolizidine alkaloids is a tandem nitroalkane cycloaddition developed by Denmark[4] and a number of pyrrolizidine derivatives have been synthesized using this method.[5] Another elegant synthetic route was described by White and is based on a ring-closing metathesis and a transannular cyclization.[6] Due to their highly oxygenated architecture, saccharides are obvious starting materials for the synthesis[7] of polyhydroxylated pyrrolizidine alkaloids. Recently, Yoda reviewed the synthesis of polyhydroxylated alkaloids.[8] Grierson and co-workers prepared the perhydropyridino-thiazole analogue of castanospermine,[9] while Beaupere and co-workers obtained perhydropyridino- and pyrrolo-thiazoles as analogues of castanospermine and australine, respectively.[10] Berges and co-workers used D-xylose[11] and D-lyxose[12] as chiral precursors for the synthesis of perhydropyridino-thiazoles. In all cases the separation of the two thiazole isomers was problematic. Herein we describe a ring contraction, which transforms a 7,5-fused thiazolidinelactam selectively into a single hexahydropyrrolo[2,1-*b*]thiazole. Numerous thio-analogues of polyhydroxylated-pyrrolizidines should be accessible using this route.

Highly regioselective α-triflation gives the octahydro-5-oxo-thiazolo[3,2-*a*]azepines **2** from its tetrahydroxylated precursor **1**.[13,14] The nucleophilic exchange of the triflate group with azide is the next reaction step towards the dipeptide mimetics. The reactivity of triflate **2a** in the presence of different nucleophiles was investigated in order to learn more about alternative reaction paths. When **2a** was dissolved in methanol in the presence of potassium carbonate, a single product formed within 2 h. The ring contraction of the thiazolidinelactam **2a** into a bicyclic hexahydropyrrolo[2,1-*b*]thiazole was indicated by the heteronuclear long-range CH-correlations in the HMBC spectrum, but the stereochemistry of **3a** could not be determined unambiguously by NMR methods, leaving the stereochemistry of the exocyclic stereocentre unassigned, until the subsequent X-ray structure analysis of **6a** (Scheme 1). In an effort to



Scheme 1. (a) R = OMe and OEt lit.[14], R = H lit.[15], (b) R = OMe and OEt lit.[14], R = H lit.[15], (c) K_2CO_3, MeOH, 2 h, (**3a** 85%; **3b** 83%), or 7 M NH_3 in MeOH, MeOH, 8 h, (**3a** 70%; **3b** 76%).

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characterize intermediates of the transformation, the less basic sodium hydrogen carbonate was added to a methanolic solution of **2a**. The same final product **3a** was obtained and an intermediate was observed in the NMR spectrum but it could not be isolated due to its transient character. In the 2-D CH-correlation of the reaction mixture an epoxide intermediate was identified. Treatment of **2a** with 7 M ammonia in methanol gave the same product **3a**. The aminolysis of the methyl esters was observed only after a prolonged reaction time of 1 day. Methyl ester **3a** was the only product when the ring contraction was carried out with ethyl ester **2b**; similarly, azepine **2c**[15] yielded **3b** in good yield.

Several derivatives of **3** were synthesized in order to test the chemical stability of the trihydroxyhexahydropyrrolo[2,1-*b*]thiazoles and to investigate the applicability of this new approach, which yields highly functionalized alkaloids without the necessity of using any protecting group. Another aim was to obtain crystals to assign unambiguously the absolute stereochemistry of the ring-constrained products **3**. Compounds **3a** and **3b** were converted into **4a** and **4b**, respectively, by saponification with lithium hydroxide (Scheme 2). The carboxylic acids were obtained after treatment of the reaction mixture with ion-exchange resin. Co-crystals with LiOH with sufficient quality for X-ray analysis were obtained for **4a** directly from the reaction mixture.[16] Reduction of the ester function of **3a** and **3b** with lithium aluminium hydride afforded primary alcohols **5a** and **5b**, respectively. Treatment of **3a** and **3b** with aqueous ammonia resulted in **6a** and **6b**, respectively, in good yields. Compound **6a** was crystalline too,[17] allowing us to fully assign the structure of the ring-contracted products (Fig. 1); its stereochemistry also matched that of **4a**.

A mechanism for the ring contraction is proposed in Scheme 3. In a first step, methanolysis of the amide bond opens the seven-membered lactam ring. Unrestricted rotation about the Cβ–Cγ bond of the newly formed ester then brings Cβ–OH into the right orientation for epoxide formation. *N*-Acylated thiazolidinelactams are configurationally stable but the thiazolidines quickly epimerize in protic solvents.[18] Opening of the thiazolidine ring gives an imino group, which subsequently attacks the epoxide leading to the iminium ion, which finally closes and forms the hexahydropyrrolo[2,1-*b*]thiazole diastereoselectively. The attack of the imine on the epoxide, as well as the final ring closure of the thiazolidine, are both highly selective ring forming reactions. No other isomers were observed in the ^{1}H NMR of the crude reaction mixture.

