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Double Cycloisomerization as a Novel and Expeditious Route to Tricyclic Heteroaromatic Compounds: Short and Highly Diastereoselective Synthesis of (±)-Tetraponerine T6

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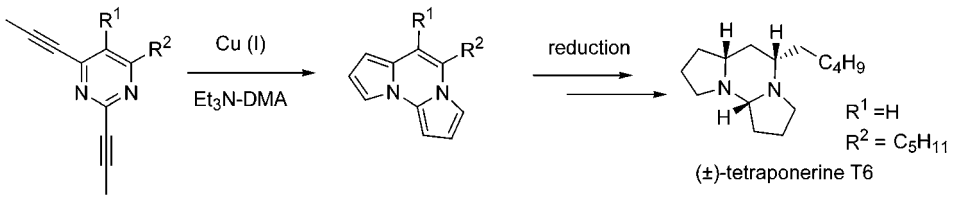
ABSTRACT



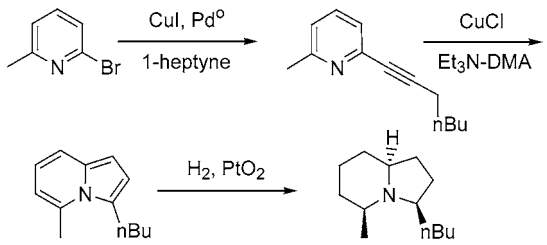
Cu-Assisted double cycloisomerization of bis-alkynylpyrimidines afforded the 5–6–5 tricyclic heteroaromatic skeleton. This transformation was used as a key step in the highly diastereoselective total synthesis of (±)-tetraponerine T6.

We have recently reported a novel, general, and efficient method for the construction of 2-monosubstituted and 2,5-disubstituted pyrroles, as well as fused aromatic heterocycles containing a pyrrole ring, via the Cu-assisted cycloisomerization of alkynyl imines. The generality and synthetic usefulness of this novel methodology was demonstrated by achieving the shortest synthesis of (±)-monomorine in three steps and 47% overall yield[1] (Scheme 1). This successful result encouraged us to investigate a possible multiple pyrrolization protocol. If this unprecedented cascade transformation proves to be successful, combined with a further functionalization sequence, it can provide us with a conceptually novel and expeditious route to various polycyclic alkaloid skeletons.

Herein, we report the first example of double pyrrolization of pyrimidine derivatives into the bis-pyrrolopyrimidines and employment of this transformation in the short and highly diastereoselective synthesis of (±)-tetraponerine T6.

To examine the possibility of assembling a 5−6−5 tricyclic heteroaromatic skeleton, we synthesized bis-propynylpyrimidine derivatives **1a**−**c** and tested them under pyrrolization conditions. A sequential double pyrrolization of **1** posed a certain challenge. Indeed, as shown in Scheme 2, the first pyrrolization of **1** can proceed in three possible ways (paths **A**−**C**). Among them, paths **A** and **B**, after the first cycloisomerization, will produce pyrrolopyrimidines **3** and **4**, which after the second pyrrolization will be converted

Scheme 1. Short Synthesis of (±)-Monomorine



(1) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.

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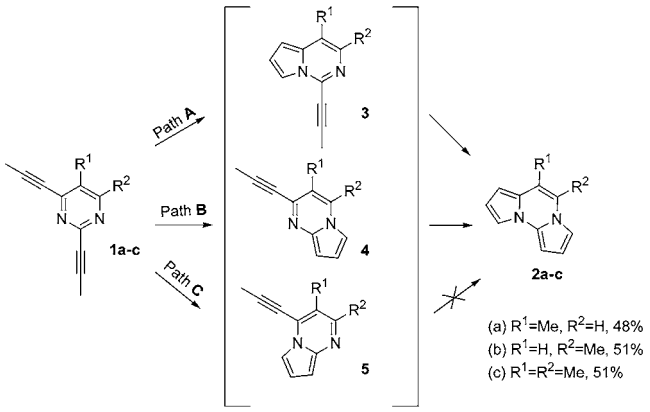
Scheme 2. Sequential Double Pyrrolization[a]

