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First Synthesis of [5-5-6-6] Tetracyclic Framework of Spiropreussione B

Bhavani Shankar Chinta[a] and Beeraiah Baire*[a]

Abstract: Rapid synthesis of [5-5-6-6]-tetracyclic system present in a novel spirobionaphthalene natural product spiropreussione B has been achieved. An intramolecular, thermal dehydrogenative Diels-Alder reaction has been employed as the key step. Furthermore, this approach was extended for the generation of library of structurally novel linear tetracyclic systems of spiropreussione B in a highly efficient manner. This report constitutes the first synthetic approach to the spiropreussione B natural product.

Introduction

The endophytic fungus *Preussia* sp. was isolated from a stem of *Aquilaria sinensis* (Lour.) Gilg (Thymelaeaceae), collected from Guangxi Medicinal Arboretum. The ethyl acetate and petroleum extracts of the ethanol extracts of dry mycelium showed inhibitory activities against *Candida albicans* and *Staphylococcus aureus*. A series of column chromatographic purifications of the EtOAc extract resulted in the isolation of three new spirobionaphthalene analogues, spiropreussione B **1**, spiropreussione A **2**, and spiropreussomerin A **3**.[1] Among these three natural products, spiropreussione B **1** possesses novel and unique structural features, with a pentacyclic system **4,** spiro fused to 1,8-dihydroxynaphthalene (Figure 1).

To the best of our knowledge so far, there are no reports appeared in the literature either on the synthesis of partial frameworks or on the total synthesis of the natural product spiropreussione B **1**. Inspired by the presence of novel and complex structural unit coupled with the bioactivities of the spirobionaphthalene derivatives,[2] we aimed at the development of a rapid synthetic strategy for the pentacyclic framework present in spiropreussione B **1**. We chose a thermal intramolecular dehydrogenative Diels-Alder cyclization[3] reaction as the key step for the construction of the tetracyclic system.

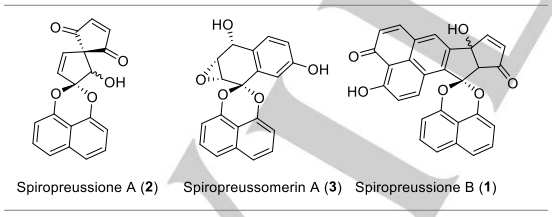
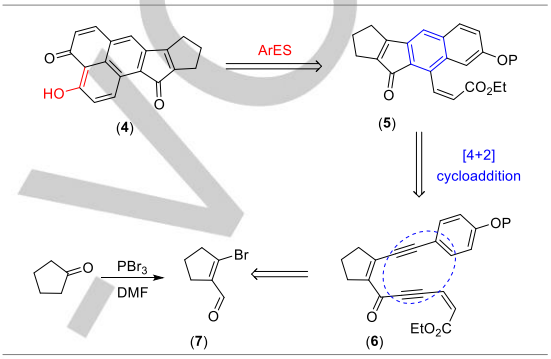


Figure 1. Spiropreussione B and other spirobionaphthalene natural products

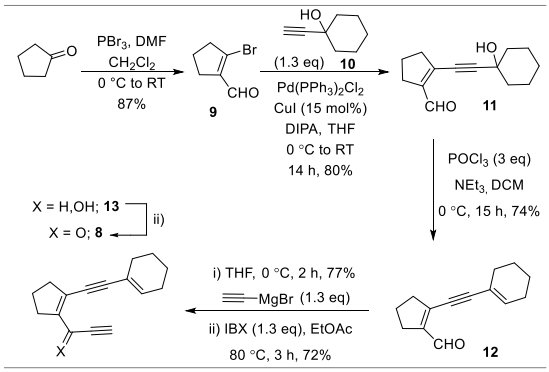
According to our retrosynthetic plan (Scheme 1), the pentacyclic system **4** of spiropreussione B **1**, can be generated from a linear [5-5-6-6] tetracyclic system **5** employing an intramolecular aromatic electrophilic substitution reaction. This **5** can be obtained *via* an intramolecular [4+2] cycloaddition reaction of the enyne-alkyne **6**. Synthesis of **6** can be possible from bromo-aldehyde **7**, employing few simple synthetic transformations including Sonogashira cross coupling.



