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Cis- and *Trans*-1,7,9-Trioxadispiro[5.1.5.3]hexadecane: Synthetic Studies

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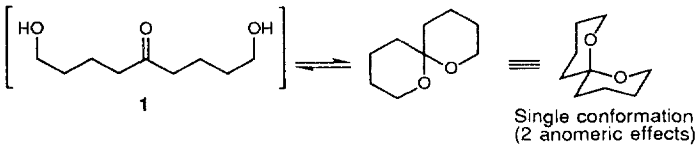
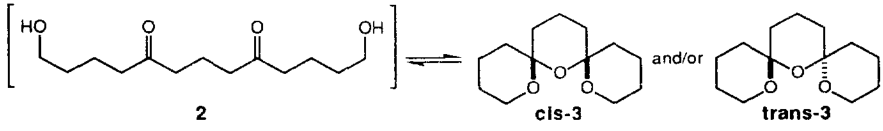
Abstract: The first synthesis of the title compounds via thermodynamic spirocyclization of a diketodiol **2** is described. Three convergent synthetic approaches to protected derivatives of **2** have been developed, all of which have been converted into a 1.70 : 1.00 mixture of ***trans*-3**:***cis*-3**. A practical consequence of these studies is the availability of the title compounds from dihydropyran and 1,5-pentanediol in 28% and 32% overall yields, respectively.

The design and study of strategically functionalized molecular arrays has proven to be an exceptionally fertile context for chemical discovery. Difficulties in obtaining compounds that incorporate the desired spatial characteristics are often a significant obstacle to such studies. We have been interested in identifying and exploiting stereocontrolled self-organization processes as a means of efficiently preparing spatially defined molecules that embody new and unique properties. With this in mind, the 1981 report by Deslongchamps and co-workers on the cyclization of ketodiol **1** to afford a spiroketal which exists in a single conformation is specially intriguing (eq 1).[1] The exclusive selection of only one of three possible conformations is a consequence of the stabilizing anomeric and exo-anomeric effects that direct both C-O bonds to axial positions on the respective rings. This is a clear demonstration of how stereoelectronic effects can define the three-dimensional space of polycyclic compounds.[2]



(1)

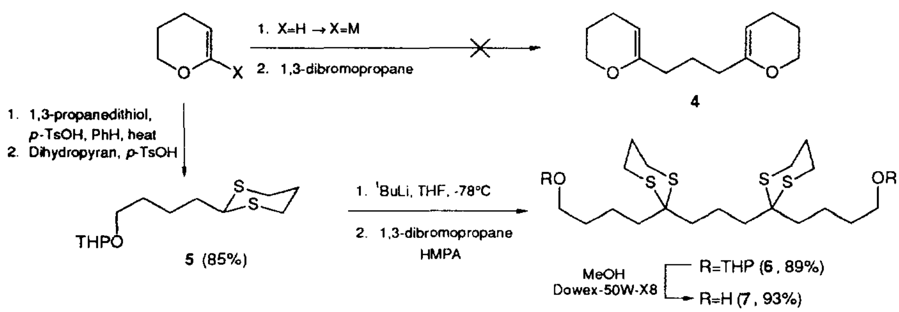


(2)

We have been interested in exploiting these stereoelectronic effects to define the geometry of higher-order polycyclic spiroketals. As a prelude to realization of more highly substituted functional arrays, we have examined the characteristics of the thermodynamically controlled polycyclization of diketodiol **2** to afford the parent *bis*-spiroketals (***cis*-3** and ***trans*-3**, eq 2). The stereochemical complexity of this cyclization process is increased significantly with respect to the Deslongchamps example as diastereomeric products are possible in addition to increased conformational ambiguity. While some studies on the synthesis of polyspiroketals have been reported, most notably the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene spiroketal core of members of the polyether antibiotics,[3] the unnatural 1,7,9-trioxadispiro[5.1.5.3]hexadecane system has received scant attention to date.[4] It was the objective of these studies to gain an understanding of the interplay of steric and stereoelectronic effects on the stability of these isomeric *bis*-spirocyclic arrays in the absence of additional substituent effects.

