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Highly Diastereoselective Approach toward (±)-Tetraponerine T6 and Analogues via the Double Cycloisomerization−Reduction of Bis-alkynylpyrimidines

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A new, short, and efficient approach toward tricyclic alkaloids, involving the double cycloisomerization−reduction of bis-alkynylpyrimidines **3a**−**m**, has been developed. The requisite bis-alkynylpyrimidines **3a**−**m** were readily prepared via regioselective sequential Sonogashira coupling reactions of dibromopyrimidines **1**. Bis-alkynylpyrimidines **3a**−**m** were converted into the 5−6−5 tricyclic heteroaromatic cores **4a**−**m** via the Cu(I)-assisted double cycloisomerization reaction. The reaction proceeded stepwise, which was confirmed by the isolation of the mono-pyrrolization intermediate **5**. The structure of **5** was assigned by 2D NMR and by independent synthesis. Cycloisomerization of **5** under standard conditions afforded tricyclic **4g** in 89% yield. The PtO_2-catalyzed hydrogenation of bis-pyrrolopyrimidines **4d**, **4g**, and **4i** in acidic media afforded stable amidinium derivatives, **11a**, **11b**, and **11c**. Further reduction of the latter with $LiAlH_4$ allowed for the highly diastereoselective total synthesis of (±)-tetraponerine T6 and its analogues.

Introduction

The tetraponerines are a group of eight toxic alkaloids that are found in the venom of the New Guinean pseudomyrmecine ant *Tetraonera sp.*[1] and are composed of 1,3-diaza tricyclic systems (5−6−5 and 6−5−6), highly unusual cores for alkaloids isolated from animals. Moreover, these alkaloids represent the major constituents of the contact poison, showing profound insecticidal activities (LD_{50} of 5×10^{-9} mol/ant mg). The unprecedented tricyclic skeleton, along with the interesting insecticidal activities of the tetraponerines, has made them attractive targets for total synthesis. Tetraponerine T6 is made of a 5−6−5 skeleton and is one of the major venom alkaloids. Prior to our studies, four diastereo- and enantioselective syntheses of tetraponerine T6 had been reported.[2] These syntheses, representing two synthetic approaches toward assembling a tricyclic core of tetraponerine T6, are summarized in Scheme 1. Blechert assembled the tricyclic 5−6−5 core via a cascade Pd-catalyzed cyclization.[2a] Another approach, utilized by Plehiers,[2b] Royer,[2c] and Devijver,[2d] employed different modes of double condensation of proline homologues with cyclic imines. We have recently communicated a short and highly diastereoselective synthesis of (±)-tetraponerine T6, employing a totally different approach[3] involving exhaustive hydrogenation/reduction of the bis-pyrrolopyrimidine skeleton obtained via the double cycloisomerization of bis-alkynylpyrimidine (Scheme 1). This strategy represents a conceptually novel and highly expeditious route toward certain polycyclic alkaloid skeletons. Herein, we provide a full account of this work as well as additional mechanistic studies and syntheses of tetraponerine analogues.

Results and Discussion

Recently, we developed a novel, general, and efficient method for the construction of pyrrole rings and fused aromatic pyrroloheterocycles via the Cu-assisted cycloisomerization of alkynyl imines.[4] The synthetic usefulness of this novel methodology was further demonstrated by achieving the shortest synthesis of (±)-monomorine in three steps and 47% overall yield (Scheme 2). This successful result encouraged us to investigate the prospect of multiple pyrrolization protocols en route to tricyclic alkaloid structures. To test this idea, we investigated the possibility of constructing a 5−6−5 tricyclic heteroaromatic skeleton via the double Cu(I)-assisted cycloisomerization of bis-alkynylpyrimidines.

To this end, we synthesized various bis-alkynylpyrimidine derivatives **3a**−**m** employing Sonogashira coupling reactions[5] of 1,3-dibromo-pyrimidines **1** (Table 1). Double-fold Sonogashira coupling of dibromopyrimidines[6] with propyne proceeded smoothly to give bis-propynylpy-

(1) (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., C: Biosci.* **1987**, *42c*, 627.