Scheme 1. Our designed retrosynthetic plan for functionalized pentacyclic framework of spiropreussione B

Results and Discussion

To begin with, we focused to understand the feasibility of the proposed dehydrogenative Diels-Alder cyclization for the generation of [5-5-6-6]tetracyclic systems. Accordingly, we chose an enyne-alkyne **8** as a model substrate. The synthesis of enyne-alkyne **8** from commercially available cyclopentanone is depicted in scheme 2. Treatment of the cyclopentanone with PBr_3 and *N,N*-dimethylformamide (DMF) in CH_2Cl_2 at 0 °C gave the 2-bromo-enal **9** in 87% yield.[4] Sonogashira cross coupling[5] of **9** with propargylic alcohol **10** in presence of $PdCl_2(PPh_3)_2$ and CuI gave the coupled product **11** in good yield.



Scheme 2. Synthesis of enyne-alkyne precursor for TDDA reaction

Next, dehydration of *tert*-alcohol present in **11**, with $POCl_3$ and triethylamine in CH_2Cl_2 at 0 °C afforded the enyne-aldehyde **12**. Treatment of the aldehyde **12** with ethynylmagnesium bromide (0.5 *M* in THF) in THF resulted in the formation of the *sec*-propargylic alcohol **13** in 77% yield. Further oxidation of the

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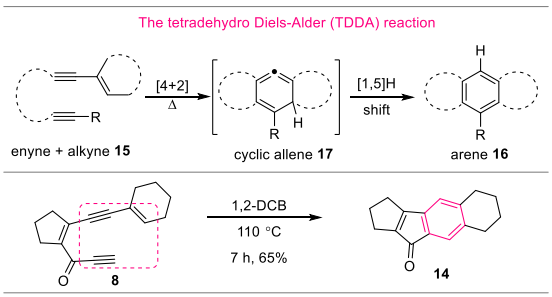
secondary alcohol of **13** with IBX[6] at 80 °C in EtOAc gave the required enyne-alkyne **8**. With the key precursor **8** in hand, we next planned for the intramolecular Diels-Alder cyclization to generate the tetracyclic system **14**.

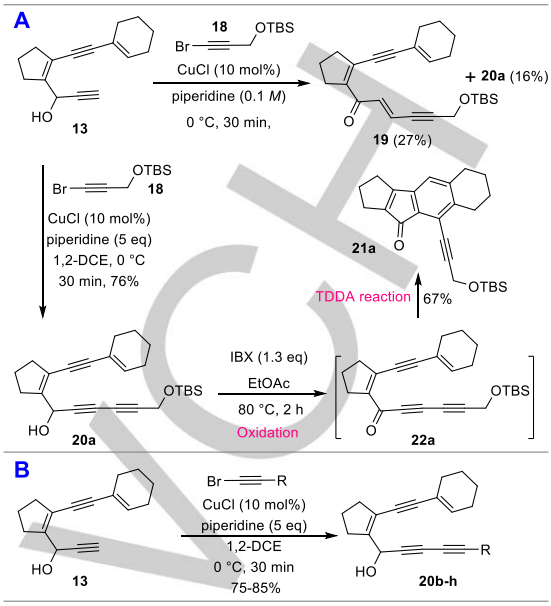
The [4+2] cycloaddition[7] reaction between an enyne (4π) and alkyne (2π) **15** would result in an arene derivative **16** *via* a [1,5]H shift of the initially formed cyclic allene intermediate **17** (Scheme 3). Based on the unsaturation present in the 4π and 2π components as well as in the product arene **16**, the above reaction is a tetra-dehydrogenative version of the classical Diels-Alder reaction and termed as the tetradehydro Diels-Alder reaction (TDDA).[3] Accordingly, the enyne-alkyne **8** upon heating in 1,2-dichlorobenzene (1,2-DCB) at 110 °C for 7 h, to our delight resulted in the formation of the expected cyclised product **14** in 65% yield (Scheme 3).[8]



Scheme 3. The tetradehydro Diels-Alder reaction and generation of [5-5-6-6] tetracyclic system of spiropreussione B

