Rapid Access to Dispirocyclic Scaffolds Enabled by Diastereoselective Intramolecular Double Functionalization of Benzene Rings

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Abstract: Here we describe the diastereoselective synthesis of (5r,8r)-1,9-diazadispiro[4.2.4.2]tetradecatienes via domino double spirocyclization of N-arylamide derivatives. This reaction can serve as a fast way to synthesize dispirocycles, which are found in the core structures of bioactive natural products. Product diversification via Suzuki–Miyaura cross coupling and application to the synthesis of 1-oxa-9-azadispiro[4.2.4.2]tetradecatienes were also conducted.

Dearomative transformations play a significant role in organic chemistry,[1] In particular, a double cyclization reaction via dearomatization is attractive because it can facilitate a single-step formation of two cycles (Figure 1a). However, to date, the application of this method has been limited to angularly fused[2,3] and bridged[4] cycles. To the best of our knowledge, dispirocycles have not been synthesized despite the attention they have received in the field of chemical sciences.[5] Here, we report a diastereoselective domino double spirocyclization via dearomatization.

In this context, we planned to construct a (5r,8r)-1,9-diazadispiro[4.2.4.2]tetradecatiene scaffold, which is found in the core structures of grandilodine C (1),[6a] lundurine A (2),[6d] and lapidilectam (3)[6e] (Figure 1b). These are known as pyrroloazocine indole alkaloids,[6] which can reverse drug resistance[7] in vincristine-resistant cell lines. The characteristic diazadispirocyclic scaffold is considered a fascinating synthetic target because, in general, some of the drug seeds and molecular probes are inspired by low-molecular-weight fragments derived from natural products.[8] However, the cyclic structures have rarely been synthesized,[9] and their diastereoselective synthesis, to the best of our knowledge, has not been reported.

Based on advances in dearomative ipso-cyclization chemistry,[10] especially in the synthesis of cyclohexadienes,[11,12] we hypothesized that the following process from 4-H toward 6 would occur in one step (Figure 1c). The reaction consists of three steps. Iodination of the terminal alkyne of 4-H would give 4-I, and the subsequent ipso-iodocyclization[13] would afford cyclohexadienyl cation 5. Moreover, the resulting cation would be captured[14] by the nitrogen atom of the side chain in a diastereoselective manner. Along with the desired cyclization reaction, quinolinolone 7[14] and tetraene 8[15] might be produced. The diastereoselectivity between 6 and 9 would be varied by substituents R1 and R2. Furthermore, derivatives 10 would be obtained via a cross-coupling reaction employing two iodine atoms as chemical handles incorporated in 6.

As illustrated in Scheme 1, the synthesis of cyclization precursor 4-Hb was commenced with commercially available carboxylic acid 11. 11 was converted into carbamate 12 via a Curtius rearrangement in 95% yield, and the nitro group of 12...
was reduced with ammonium chloride and iron powder to give aniline 13 quantitatively. Then 13 was condensed with propionic acid to synthesize amide 4-Ha followed by N-benzylation to afford cyclization precursor 4-Hb.

After synthesizing the cyclization precursor 4-Hb, we began our studies on the double cyclization (Table 1). As shown in entry 1, treatment of 4-Hb with 2.2 equivalent of NIS and AgNO₃ in MeCN solvent gave (5r,8r)-dispirocyclo 6b in 21% ¹H NMR yield, whose stereochemistry was established by the NOESY experiment. Next, the reaction was performed with NIS and AgNO₃ in various solvents (entries 2–4). Acetone or CH₂Cl₂ was inefficient, while MeNO₂ worked efficiently and gave relatively clean crude material. Two diastereomers, 6b and 9b, could be separated through conventional silica gel column chromatography, and 6b was isolated in 46% yield. The results of the solvent screening experiment indicated that polar and low-nucleophilic solvents are suitable for the reaction. Therefore we turned to test fluorinated alcohols (i.e., TFE, TFP, and HFIP), which are known to enhance the halogenation of both aromatics and olefins.[¹⁴] As shown in entries 5–7, both yields and dr were improved as the polarity of the solvent increased, and HFIP gave the best result to give 6b in 54% yield with 73:27 dr. The amount of AgNO₃ could be reduced to 0.1 equivalent without affecting the outcome (entry 8), and performing the reaction at 0°C improved the yield by 68% (entry 9). As in entry 10, replacing the counter anion of silver reagent from nitrate to trifluoroacetate improved the yield by 75%, while the diastereoselectivity did not change. The importance of silver reagents was explored in entries 11 and 12. The reactions with catalytic nitric acid or without any catalysts did not reach completion, although retained diastereoselectivity with 75:25 dr. Lastly, as in entry 13, the reaction without silver catalyst in MeNO₂ did not give 6b or even intermediate 4-ib, resulting in the recovery of 4-Hb. Through the optimization of the reaction conditions, the product derived from the direct spirocyclization of 4-Hb before the formation of 4-ib was not detected.