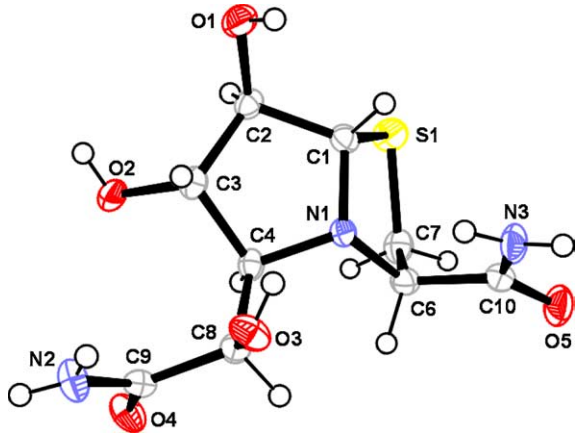
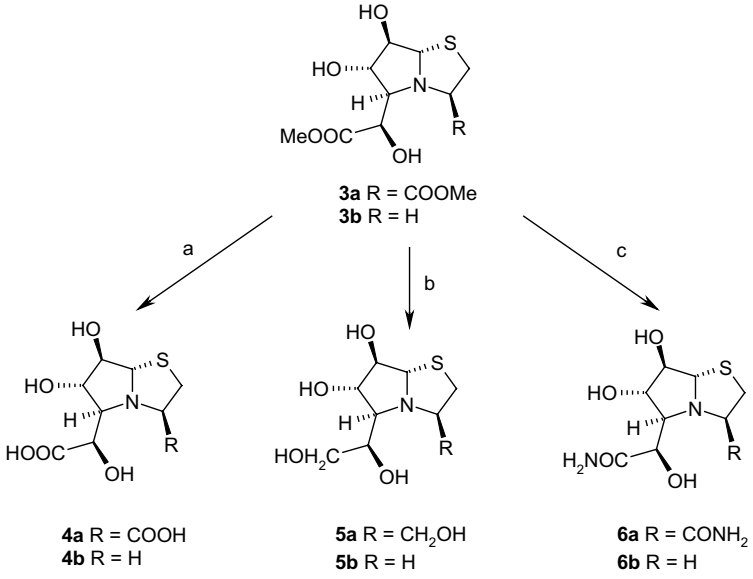
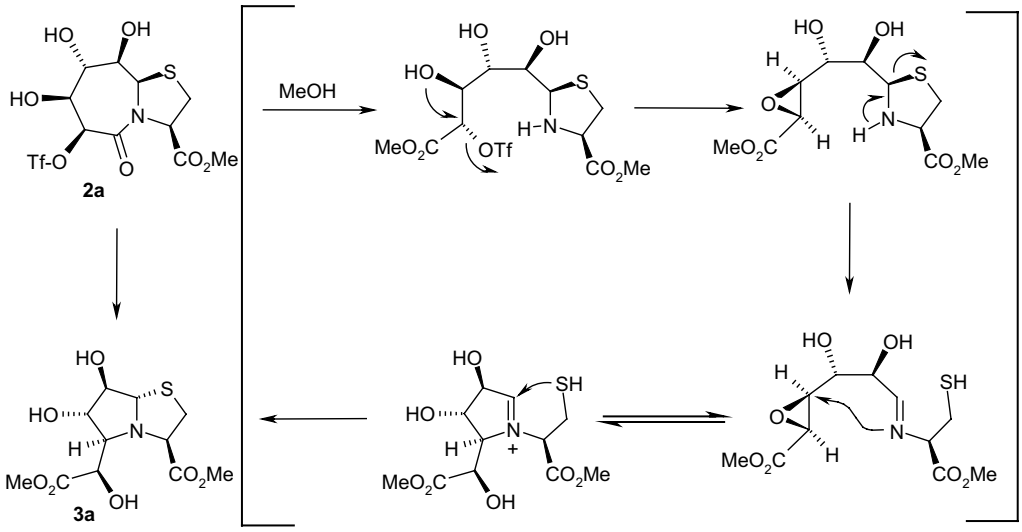


Figure 1. The crystal structure of compound **6a**.

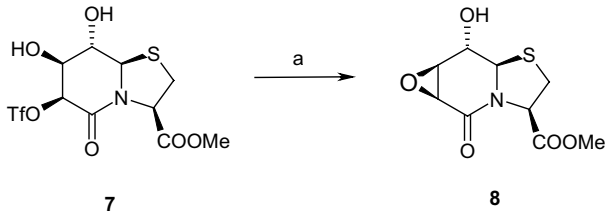
To test whether such a multi-step transformation exists for bicyclic thiazolidinelactams of different ring size, we treated the 6-O-triflate **7**[19] with K_2CO_3 as described above for **3a**. From the reaction mixture epoxide **8** (Scheme 4) was isolated in good yield but no opening of the lactam was observed, even at elevated temperatures. Above 50 °C, **8** decomposes in the presence of potassium



Scheme 2. (a) LiOH, water, 1 h, (**4a** 92%; **4b** 91%), (b) $LiAlH_4$, THF, 30 min, (**5a** 82%; **5b** 70%), (c) NH_3, water, 8 h, (**6a** 70%; **6b** 73%).



Scheme 3. The proposed mechanism of the rearrangement.



Scheme 4. (a) K_2CO_3, MeOH, 2 h, 85%.

carbonate. Presumably, **8** forms after epimerization of the α-carbon, which bears the *O*-triflate substitutent. Epimerization of the α-position was observed for other 6,5-fused thiazolidinelactams,[18] but must not happen in the case of **2a** because an inverted stereochemistry of the exocyclic carbon of **3a** would have been observed.

In summary, we present the unique ring contraction of a polyhydroxylated thiazolidinelactam into a hexahydropyrrolo[2,1-*b*]thiazole, which opens up a new synthetic approach towards polyhydroxylated pyrrolizidine analogues. Biological testing of the glycosidase inhibition activity of compounds **3–6** is in progress.

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