(2) (a) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (b) Plehiers, M.; Heilporn, S.; Ekelmans, D.; Leclercq, S.; Sangermano, M.; Braekman, J. C.; Daloze, D. *Can. J. Chem.* **2000**, *78*, 1030. (c) Yue, C.; Gauthier, I.; Royer, J.; Husson, H. P. *J. Org. Chem.* **1996**, *61*, 4949. (d) Devijver, C.; Macours, P.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *Tetrahedron* **1995**, *51*, 10913.

(3) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697.

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

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SCHEME 1. Approaches toward Tetraponerine T6

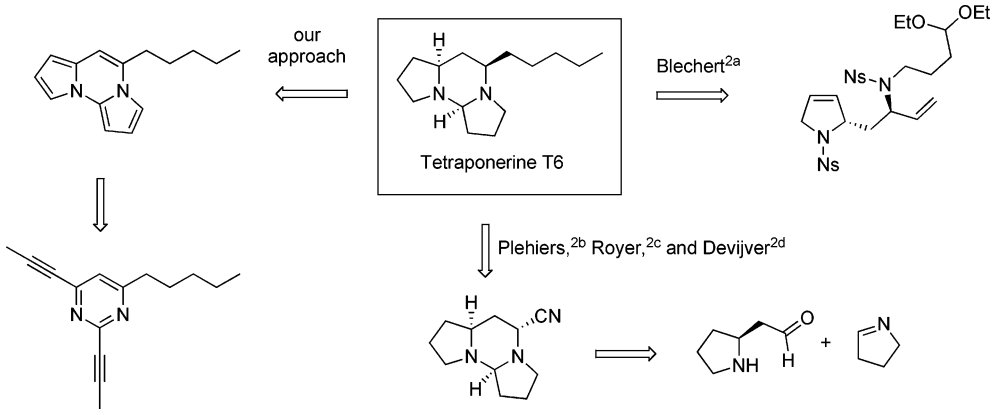
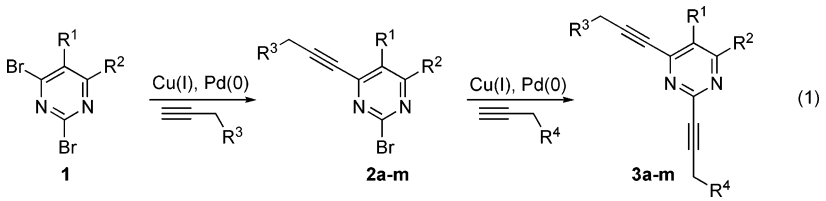


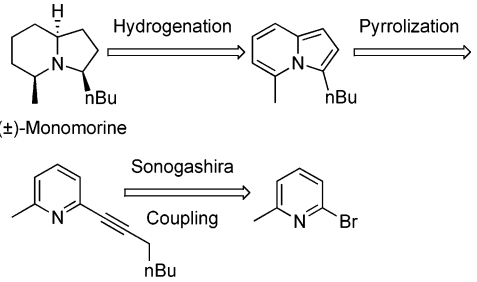
TABLE 1. Synthesis of Bis-alkynylpyrimidines



					yield[a] (%)	
entry	R^1	R^2	R^3	R^4	**2**	**3**
1	H	H	H	H		100 (**a**)
2	H	CH_3	H	H		100 (**b**)
3	CH_3	H	H	H		100 (**c**)
4	H	C_5H_{11}	H	H		100 (**d**)
5	CH_3	CH_3	H	H		100 (**e**)
6	H	H	C_2H_5	C_2H_5		77 (**f**)
7	H	C_5H_{11}	C_3H_7	C_3H_7		79 (**g**)
8	CH_3	H	C_2H_5	C_2H_5		100 (**h**)
9	CH_3	CH_3	C_2H_5	C_2H_5		100 (**i**)
10	CH_3	CH_3	$(CH_2)_2Ph$	OCH_3	80	82 (**j**)
11	CH_3	CH_3	OCH_3	$(CH_2)_2Ph$	46[b]	100 (**k**)
12	CH_3	CH_3	$(CH_2)_2Ph$	C_3H_7	*c*	100 (**l**)
13	CH_3	CH_3	C_3H_7	$(CH_2)_2Ph$		75 (**m**)[d]

