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SYNTHETIC STUDIES ON DIDYMELINE USING SPIROCYCLIZATION OF PHENOLS WITH DIAZO FUNCTIONALITY

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Dedicated with respect to Professor Yasuyuki Kita on his 77th birthday

Abstract – Didymeline is an alkaloid with an azaspiro tricyclic skeleton with various functionalities. Despite the fact that its unique architecture is synthetically attractive, its total synthesis has never been achieved before. Herein, we present synthetic studies on the core structure of didymeline. Accordingly, a spiro ring system was constructed through dearomatization of a phenol derivative with α-diazoamide unit. Based on the resulting 2-azaspiro[4,5]decane variant, a tricyclic molecule was synthesized via base-promoted intramolecular ring closure. For an asymmetric synthesis, an enantioselective dearomatization was also examined under silver catalysis, which led to the formation of an all-carbon substituted quaternary stereogenic center.

Didymeline and dihydrodidymeline were isolated from the leaves of *Didimeles madagascariensis* by Ahond and Poupat group in 1987 (Figure 1).[1] The chemical structure of these alkaloids includes a tricyclic ring system comprising a 2-azaspiro[4,5]decane with multiple contiguous stereocenters; this is a characteristic architecture also found in bioactive steroidal alkaloids, such as (+)-conessine (a histamine H_3 antagonist)[2] and holadienine. However, to date, the total synthesis of didymeline or dihydrodidymeline has not been achieved due to their structural complexity; thus, their pharmaceutical activities have remained unclear.

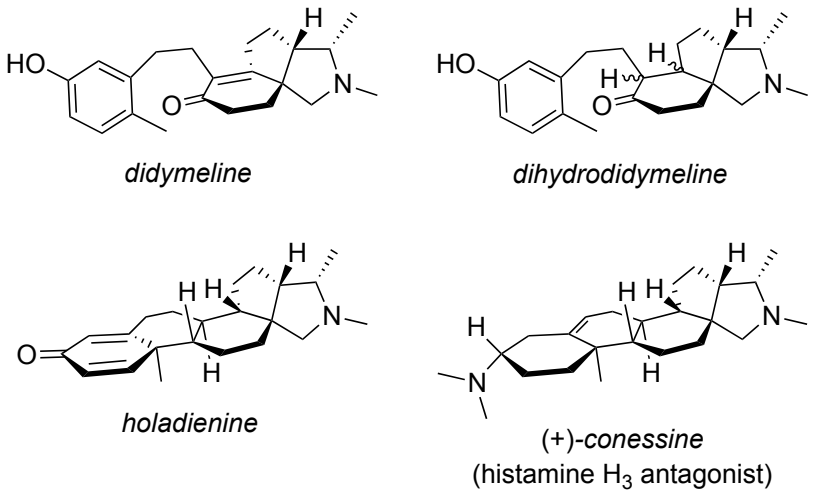
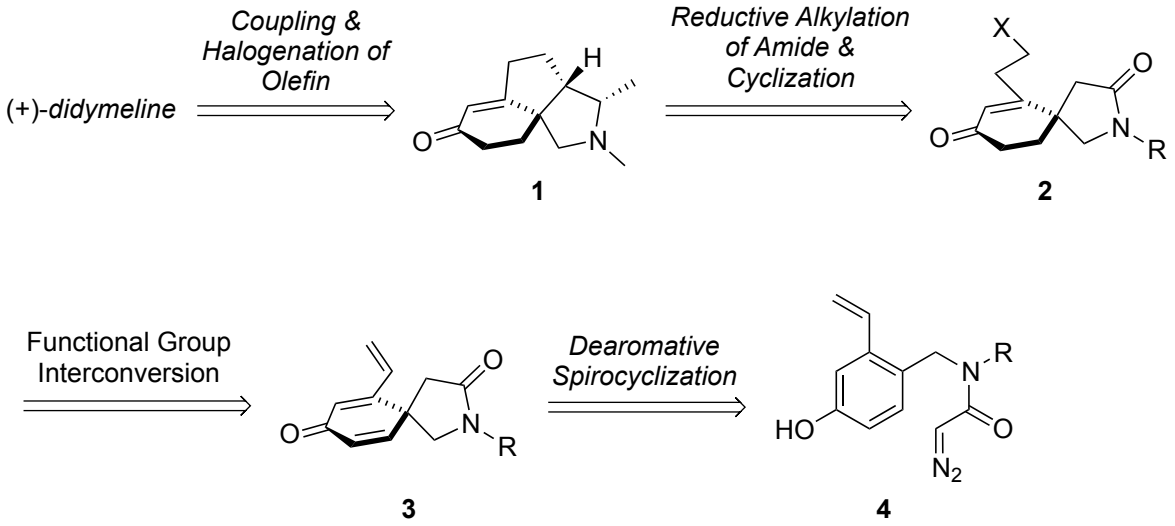


