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SYNTHESIS OF 1,5-DIOXASPIRO[3.4]OCTANE THROUGH BROMOCATION-INDUCED CASCADE CYCLIZATION

Atsuo Nakazaki, Yoshiki Nakane, Yuki Ishikawa, and Toshio Nishikawa*

Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa, 464-8601, Japan. nisikawa@agr.nagoya-u.ac.jp

Abstract – A new approach to the synthesis of 1,5-dioxaspiro[3.4]octane, *spiro*-oxetane having acetal moiety, via the bromocation-induced cyclization is described. This reaction underwent to furnish *spiro*-oxetane in one-pot manner with a high degree of diastereoselectivity.

Much attention has been centered on bicyclic oxetane containing an acetal carbon in the cyclic framework because of unique structural features and their biological activities (Figure 1).[1] A representative example is thromboxane A_2, which is known to be a platelet aggregation factor and extremely labile substance ($T_{1/2}$ = 32 sec in aqueous Krebs medium at pH 7.4).[2-4] Owing to the highly strained nature of oxetane nucleus, synthetic approaches are limited.[1] In particular, bicyclic oxetane containing an acetal should be constructed through kinetically controlled reactions in order to avoid decomposition of the formed oxetane which potentially bears thermodynamic instability originated from acetal moiety. Bicyclic oxetane **A** in Figure 1 is available via Williamson ether synthesis[4,5] or Mitsunobu reaction.[3] In contrast, bicyclic oxetane **B**[6] and spirocyclic oxetane **C** (1,5-dioxaspiro[3.4]octane)[7] are known to be constructed by utilizing [2+2] cycloaddition of carbonyl compound and alkene.

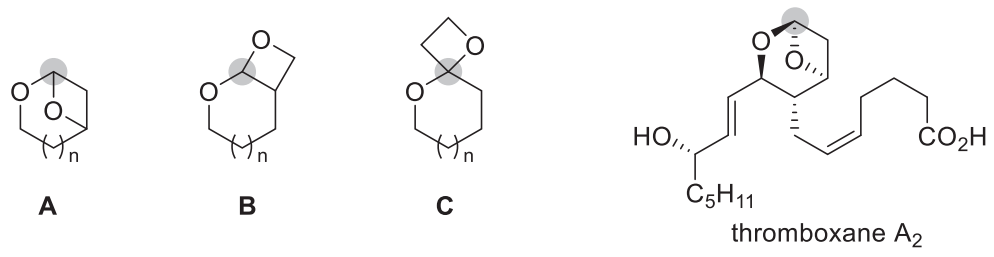
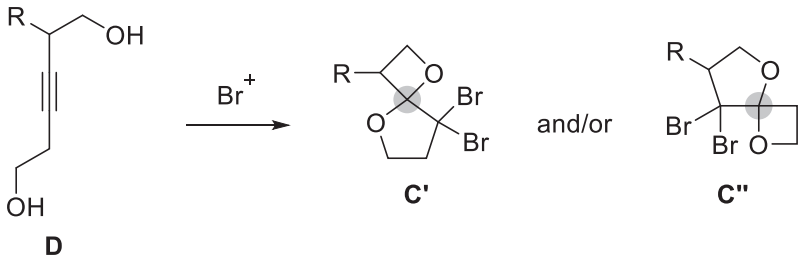