[a] Isolated yields. All reactions were performed with 0.4 mol % of CuI and 0.2 mol % of $Pd(PPh_3)_2Cl_2$ in Et_3N. See the Experimental Section for details. [b] 18% of the starting material was recovered. [c] Monoalkynyl pyrimidine **2j**, which was obtained in 80% yield (entry 10), was subjected to the reaction with 1-pentyne in stepwise fashion. [d] The reaction was performed under one-pot procedure conditions.

SCHEME 2. Short Synthesis of (±)-Monomorine



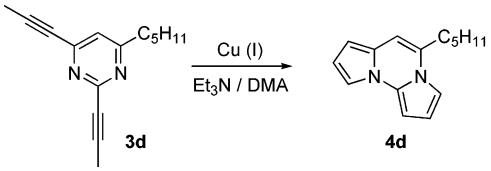
rimide derivatives in quantitative yields (Table 1, entries 1−5). Analogously, employment of higher alkyne analogues, such as pentyne and hexyne, allowed for the efficient syntheses of symmetric bis-alkynylpyrimidines **3f**−**i** (Table 1, entries 6−9). Next, we synthesized bis-alkynylpyrimidines **3j**−**m**, possessing different alkynyl substituents (Table 1, entries 10−13). Here, we took advantage of the known, different reactivity of bromides in dibromopyrimidines **1**.[7] First, we accessed bis-alkynylpyrimidines **3j**−**l** in stepwise fashion. Accordingly, employment of 1 equiv of alkyne allowed for selective coupling at the C-4 position to give the corresponding bromopyrimidine **2** in reasonable to good yields. Subsequent coupling of the C-2 bromide with another alkyne provided the unsymmetrical bis-alkynylpyrimidines in excellent overall yield (Table 1, entries 10−12). It was

(5) (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.

(6) For the syntheses of dibromopyrimidines, see Experimental Section. Janin, Y. L.; Roulland, E.; Beurdeley-Thomas, A.; Decaudin, D.; Monneret, C.; Poupon, M. F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 529.

(7) For selective mono cross-coupling reactions of pyrimidine dihalides, see: (a) Tullis, J. S.; VanRens, J. C.; Natchus, M. G.; Clark, M. P.; De, B.; Hsieh, L. C.; Janusz, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1665. (b) Simkovsky, N. M.; Ermann, M.; Roberts, S. M.; Parry, D. M.; Baxter, A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1847. (c) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829. (d) Mangalagiu, I.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1996**, *50*, 914.

TABLE 2. Optimization of the Cu(I)-Assisted Double Cycloisomerization of 3d

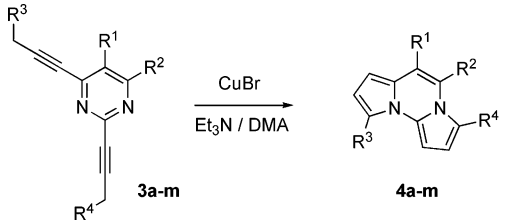


(2)

entry	Cu(I) (equiv)	concn (M)	temp (°C)	time (h)	yield[a] (%)
1	CuI (2)	0.5	130	12	<5
2	CuI (2)	0.1	110	9	<5
3	CuI (2)	0.1	80	2	NR
4	CuI (1)	0.1	150	6	27
5	CuI (0.5)	0.1	150	6	30
6	CuI (0.3)	0.1	150	12	24
7	CuI (0.3)	0.1	110	5	<5
8	CuCl (1)	0.1	150	6	28
9	CuBr (1)	0.1	150	6	34
10	CuBr (1)	0.02	150	6	50
11	CuBr (1)	0.02[b]	150	10	52
12[c]	CuBr (1)	0.02[d]	150	22	34
13	CuBr (1)	0.02[e]	150	12	47

[a] Isolated yields. [b] Slow addition of **3d** via syringe pump over 5 h at 150 °C. [c] Bu_3N was used instead of Et_3N. [d] Slow addition of **3d** via syringe pump over 20 h at 150 °C. [e] Slow addition of **3d** via syringe pump over 12 h at 150 °C.

