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Synthesis of 3′-Deoxyribolactones using a Hydrolysis-Induced Lactonization Cascade Reaction of Epoxy Cyanohydrins

Danielle J. Vugts,[a] Halil Aktas,[a] Kanar Al-Mafraji,[a] Frans J. J. de Kanter,[a] Eelco Ruijter,[a] Marinus B. Groen,[a] and Romano V. A. Orru*[a]

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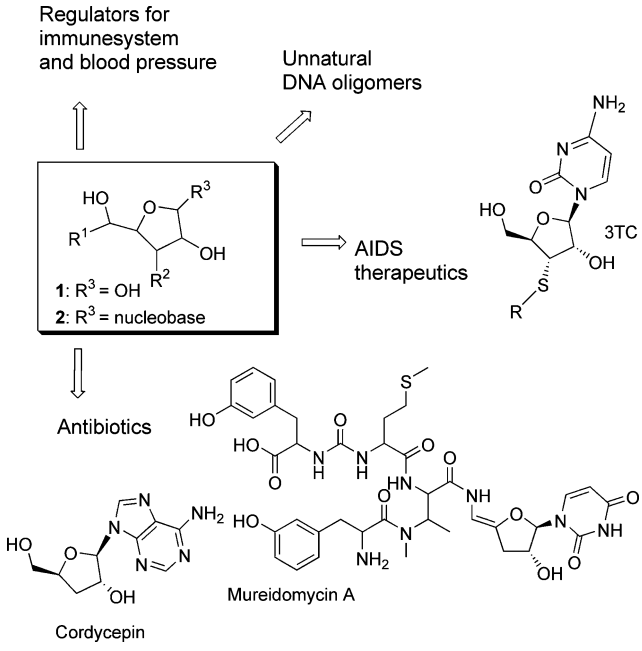
The synthesis of 3′-deoxyribolactones was accomplished in a few steps from the commercially available 3-decyn-1-ol in 44 % overall yield. The key transformation comprises a one-pot four-reaction hydrolysis-induced lactonization cascade. The strategy was employed to efficiently access optically active 5′-chloro-3′-deoxyribolactones.

Introduction

3′-Deoxyriboses **1** are valuable building blocks for the synthesis of pharmaceutically important nucleosides of type **2** (Scheme 1). Several of these nucleosides show antitumor, antiviral, and antiparasitic activities. For example, they can specifically interfere with DNA/RNA biosynthesis and inhibit reverse transcriptases involved in HIV replication.[1] Due to the lack of the 3′-hydroxy group, these nucleosides act as chain terminators by blocking elongation of nascent DNA, leading to inhibition of viral replication.[1a] As such, they represent one of the main drug families used against AIDS, which is exemplified by 3TC.[1c] Several antibiotics, such as cordycepin and the recently discovered mureidomycins, also have **2** as a key component.[2] Further, nucleosides of type **2** have been reported as regulators of both the immune system and blood pressure.[3] Finally, **2** can be utilized in the synthesis of unnatural DNA oligomers.[4] Oligonucleotides with modifications in the phosphodiester backbone unit, especially in the carbohydrate part, show significant increase in RNA affinity and play a central role in the development of genetic therapies such as triplex (antigene) and antisense strategies.[4a,4b]



Scheme 1. Some applications of 3′-deoxyriboses.

Thus, the 3′-deoxyribose moiety is an interesting carbohydrate motif, and general methodology for its stereoselective synthesis is of importance and widespread interest. Suitably functionalized lactones are generally considered convenient precursors to access these types of carbohydrates.[5] For example chiral sultams have been employed to efficiently give diastereomeric mixtures of 3′-deoxyribolactones.[7,8] Another approach describes the asymmetric synthesis of 3′-deoxyribolactones from γ,δ-unsaturated α-hydroxy esters as common precursor.[9] Alternatively, many approaches for the syntheses of modified 3′-deoxyribose-based carbohydrates and nucleosides rely on the chiral pool for starting materials.[6] The advantage is that the stereochemistry is already set. On the other hand, these synthetic routes are often lengthy, include difficult separations, and are inherently inefficient. Consequently, extensive protection and deprotection reactions are often necessary.