Figure 1. Structures of Didymeline, Dihydrodidymeline, Holadienine, and Conessine

The research groups of Jonhson,[3] Stork,[4] and Nagata[5] independently succeeded in the construction of a 2-azaspiro[4,5]decane system and achieved total syntheses of the racemic form of (±)-conessine in the 1960s by consistently using tetralone derivatives as starting compounds. In 1996, Meyers succeeded in the asymmetric formal synthesis of (+)-conessine from a chiral lactam.[6] Their key reaction sequence was diastereoselective [3+2] cycloaddition of the lactam with an azomethine ylide; this was followed by intramolecular cyclization, thereby constructing an azaspiro ring system. In 2004, Jiang also reported a stereoselective synthesis of tetracyclic pyrrolidines via Pauson-Khand reaction[7] of a chiral 1,6-enyne using a [$Co_2(CO)_8$] reagent.[8]

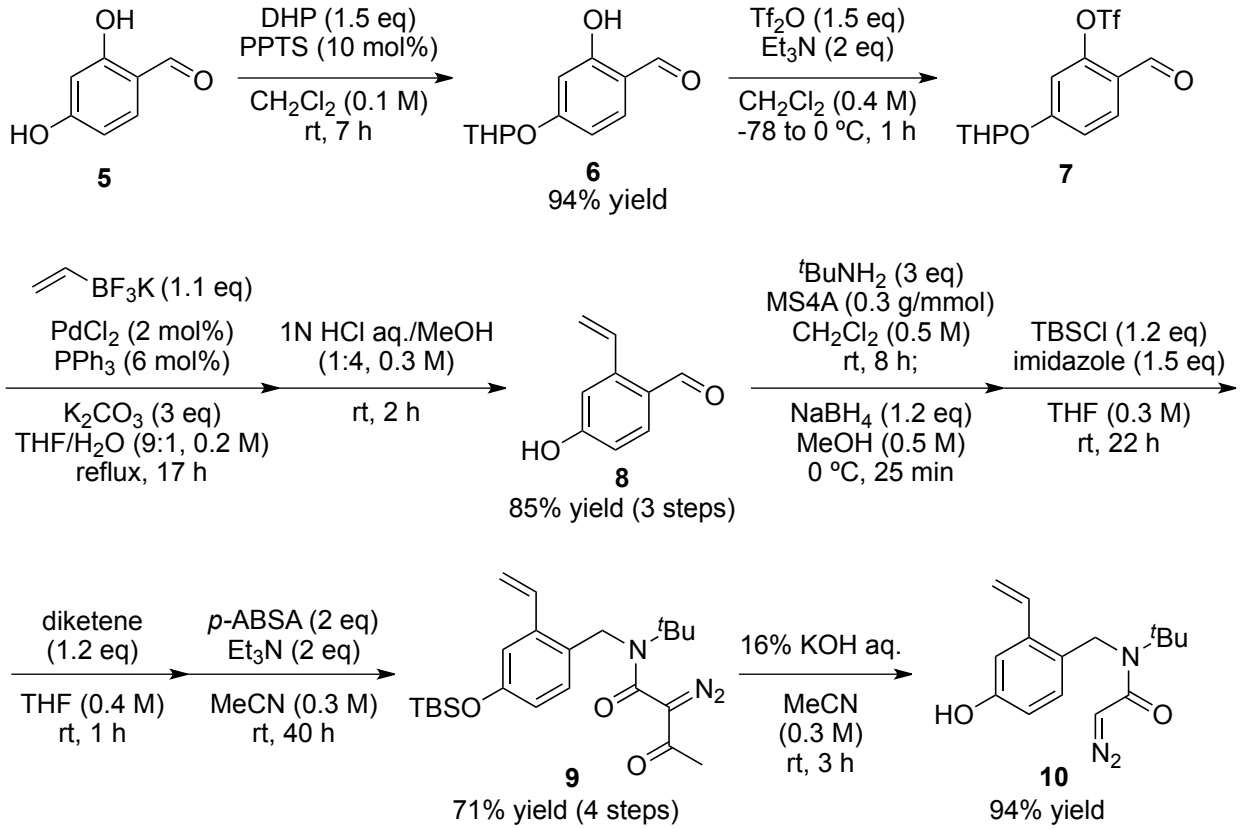
Metal-carbenes are highly reactive carbon species capable of diverse molecular transformations. The metal-carbene chemistry that dates back to the late 1800s[9] is still at the forefront of research.[10] As a part of our ongoing exploration of metal−carbene species, we reported a dearomatization reaction[11,12] of phenols with diazo functionality using silver-carbene species.[13,14] In a series of studies, silver-carbenes have been proven to possess unique reactivities, which are totally distinct from those of rhodium or copper carbenes. For instance, in an intermolecular reaction of phenols, silver catalyst with phosphate ligand[15] promoted chemo- and enantioselective phenol dearomatization, whereas a Rh or Cu catalyst caused C–H insertion and a Büchner reaction.[16-18] The catalytic asymmetric dearomatization[19] based on the *ipso*-Friedel−Crafts reaction process is a powerful method for assembling non-flat polycyclics from aromatic feedstocks with high availability. The resulting spiro compounds with various functionalities are privileged scaffolds for molecular synthesis.[20] With these background studies in mind, we started the synthetic studies on didymeline based on phenol dearomatization.