As the only available synthesis of ***cis*-3** and ***trans*-3** suffered from low overall yields[4] and appeared ill-suited to our future goals, we sought to develop a more efficient means of preparing these compounds. Having selected a strategy that features spirocyclization (see eq 2), synthetic approaches to protected derivatives of diketodiol **2** were examined. The highly symmetrical nature of **2** suggested that a rapid assembly of the carbon skeleton could be realized by treating the easily prepared anion of dihydropyran[5] with an appropriate *bis*-electrophile. Unfortunately, we were unable to define conditions to couple anionic derivatives of dihydropyran to 1,3-dibromopropane to afford the *bis*-enol ether **4** (Scheme I).[6] However, it was found that the derived dithiane **5** provided a very effective nucleophile for alkylation with this *bis*-electrophile to afford the intact carbon skeleton **6** in high yield (89%). Removal of the THP protecting groups resulted in a suitable spirocyclic precursor **7**.

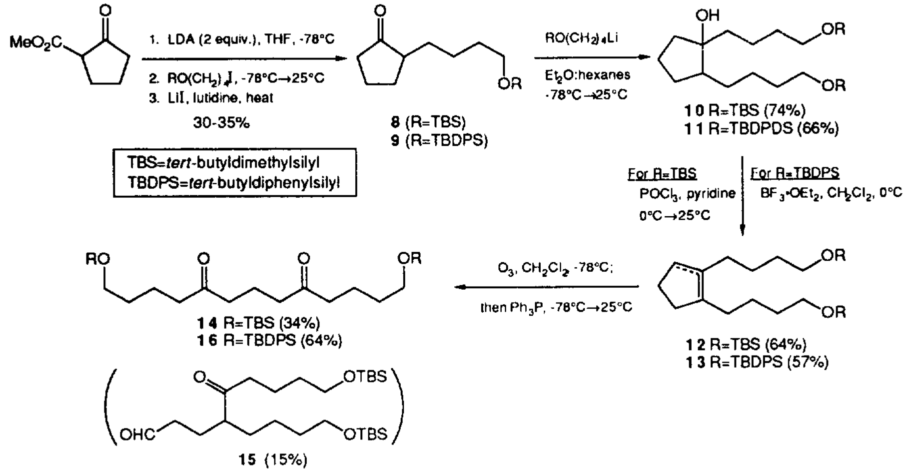
Scheme I



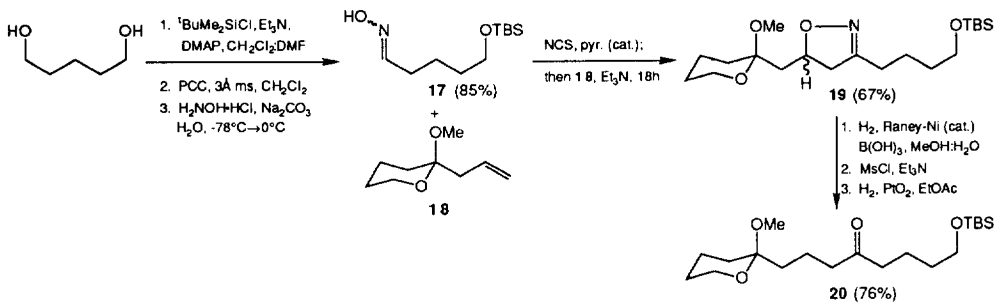
While this scheme offers a very concise approach to a protected derivative of **2**, our future needs dictated a synthetic strategy that would accommodate the introduction of additional substitution, including asymmetry. Consequently, other less symmetric synthetic approaches were explored. Viewing the two ketones in **2** as available from the oxidative cleavage of an olefin, a 1,2-disubstituted cyclopentene became an attractive candidate as a precursor to **2**. Toward this end, the dianion of 2-carbomethoxycyclopentanone[7] could be alkylated with a silyl-protected iodobutanol,[8] followed by Krapcho decarboxylation[10] to afford compounds **8** and **9** (Scheme II). Exposure of the ketone to $RO(CH_2)_4Li$[11] affords tertiary alcohols **10** and **11**. Dehydration of the *tert*-butyldimethylsilyl protected compound using $POCl_3$/pyridine resulted in a mixture of double bond isomers **12**. Alternatively, the more robust *tert*-butyldiphenylsilyl could be dehydrated using Posner's $BF_3{\bullet}OEt_2$ conditions[12] to give a single olefin **13**, though in modest yield. Oxidative cleavage of compounds **12** gave a 49% yield of a 3:1 mixture of desired diketone **14** and the isomeric ketoaldehyde **15**, while similar treatment of **13** afforded only diketone **16** in 64% yield.