Here we describe a method for the synthesis of 3′-deoxyribolactones of type **4** as convenient precursors for **1** (or **2**) using a combination of chemical and enzymatic transformations (Scheme 2). Our approach employs β,γ-unsaturated aldehydes **3** as convenient starting materials for a stereose-

[a] Department of Chemistry & Pharmaceutical Sciences, Faculty of Science, Vrije Universiteit,
De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands
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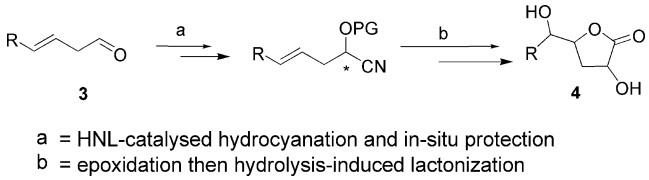
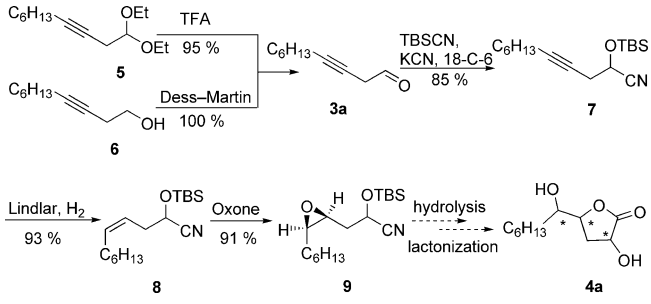
lective hydrocyanation using a hydroxynitrile lyase (HNL) as the enzyme catalyst.[10] We envisioned that selective epoxidation of the resulting optically pure cyanohydrins followed by hydrolysis-induced lactonization should efficiently result in the desired optically pure 3′-deoxyribolactones.



Scheme 2. Chemo-enzymatic approach to 3′-deoxyribolactones.

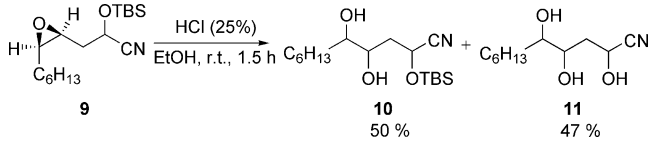
Results and Discussion

To arrive at the desired optically active 3′-deoxyribolactones of type **4**, enantiopure cyanohydrins were required. However, we first studied the feasibility of our approach. For practical reasons, β,γ-unsaturated aldehyde **3a** was chosen as starting material. The route depicted in Scheme 3 should then lead to the 3′-deoxyribolactone **4a**. Aldehyde **3a** can either be obtained from diethyl acetal[11] **5** or homopropargylic alcohol **6**.[12] Cleavage of the acetal function of **5** under acidic conditions using CH_2Cl_2/TFA/H_2O (4:1:1) gave **3a** in 95% yield.[13] Alternatively, oxidation of **6** using Dess–Martin periodinane gave **3a** in quantitative yield. Subsequent transformation of **3a** to the corresponding protected cyanohydrin **7** using TBSCN, KCN and 18-crown-6 ether went smoothly in 85% yield.[14] After hydrogenation of the triple bond in **7** with Lindlar catalyst[15] in ethanol, the resulting (*Z*)-alkene **8** was epoxidized with Oxone®.[16] This resulted in a 1:1 mixture of two diastereomeric epoxides **9**.