Our retrosynthetic plan is outlined in Scheme 1. First, the development of a synthetic method for assembling the structure of **1** would provide the common synthetic scaffold for synthesizing didymeline and dihydrodidymeline. We surmised that spiro molecule **2** could be a viable intermediate to produce **1** through a base-promoted ring closure for constructing the tricyclic system followed by reductive alkylation of an amide. Further, **2** could be accessible *via* site-selective reduction of cyclohexadienone **3** and functional group interconversions. The key dearomatization reaction of phenol variant **4** with a diazo functionality could provide **3** based on the previously developed method.



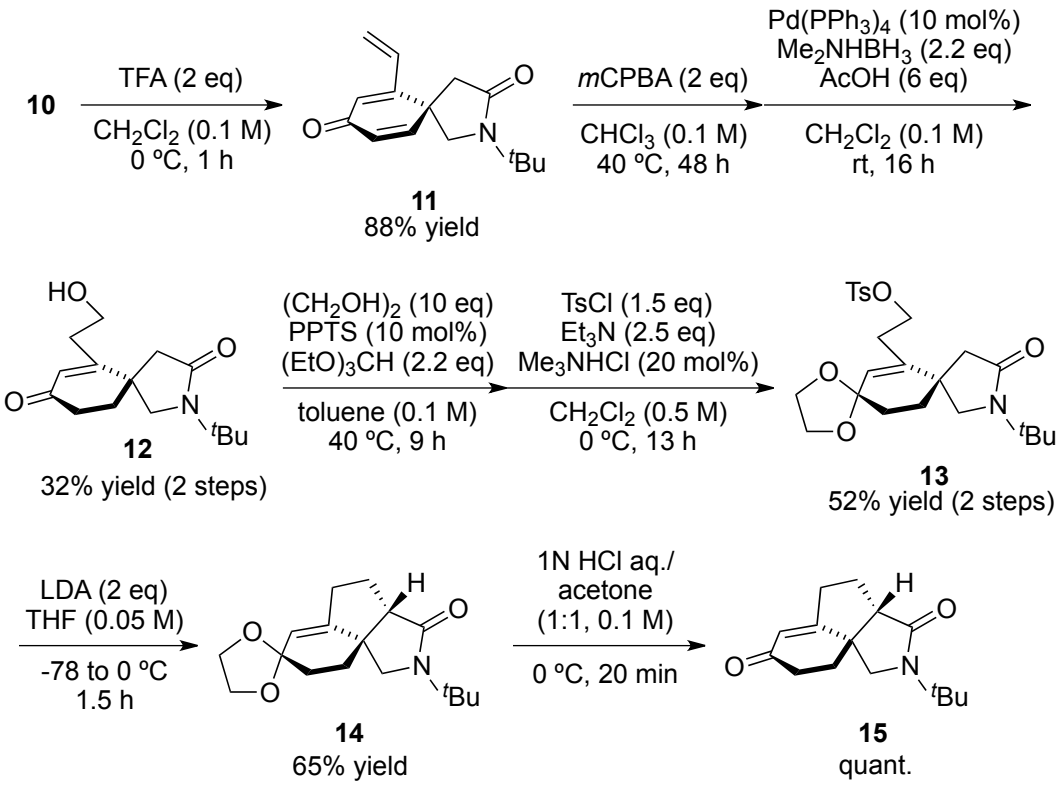
Scheme 1. Retrosynthetic Analysis of Didymeline

We started our synthetic studies using commercially available 2,4-dihydroxybenzaldehyde **5** (Scheme 2). The phenolic hydroxy group at a less hindered position was transformed into 2-tetrahydropyranyl (THP-) ethers,[21] giving **6** in 94% yield. The other hydroxy group was converted to a triflate functionality. The subsequent Suzuki-Miyaura cross-coupling reaction with a vinyltrifluoroborate, which was followed by an acid treatment, provided a styrene variant **8** in 85% yield (3 steps). In 4 more steps, **9** was furnished without purification of intermediate products in 71% yield through a reductive amination of **8** with *tert*-butylamine, TBS protection, acetoacetylation of the resulting secondary amine, and the Regitz diazo transfer reaction using *p*-ABSA successively. The stage was set for the dearomative cyclization after **9** was subjected to a basic treatment.



