Keywords: cobalt · coordination modes · dinuclear complexes · macrocyclic ligands

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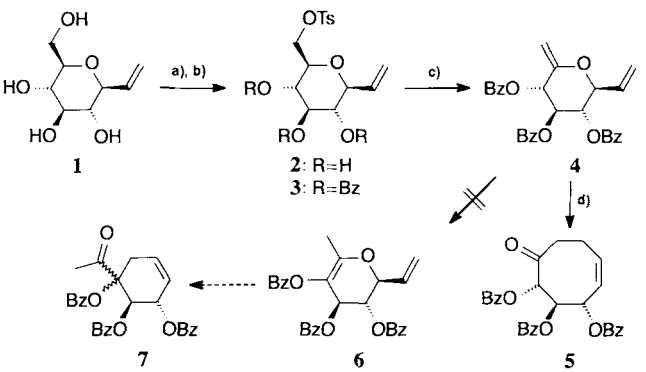
From D-Glucose to a New Chiral Cyclooctenone**

Barbara Werschkun and Joachim Thiem*

Eight-membered carbocycles have increasingly attracted the interest of natural product chemists in recent years. The discovery of a growing number of naturally occurring compounds with eight-membered rings as a structural feature especially among the diterpenes, of which particularly the highly functionalized taxane derivatives show exceptional biological activity, has led to a significant increase in synthetic efforts in this area. The formation of eight-membered rings is a special problem in organic chemistry: owing to the unfavorable energetic relations that are caused by Pitzer strain and transannular interactions, the usual ring-closing methods can often only be applied with low product yields, if at all.[1] Thus alternative synthetic routes such as fragmentations or ring enlargements are of great importance. An elegant variation of the latter reaction is the Claisen rearrangement of 2-methylene-6-vinyl-tetrahydropyrans to cyclooctenone derivatives used by Paquette et al. in the synthesis of several natural products.[2,3]

The tetrahydropyran structure of the starting material and the complex oxygen-rich chiral eight-membered rings that are difficult to obtain by other methods, which were expected as products of the rearrangement, made it seem reasonable to apply the reaction to carbohydrates. The Claisen rearrangement has been used in carbohydrate chemistry as an efficient C–C coupling method for a long time, but its application was restricted to the introduction of alkyl branches and the synthesis of C glycosides.[4] A skeletal rearrangement with loss of the sugar structure was hitherto unknown as was the synthesis of 5,6-unsaturated *C*-vinylglycosides such as **4**, which we have achieved by a simple sequence of well-known reactions (Scheme 1).



Scheme 1. Synthesis and rearrangement of **4**. a) TsCl, pyridine, 62%; b) BzCl, pyridine, 89%; c) DMSO, 80°C, 1. NaI, Bu_4NI, 2. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 52%; d) xylene, reflux, 60%.

The β-*C*-vinylglycoside **1** is available as a pure anomer from the Grignard reaction of acetobromoglucose with vinylmagnesium bromide in approximately 30% yield.[5] The selective reaction of the primary hydroxy group with tosyl chloride (TsCl) to give **2**, and the subsequent perbenzoylation with benzoyl chloride (BzCl) to afford the protected tosylate **3** are standard methods. In a one-pot reaction introduced by Sato et al.,[6] the sulfonate moiety is first replaced by an iodine substituent, followed by base-catalyzed elimination of hydrogen iodide, during which the exocyclic double bond is formed. The allyl enol ether **4**, which is obtained in 50% yield, is stable enough to be purified on silica gel and kept for several weeks at -18°C.

