A novel hydride rearrangement of the acetal group of tetraacetal tetraoxa-cages mediated by Lewis acids

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Treatment of tetraoxa-cages 1a–f with Lewis acids such as $TiCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$ and $MeSO_3H$ in dichloromethane at 25 °C gives the rearrangement products 2a–f in 90% yields regioselectively and stereoselectively; a novel hydride rearrangement of the acetal group of tetraacetal tetraoxa-cages mediated by Lewis acids.

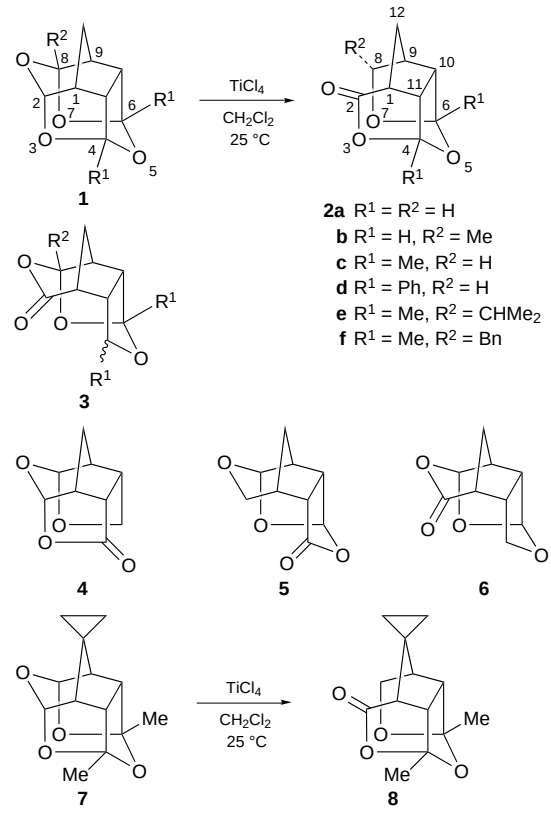
The reaction chemistry of acetals has been greatly expanded by the use of Lewis acidic promoters, particularly in conjunction with silicon-containing nucleophiles.[1,2] Usually, acyclic and monocyclic acetals, especially the acetal groups in monosaccharide derivatives, are the objects for study. Recently, we accomplished the synthesis of novel oxa-cage compounds, such as diacetal trioxa-cages,[3] triacetal trioxa-cages,[4] tetraacetal tetraoxa-cages,[5] tetraacetal pentaoxa-cages[6] and pentaacetal pentaoxa-cages (the pentaoxa[5]peristylanes).[7] All these oxa-cages contain acetal and ketal groups. As part of a program that involves the synthesis, chemistry and applications of new heterocyclic cages, we report here a novel hydride rearrangement of the acetal group of the tetraacetal tetraoxa-cages **1** mediated by Lewis acids.

Reaction of the tetraacetal tetraoxa-cages **1a–f** with two equivalents of Lewis acids, such as $TiCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$ and $MeSO_3H$ in dichloromethane at 25 °C for 3 h gave the novel hydride rearrangement products **2a–f** in 90–95% yields regioselectively and stereoselectively (Scheme 1). No detectable amount of the other regioisomer **3** was obtained. In the case of the unsubstituted (parent) compound **1a**, no detectable amount of the other regioisomers **4**, **5** or **6** was obtained. We attribute the high regioselectivity of the hydride rearrangement to the angle strain of the unusually large bond angle of C(2)–O(13)–C(8) of the tetraoxa-cages **1a–f**. While the other C–O–C bond angles of the tetraoxa-cages **1** are between 111°–108°, the C(2)–O(13)–C(8) bond angle is 117.5°, remarkably larger than ordinary bond angles about sp^3-hybridized atoms.[5a] In the cases of both **1a** and **1b**, with no alkyl substituents on C(4) and C(6), the hydride rearrangement still took place regioselectively between C(2) and C(8). Thus, a steric hindrance factor for the regioselective hydride rearrangement of **1** to **2** was excluded. Treatment of the tetraoxa-cage **7** with $TiCl_4$ under the same reaction conditions gave **8** in 90% yield. A three-membered spiro ring on the apical carbon did not interfere with the hydride rearrangement.