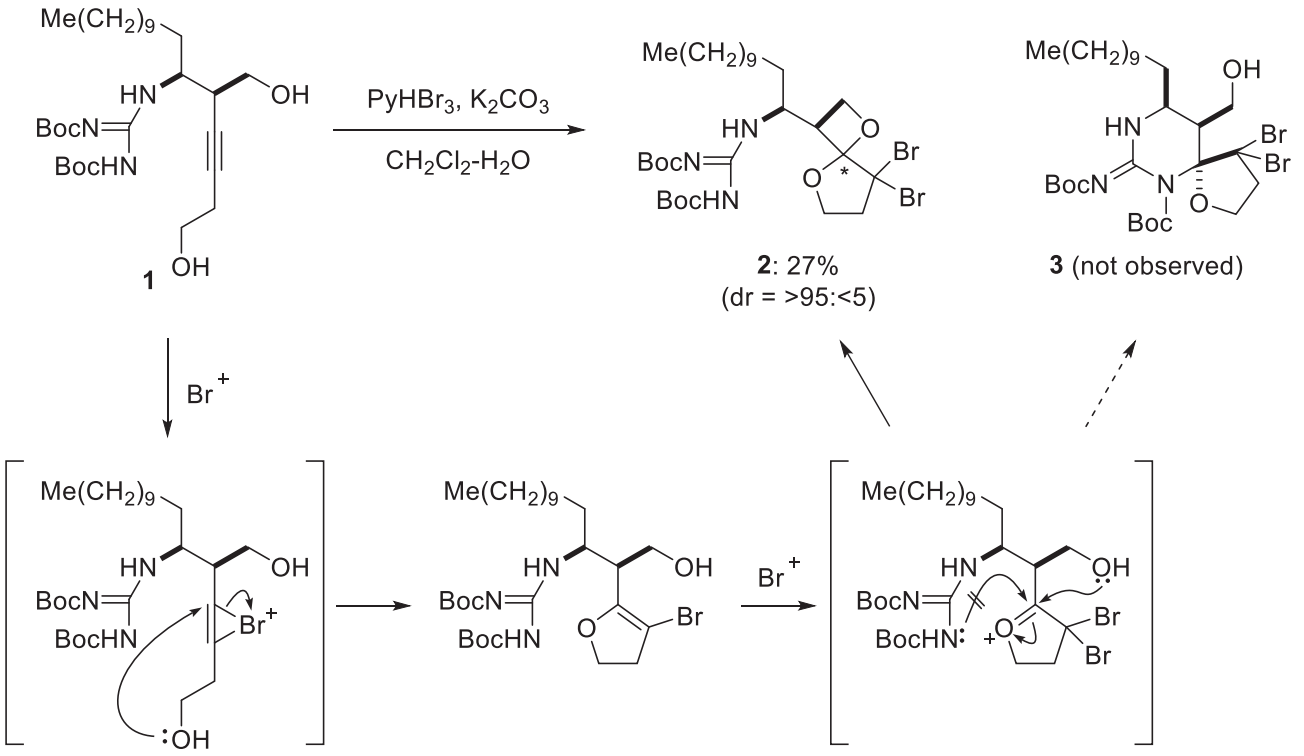
Figure 1. Reported structures of bicyclic oxetane containing an acetal carbon and the structure of thromboxane A_2

In this communication, we describe a new approach to the synthesis of 1,5-dioxaspiro[3.4]octane via the cascade bromocyclization (Scheme 1).[8,9] Although used unsymmetrical diol **D** would mechanistically provide two 1,5-dioxaspiro[3.4]octanes **C'** and **C''** through bromocation-induced 5-*endo-dig* followed by 4-*exo-trig* cyclizations,[10] only *spiro*-oxetane **C'** was observed.



Scheme 1. General scheme for the formation of 1,5-dioxaspiro[3.4]octanes **C'** and/or **C''** by a bromocation-induced cascade cyclization in this report

