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# Oxonium ion-mediated synthesis of 4-substituted spiro-isoxazolines

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## ABSTRACT

The stereoselective synthesis of 4-bromo-spiro-isoxazolines was achieved in one step through the bromination of various isoxazoles that contain a pendant alcohol or carboxylic acid functional group. Isoxazole bromination leads to a bromonium ion intermediate, which opens either by neighboring oxygen lone pair electrons or by intramolecular nucleophilic attack. Single X-ray crystal data provide evidence that the two contiguous stereocenters of the spiro-isoxazoline are formed by the *anti* intramolecular attack of the nucleophile relative to bromine, since there is an *anti* stereochemical relationship between the spirocyclic ring oxygen and the bromine atom.

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Spiro-isoxazolines are found in a number of natural products,<sup>1</sup> and due to their biological activity,<sup>1a,c-f,2</sup> many compounds within the psammaplysin and ceratinamide families have the potential to serve as a structural template that could lead to synthetic analogues that target a variety of diseases. The spiro-isoxazoline ring core is the central structural feature within the aforementioned natural products, and only a few publications address the synthesis of this unique ring system.<sup>3,4</sup> In the psammaplysin natural products, the oxepine oxygen and the 4-hydroxy group on the isoxazoline are *anti* to each other. A synthetic methodology that provides a stereoselective construction of spiro-isoxazolines that mimic the stereochem-

ical features of the psammaplysin natural product is warranted. Herein, we report the application of an oxonium-mediated stereoselective intramolecular cyclization of a brominated isoxazole intermediate by a pendant alkoxide or carboxylate ion (Fig. 1).

Since the spiro-isoxazoline of the psammaplysin family of natural products contains an isoxazoline ring that has a substituent on the 4-position, the exploration of the possibility of reacting an isoxazole possessing a pendant nucleophilic functional group with an electrophile was performed in order to determine if an intramolecular cyclization would take place.<sup>5</sup> Our retrosynthetic rationale is depicted in Scheme 1.



Figure 1. Psammaplysin and ceratinamide family of natural products.

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Scheme 1. Retrosynthetic analysis of 4-bromo-substituted spiro-isoxazolines.



Scheme 2. Synthesis of furan and pyran-based spiro-isoxazolines.



Scheme 3. Synthesis of lactone containing spiro-isoxazolines.

In order to test our hypothesis, alkyne **1** was reacted with the nitrile oxide that was generated in situ from the base-promoted reaction of  $\alpha$ -chlorobenzaldoxime with triethyl amine to afford isoxazole<sup>6</sup> (**3**) regioselectively.<sup>7</sup> Spiro-isoxazolines **5** and **6** were effectively formed as single diastereomers upon the respective treatment of **3** and **4** with pyridinium tribromide (Scheme 2).

Extension of this methodology to the synthesis of spiro-isoxazolines with an inherent lactone ring system commenced from the 1,3-dipolar cycloaddition of **7** with the nitrile oxide from  $\alpha$ -chlorobenzaldoxime to afford **9**.<sup>4,8</sup> Pyridinium tribromide-promoted spirolactonization of **9** stereoselectively afforded **11** as shown in Scheme 3.<sup>9</sup> Spiro-isoxazoline (**12**) was also obtained in an analogous manner. Compound **12** was also assembled as a single isomer based upon the NMR of the unpurified material. Fortunately, compound **11** was a crystalline solid, and X-ray crystallographic analysis of **11** showed that the bromine and the lactone oxygen are *anti* to each other<sup>10</sup> (Fig. 2). Based upon this stereochemical evidence, a mechanism describing the formation of **11** is proposed in Scheme **4**.

In our proposed mechanism, bromination of carboxylate ion (13) affords the bromonium ion intermediate (14). If intermediate 14 follows pathway **A**, oxonium ion intermediate (15) is formed. Intramolecular cyclization of 15 by the carboxylate ion gives rise to 11. Likewise, 14 can potentially follow route **B** where the bromonium ion is directly attacked in an intramolecular fashion by the carboxylate ion. In both pathways, the large bromine atom likely controls the direction of nucleophilic attack to form the corresponding spiro-isoxazoline, where the bromine and spirocyclic lactone oxygen atom have an *anti* relationship.



Figure 2. Thermal ellipsoid plot of the structure of 11.

In summary, this investigation shows the application of an oxonium ion-mediated synthesis of 4-bromo-spiro-isoxazolines, where two contiguous stereocenters are formed stereoselectively through the bromination and intramolecular cyclization of isoxazoles possessing a pendant alcohol or carboxylic acid. Future investigations involving the enantioselective synthesis of spiroisoxazolines with substituents other than bromine on the 4-position, and a mechanistic theoretical study of the intramolecular cyclization are currently underway.



Scheme 4. Proposed mechanism for the stereoselective formation of compound 11.

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- General procedure for 1,3-dipolar cycloaddition of the alkynol: A solution of the alkynol (3 mmol) and the hydroximoyl chloride (3 mmol) in 10 mL of dichloromethane was treated with triethylamine (0.46 mL, 3.3 mmol). The

reaction mixture was stirred at rt until the disappearance of the starting materials, as evidenced by TLC. After the reaction was complete, a minimum amount of silica gel was added, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel using 1:1 hexanes–ethyl acetate ratio as an eluant system.

- 8. General procedure for 1,3-dipolar cycloaddition of the alkynoic acid: Deionized water (3.5 mL) was added into a round-bottomed flask containing the hydroximoyl chloride (6.5 mmol) with stirring. The alkynoic acid (3.25 mmol) was added into this mixture. Potassium carbonate (4.88 mmol) was then added in small portions. The reaction mixture was stirred at rt until the reaction was complete as evidenced by TLC/NMR analysis. The reaction mixture was acidified with 4 N HCl and treated with diethyl ether and water (1:1, 20 mL). Sodium hydroxide was added to this mixture until the mixture was basic (litmus paper). The mixture was extracted with diethyl ether (3 × 10 mL), and 4 M HCl was then added to the acidified aqueous layer with ethyl acetate (3 × 15 mL), and the resulting organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the crude product which was purified via column chromatography over silica gel using 1:1 hexanes-ethyl acetate ratio as an eluant system.
- 9. General procedure for bromination/intramolecular cyclization: A solution of the isoxazole (2 mmol) and K<sub>2</sub>CO<sub>3</sub> (4 mmol) in 5 mL of dry dichloromethane was stirred in an ice-water bath. Pyridinium tribromide (4 mmol) was added slowly to the cold mixture. The reaction mixture was stirred for 2 h at 0 °C, and was allowed to slowly warm to rt overnight. The reaction mixture was stirred at rt until the disappearance of the starting materials, as evidenced by TLC. The reaction mixture was poured into a cold, saturated NH<sub>4</sub>Cl solution (5 mL), extracted with ethyl acetate (3 × 10 mL), and washed with saturated CuSO<sub>4</sub> solution (3 × 10 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography over silica gel using the appropriate hexanesethyl acetate ratio as an eluant system.
- Structural information for 11 has been deposited with the CCDC as 695718, available free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).