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Synthesis of Furo[2,3*b*]furans and Furo[2,3*b*]pyrans via Rhodium-Catalyzed Tandem Hydroformylation/Acetalization

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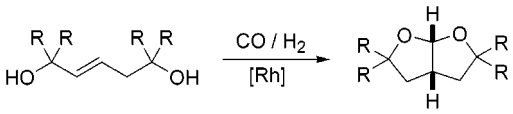
ABSTRACT



Rhodium-catalyzed tandem hydroformylation/acetalization of α,ω-alkenediols gives facile access to perhydrofuro[2,3*b*]furans and perhydrofuro-[2,3*b*]pyrans in good yields. Similarly, benzoannelated tetrahydrofuro[2,3*b*]furans are obtained by hydroformylation of *o*-hydroxy cinnamyl alcohols.

Fused polycyclic acetals are embodied in a wide range of natural products. Among bicyclic acetals, the tetrahydrofuro-[2,3*b*]furans are of special interest since both aliphatic and benzoannelated compounds of biological and pharmaceutical activity are known. Therefore, these oxabicycles are attractive targets for total synthesis.[1]

Important groups of compounds with the furo[2,3*b*]furan skeleton are clerodane-type diterpenes[2] with their insect antifeedant and antibacterial activity,[3] and the aflatoxins,[4] mycotoxins with a high toxicity and carcinogenicity that are produced by *Aspergillus flavus* and are able to contaminate different types of food[5] (Figure 1).

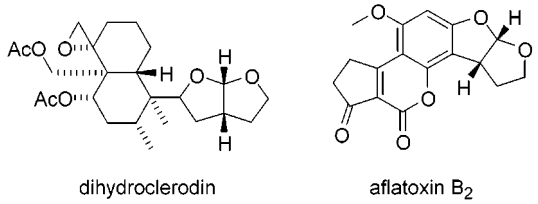


Figure 1. Natural products containing bicyclic acetal units.

Several routes toward these bicyclic acetals proceed via the formation of dihydroxy aldehydes,[6] which undergo spontaneous acetalization forming cis-fused bicyclic acetals. These aldehydes should be easily accessible by hydroformylation of adequately substituted olefins omitting the otherwise necessary protective strategies.

It is known that hydroformylation of unsaturated alcohols results in cyclic hemiacetals.[7] These reactions can be performed in the presence of various functional groups enabling the synthesis of complex target molecules.[8] Thus, we expected the direct formation of bicyclic acetals via a

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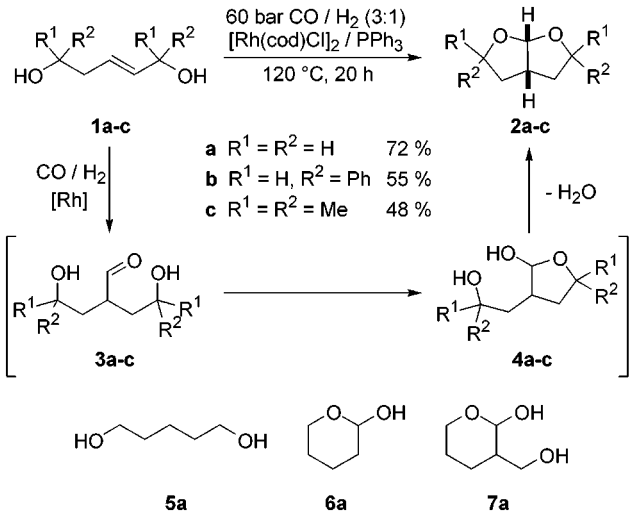
previously unknown tandem hydroformylation/acetalization of alkenediols (Scheme 1).

Scheme 1



Starting with pent-2-ene-1,5-diol (**1a**)[9] as a model compound, we obtained perhydrofuro[2,3*b*]furan (**2a**) in up to 72% yield. The optimal reaction conditions are found at a reaction temperature of 120 °C and a total pressure of 60 bar syngas ($CO:H_2$ = 3:1) using the catalyst system [Rh(cod)Cl]$_2$/PPh_3 with dichloromethane as the solvent.[10] A coupling constant of 5.0 Hz for the bridgehead protons demonstrates the exclusive formation of cis-fused bicycles.