The low overall yield of this sequence prompted a search for a more efficient, convergent route to protected diketodiols **2**. A strategy featuring the assembly of the carbon skeleton via a nitrile oxide cycloaddition reaction was successfully realized as shown in Scheme III. 1,5-Pentanediol was routinely converted into oxime **17**[13] which was subsequently transformed to the desired nitrile oxide.[14] Cycloaddition with the known ketal **18**[15] afforded a diastereomeric mixture of isoxazolines **19** in good yield. Reductive cleavage of the N-O bond[16] results in a β-hydroxy ketone which was deoxygenated via straightforward dehydration/hydrogenation to give a protected spiroketalization substrate in the form of **20**.

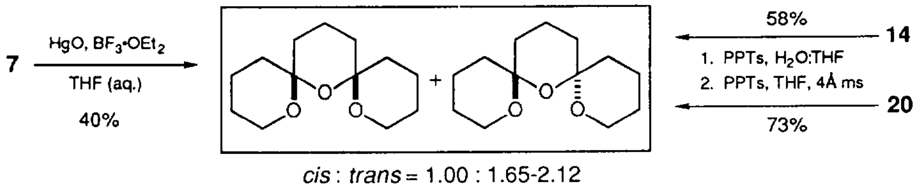
Scheme II



Scheme III



With compounds **7**, **14** (**16**), and **20** in hand, the stage was set to examine the self-organizational characteristics of the *bis*-spiroketalization reaction described in equation 2. The preparation of diketodiol **2** was realized from compound **7** through HgO-mediated removal of the thioketals[17] to result in direct spirocyclization to compounds **3** in 40% yield (eq 3). Alternatively, compounds **14** and **20** could be sequentially deprotected (to afford **2**) using aqueous pyridinium *p*-toluenesulfonate (PPTS), then cyclized to *bis*-spiroketals **3** through exposure to catalytic pyridinium *p*-toluenesulfonate under anhydrous conditions in 58% (**14**) and 73% (**20**) overall yield. With the success of these cyclizations, the goal of synthetic availability of the isomeric *bis*-spiroketals **3** is met with overall yields of 28% and 32% from dihydropyran and 1,5-pentanediol, respectively.



(3)

The stereochemical features of these polyspirocyclizations were examined by HPLC analysis of the crude reaction mixtures. In every instance, the *trans*-isomer was found to predominate in ratios ranging from 1.65:1 (from **7**) to 2.12:1 (from **20**). This observation is consistent with reports on related spiroketalization reactions[3,4] and apparently reflects the influences of stereoelectronic effects on the relative stability of ***cis*-3** and ***trans*-3**. It can be expected, therefore, that the diastereoselection expressed in spiroketalization reactions to give substituted 1,7,9-trioxadispiro[5.1.5.3]hexadecanes will also be affected by this stereoelectronic bias favoring a *trans*-relationship of the spirocyclic centers. The structural consequences of these stereoelectronic effects were examined in more detail in studies that are described in the following Communication.

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