Tetrahydrofurans from Substituted Hex-5-yne-1,4-diols

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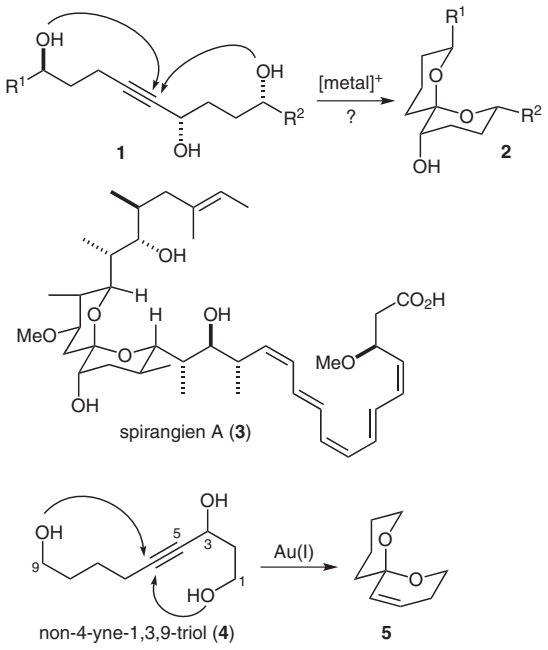
Abstract: It was discovered that substituted hex-5-yne-1,4-diols like **16**, **28**, and **30** undergo a domino sequence of Meyer–Schuster rearrangement followed by Michael addition forming 2,5-disubstituted tetrahydrofurans in presence of $PtCl_2$.

Key words: alkynes, domino reaction, Michael addition, organometallic reagents, rearrangement

The carbon–carbon triple bond represents an extremely versatile functional group in organic synthesis. In particular it can engage in a number of unique transformations. For example, metallacyclopentenes and metallacyclopentadienes are key intermediates in classical transformations involving alkynes. But alkynes can also be considered dehydrated ketones. The well-known hydration of alkynes is typically performed in presence of Hg(II) salts and strong acids.[1] In recent years the chemistry of alkynes has been extended by employing other soft electrophilic metals, like Au(I) or Pt(II) salts for promoting nucleophilic attack.[2] Thus, with internal hydroxyl functions, enol ethers and related compounds could be obtained from alkynols.[3] Furthermore, such metal-promoted additions of internal oxygen-based nucleophiles have been exploited for some unique domino reactions.[4] Some groups already reported on the synthesis of spiroacetals[5] and bridged ketals[6] from alkynediols. Spiroactals are frequently found in polyketide-based natural products.[7] They provide a unique shape and curvature for a molecule. In this regard they can also be considered as a natural scaffold.[8] With a view to the synthesis of the spiroacetal fragment of spirangien A, we conceived the cyclization of substrates containing a non-5-yne-1,4,9-triol subunit (**1** → **2**, Scheme 1). The spirangiens were described in 2005 by Höfle et al.[9] Spirangien A (**3**) displays potent antifungal and cytotoxic properties. In addition to the complex highly unsaturated side chain there is a hydroxyl group next to the spiro acetal function. The known routes to the spirangien spiroacetal rely on the classical acetalization of a dihydroxyketone precursor.[10,11] A related substrate **4** containing also a propargylic alcohol substructure was recently reported to cyclize to spiroacetal **5**.[5c]

A corresponding model substrate **16** could be easily assembled from methyl (3*R*)-hydroxybutanoate[12] **6** (Scheme 2). Via silylation of the alcohol[13] and reduction of the ester function alcohol **8** was obtained.[14] The alcohol



Scheme 1 Planned metal-catalyzed cyclization of non-5-yne-1,4,9-triols to spiroacetals. Structure of spirangien A (**3**) and example for a Au(I)-catalyzed spiroacetal formation