Simple heating of a solution of **4** in boiling xylene leads to the carbocycle **5** in 60% yield after 12 h, as the expected product of the sigmatropic rearrangement. In spite of the well-known tendency of 2-methylene-substituted tetrahydropyrans to isomerize under conversion of the exo- into an endocyclic double bond,[7] neither the derivative **6** nor its hypothetical reaction product **7** was found. It has to be emphasized that due to the β configuration of the C-glycosidic vinyl group a

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sigmatropic rearrangement can only occur out of the $^1C_4$ conformation of the carbohydrate ring, and that this is the first example of a Claisen rearrangement of such a configured compound. The boat–chair conformation of **5** shown in Figure 1 can be deduced from the ^3J couplings in the ^{1}H NMR

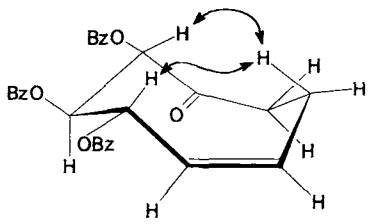

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Figure 1. Boat–chair conformation of **5** deduced from NMR data. The arrows reproduce the observed NO effects.

spectrum and is supported by the transannular NOEs observed in the two-dimensional experiment. The very sharp signals point to the fact that the flexibility is strongly reduced by the three sp^2 carbon centers, which for less substituted systems has already led to remarkable stereoselectivity in follow-up reactions.[8]

This fact together with the three defined chiral centers from the original carbohydrate framework and the high density of oxygen-containing substituents, which can be readily modified synthetically, make compounds like **5** attractive as useful synthetic building blocks, particularly since they are now available from the simple and common starting material D-glucose in few steps.

Experimental Section

5: A solution of **4** (52 mg, 0.11 mmol) in dry xylene (5 mL) was heated to reflux for 12 h. After evaporation of the solvent the residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate (5/1) as eluent. This afforded **5** (31 mg, 60%) as a colorless syrup. $[\alpha]_{20}^{D} = -49.5$ ($c = 1$, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.43-2.50$ (m, H-7eq), 2.60 (ddd, H-8ax, $J = 4.6$, 12.7, 13.2 Hz), 2.85–2.95 (m, H-7ax), 3.13 (ddd, H-8eq, $J = 4.1$, 12.7 Hz), 5.53 (d, H-2, $J = 8.6$ Hz), 5.62 (dd, H-5, $J = 7.1$, 11.2 Hz), 5.71 (dd, H-3, $J = 8.6$, 10.7 Hz), 5.92 (m, H-6), 6.22 (ddd, H-4, $J = 1.5$, 7.1, 10.2 Hz), 7.20–7.47, 7.79–7.85 (2 × m, 9H, 6 H, aryl). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.01$ (C-7), 42.08 (C-8), 68.91 (C-4), 69.51 (C-3), 76.32 (C-2), 126.88–132.63 (C-5, C-6, aryl-C), 164.45, 164.48, 164.74 (3 × CO_2), 203.78 (C-1).

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Synthesis of an ABC Ring Analogue of Kapurimycin A_3 as an Effective DNA Alkylating Agent**

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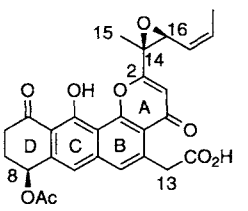
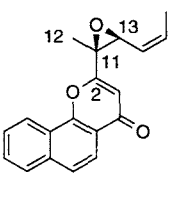
The antitumor antibiotic kapurimycin A_3 (**1**),[1] whose structure is closely related to that of pluramycins,[2] alkylates DNA by attacking the epoxide subunit on guanine at N7 to form a kapurimycin–DNA adduct.[3] The high efficiency of the selective alkylation of guanine at N7 implies that the epoxide subunit is placed in the major groove of DNA with an appropriate alignment to N7 of guanine through precovalent intercalation of the aromatic moiety, as previously suggested for aflatoxin B_1[4] and altromycin B.[5,6] To identify the factors responsible for such an efficient and selective guanine alkylation and to devise new DNA-alkylating agents possessing an epoxide subunit, we synthesized the truncated kapurimycin analogues **2** and **3** as well as their epoxy alcohol and



kapurimycin A_3 **1**



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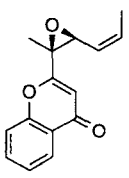

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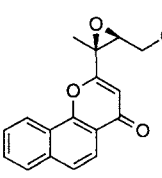

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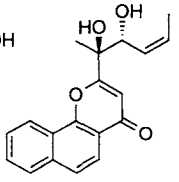

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