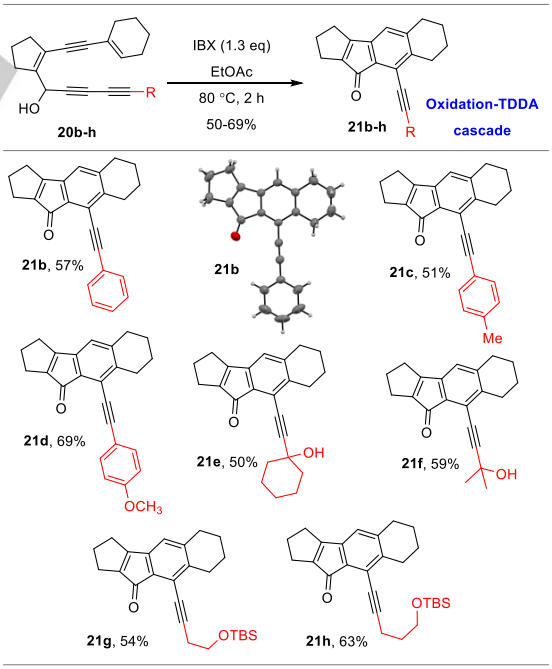
Encouraged by this result, we next planned to generate a library of diversely functionalized [5-5-6-6]-tetracyclic systems of spiropreussione B **1**. Accordingly, a three-step Cadiot-Chodkiewicz coupling–oxidation–TDDA cyclization strategy was developed, starting from the propargylic alcohol **13** (Scheme 4). In view of this, the alkyne **13** upon subjection to Cadiot–Chodkiewicz coupling reaction[9] with bromoalkyne[10] **18** in presence of CuCl (10 mol%) and piperidine (solvent as well as base) at 0 °C gave after 30 min., a mixture of two compounds, the unexpected enynone **19** in 27% yield along with the expected diynol **20a** in 16% yield. The formation of **19** can be possible *via* an initial formation of the diynol **20a** followed by the base (piperidine) promoted isomerisation of the propargylic alcohol to enone.[11] Since the standard conditions for the formation of diyne **20a** failed, subsequently, we employed a modified procedure for the same transformation.[12] Therefore, treatment of the alkyne **13** and alkynyl bromide **18** with 5 equiv. of piperidine (base) and 10 mol% of CuCl at 0 °C in 1,2-dichloroethane resulted in clean formation of the expected diynol **20a** in 79% yield after 30 min. (Scheme 4). Next oxidation of the secondary alcohol **20a** with IBX in EtOAc at 80 °C for 2 h, gave directly the tetracyclic product **21a** in 67% yield (for two steps), *via* the TDDA cyclization reaction of the initially formed ketone **22a**.

Having developed a three step strategy for the functionalized [5-5-6-6] tetracyclic system **21a** from **13**, we further extended this strategy for the synthesis of divergent tetracyclic systems **21b-h** (Scheme 5) *via* corresponding diynols **20b-h**.



Scheme 4. Synthesis of structurally divergent enyne-alkyne precursors

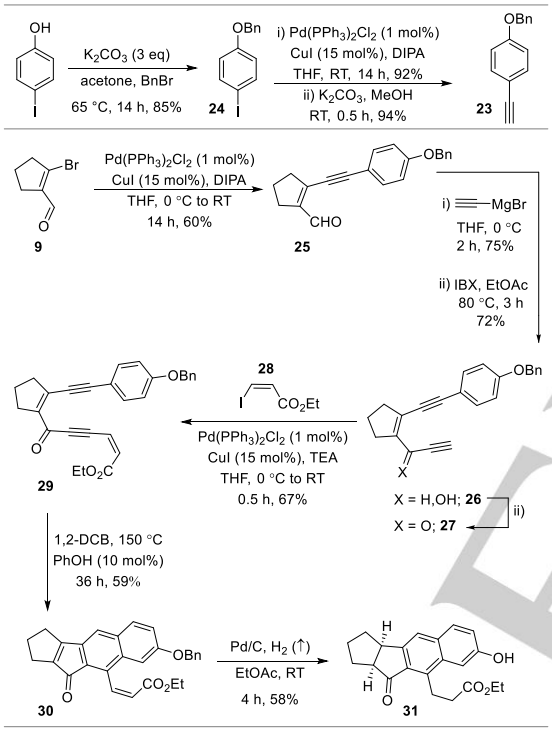
Alkynyl bromides consisting of aryl acetylenes, propargylic alcohols, homo-propargylic alcohols, and -OTBS ethers were utilized in the cross coupling reaction to generate the diynols **20b-h**. All these substrates **20b-h**, when subjected to IBX oxidation conditions at 80 °C, cleanly and smoothly underwent the oxidation-cycloaddition cascade to afford the corresponding cyclised products **21b-h** in moderate to good yields (Scheme 5).



