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Addition of Metalated Pyrones to β-Alkoxy Aldehydes: Synthesis of Hydroxylated Spiroketals

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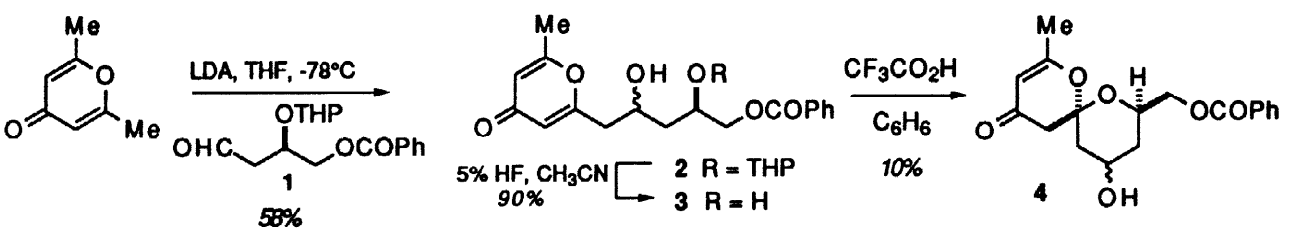
Abstract: Addition of lithiated γ-pyrones to β-alkoxy aldehydes followed by acid catalyzed spiroketalization provides a rapid efficient entry to functionalized hydroxylated spiroketals. The efficiency of the spiroketalization step is dependent on the substituents, particularly unprotected hydroxyls, on the chain which becomes the second ring of the spiroketal.

The 1,7-dioxaspiro[5.5]undecane (6,6-spiroketal) moiety is commonly found in natural products of biological interest.[1] The most common synthetic approach to spiroketals has been through the intramolecular ketalization of the fully elaborated dihydroxyketones in which the acyclic stereogenicity dictates the configuration of the anomeric center.[2] However, the conformational rigidity and thermodynamic stability of spiroketals also create the possibility for the use of the spiroketal scaffold as a template for stereocontrol.[3-5] An efficient approach to spiroketals with appropriate functionality for further elaboration would be of substantial utility in the construction of highly substituted spiroketals. We have previously demonstrated that the cyclization of hydroxy pyrones, prepared by the addition of the lithium acetylide of methoxybutenyne to lactones, provides an efficient entry into spiroketal enones.[6] In the search for an even more direct approach, the addition of metalated pyrones to β-alkoxy aldehydes followed by acid catalyzed cyclization of the hydroxy pyrones has been investigated as a method for the construction of highly functionalized spiroketal subunits.

Scheme 1



Metalation of 2,6-dimethylpyrone with LDA,[7] followed by addition of β-alkoxy aldehyde **1** (Scheme 1) gave the pyrone **2**[8] in 58% yield, however, attempts to effect cyclization of the hydroxy pyrone **3** to the spiroketal **4** met with limited success even after extended exposure to acid. The low conversion in the cyclization was attributed to the free hydroxyl in **3** which was thought to stabilize the open chain pyrone through extended hydrogen bonding. In an effort to reduce the intramolecular hydrogen bonding and improve the spiroketalization, pyrone **6** was constructed from the homologous aldehyde **5** and the free hydroxyl was

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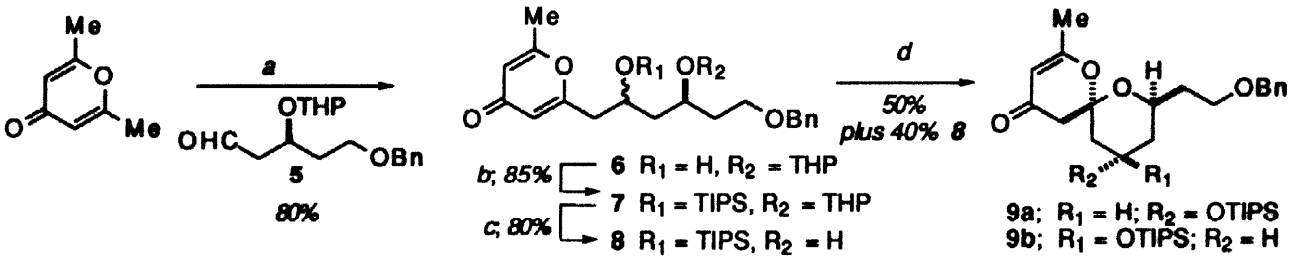
protected to give the TIPS ether **7** as shown in Scheme 2. When the THP protecting group was removed from pyrone **7** the cyclization occurred more readily providing spiroketal **9** in 50% yield for two steps accompanied by 45% of the hydroxypyrone.[8] The pyrone and spiroketal are readily separated by chromatography to allow easy recycling of the unreacted pyrone.

