Novel Spiroacetal Synthesis via Hydroboration of Alkynediols

Keigo Fugami, Nobuhito Hagiwara, Takeaki Okeda, and Masanori Kosugi*
Department of Chemistry, Faculty of Engineering, Gunma University, Kiryu, Gunma 376

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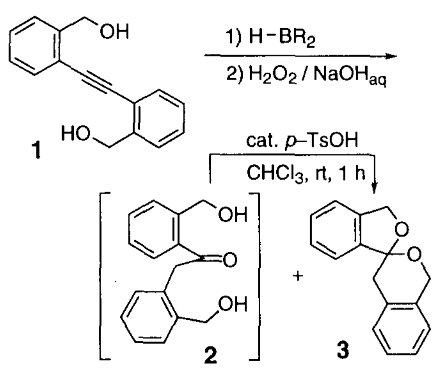
Alkynediols were transformed to the corresponding spiroacetals by the sequence of hydroboration with disiamylborane, oxidation of the resulting alkenylboron intermediate with alkaline hydrogen peroxide, and catalytic treatment with *p*-TsOH. By this transformation, 6-(2-hydroxymethyl)phenyl-3-methyl-5-hexyn-1-ol was converted to spiro[3,4-dihydro-1*H*-2-benzopyran-3,2'-[4']methyl[3',4',5',6']tetrahydro-2'*H*-pyran] as a single diastereomer.

Hydroboration of internal alkynes with less reactive boranes such as disiamylborane, dicyclohexylborane, and catecholborane affords the corresponding alkenylboranes. On the other hand, that with more reactive boranes such as borane-tetrahydrofuran (THF) complex and 9-BBN may proceed further to the corresponding *gem*-diboroalkanes.[1a] By the oxidation with alkaline hydrogen peroxide, the former provide the corresponding ketones,[1b] while the latter give the alcohols via the partial hydrolysis of the carbon-boron bonds.[2] The latter can also lead to the ketones if an excess of borane-THF complex was used for the hydroboration.[2]

Spiroacetal skeletons are often found in a variety of biologically intriguing compounds.[3,4] One of the representative synthetic strategies to spiroacetals is acetalization of the corresponding ketodiols or its equivalents.[3,4] Palladium(II) catalyzed spiroacetal synthesis under wet conditions has brought alkynediols into consideration as a precursor.[5] Here we disclose our results on a novel spiroacetal synthesis via hydroboration of unprotected alkynediols.[6]



Scheme 1.

After hydroboration of the alkynediol **1**, the reaction mixture was treated with alkaline hydrogen peroxide,[7] and then the products were extracted with $CHCl_3$. Since the ketodiol **2** if formed was prone to the dehydrative spiroacetalization, the $CHCl_3$ extract was treated with *p*-TsOH (3 mol% to **1**, rt, 1h) to complete the conversion of **2** to **3**. The results varied with the conditions of hydroboration as shown Table 1. Whenever borane-THF was used as the hydroborating agent, the reaction sequence afforded the triol **4**, predominantly. To our surprise, the tendency was retained even when an excess of borane was employed for the hydroboration.[2] This result may suggest that the benzylic carbon-boron bond is extraordinary sensitive to hydrolysis. The course of the reaction was quite altered by switching the hydroborating agent from borane-THF complex to disiamylborane. The reaction sequence provided the desired spiroacetal **3** in good yield, when the hydroboration was performed under refluxing THF. The triol **4** was not detected.

Table 1. Spiroacetal Synthesis via Hydroboration of **1**

run	HBR_2 (mmol)[a]	temperature[b]	yield / % **3**	yield / % **4**
1	H_3B•THF (2.4)	rt	14	62
2		reflux	17	63
3		120 °C	complex mixture	
4	(6.0)	0 °C	6	18[c]
5		reflux	11	49
6	$HB(sia)_2$ (4.8)	rt	28	0
7		reflux	89	0
8		120 °C	20	0

a Used to convert 1 mmol of **1** to the products.
b At which the hydroboration was performed.
c Alkynediol **1** was recovered in 27% yield.

