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anti-Oligoannelated THF Moieties: Synthesis via *Push*−*Pull*-Substituted Cyclopropanes‡

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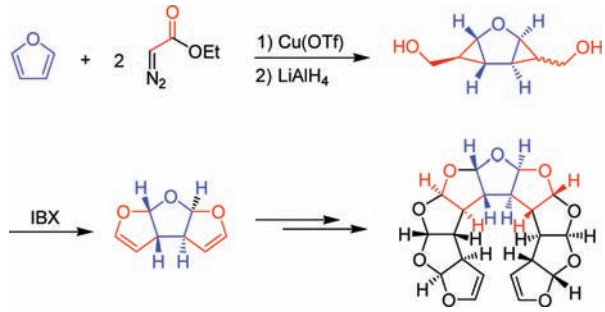
ABSTRACT



The first synthesis of *anti*-fused oligoannelated THF moieties is reported. The key transformation of the synthetic sequence, consisting of cyclopropanation, reduction and oxidation, is the expansion of a *push*−*pull*-substituted three-membered ring into a five-membered enol ether system. A repetition of the sequence allows the creation of oligoacetals up to a nonacyclic system.

Symmetric molecules have attracted the interest of chemists for decades. One motivation behind the interest in these compounds is certainly their aesthetic appearance. Many of them are formed by the repetitive arrangement of subunits. Examples are triangulanes (a type of σ-helicenes),[1] cyclacenes,[2] pericyclynes,[3] and elastic macrocycles,[4] to name just a few. A variety of highly aesthetic structures[5] was also obtained by the repetitive arrangement of tetrahydrofuran (THF) moieties. 2,5-Connected oligotetrahydrofurans are known to occur in several natural products.[6] Non-natural derivatives such as compound **1** have recently been prepared and reveal channel-like cation-transport behavior.[7] Spiro-annelated THF moieties of type **2** proved to be the first primary helical molecules based upon the shape of the THF

‡ Dedicated to Professor Dr. Armin de Meijere on the occasion of his 70th birthday.

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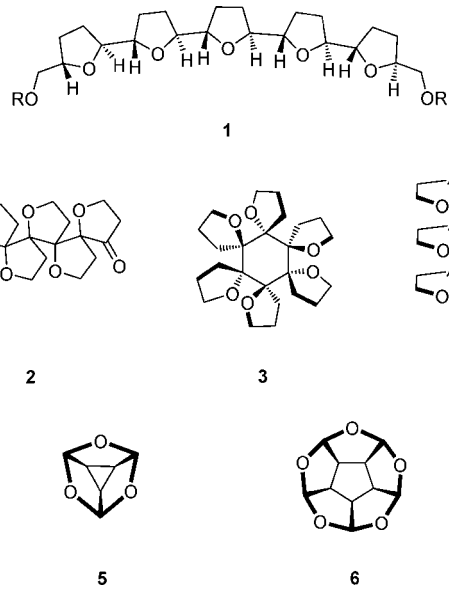
ring system.[8] Cyclic and acyclic oligospiro-THF systems such as **3** and **4** were synthesized and revealed deeper insights into the *gauche* effect.[7] Highly elegant synthetic routes led to the creation of so-called oxa-bowls of type **5**and **6**.[10] Systems of such a molecular architecture are not only known for three and five, but also for four and six *syn*-fused THF moieties.[10]

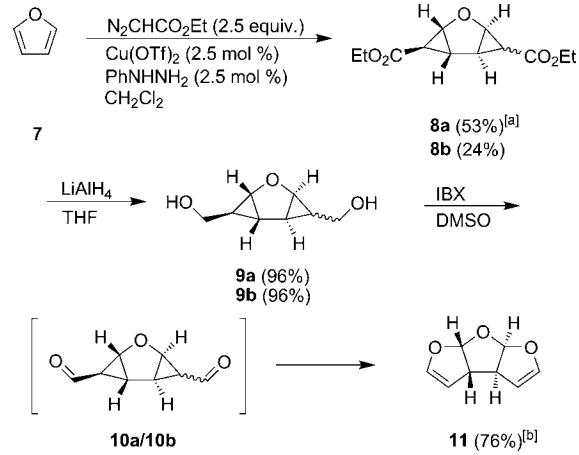


In this communication, we report on the synthesis of a further motif of repeating THF moieties. In contrast to the oxa-bowls **5** and **6** showing a *syn*-arrangement of the THF units, the molecules we prepared exhibit an *anti*-orientation of the fused five-membered rings.

To reach this goal, we made use of the unique tendency of *push*−*pull*-substituted three-membered rings to open the bond between the electron-donating and electron-withdrawing substituent.[11] This property has been intensively investigated[11] and has already been used in a variety of natural product syntheses.[12] It has been shown that donor−acceptor-substituted cyclopropanes can be used as 1,3-dipolar building blocks in acid-mediated rearrangement reactions,[13] in retro-aldol reactions[14] and in ring-opening reactions with electrophilic and nucleophilic double or triple bond systems.[15] Ester groups have especially been used as acceptor substituents, fewer reactions have been performed with aldehydes as acceptors.[16] We envision a sequence involving cyclopropanation, reduction of the ester moieties and oxidation to the aldehyde with subsequent rearrangement to the five-membered ring[17] should be applicable for the preparation of *anti*-fused THF moieties.