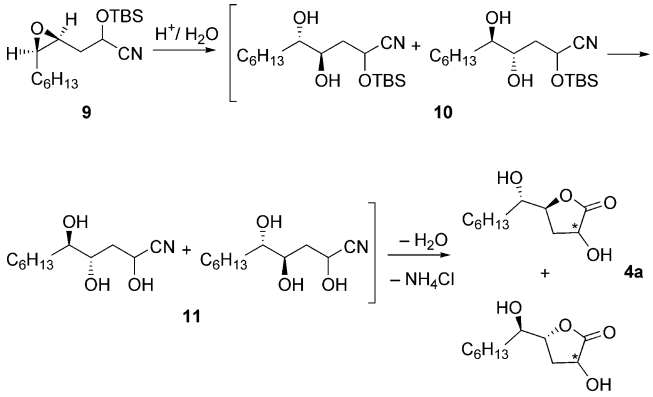


Scheme 3. Racemic synthesis of epoxide precursors.

At this point, the key transformation, a hydrolysis-induced lactonization of epoxides **9** to form the desired lactones **4a**, was performed. In an initial attempt, an ethanolic solution of epoxides **9** was treated with 20 equiv. of acid (using 25% aq. HCl) at room temperature (Scheme 4). Although such conditions had been reported to give efficient hydrolysis-induced lactonization of similar TMS-protected cyanohydrin derivatives,[17] we only found the ring-opened cyanohydrins **10** and **11** in 50% and 47% yield, respectively. In a further test reaction, **9** was allowed to react with excess HCl (25%) in refluxing ethanol for 6 h. After this reaction we could isolate a diastereomeric mixture of the desired lactones **4a** in about 20% yield. This can only be the result of a reaction sequence including four successive steps starting from **9** (Scheme 5). The sequence starts with acid-catalyzed epoxide ring opening of **9**, that results in *threo*-diols **10** by an *anti* addition of water. Under the rather acidic conditions the TBS group is then cleaved to give the deprotected cyanohydrins **11**. At this stage the cyano group is still intact, but under reflux conditions this can undergo hydrolysis and intramolecular lactonization (not necessarily in this order) to ultimately give the lactones **4a**.



Scheme 4. Initial attempts to hydrolyze epoxides **9** selectively.

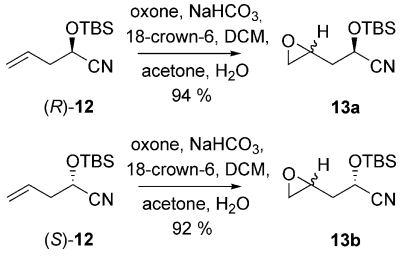


Scheme 5. Hydrolysis-induced lactonization to form lactones **4a**.

Further optimization of the reaction sequence led to a procedure using dioxane as the solvent. In this way, only a minimal amount of side products were observed, while **4a** was formed in 84% according to GC analysis. An additional advantage of the hydrolysis-induced lactonization reaction performed in dioxane is that the NH_4Cl salt formed during reaction precipitates, which drives the reaction to completion and simplifies workup. When the optimized conditions were used for the hydrolysis-induced lactonization of **9** on a preparative scale, the lactones **4a** were obtained as a mixture of four isomers in a ratio of 1:5:6:1 in 61% total isolated yield. The formation of four isomeric lactones may be explained by some temperature-induced epimerization of the lactone products or by suboptimal regio- or stereoselectivity in the initial hydrolysis of epoxide **9**, which is the first step in the cascade process. It should