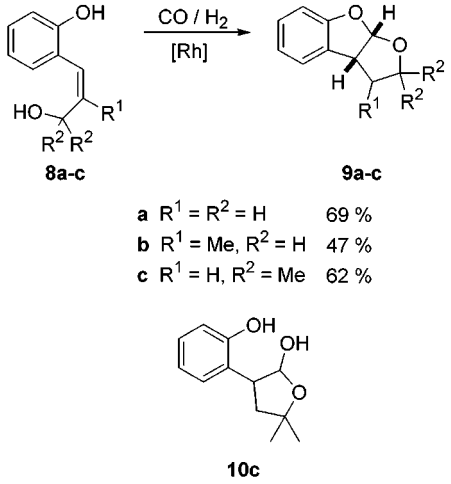
Under nonoptimized conditions, several byproducts can be observed, among them the hydrogenation product **5a**, tetrahydropyran-2-ol (**6a**), which is formed via a rhodium-catalyzed double-bond migration to the enol and addition of the second hydroxy group to the enol forming the hemiacetal. The saturated diol **5a** was only observed when the phosphine ligand was omitted. Furthermore, a regioisomeric hydroformylation product **7a** can be formed, which undergoes only hemiacetalization. This regioisomer was only observed when using 1,4-dioxane as the solvent.

This reaction sequence can also be applied to substituted alcohols. The 1,5-diphenyl-substituted alkenediol **1b**[11] affords the desired furofuran **2c** in 55% yield. The 2,2,5,5-tetramethyl-substituted furofuran **2c** is obtained in 48% yield starting from the alkenediol **1c**.[11]

The decline of the yields can be attributed both to steric shielding of the double bond and to side reactions of the higher-substituted alcohols, especially dehydration of the diol and subsequent reactions to be expected thereof. Thus, further optimization is required here for each individual substrate.

For the synthesis of benzoannelated tetrahydrofuro[2,3*b*]furans we used *o*-hydroxy cinnamyl alcohols **8** as starting compounds, which can be easily prepared starting from coumarins.[12] Unlike the aliphatic pentenediols, these cinnamyl alcohols undergo regioselective hydroformylation, as shown by Nozaki et al.[13] for the formation of phenyl-substituted tetrahydrofuran-2-ols. Under optimized conditions, the desired *cis*-2,3,3a,8a-tetrahydrofuro[2,3*b*]benzofuran (**9a**)[14] is obtained starting from the unsubstituted diol **8a** in 69% yield (Scheme 2) at 60 °C using the Rh(acac)$(CO)_2$/PPh_3 catalyst system with 1,4-dioxane as the solvent.

Scheme 2



Similar to the aliphatic olefins, isomerization and hydrogenation products are observed and their ratio increases if the reaction is performed at higher reaction temperatures in the absence of phosphine ligands.

Substituents at the double bond or at the aliphatic alcohol moiety enable the formation of substituted tetrahydrofurobenzofurans. Since these cinnamyl alcohols are less reactive than the unsubstituted olefin **8a**, we examined their reactions only at 120 °C.

Under these conditions 2,3,3a,8a-tetrahydro-3-methylfuro[2,3*b*]benzofuran (**9b**) is obtained in 47% yield starting from the trisubstituted olefin **8b**. The substituted tetrahydrofuro[2,3*b*]benzofuran **9b** is obtained as a 7:1 mixture of two diastereomers, where the heterocyclic rings are cis-fused.