could be extended to nitrile **10** via mesylate **9** followed by substitution with cyanide (78%, 2 steps). A substitution of the alcohol under Mitsunobu conditions[15] (DEAD, acetone cyanohydrin toluene) gave nitrile **10** in 67% yield. Treatment of nitrile **10** with DIBAL-H (1.4 equiv) in toluene furnished the key aldehyde **11**. Part of this aldehyde was converted to alkyne **13** employing dimethyl 1-diazo-2-oxopropylphosphonate[16] (**12**) as C-1 building block. In the next step alkyne **13** was added under Carreira conditions to aldehyde **11** using zinc triflate and (–)-*N*-methylephedrine (**14**) as additives.[17] This way a 60% yield of alkynol **15** could be realized. Cleavage of the two silicon protecting groups gave rise to undec-6-in-2,5,10-triol (**16**). The fact that **16** only shows one set of signals in the ^{13}C NMR spectrum indicates the high selectivity in the Carreira reaction. Alkynetriol **16**, dissolved in toluene, was then subjected to some metal catalysts. While Ph_3PAgCl and Ph_3PAuCl left the substrate unchanged, $PtCl_2$ (40 mol%) in toluene induced the formation of a new product. Inspection of the ^{13}C NMR indicated the lack of an acetal C but the presence of a keto function (209.3 ppm). Acetylation (Ac_2O, pyridine) showed that one of the OH groups was free. These data, the DEPT and COSY spectrum led to the conclusion that tetrahydrofuran

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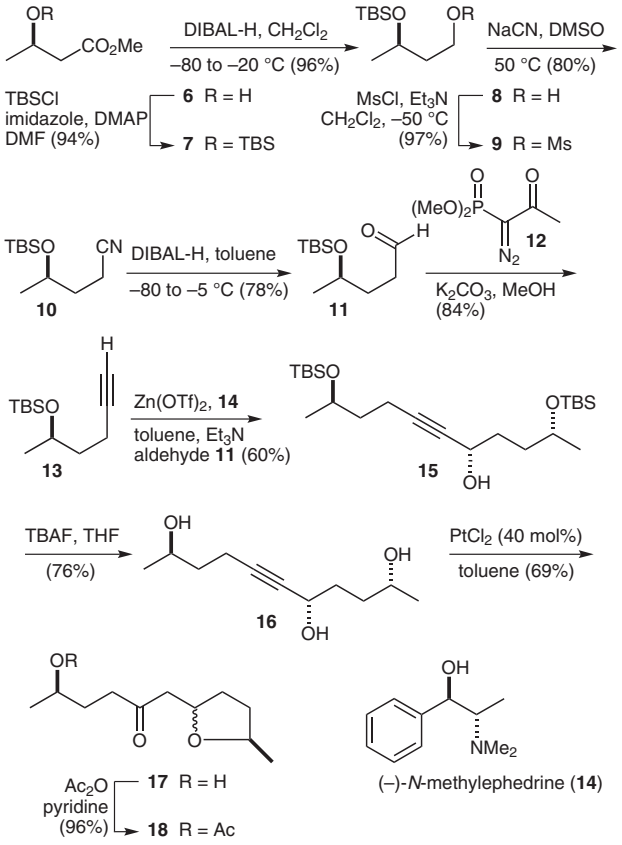
17 was formed from alkynetriol **16**. Alcohol **17** and acetate **18** showed the presence of diastereomers (62:38).

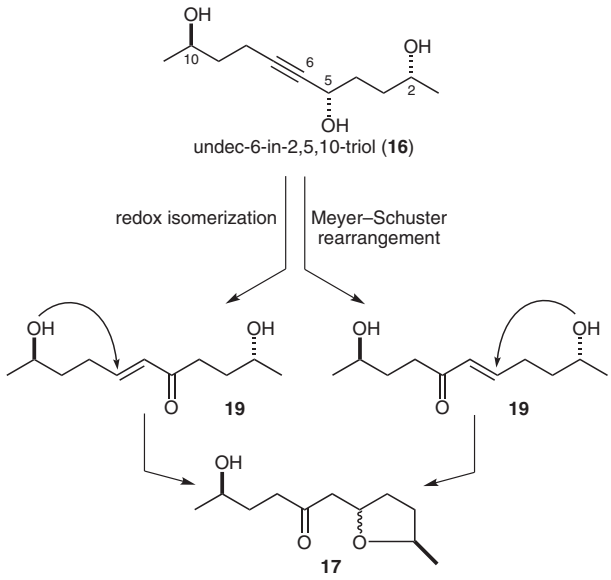


Scheme 2 Conversion of butanoate **6** to undec-6-in-2,5,10-triol (**16**) and its $PtCl_2$-catalyzed formation of tetrahydrofuran **17**

The formation of tetrahydrofuran **17** can be explained by an intramolecular oxa-Michael addition to enone **19** (Scheme 3). Due to partial symmetry within substrate **16** it was however not possible to distinguish between a metal-catalyzed redox isomerization[18] or a Meyer–Schuster rearrangement[19] of the central alkynol to the enone.