Scheme 5. Generation of library of functionalized [5-5-6-6]tetracyclic systems of spiropreussione B **1**, and ORTEP diagram for compound **21b**

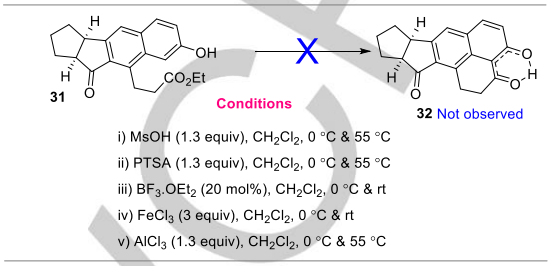
In order to confirm the presence of the tetracyclic framework, X-ray diffraction analysis was performed for the compound **21b** and its ORTEP diagram[13] is presented in Scheme 5.

Subsequently, after successful generation of the library of novel tetracyclic systems we turned our attention to construct the pentacyclic framework, having appropriate functional groups (Schemes 6 & 7). Accordingly, *p*-benzyloxyphenylacetylene **23** was prepared from the commercially available *p*-iodophenol in three steps. Initial protection of the hydroxy group with K_2CO_3 and BnBr in acetone at 65 °C, gave the benzylether **24** in 85% yield. Sonogashira coupling of **24** with trimethylsilylacetylene followed by the deprotection of trimethylsilyl- group with K_2CO_3, MeOH gave the phenylacetylene derivative **23**.



Scheme 6. Synthesis of advanced [5-5-6-6]tetracyclic system

Next, the Sonogashira coupling of the bromo-enal **9** with the arylalkyne **23** gave the arenyne-aldehyde **25**. Addition of an ethynylmagnesium bromide to the aldehyde **25** at 0 °C in THF followed by oxidation of the resultant propargylic alcohol **26** with IBX in EtOAc, gave the enynone **27** in 50% yield (for two steps). At this stage, we envisioned an acrylate as the three carbon unit, for the creation of the fifth ring, after the TDDA cyclization. Hence, a Sonogashira coupling reaction of the ynone **27** with (*Z*)-2-iodoacrylate[14] **28** gave the enynonate **29**. Further heating the **29** in 1,2-DCB and phenol (10 equiv.) at 150 °C for 3 h, resulted in the exclusive formation of the linear tetracyclic product **30** in 59% yield. Upon subjection to hydrogenolysis conditions with 10% Pd/C in EtOAc at RT, the cyclic compound **30** underwent the reduction of enone and ynoate double bonds as well the deprotection of benzyl group to give the saturated phenol derivative **31**. Having the required 3-carbon ester and phenol functional groups at the appropriate positions in **31**, we attempted for the intramolecular ring closure reaction to create the pentacyclic system **32** (Scheme 7). But to our disappointment, none of the employed conditions gave the expected product **32**. In some cases the starting material **31** was recovered and few cases there was a decomposition of **31** observed.



Scheme 7. Attempts for the pentacyclic system of spiropreussione B

Conclusions

In summary, we have developed a linear synthetic strategy for the first synthesis of functionalized [5-5-6-6] tetracyclic framework of the natural product spiropreussione B. The tetradehydro Diels-Alder reaction between an enyne and alkyne was employed as the key step. Further this strategy was extended for the generation of library of structurally novel, highly functionalized [5-5-6-6] tetracyclic systems. Various attempts for the generation of pentacyclic system have failed.

Acknowledgements

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Keywords: Alkynes • Dehydrogenative Diels-Alder reactions • Enynes • Natural products • Polycyclic compounds.

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[8] At 70 °C the reaction was very slow. After 48 h, there was only about 35% conversion of **8** to **14** was observed. At 130 °C and 150 °C though the reaction was quicker, yields of **14** were only ~50%.

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[13] Crystallographic data information for **21b** has been deposited with the Cambridge Crystallographic Data Centre with CCDC1540073. Further details are given in the supporting information file.

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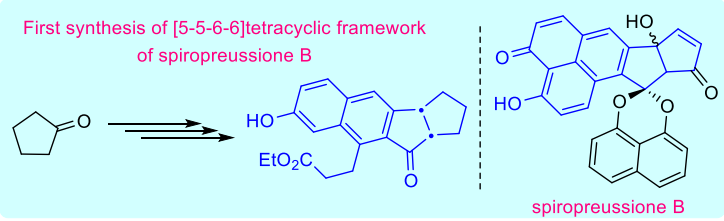

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