Analogously, the tandem hydroformylation acetalization of 2-((*Z*)-3-hydroxy-3-methylbut-1-enyl)-phenol (**8c**) gives access to 2,3,3a,8a-tetrahydro-2,2-dimethylfuro[2,3*b*]-benzofuran (**9c**) in 62% yield. Under milder reaction conditions at 60 °C, only the hemiacetal **10c** as a 1:1 mixture of two

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(10) **Typical procedure.** A solution of 512 mg (5.0 mmol) of pent-2-ene-1,5-diol (**1a**), 12 mg (25 μmol) of [Rh(cod)Cl]$_2$, and 40 mg (150 μmol) of PPh_3 in 10 mL of dichloromethane is heated for 20 h at 120 °C in an autoclave under an atmosphere of 45 bar carbon monoxide and 15 bar hydrogen. Purification of the crude product by column chromatography on basic alumina with MTBE followed by ethanol as eluants gives 411 mg (3.6 mmol) of perhydrofuro[2, 3*b*]furan (**2a**).

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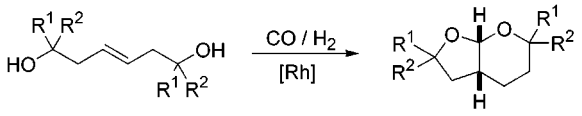
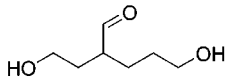
Scheme 3



11a-d **12a-d**

a $R^1 = R^2 = H$ 92 %
b $R^1 = R^2 = Me$ 96 %
c R^1-R^2 = -$(CH_2)_5$- 74 %
d $R^1 = H$, $R^2 = Ph$ 40 %



13a

diastereomers is observed. This intermediate is completely transformed to the acetal **9c** by acid-catalyzed acetalization using *p*-toluenesulfonic acid at elevated temperatures.

This new tandem reaction is not limited to the synthesis of tetrahydrofurofurans, but can also be used for the preparation of perhydrofuro[2,3*b*]pyrans from 3-alkene-1,6-diols.

With these symmetric olefins, only one hydroformylation product can be expected. Therefore, higher yields for both the unsubstituted hex-3-ene-1,6-diol (**11a**)[15] and the substituted tertiary alcohols **11b** and **11c**[16] are obtained. The unsubstituted perhydrofuro[2,3*b*]pyran (**12a**) is generated in 92% yield. The only observed byproduct is the aldehyde **13a**, an intermediate of the reaction sequence, which is obtained in 6% yield (Scheme 3). The aldehyde **13a** is transformed into the bicyclic acetal **12a** as the sole product analogous to the aryl-substituted hemiacetal **10c** in an acid-catalyzed cyclization. NMR experiments once again affirm the exclusive formation of cis-fused bicycles.

In this case, excellent yields are also observed for the tertiary alcohols **11b** und **11c**. These are explained by the reduced steric hindrance due to the additional methylene group in the starting olefin in comparison to the 1,5-alkenediols. 2,2,6,6-tetramethyl-(3a*S**,7a*R**)-perhydrofuro[2,3*b*]-pyran (**12b**) is obtained in 96% yield; the tetracyclic spiroannelated acetal **12c** is obtained in 74% yield.

The 1,6-diphenyl-substituted hexenediol **11d**, however, up to now provided the furopyran **12d** in lower yields than the related furofuran **2b**. Apparently, the formation of conjugated olefin via dehydration of the benzylic alcohols causes a reduced chemoselectivity of the hydroformylation of **11d**. Therefore, for this alkenediol, further optimization of the reaction conditions is necessary.

In conclusion, a new viable method for the construction of aliphatic and benzoannelated furo[2,3*b*]furans and furo-[2,3*b*]pyrans has been introduced. Starting from easily accessible alkenediols, these heterocycles are selectively formed in a new rhodium-catalyzed tandem hydroformylation/acetalization reaction. Since hydroformylation tolerates various functionalized groups,[8] it should also be possible here to introduce different substituents into the starting olefins, enabling the synthesis of interesting building blocks for target molecules. Further investigations leading to the total synthesis of selected natural products are currently underway in our laboratories.

Supporting Information Available: Experimental procedures and full spectroscopic and analytical characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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