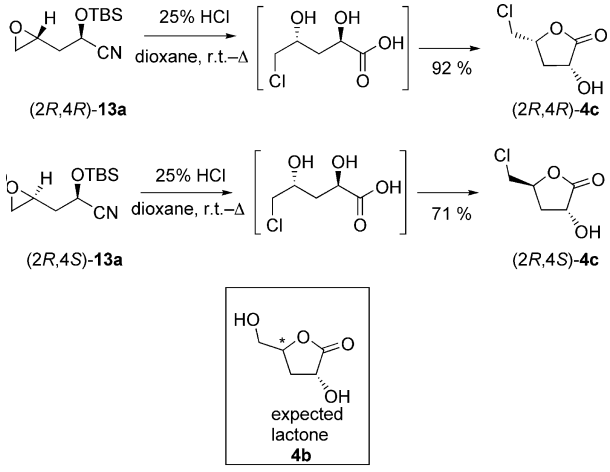
be noted that no δ-lactone formation was observed. Formation of γ-lactones is usually much faster, compared to formation of corresponding 6-membered lactones.[18] Furthermore, upon comparison of the C=O stretch frequencies of the IR spectra of the lactones **4a** with those reported for similar lactones, the data confirm that these are indeed γ-lactones. Generally, saturated γ-lactones show a C=O stretch frequency between 1780 and 1760 cm^{-1}.[19] For δ-lactones and also the open-chain analogs characteristic C=O stretch frequencies are observed between 1750 and 1735 cm^{-1}.[19] In the IR spectrum of **4a** we observed C=O stretch frequencies at 1761, 1773 and 1777 cm^{-1}. In addition, the ^{13}C NMR signals of the lactone C=O group of **4a** appear between δ = 176 and 177 ppm, which is in agreement with literature data for C=O chemical shifts of γ-lactones.[20]

Thus, γ-lactones **4a** can be efficiently synthesized in 5 steps from a commercial alcohol in 44% overall yield. The key step in this sequence is a hydrolysis-induced lactonization cascade. The epoxy cyanohydrin derivative **9** is a central precursor for this one-pot four-reaction sequence. We envisioned that the application of suitably functionalized optically active derivatives of **9** would lead to enantiomerically enriched lactones. In earlier work we have shown that optically active cyanohydrin derivatives can be conveniently prepared in one pot from the corresponding alcohols by TEMPO/PhI(OAc)$_2$-mediated oxidation followed by a stereoselective HNL-catalyzed hydrocyanation-protection sequence.[10] By this chemo-enzymatic protocol, the γ,δ-unsaturated TBS-protected (*R*) and (*S*) enantiomers of the cyanohydrins **12** can be obtained by employing an (*R*)- and an (*S*)-selective HNL, respectively. Further elaboration of the cyanohydrin material by the general route described above leads to optically active 3′-deoxyribolactones. Thus, (*R*)- and (*S*)-**12** were epoxidized with Oxone® resulting in diastereomeric mixtures (1:1 ratio) of epoxides **13a** and **13b** in 94 or 92% yield, respectively (Scheme 6). When (*R*)-**12** was employed as starting material, the two diastereomers could be separated by column chromatography.



Scheme 6. Synthesis of epoxides **13**.

We then performed the hydrolysis-induced lactonization according to the protocol described for epoxide **9**. Both epoxides (2*R*,4*R*)- and (2*R*,4*S*)-**13a**, however, did not afford the expected lactones **4b** with a 5′-OH substituent. Instead the corresponding lactones with a 5′-chloro substituent were formed (Scheme 7, **4c**). The formation of the chloromethyl lactone **4c** is the result of attack of the chloride ion (from HCl) to the primary carbon atom (C1) of the epoxide function in **13a**, resulting in retention at the C2 stereocenter. Subsequent hydrolysis of the TBS-protected cyanohydrin and intramolecular lactonization in the usual manner result in the optically pure chloromethyl lactones (2*R*,4*R*)- and (2*R*,4*S*)-**4c** in excellent yields starting from (2*R*,4*R*)- and (2*R*,4*S*)-**13a**, respectively. Such optically pure halomethyl γ-lactones are useful synthetic intermediates towards a range of biologically active chiral 4-butanolides.[6,7]



Scheme 7. Synthesis of enantiomeric lactones **4c**.

Conclusions

The synthesis of 3′-deoxyribolactones was accomplished starting with simple starting materials, like β,γ-unsaturated aldehydes or the corresponding primary alcohols. The key transformation constitutes a one-pot four-reaction hydrolysis-induced lactonization cascade. In this way, 3′-deoxy-5′-hexyl lactone **4a** was synthesized in few steps from commercially available 3-decyn-1-ol in 44% overall yield. This strategy was employed for a short and efficient synthesis of enantiopure 5′-chloro-3′-deoxyribolactones **4c**.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data of the synthesized compounds

Acknowledgments

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