Therefore, furan (**7**) was treated with an excess of ethyl diazoacetate under copper catalysis to afford the tricyclic compounds **8a/8b** with two three-membered rings in an *anti*-arrangement in 77% yield (Scheme 1).[18] A reduction of the ester moieties with $LiAlH_4$ in THF gave the diols **9a/9b** in quantitative yield. The generation of the *push*−*pull*-substituted cyclopropanes in **10a/10b** (by oxidation of the hydroxy methyl units of **9a/9b**) that instantaneously opened to form a five-membered enol ether had to be performed in such a way that the oxidizing agent does not attack the newly generated enol ether system.

Scheme 1. Synthesis of the Tricyclic Bisacetal **11**



[a] **a** designates always the C_2-, **b** the C_1-symmetrical product. [b] **9a** was used as starting material.

The reagent of choice for this purpose proved to be IBX in DMSO.[19] Several other oxidizing agents such as the use of Dess−Martin periodinane, PCC or TPAP did only yield

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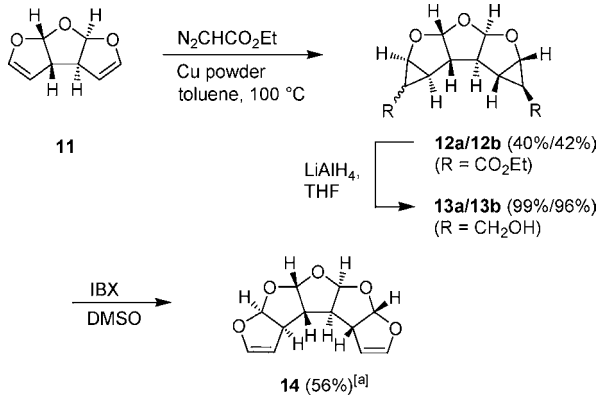
traces of the desired product. Even the use of the Swern reaction did not lead to any product formation, but showed complete destruction of the starting material. An experiment to shorten the two-step sequence of ester reduction and oxidation of the alcohol to one step by utilizing DIBAL-H proved to be unsuccessful. However, oxidation by IBX allowed the direct formation of the tricyclic bisacetal **11** that was accessible in only three steps from furan.

For the preparation of larger oligoacetal structures the newly formed enol ether moieties in **11** were subjected to the same sequence. The 2-fold cyclopropanation of **11** proceeded smoothly with high *anti*-selectivity (Scheme 2).

Scheme 2. Repetition of the Sequence Towards the Pentacyclic Tetraacetal **14**



[a] **13a** was used as starting material.

However, besides the C_2-symmetric compound **12a** (40%) the same amount (42%) of an asymmetric compound **12b** was obtained. The latter differs from **12a** in the position of the ester moiety; one of the two ester groups of **12b** is oriented toward the adjacent THF ring. The separation of **12a** and **12b** was possible via careful silica gel column chromatography (see Supporting Information). An X-ray investigation of diastereomer **12a** shows the *all-anti*-arrangement of the three- and five-membered rings (Figure 1). As

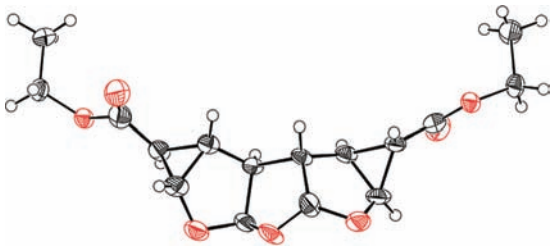
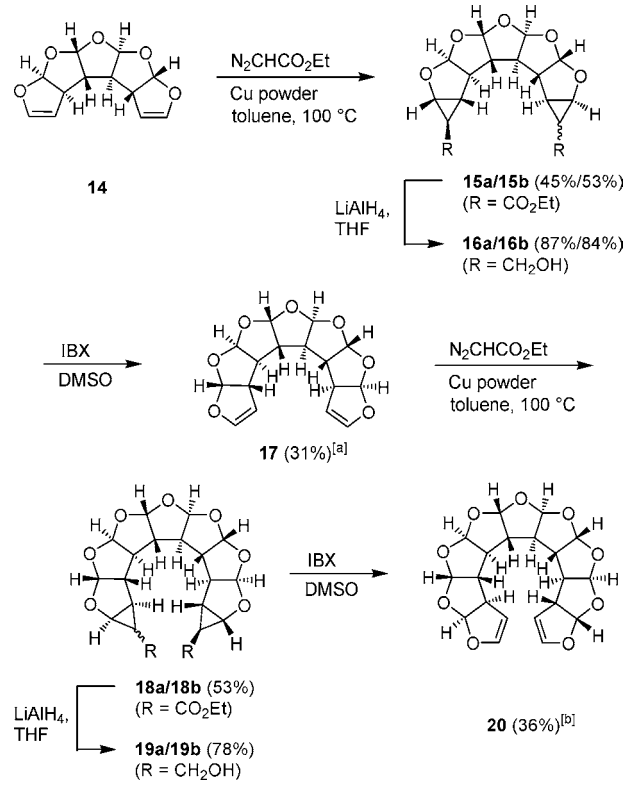