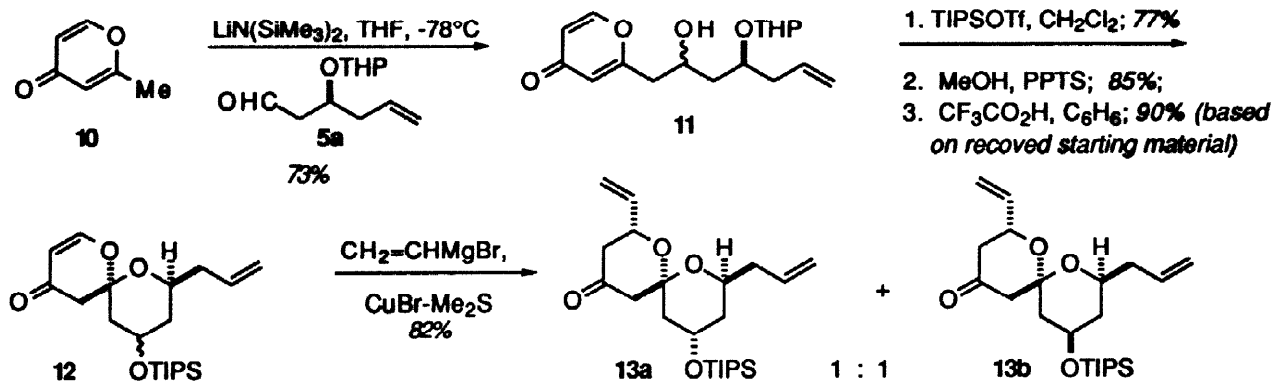
Scheme 2



Conditions: (a) LDA, THF, -78°C; (b) TIPSOTf, CH_2Cl_2; (c) MeOH, PPTS; (d) CF_3CO_2H, C_6H_6.

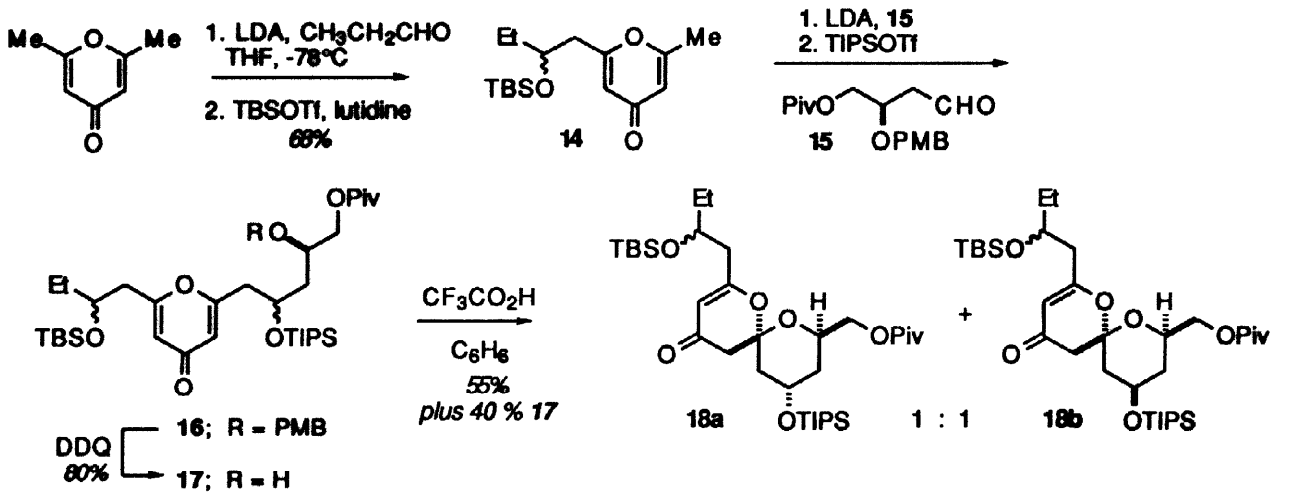
Similarly, 2-methyl-γ-pyrone **10** (prepared from Meldrum's Acid)[9] was deprotonated with $LiN(SiMe_3)_2$ followed by addition of aldehyde **5a** to afford the pyrone **11** in good yield. Protection of the secondary hydroxyl as before, followed by removal of the THP and acid catalyzed cyclization provided the spiroenone **12** in good overall yield. The spiroenone **12** was further functionalized by copper catalyzed addition of vinyl magnesium bromide to the enone with excellent stereoselectivity (95:5 d.s.).[5] The allyl group apparently functions to restrict attack from the axial face of the enone resulting in predominantly equatorial addition.