Using this condition, various alkynediols were converted to the corresponding spiroacetals as summarized in Table 2. Both reactions of unsymmetrical 4-octyne-1,8-diol and 3-heptyne-1,7-diol derivatives gave the mixtures of regioisomers (runs 1, 2, 5, and 6). The major product of the latter was 3-(2-hydroxyethyl)isocoumarin instead of the corresponding spiro-acetal, due to the ring strain of the oxetane structure (run 2). The trend of the regioselectivity was fairly close to that of 1-phenylpropyne.[8] It is worth noting that a single regioisomer was obtained by the reaction of 4-nonyne-1,9-diol and of 4-decyne-1,10-diol derivative, respectively (runs 3 and 4). No other products including isomers and triols were obtained at all. Although the origin of the regioselectivity is not clear, this result forms a striking contrast to the previous report on the similar reaction of a protected alkynediol, which gave a mixture of regioisomers.[6] In contrast with the palladium(II) catalyzed spiroacetalization which exclusively gave 2,6-dioxaspiro[4.6]undecane,[5] the present method can be regarded as a complementary procedure of spiroacetal synthesis. Run 4 gave a mixture of 3-(5-hydroxypentyl)isocoumarin and the corresponding spiroacetal, probably due to the low stability of the 7-membered spiroacetal. The reaction of the branched 4-octyne-1,8-diol derivative gave a mixture of regioisomers as described before. Interestingly, the spiroacetal of the dihydrobenzofuran type was a single diastereomer, probably due to the stereoelectronic effect,[9] while that of the dihydroisocoumarin type was a mixture of stereoisomers. A branched 4-nonyne-1,9-diol derivative was next examined. As expected from runs 3, 5,and 6, a single isomer was obtained in 42% yield.

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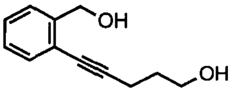
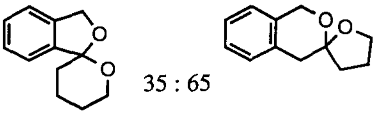
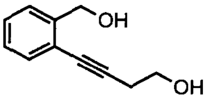
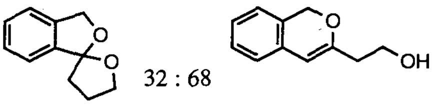
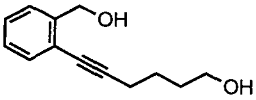
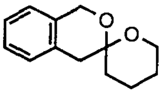
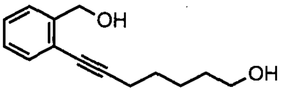
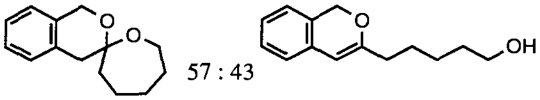
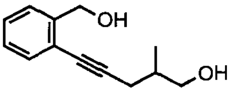
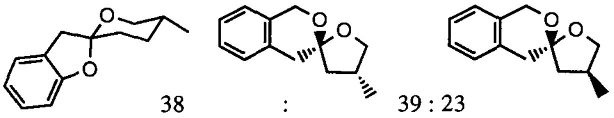
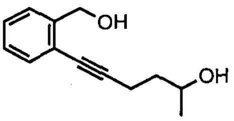
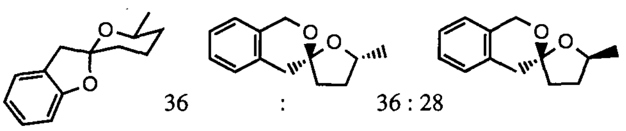
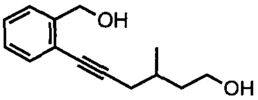
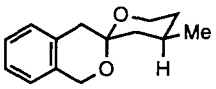
Table 2. Synthesis of various spiroacetals via the hydroboration of the alkynediols

run	substrate	yield / %	products
1		83	 35 : 65
2		47	 32 : 68
3		48	
4		35	 57 : 43
5[a]		78	 38 : 39 : 23
6[a]		80	 36 : 36 : 28
7		42	

a Stereochemistry of the products were assigned by speculation.

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