Figure 1. ORTEP plot (50% ellipsoid probability) of the molecular structure of **12a** in the solid state. Oxygen atoms are shown in red. For the sake of clarity the disorder in the two ester moieties is not shown.

anticipated according to the Walsh model[20] of cyclopropane the plane of the ester moiety is almost perpendicular (85°) to the plane of the three-membered ring. A comparison of the bond lengths within the cyclopropane unit reveals, also in accord with the Walsh model, the bond opposite the ester group is the shortest (1.490 Å compared to 1.534 and 1.535 Å).[20]

Both diastereomers **12a/12b** were reduced to the corresponding diols **13a/13b**. Compound **13a** was subjected to an oxidation by IBX to form the pentacyclic compound **14** in 56% yield (Scheme 2).[21] A further repetition of this sequence by using the pentacycle **14** as starting material led - via the diesters **15a/15b** and the corresponding diols **16a/16b** - to the heptacyclic oligoacetal **17**. The latter could be further transformed into the nonacyclic compound **20** (Scheme 3). Due to the extremely low solubility of **20** in all

Scheme 3. Synthesis of the Nonacyclic Octaacetal **20**



[a] **16a** was used as starting material. [b] Mixture of **19a**/**19b** (2:1) was used as starting material.

tested solvents, we abstained from continuing on with this sequence once more.[22] However, by using substituents that increase the solubility, even larger oligoacetal structures should be accessible.

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(21) The asymmetric diastereomer **13b** was also converted to the tetraacetal **14**; however, a significantly lower yield (7%) was obtained (under unoptimized conditions).

(22) Due to solubility problems of the larger oligoacetals, work-up is very difficult and may be the reason for the lower yields of **17** and **20**.

For the penta- and heptacyclic oligoacetals **14** and **17**, respectively, we were able to grow small single crystals suitable for X-ray crystallography to elucidate their molecular structures with an *all-anti*-arrangement of the fused THF moieties (Figure 2).[23] In contrast to linear ladderane-type

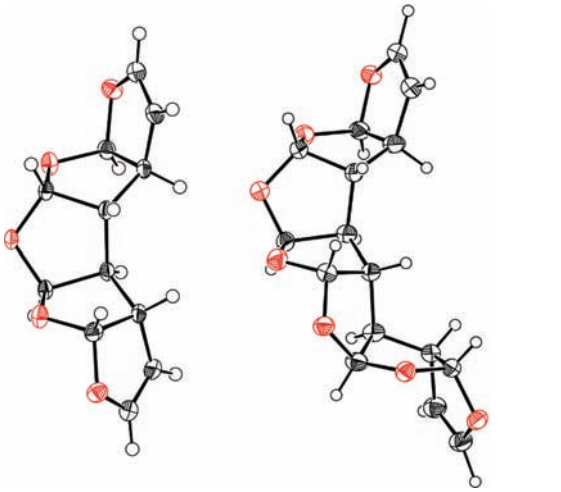

Figure 2. ORTEP plots (50% ellipsoid probability) of the molecular structures of **14** (left) and **17** (right) in the solid state. Oxygen atoms are shown in red.

structures[24] that are based on fused four-membered rings, these compounds show the arrangement of corkscrew stairs due to the *anti*-arrangement of annelated five-membered rings.

In summary, we accomplished the synthesis of oligoannelated THF moieties with *anti*-fused ring systems. As the largest assembly of this type a nonacyclic octaacetal was prepared. The common starting material of the series is furan (**7**) that was converted by a sequence of cyclopropanation, reduction and oxidation into the tricyclic compound **11**. The key step within this sequence is the ring enlargement of donor−acceptor-substituted three-membered rings into the five-membered enol ether systems. A repetition of this three-step procedure allows creation of the pentacyclic compound **14** that could be further converted to the corresponding heptacyclic and nonacyclic oligoacetals **17** and **20**. Structural investigations of **14** and **17** by means of X-ray crystallography have confirmed the *anti*-arrangement of the THF moieties. Further investigations with respect to reactive and coordinating properties of these molecules as well as the creation of spiroketals in a similar way are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. Cif files of **12a**, **14**, and **17**.[25] This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The diffractometer was equipped with a copper rotating anode (**17**) or a molybdenum micro source (**14**). Diffraction data of structure **14** also allowed an invariom refinement which led to significant improvements in the figures of merit and the physical significance of the anisotropic displacement parameters (ADPs). For the method of invariom refinement see: (a) Dittrich, B.; Hübschle, C. B.; Messerschmidt, M.; Kalinowski, R.; Girnt, D.; Luger, P. *Acta Crystallogr.* **2005**, *A61*, 314–320.

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(25) Cif files have also been deposited with the Cambridge Crystallographic Data Centre as "supplementary publication no. CCDC-725973 (**12a**), CCDC-720562 (**14**), and CCDC-720971 (**17**)". Copies can be obtained via email: data_request@ccdc.cam.ac.uk.