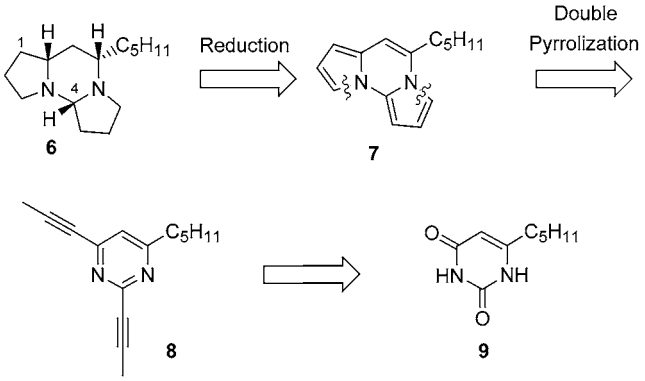


[a] Reagents and conditions: (a) CuBr, Et_3N−DMA, 150 °C, 10 h.

into the desired product **2**. In contrast to the above cases, path **C** leads to dead-end intermediate **5**. Experiments have shown that in the presence of 1 equiv of CuBr in dilute Et_3N−DMA at 150 °C, bis-propynylpyrimidines **1a**−**c** were smoothly converted into the tricyclic bis-pyrrolopyrimidines **2a**−**c** in 48−51% yield.[2] Under these reaction conditions, no other low-molecular weight compounds, besides **2**, were detected by GC-MS analyses of the crude reaction mixture. In contrast, when the reaction was performed at both reduced temperature (130 °C) and reduced copper loading (50 mol %), early stage GC-MS analyses revealed the presence of two isomeric compounds in about a 5:1 ratio, along with starting material **1** and product **2**. As the reaction progressed, the amount of tricyclic product **2** increased and the amounts of the starting material and its two unidentified isomers decreased. At this stage, it is unclear which of these three structures (**3**−**5**) corresponded to the two fleeting isomers observed by GC-MS.[3] Taking into account that the yield per each pyrrolization in the transformation **1** → **2** is about 70% and that the cycloisomerization yields for propyne derivatives are normally 10−20% lower than that of their higher homologues,[5] we considered 48−51% yield for the double pyrrolization to be a rather satisfactory result.

Encouraged by successful synthesis of 5−6−5 tricyclic bis-pyrrolopyrimidine core **2**, we attempted a total synthesis of (±)-tetraponerine T6,[6] which can be considered to be a reduced derivative of **2**. Indeed, T6 could be made by complete reduction of heteroaromatic compound **7**, a higher homologue of **2b**, which, in turn, is the double-pyrrolization product of bis-propynylpyrimidine **8**. The latter could be

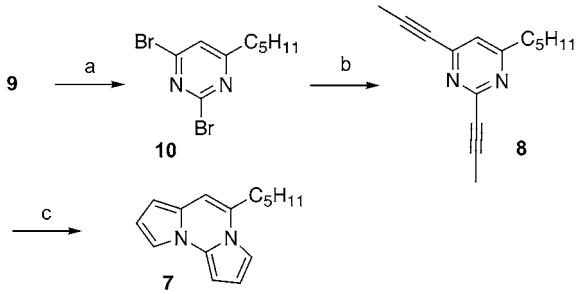
Scheme 3. Retrosynthetic Analysis for **6**



easily prepared from the known pyrimidine dione **9** (Scheme 3).

The synthesis began with pyrimidine dione **9**,[7] which was routinely prepared from ethyl acetoacetate. Treatment of **9** with phosphorus oxybromide in benzene followed by Sonogashira coupling[8] with propyne proceeded uneventfully to give bis-propynylpyrimidine **8** in excellent overall yield. The next step, a sequential double pyrrolization of **8**, gave 5−6−5 tricyclic bis-pyrrolopyrimidine **7** in 52% yield (Scheme 4).

