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A Versatile Approach to Cyclic Ethers. Synthesis of Disubstituted Oxepanes and Oxocanes

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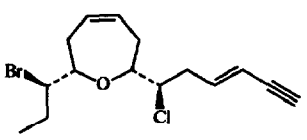
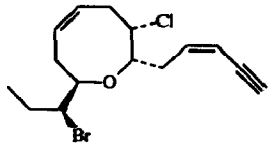
Abstract: **A synthetic sequence for the preparation of α,α'-disubstituted cyclic ethers of various ring sizes and either relative stereochemistry (*cis* or *trans*) is presented. It is based on the hetero Diels Alder reaction of a monoactivated diene and an aldehyde, yielding a silylenol pyrone which is transformed into a linear ether. This ether is cyclized by an intramolecular nucleophilic substitution reaction to the desired cyclic ethers. The viability of this route is demonstrated by the preparation of two examples, an oxocane and an oxolane.**

Cyclic ethers are found as a part of the structure of many natural products isolated from terrestrial and marine organisms, many of which show some kind of biological activity.[1] This fact, coupled with the interesting structural features present in a large number of these compounds, makes cyclic ethers attractive targets for synthesis.[2]

Most of the monocyclic compounds isolated from natural sources possess substituents at the two positions adjacent to the oxygen atom of the ether (α, α' positions). These substituents can exist in either the *cis* or *trans* relative configuration, as can be seen in the examples shown below.



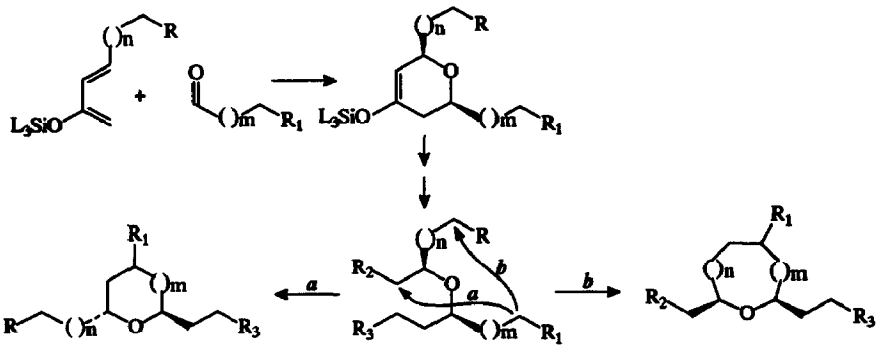
Isolaurepinnacin[3a]



cis-Dihydrorhodophytin[3b]

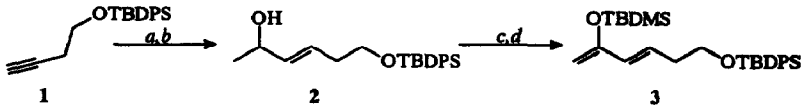
In this paper, we present our approach to the synthesis of this type of compounds, based on the intramolecular cyclization of a functionalized linear ether, which can in turn be obtained from the oxidative cleavage of dihydropyrones, resulting from the hetero Diels Alder reaction of monoactivated dienes and substituted aldehydes (Scheme 1).

The hetero Diels Alder reaction of activated dienes can be highly stereoselective when conducted under Lewis acid catalysis as demonstrated by Danishefsky et al,[4] and the relative stereochemistry of the substituents on the Diels-Alder adduct and hence on the linear ether, can be controlled by the choice of heterodienophile and whether it forms chelates with the Lewis acid or not.[5] According to Scheme 1, the length of the chain in both the diene and the dienophile (m, n) governs the size of the newly formed ring, whereas the position of the leaving group and of the carbanion stabilizing group determines the relative configuration of the substituents at the α and α' positions on the final product (paths *a* and *b* in Scheme 1).

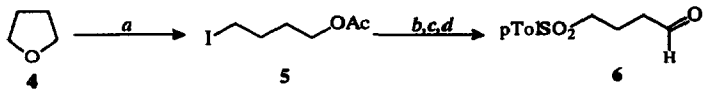


Scheme 1

In order to prove the viability of this approach, we decided to prepare two different cyclic ethers starting from the same diene and aldehyde. The preparation of the chosen diene and aldehyde is shown in Scheme 2.[6]



a) n-BuLi, THF, -78°C, CH_3CHO (94%); *b*) LAH , THF, 25°C (90%); *c*) Swern Ox. (90%); *d*) TBDMSOTf, TEA, 0°C (98%)



a) Zn, Ac_2O, HI (90%); *b*) $NaSO_2pTol$, DMF, 60°C (95%); *c*) K_2CO_3, MeOH (90%); *d*) Swern Ox. (85%)