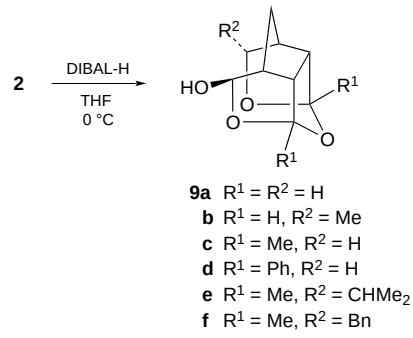
The IR spectra of **2a–f** showed strong absorption at 1770 cm^{-1} for the five-membered lactone carbonyl group. The ^1H NMR spectrum of **2a** revealed two doublets at δ 6.04 and 5.97 for the two acetal protons on C(4) and C(6) and two doublets of doublets at δ 4.13 and 3.50 for the methylene protons on C(8). The ^{13}C NMR spectrum of **2a** diplayed a singlet at δ 179.09 for the lactone carbonyl, two peaks at δ 112.31 and 106.38 for the acetal carbons C(4) and C(6) and one peak at δ 71.59 for the methylene carbon C(8).

The stereochemistry of the alkyl group on C(8) of **2b**, **2e** and **2f** was assigned on the basis of the following chemical transformation of **2a–f** and NOE experiments of **2b**. Irradiating the methyl group on C(8) of **2b** gives 8.6% enhancement of the intensity of the C(9) proton. Reduction of **2a–f** with DIBAL-H in dry THF at 0 °C gave compounds **9a–f** stereoselectively in 85–90% yields (Scheme 2). The stereochemistry of the hydroxy group and the alkyl substituent on C(8) was proven by X-ray analysis of the crystalline compound **9b** (Fig. 1).† Hence, the stereochemistry of the alkyl substituent on C(8) of **2b**, **2e** and **2f** was confirmed.

A reaction mechanism is proposed for the hydride rearrangement from **1** to **2** (Scheme 3). Coordination of $TiCl_4$ to the oxygen atom O(13) of **1** followed by cleavage of the C(8)–O(13) bond gives the oxonium ion **10**. Fragmentation of **10** to a monocyclic species **11** followed by zipping back up to



Scheme 1



Scheme 2

the stereoisomer **12** and a subsequent (fast) intramolecular hydride transfer gives **2**.

In summary, we have discovered a novel hydride rearrangement of the acetal group of tetraacetal tetraoxa-cages mediated by Lewis acids. The hydride rearrangement is found to be regio- and stereo-selective. We attribute the highly regioselective hydride rearrangement to the unusually large bond angle of C(2)–O(13)–C(8) of the tetraoxa-cages **1**.

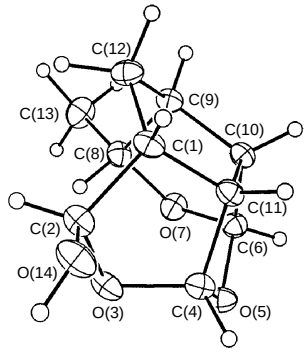
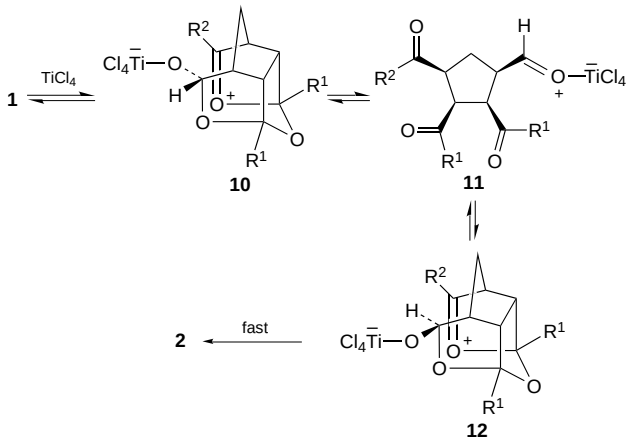


Fig. 1 ORTEP diagram of **9b**



Scheme 3

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Footnote

† *Crystal data*: for **9b**: $C_{10}H_{14}O_4$, M = 198.2, monoclinic, space group $P2_1/n$, a = 5.4843(2), b = 13.6462(7), c = 12.2570(6) Å, β = 91.865(2)°, U = 916.8(4) Å^3, Z = 4, R = 0.0422, Rw = 0.0517. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/371.

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