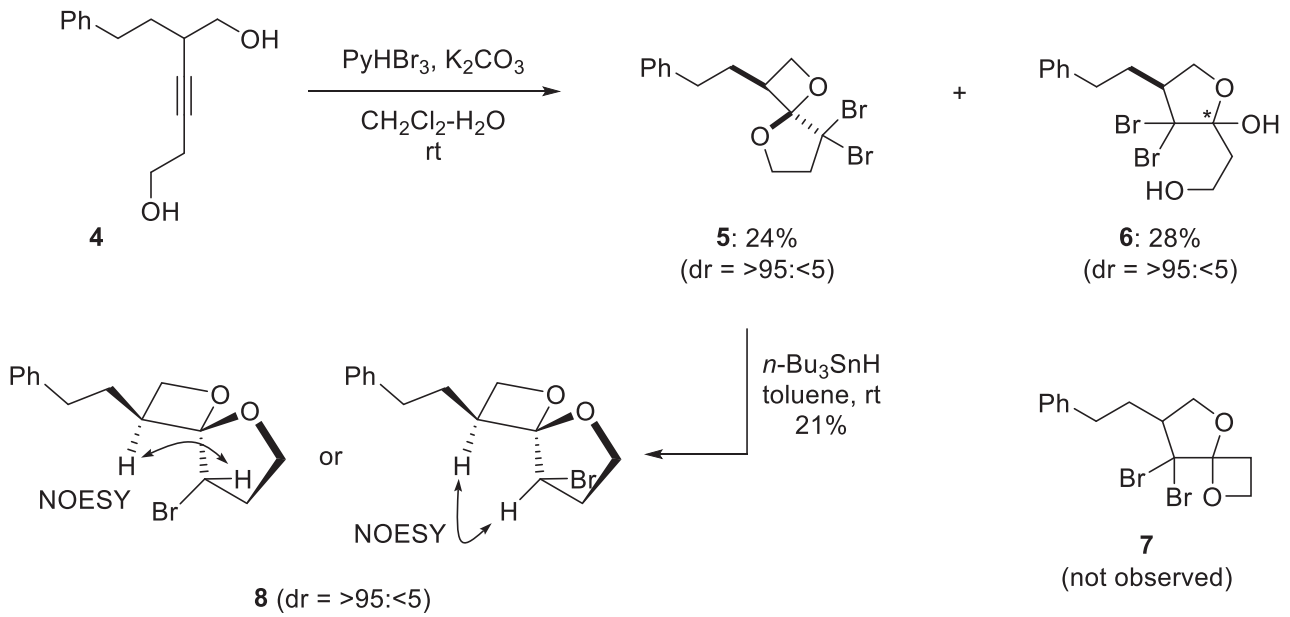
In the course of our synthetic study on spirocyclic guanidine alkaloid,[9] we have unexpectedly found the formation of a spirocyclic oxetane under the cascade bromocyclization conditions developed in this group[8] (Scheme 2). Thus, diol **1**[11] was subjected to pyridinium tribromide ($PyHBr_3$) in the presence of



Scheme 2. Preliminary result for the formation of 1,5-dioxaspiro[3.4]octane **2** through the bromocyclization of diol **1**

K_2CO_3 in a biphasic solvent system (CH_2Cl_2 and H_2O, 1:1) to furnish 1,5-dioxaspiro[3.4]octane **2**[12] in 27% yield as a single diastereomer instead of the expected *spiro*-hemiaminal **3**. Interestingly, the obtained *spiro*-oxetane **2** was found to be stable enough to be isolated by neutral silica gel column chromatography probably due to the effect of geminal dibromomethylene by destabilizing oxonium ion.[3,4] In this process, guanidino-diol **1** underwent bromocation-induced cyclization to generate a cyclic enol ether, which was further reacted with bromocation to form oxonium ion intermediate. And then the oxonium ion would be intercepted by an internal hydroxy group to furnish *spiro*-acetal **2** having an oxetane ring.[13] No observation of the expected *spiro*-hemiaminal **3** would be attributed to sluggish rate of the nucleophilic addition of a nitrogen atom of the (biscarbamoyl)guanidino group. To the best of our knowledge, this is the first example for the construction of a 1,5-dioxaspiro[3.4]octane scaffold through electrophilic cyclization.

