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Double Cycloisomerization as a Novel and Expeditious Route to Tricyclic Heteroaromatic Compounds: Short and Highly Diastereoselective Synthesis of ($\pm$)-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 ($\pm$)-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 ($\pm$)-monomorine in three steps and 47% overall yield¹ (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 ($\pm$)-tetraponerine T6.

To examine the possibility of assembling a 5–6–5 tricyclic heteroaromatic skeleton, we synthesized bis-pro-pynylpyrimidine 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 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 Et₃N–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 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 coupling⁸ 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).

Direct complete hydrogenation of heteroaromatic compound **7** to **6** proved not to be simple 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 PtO₂ 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 LiAlH₄ to give **6** as the sole stereoisomer in 64% yield for two steps (Scheme 5).

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 ¹H NOE experiments.¹²

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Scheme 1.
Short Synthesis of (±)-Monomorine

Scheme 2.
Sequential Double Pyrrolization^a

^a Reagents and conditions: (a) CuBr, Et₃N-DMA, 150 °C, 10 h.

Scheme 3.
Retrosynthetic Analysis for **6**

Scheme 4.

Synthesis of Bis-pyrrolopyrimidine 7a

^a Reagents and conditions: (a) $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$, POBr_3 , benzene, reflux, 2h, 81%; (b) CuI , $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, propyne, Et_3N , 50 °C, 3 h, 100%; (c) CuBr , Et_3N -DMA, 150 °C, 10 h, 52%.

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

^a Reagents and conditions: (a) H₂ (50 psi), PtO₂, HBr, MeOH, rt, 40 h; (b) LiAlH₄, THF, 4 Å MS, from 0 °C to rt, 2 h, 64% yield for two steps.