With the optimized conditions in hand, we evaluated the effects of the R₁ and R₂ groups on diastereoselectivity (Table 2). The precursors 4-Hc–4-Hk were readily prepared via similar synthetic routes for 4-Hb. First, we examined the effect of R₁ on diastereoselectivity, and the substrate 4-Hc bearing the t-butoxycarbonyl group showed results comparable to those of 4-Hb (entry 1, 2). The reaction employing 4-Hd with the p-toluenesulfonyl group for R₁ proceeded smoothly, although dr decreased to 58:42 (entry 3). Next, we tested the effect of the electron density of R₁ on diastereoselectivity. Thus we performed cyclization with substrates bearing an electron-donating group (entries 4, 5) or an electron-withdrawing group (entry 6). Only slight differences were observed among the yields and selectivities among 4-He–4-Hg. Lastly, the size of the R₂ was investigated (entries 7–10). While the methyl group showed low diastereoselectivity, the 2-naphthylmethyl group gave high selectivity. The best result was obtained when the 1-naphthylmethyl group was employed, providing (5r,8r)-diaspirocycle 6k with 91:9 dr.

The observed stereoselectivity can be explained by considering the conformation of the cationic intermediates produced by the first spirocyclization reaction (Figure 2a). In the second spirocyclization, C–N bond formation should occur to minimize the steric interaction between the R₂ group of the side chain and the R₁ or R₂ group of the lactam ring. The intermediate A, leading to the desired isomer 6, would be predominant if the R₂ group is more sterically hindered than the R₁ group, so that the substrate 4-Hk with the R₁ group for a bulkier substituent (R₁ = 1-naphthylmethyl, R₂ = iodine) resulted in the high selective (91:9 dr) formation of the desired (5r,8r)-diaspirocycle 6. In contrast, (5s,8s)-isomer was predominant when the precursor with the R₁ group for a bulkier substituent (R₁ = methyl, R₂ = phenyl) was employed. Thus, the treatment of 4-Ph under the same reaction conditions gave 9-Ph as a major product with 60:40 dr, as shown in Figure 2b.

Next, derivatization was conducted by a modification of the diodo moiety (Scheme 2). Thus, diarylethenes[¹⁵] with electron-rich and electron-poor aromatics were synthesized via Suzuki-Miyaura cross coupling in the presence of Pd(PPh₃)₄ catalyst.

### Table 1. Optimization of cyclization using 4-Hb.

| entry | additive (equiv) | sol. temp. (°C) | yield (%)[¹][²] | dr[¹][²] |
|-------|-----------------|-----------------|----------------|---------|
| 1     | AgNO₃ (1)       | MeCN            | 21             | –       |
| 2     | AgNO₃ (1)       | acetonitrile    | 21             | –       |
| 3     | AgNO₃ (1)       | CH₂Cl₂          | 30             | –       |
| 4     | AgNO₃ (1)       | MeNO₂           | 46             | 51:49   |
| 5     | AgNO₃ (1)       | TFE             | 46             | 59:41   |
| 6     | AgNO₃ (1)       | TFP             | 49             | 63:37   |
| 7     | AgNO₃ (1)       | HFIP            | 54             | 73:27   |
| 8     | AgNO₃ (0.1)     | HFIP            | 56             | 73:27   |
| 9     | AgNO₃ (0.1)     | HFIP            | 68             | 75:25   |
| 10    | AgTFA (0.1)     | HFIP            | 75             | 75:25   |
| 11    | HNO₃ (0.1)      | HFIP            | 36             | 75:25   |
| 12    | –               | HFIP            | 41             | 75:25   |
| 13    | –               | MeNO₂           | 0              | –       |

[a] isolated yield of 6b; [b] diastereomeric ratio determined by ¹H NMR of crude material; [c] yield determined by ¹H NMR of crude material; [d] the reaction did not complete; [e] no reaction: 4-Hb was recovered. NIS = N-iodosuccinimide, TFE = 2,2,2-trifluoroethanol, TFP = 2,2,3,3-tetrafluoro-1-propanol, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.
Ag₂O, and CsF. The reaction was completed at room temperature within 2 hours, and 6e was converted into diarylethene 10e–1, having two p-nitrophenyl groups in 78% yield, while the use of an organic base such as K₃PO₄ instead of Ag₂O resulted in partial decomposition. Next, under similar conditions, derivative 10e–2 with two p-methoxyphenyl groups was synthesized in 62% yield.

Finally, we extended the above-developed method to the synthesis of both (5r,8r)- and (5s,8s)-diastereomers of 1-oxa-9-azadispiro[4.2.4.8]tetradecatrienes (Scheme 3). First, readily available carboxylic acid 14 was treated with AgTFA and NIS in HFIP, providing (5r,8r)-isomer of dispirocyle 15 as a major product in 59% isolated yield with 65:35 dr. Second, cyclization of phenylpropiolate 16 afforded (5s,8s)-isomer of the dispirocyle 17 in 57% yield with 66:34 dr. The stereochemical outcome can be explained in the same way as the corresponding diadispirocyclazines in Figure 2.

In conclusion, we have developed a diastereoselective double spirocyclization reaction, enabling the one-step construction of the diazadispirocyclic core found in the structures of the pyrroloazocine indole alkaloids family. Our discovery...
indicated that HFIP and silver catalyst could promote both the iodination and spirocyclization processes with NIS, and HFIP appeared to be essential for the high level of diastereoselectivity. The spirocyclization seemed to be triggered by the iodination of terminal alkyne, since no trace of direct cyclization was observed before the iodination. The stereoselectivity was affected by the steric sizes of the lactam ring's substituents but was not affected by the electronic properties. The cyclized product was modified to expand the product diversity. Furthermore, the method developed was applied to the synthesis of tetradecatrienes. More extensive applications of the reaction including the total synthesis of pyrroloazocine indole alkaloids are now under way in this laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

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