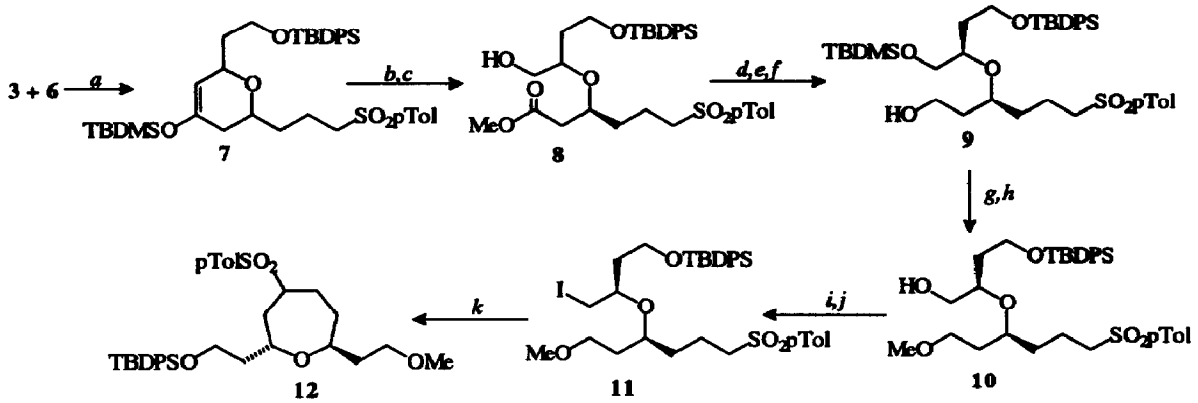
Scheme 2

The diene **3** contains a protected hydroxyl group suitable for transformation into a leaving group, whereas the sulfone present in the aldehyde **6** will serve as the carbanion stabilizing group needed for the cyclization step.

The hetero Diels Alder reaction between **3** and **6** was carried out at room temperature, using $LiBF_4$ as the Lewis acid and benzene/acetonitrile as the solvent[7] (Scheme 3). The mixture of diastereoisomeric dihydropyrones **7** (70:30 by NMR analysis) was subjected to ozonolysis in methanol followed by the addition of excess $NaBH_4$ and treatment of the crude reaction mixture with diazomethane to facilitate the work-up. The two diastereoisomers were readily separated at this point by column chromatography, and the racemic major compound (the *cis* isomer) was used in the following steps.

The preparation of the seven-ring system with a *trans* stereochemistry was undertaken in the first place, following path *a* of Scheme 1. The hydroxyl group present in **8** was protected and the ester reduced with excess DIBAL. At this point, we decided to protect the resulting hydroxy group as a methyl ether for simplicity, but a different protecting group can be introduced if further elaboration of the cyclic ether is

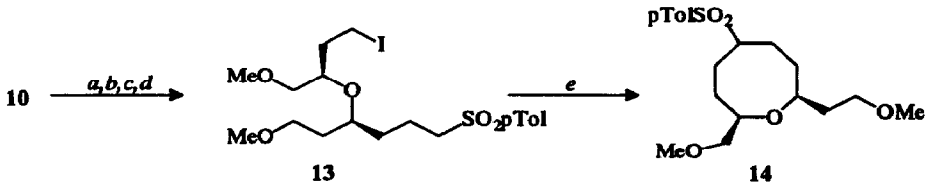
desired. After treatment with NaH and MeI, the resulting compound was selectively deprotected, and the hydroxy group was transformed into the iodide **11** by tosylation and treatment with NaI (Scheme 3).



a) $LiBF_4$, Be/CH_3CN (77%); *b*) *i* O_3, MeOH, -78°C, *ii* $NaBH_4$; *c*) CH_2N_2, ether (74%); *d*) Isomer separation; *e*) TBDMSCl, imidazole, THF (95%); *f*) DIBAL, THF (95%); *g*) NaH, MeI, THF (96%); *h*) AcOH, THF, H_2O, 3:1:1 (85%); *i*) TsCl, DMAP, TEA , THF (99%); *j*) NaI, $(CH_3)_2CO$, 40°C (86%); *k*) LDA, THF, -78°C→-40°C (21%)

Scheme 3

Iodide was chosen as the leaving group since the use of tosylate did not yield any cyclization product. After several attempts, compound **12**[8] was obtained, as a single isomer in a 21% yield, by treatment with excess LDA (4.5 eq.) in THF at -80°C, and allowing the reaction mixture to warm up to -40°C (2h.). Difficulties for the coupling of similarly substituted systems (tosylates and iodides bearing a β-alkoxy substituent) with alkinyllithiums have been reported previously,[9] and this prompted us to try out the preparation of the eight-member ring system (path *b* in Scheme 1), since in this case the oxygen is located in the γ position from the leaving group. Compound **10** was transformed into the iodide **13** as shown in Scheme 4. As before, the tosylate showed little reactivity towards cyclization. However, when **13** was treated with excess of LDA under the same conditions as before, the desired oxocane **14**[10] was isolated in 80% yield, as a single isomer.



a) NaH, MeI, THF (89%); *b*) Bu_4NF, THF 0°C (81%); *c*) TsCl, DMAP, TEA (90%); *d*) NaI, $(CH_3)_2CO$, 25°C (75%); *e*) LDA, THF, -78°C → -40°C (80%).

Scheme 4

It is interesting to note that the substitution of the tosylate by the iodide requires somewhat stronger reaction conditions in the preparation of **11** (40°C) than in the case of **13** (room temperature), supporting the

idea that the presence of a β-alkoxy substituent is responsible for the difficulties encountered in the nucleophilic substitution reaction and hence for the low yield attained in the cyclization of **11**.

The successful preparation of **12** and **14** demonstrates the viability of the proposed synthetic scheme, which yields polysubstituted cyclic ethers with functional groups in their skeleton that can be used as synthons to prepare monocyclic natural products, or when carried out with more substituted starting material (diene and dienophile), can serve as precursors of polycyclic compounds.

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