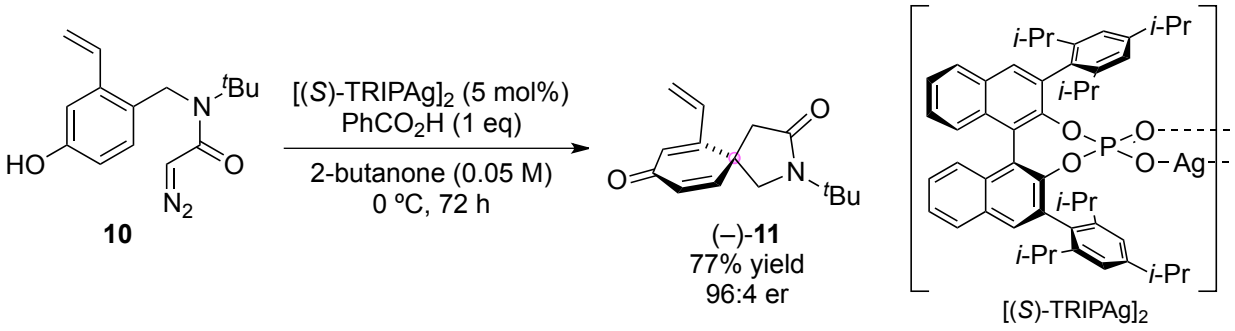
Scheme 2. Synthesis of Diazoacetamide Derivatives **10 (**DHP represents 3,4-dihydropyran. PPTS represents pyridinium *p*-toluenesulfonate. *p*-ABSA represents *p*-acetamidobenzenesulfonyl azide**)**

Next, we ventured into synthetic studies on a tricyclic lactam (Scheme 3). In order to establish a synthetic pathway, an achiral promoter was initially used for phenol dearomatization. The spirocyclization of **10** using trifluoroacetic acid (TFA) was performed at 0 °C for 1 h, thereby furnishing the desired spiro lactam **11** in 88% yield. A site-selective oxidation of the vinyl group of **11** using *m*CPBA gave an epoxide (undrawn). The epoxide was relatively unstable; therefore, the next operation was promptly conducted without purification. The subsequent reductive epoxide ring-opening and the site-selective reduction of disubstituted olefin, using $Pd(PPh_3)_4$, $Me_2NH \cdot BH_3$, and AcOH, provided primary alcohol **12** in 32% yield over two steps. Ketal protection of the ketone with ethylene glycol, which was followed by the activation of the terminal hydroxy group as a leaving group, formed a sulfonate ester **13** in 52% yield (2 steps). Then, the intramolecular cyclization of **13** using LDA provided the corresponding tricyclic lactam **14** as a single diastereomer in 65% yield. The deprotection of the cyclic acetal under acidic conditions gave **15**, whose structure was similar to that of didymeline. Unfortunately, further attempts to develop a synthetic route to **1** were unsuccessful.[22]



Scheme 3. Synthesis of Tricyclic Lactam **15**

For asymmetric synthesis, a silver-catalyzed asymmetric dearomatization reaction of diazoacetamide **10** was attempted (Scheme 4). In the presence of 5 mol% [(*S*)-TRIPAg]$_2$ catalyst and benzoic acid in 2-butanone at 0 °C for 3 d, the phenol dearomatization produced (–)-**11** bearing an all-carbon quaternary stereogenic center in 77% yield with 96:4 er. In this reaction, none among C–H insertion, cyclopropanation, or Büchner reaction was observed, indicating high chemoselectivity.[23]



Scheme 4. Asymmetric Phenol Dearomatization

In summary, we have succeeded in synthesizing the core structure of didymeline. The tricyclic lactam **15** was constructed from commercially available **1** through a 16-step reaction sequence. Chemoselective dearomatization of phenol **10** with diazoacetamide using a chiral silver catalyst was made possible with a

high level of enantiocontrol, which led to the formation of a corresponding spiro lactam in an asymmetric format. However, further transformation of **15** into didymeline was unsuccessful. The research for the development of another synthetic route for the total synthesis of didymeline and related alkaloids is continuing in our laboratory.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Supplementary (typical procedure for Michael reaction, HPLC chromatograms, ^{1}H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27092/103/2

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22. A removal of the *t*-Bu group of **15** using TFA or $Cu(OTf)_2$ was unsuccessful.
23. Reaction of **10** using $Rh_2(OAc)_4$ did not give **11** at all, instead a C–H insertion product was obtained.