Therefore some other substrates were prepared that would allow to probe the isomerization mechanism. The general sequence is shown in Scheme 4. Substituted acetaldehydes **20a**,**b** were subjected to a one-pot proline-catalyzed α-aminoxylation, Wittig–Horner reaction and cleavage of the N–O bond leading to 4-hydroxy enoates **22a**,**b**.[20] A final catalytic hydrogenation furnished the 4-hydroxy esters **23a**,**b**. For the examples studied, the ee values of **22a**,**b** were very high. Via silylation of the hydroxyl function, ester reduction and Dess–Martin oxidation, aldehydes **26a**,**b** could be secured.

Using the two aldehydes **26a**,**b** addition of propynyllithium, generated by metalation of propenyl bromide,[21] followed be removal of the silyl protecting group led to alkynediols **28** with an inner triple bond. Aldehyde **26a** was also reacted with (phenylethynyl)lithium leading to propargylic alcohol **29** and after deprotection to 1,7-diphenylhept-6-yne-2,5-diol (**30**).



Scheme 3 Redox isomerization as well as Meyer–Schuster rearrangement might explain the formation of furanon **17**

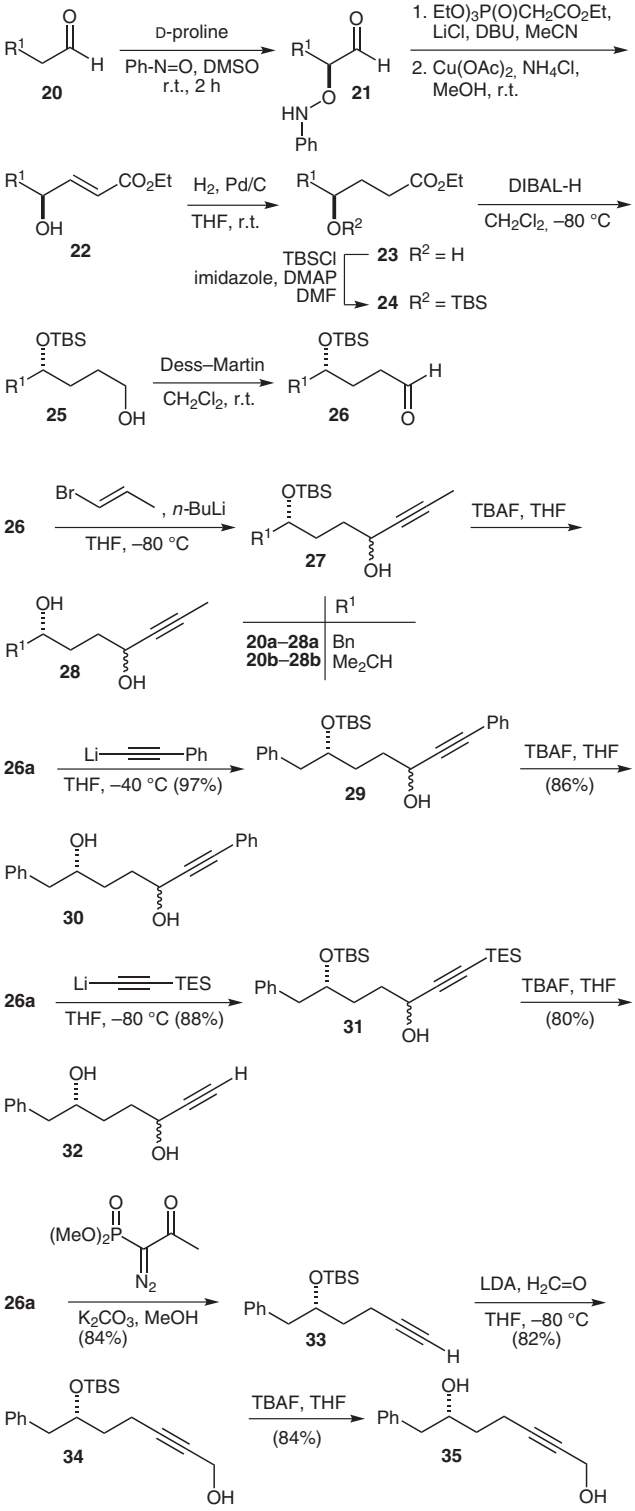
In order to probe the effect of an inner alkyne versus a terminal one, propargyl alcohol **32** was prepared from aldehyde **26a** by addition of lithium acetylide (THF, –80 °C) followed by cleavage of the silyl ether.