Scheme 3



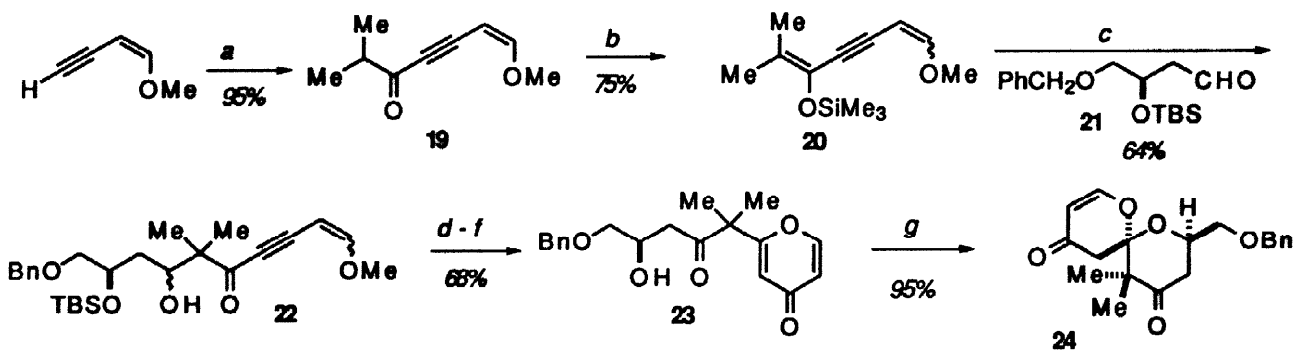
An important feature of the pyrone approach is the potential for carbon-carbon bond formation at each of the two methyl groups of 2,6-dimethylpyrone. To accomplish the chain extension, the pyrone **14** (Scheme 4) was lithiated with LDA and exposed to aldehyde **15** affording a good yield of the pyrone **16** after protection of the secondary hydroxyl as a TIPS ether. Subsequent removal of the PMB ether with DDQ produced the hydroxypyrone **17** which was cyclized under the usual conditions to give spiroketals **18a,b**.

Scheme 4



An attempt to metalate 2-isopropyl-γ-pyrone[9] as a method to prepare gem-dimethyl substituted spiroketal systems failed because of competing conjugate addition of the base to the pyrone. Due to the inability to efficiently metalate 2-isopropyl-γ-pyrone without competing conjugate addition of the base to the 6-position of the pyrone, an alternate approach to the synthesis of the more highly substituted spiroketal building blocks was undertaken (Scheme 5). Rather than starting with the pyrone, a pyrone precursor **20** was constructed from ketone **19**. Ketone **19** was prepared from 1-methoxy-1-butene-3-yne by addition of the acetylide (*n*-BuLi, THF, -78° C) to isobutyric anhydride.[10] The ketone **19** was readily converted to its silyl enol ether by exposure to chlorotrimethylsilane and triethylamine.[11] A Lewis acid catalyzed condensation[12] of silyl enol ether **20** with β-alkoxy aldehydes was then investigated. Treatment of a mixture of **20** and the aldehyde **21** with $TiCl_4$ at -78°C gave the acetylenic ketone **22** which was converted to the ketopyrone **23** and subsequently cyclized to the spiroketal **24** in excellent yield. The spiroketal **24** or a similar variant could serve as the key building block for

Scheme 5



Conditions: (a) *n*-BuLi, THF, $[(CH_3)_2CHCO_2]_2O$, -78°C; (b) TMSCl, Et_3N; (c) $TiCl_4$, CH_2Cl_2, -78°C; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (e) K_2CO_3, MeOH; (f) 5% HF, CH_3CN; (g) Cl_3CCO_2H, C_6H_6

both the C1 to C12 fragment and the C14 to C27 fragment of bryostatin 11.[13] Use of silyl enol ether **20** is somewhat less efficient than direct addition of metalated pyrones, but provides access to more highly susbstituted spiroketals in good overall yields. The application of this general approach to the preparation of spiroketal fragments for a variety of hydroxylated spiroketal fragments found in natural products is currently in progress.

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References and Notes

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