Scheme 4. Synthesis of Bis-pyrrolopyrimidine **7**[a]



[a] Reagents and conditions: (a) $C_6H_5N(CH_3)_2$, $POBr_3$, benzene, reflux, 2h, 81%; (b) CuI, $Pd(PPh_3)_2Cl_2$, propyne, Et_3N, 50 °C, 3 h, 100%; (c) CuBr, Et_3N−DMA, 150 °C, 10 h, 52%.

Direct complete hydrogenation of heteroaromatic compound **7** to **6** proved not to be simple. It is well-known that

(2) Double pyrrolization of the unsubstituted bis-propynylpyrimidine proceeded with a somewhat lower yield, probably due to a competing polymerization process.

(3) Possible allenic structures for the observed isomers were discounted, since propargyl−allenyl isomerization is a rate-determining step in the entire cycloisomerization; thus, allenyl intermediates were never detected during the reaction course. See refs 1 and 4.

(4) Kel'in, A.; Gevorgyan, V. *J. Org. Chem*. **2002**, *67*, 95.

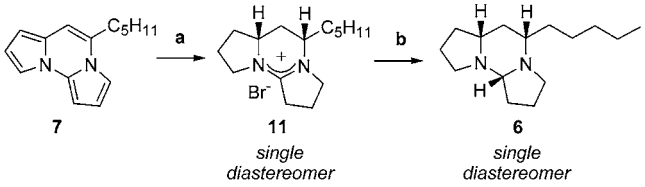
(5) For lower thermal stability of the terminal allenic intermediates, see refs 1 and 4.

(6) T6 Tetraponerine T6 is the one of the major venom alkaloids isolated from the poison gland of the Neo Guinean ant *Tetraponera* sp. For isolation of tetraponerines, see: (a) Merlin, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *J. Chem. Ecol*. **1988**, *14*, 517. (b) Braekman, J. C.; Daloze, D.; Pasteels, J. M.; Vanhecke, P.; Declercq, J. P.; Sinnwell, V.; Franke, W. Z. *Naturforsch*. **1987**, *42c*, 627. Tetraponerines are made of the tricyclic skeletons (6−6−5 and 5−6−5), which are unprecedented alkaloid cores isolated from animals. Moreover, their interesting insecticidal activities (LD_{50} = 2 × 10^{-9} mol/ant mg) have made them attractive synthetic targets for chemists; see refs 2b and 4. To date, four diastereo- and enatioselective syntheses of tetraponerine T6 have been described; see: (a) Stragies, R.; Blecher, S. *J. Am. Chem. Soc*. **2000**, *122*, 9584. (b) Yue, C.; Gauthier, I.; Royer, J.; Husson, H. P. *J. Org. Chem*. **1996**, *61*, 4949. (c) Plehiers, M.; Heilporn, S.; Ekelmans, D.; Leclercq, S.; Sangermano, M.; Braekman, J. C.; Daloze, D. *Can. J. Chem*. **2000**, *78*, 1030. (d) Devijver, C.; Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron*, **1995**, *40*, 10913.

(7) See Supporting Information for details.

catalytic hydrogenation of pyrimidine derivatives in acidic media is cis diastereoselective and stops at the stage of formation of stable amidinium derivatives.[9] Accordingly, as expected, catalytic hydrogenation of **7** over PtO_2 under acidic conditions gave amidinium salt **11** as a single cis isomer.[10] The total synthesis of (±)-tetraponerine T6 was completed by highly diastereoselective reduction of crude **11** with $LiAlH_4$ to give **6** as the sole stereoisomer in 64% yield for two steps (Scheme 5).