For the Bn series we also prepared the isomer where the triple bond is between the two hydroxyl groups, namely propargyl alcohol **35**. This substrate could be obtained from **26a** via Bestmann–Ohira alkyne formation (82%) yielding alkyne **33**. The corresponding lithium acetylide (LDA, THF, –80 °C) was added to paraformaldehyde to provide ultimately propargyl alcohol **35**.

The five compounds (**32**, **35**, **28a**,**b**, and **30**) were then subjected to a substoichiometric amount of $PtCl_2$ in toluene at room temperature (Scheme 5). In case of **32** the classical hydration product, hemiacetal **36** was formed as a mixture of diastereomers. From propargylic alcohol **35** the tetrahydrofuran would result if a redox isomerization would be induced by $PtCl_2$. However, with this substrate a complex mixture of products was formed that was not further analyzed. In contrast, the hexyne diol **28a** furnished a reasonable yield (48%) of 2,5-disubstituted furan **37a**. This shows that $PtCl_2$ had induced a Meyer–Schuster rearrangement prior to the oxa-Michael addition. Better results were obtained with the combination $(Ph_3P)AuCl/AgBF_4$ in toluene. Under these conditions the tetrahydrofuran **37a** was formed in 74% yield.

In the same manner substrate **28b** could be converted to the corresponding tetrahydrofuran **37b**. The diastereomeric ratio was in the range 1:1 (84% yield). The reaction did also work with the phenyl-substituted substrate **30** producing tetrahydrofuran **38** (50% yield, dr = 1:1).

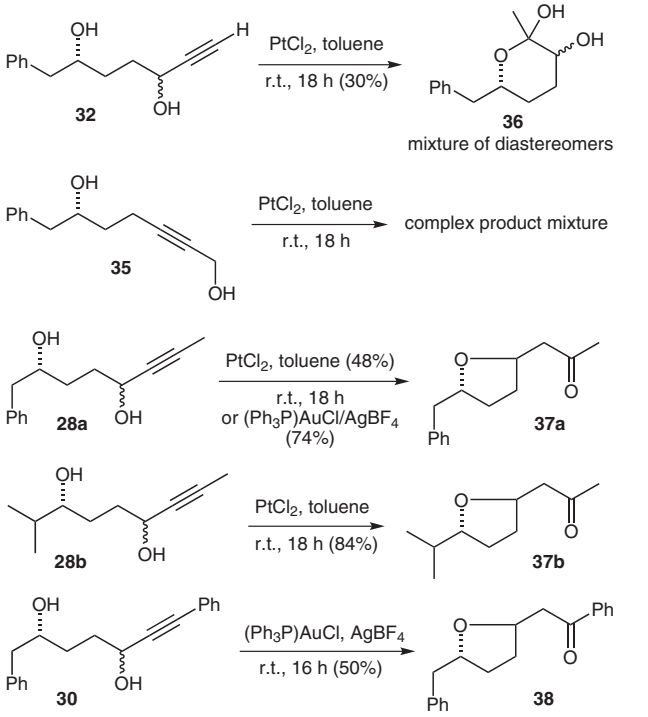
Thus, we could show that metal cations like Pt(II) or Au(I) are able to promote a formal Meyer–Schuster rearrangement of propargylic alcohols. With a suitably positioned hydroxyl function a subsequent oxa-Michael addition



Scheme 4 Synthesis of substrates for probing the alkynol isomerization mechanism

gave 2,5-disubstituted tetrahydrofurans. Possibly, this interesting domino sequence can be extended to other heterocycles or applied in a transannular fashion.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.



Scheme 5 Reactions of alkynediols **32** and **35** with $PtCl_2$. Cyclization of the alkynediols **28a**, **28b**, and **30** to the tetrahydrofurans **37a**, **37b**, and **38**, respectively, via metal-induced Meyer–Schuster rearrangement and oxa-Michael addition

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