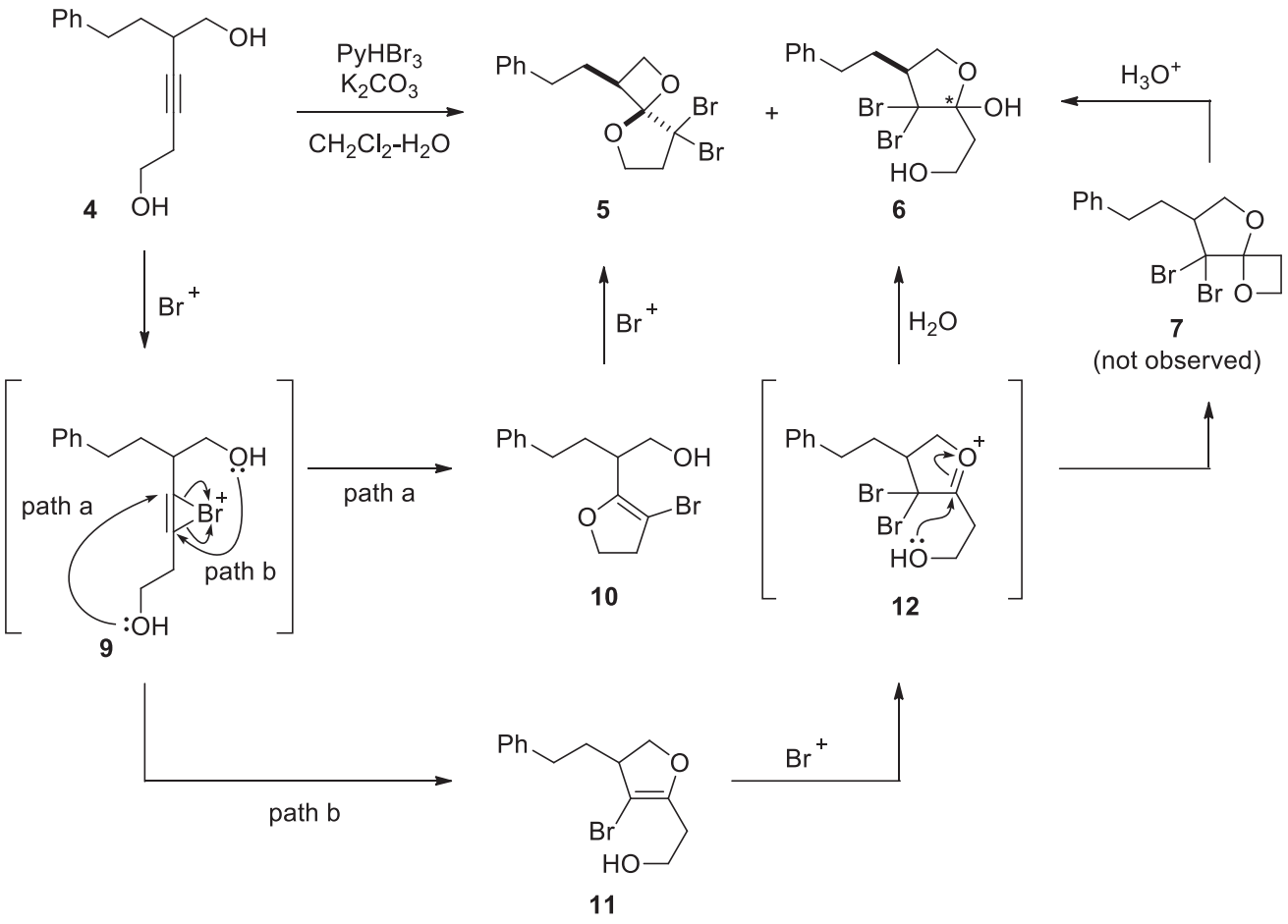
We next investigate the related reaction by utilizing simplified diol **4** without guanidine functionality in order to clarify a generality of the reaction (Scheme 3). Thus, the cascade bromocyclization using diol **4**[14] took place to afford *spiro*-oxetane **5** in 24% yield along with hemiketal **6** in 28% yield; *spiro*-oxetane **7** was not detected. Both compounds were obtained as a single diastereomer. Relative stereochemistry of the resulting oxetane **5** was confirmed by NOESY analysis of monobromo compound **8** via reductive debromination of **5**.[15] The stereogenic center of the methine proton adjacent to the bromo substituent in **8** could not be determined because of almost the same distance between both methine protons in the most stable conformer calculated by molecular mechanics. Spirocyclic monobromo oxetane **8**[16] was found to