Scheme 5. Reductive Transformations of **7**[a]



[a] Reagents and conditions: (a) H_2 (50 psi), PtO_2, HBr, MeOH, rt, 40 h; (b) $LiAlH_4$, THF, 4 Å MS, from 0 °C to rt, 2 h, 64% yield for two steps.

The highly stereoselective reduction of **9**, which we believe is stereoelectronically controlled, deserves a special note.[11] Two possible transition states can account for the delivery of hydride to the newly formed stereogenic center at the C-4 position. Obviously, the nucleophilic attack of a hydride proceeds from the β-face to give (±)-T6 through the most favorable "chairlike" transition state ***i*** instead of an α-face delivery of a hydride through the disfavored "boatlike" transition state ***ii*** to form an epi (±)-T6 (Figure 1). The relative configuration of (±)-tetraponerine T6 was confirmed by NOESY and ^{1}H NOE experiments.[12]

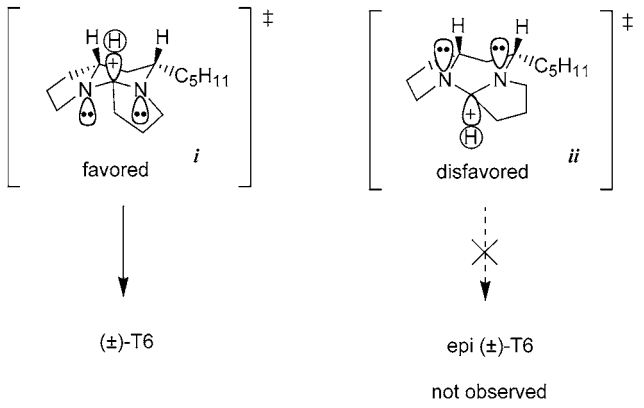


Figure 1. Transition states for the nucleophilic attack of hydride at the amidinium ion **11**.

In conclusion, the first Cu-assisted double pyrrolization of bis-alkynylpyrimidine to the 5−6−5 heteroaromatic core was demonstrated. Highly selective hydrogenation/reduction of the resulting bis-pyrrolopyrimidine allowed for the short, efficient, and highly diastereoselective total synthesis of (±)-tetraponerine T6 in five steps and 27% overall yield. The multiple pyrrolization−reductive functionalization protocol can serve as a new, short, and efficient approach toward various polycyclic alkaloid structures.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (GM-64444). We also thank Dr. Michael Rubin for fruitful discussions and Dr. John Harwood for the NOE experiment.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991, Vol. 3, p 521.

(9) For hydrogenation of pyrimidines, see: (a) Brown, D. J. The Pyrimidines. In *The Chemistry of Heterocyclic Compounds*; Wiley & Sons: New York, 1994; Vol. 52, pp 790−793. (b) Brown, D. J. T. The Pyrimidines Supplement I. In *The Chemistry of Heterocyclic Compounds*; Wiley & Sons: New York, 1970; pp 337−341.

(10) ^{13}C NMR analysis of crude **9** revealed that it is a single diastereomer. The relative configuration of its stereogenic centers was proved by a NOE experiment after the subsequent reduction step.

(11) For stereoelectronic control in addition of nucleophiles to an amidinium ion, see: (a) Perrin, C. L.; Young, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 4451. (b) Fülöp, F.; Simon, K.; Tóth, G.; Hermecz, I.; Mészáros, Z.; Bernáth, G. *J. Chem. Soc., Perkin Trans.* **1982**, *12*, 2801. (c) Kirby, A. J. *Stereoelectronic Effects*, Oxford Chemistry Primer no. 36; Oxford University Press: Oxford, 1996; pp 54−55. (d) Barluenga, J.; Tomás, M.; Kouznetsov, V.; Rubio, E. *J. Org. Chem.* **1994**, *59*, 3699.

(12) For the NOESY and ^{1}H NOE experiments of **6**, see Supporting Information.