Scheme 3. Cascade bromocyclization of simplified diol **4**

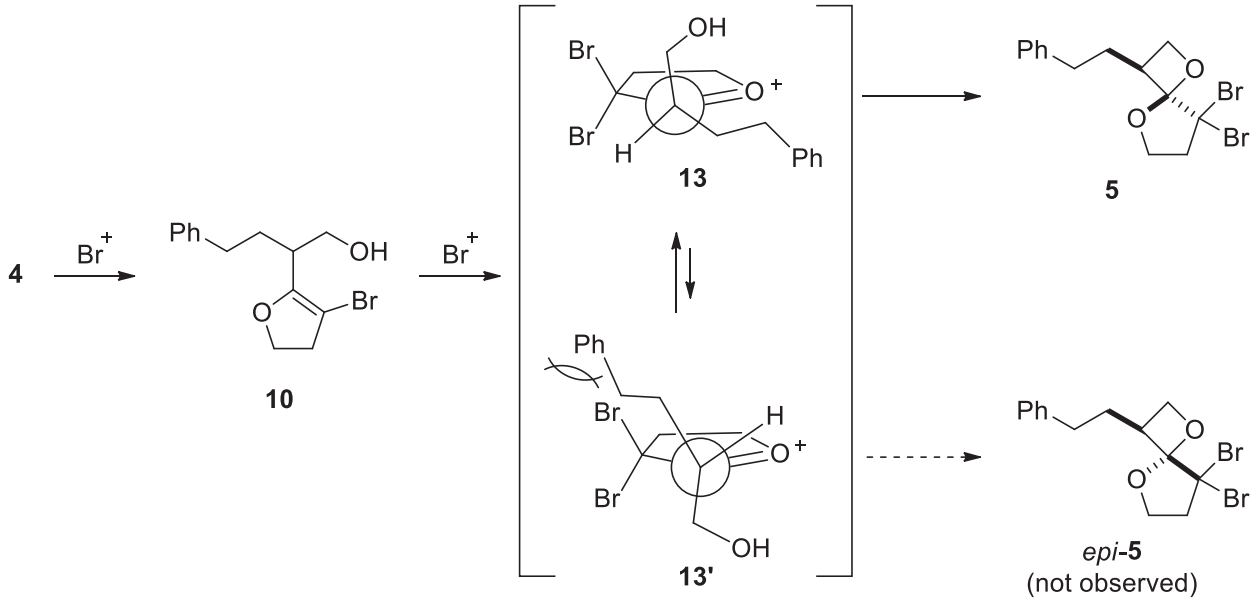
be more labile than the corresponding dibromo oxetane **5** because of less electronegative nature of the monobromo-substituted carbon.

A plausible reaction mechanism of the cascade bromocyclization of diol **4** is shown in Scheme 4. Bromocation activates alkyne of **4** providing bromonium ion intermediate **9**, in which less hindered hydroxy group cyclizes through path a in a 5-*endo-dig* manner, leading to dihydrofuran **10**. The second activation of **10** by bromocation with concomitant cyclization again furnishes *spiro*-oxetane **5**. The side-chain substituent might promote the rate of cyclization owing to compressing the angle of its substituted carbon.[17] In contrast, path b affords dihydrofuran **11**, which would be activated by bromocation to generate oxonium ion intermediate **12**. At this stage, 4-*exo-trig* cyclization of the remaining hydroxy group would be retarded probably due to no substituent effect compressing the angle at that carbon, and intermolecular attack of water proceeds to form hemiketal **6**. Formation of **7** and its subsequent hydrolysis might also be possible for explaining production of **6**.



Scheme 4. A plausible reaction mechanism for the formation of 1,5-dioxaspiro[3.4]octane **5** and hemiketal **6** from diol **4**

Stereochemical outcome of *spiro*-oxetane **5** indicates that the second cyclization would proceed through sterically less-hindered conformer **13**, instead of the conformer **13'** involving a steric repulsion between *gem*-dibromomethylene moiety and phenylethyl group, leading to **5** as a sole diastereomer (Scheme 5).



Scheme 5. Rationale for the stereoselective formation of spirocyclic octane **5**

In conclusion, we described a unique access to the synthesis of spirocyclic oxetane acetal under the bromocation-induced cyclization conditions. The feature of this method is that the cyclization underwent to furnish *spiro*-oxetane in one-pot manner with a high degree of diastereoselectivity. A geminal dibromomethylene group might play an important role for stabilizing substituent of the acetal moiety.

ACKNOWLEDGEMENTS AND NOTES

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11. Cyclization precursor **1** was synthesized by the similar way as previously reported method.[9] See Supporting Information for details.
12. Relative stereochemistry of **2** was not determined.
13. An alternative reaction mechanism leading to **2** can be imagined involving bromocation-induced 4-*exo*-dig cyclization of guanidino-diol **1** followed by 5-*exo*-trig cyclization. However this reaction would be suppressed because of instability of an oxonium ion intermediate having oxetane scaffold which would be generated after the first cyclization.
14. Cyclization precursor **4** was synthesized from hydrocinnamaldehyde in four steps. See Supporting Information for details.
15. Both recovered oxetane **5** and totally reduced product were not observed in this reaction.

16. Monobromide **8** was found to be stable during the separation using alumina or neutralized silica gel (Silica gel 60N, Kanto) with 10% of *i*-Pr_2NH as a co-eluent, however decomposition of **8** was observed on TLC plate (Silica gel 60, Merck).
17. For review of Thorpe-Ingold effect as a related effect, see: M. E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735.