TABLE 3. Cycloisomerization of Differently Substituted Bis-alkynylpyrimidines



(3)

entry	R^1	R^2	R^3	R^4	yield[a] (%)
1	H	H	H	H (**a**)	37
2	H	CH_3	H	H (**b**)	51
3	CH_3	H	H	H (**c**)	48
4	H	C_5H_{11}	H	H (**d**)	52
5	CH_3	CH_3	H	H (**e**)	51
6	H	H	C_2H_5	C_2H_5 (**f**)	41
7	H	C_5H_{11}	C_3H_7	C_3H_7 (**g**)	68
8	CH_3	H	C_2H_5	C_2H_5 (**h**)	40
9	CH_3	CH_3	C_2H_5	C_2H_5 (**i**)	70
10	CH_3	CH_3	$(CH_2)_2Ph$	OCH_3 (**j**)	40
11	CH_3	CH_3	OCH_3	$(CH_2)_2Ph$ (**k**)	43
12	CH_3	CH_3	$(CH_2)_2Ph$	C_3H_7 (**l**)	75
13	CH_3	CH_3	C_3H_7	$(CH_2)_2Ph$ (**m**)	64

[a] Isolated yields.

also found that the cross-coupling of **1** with two different alkynes can efficiently be performed under a one-pot procedure condition without isolation of monobromopyrimidine intermediate **2** (Table 1, entry 13).

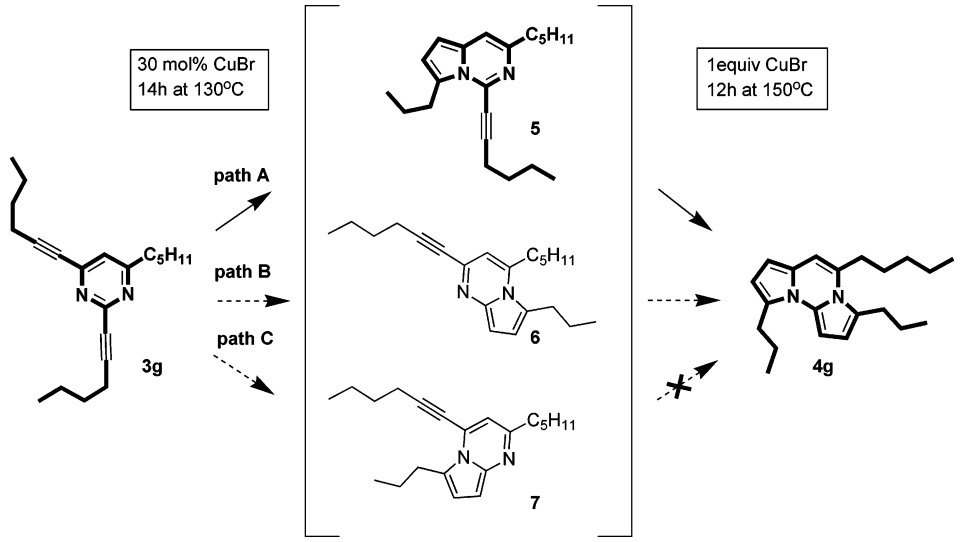
Next, bis-alkynylpyrimidine **3d**, a potential precursor of tetraponerine T6, was chosen for optimization of the double cycloisomerization process (Table 2). The attempts at double cycloisomerization of **3d** in the presence of 2 equiv of CuI at various temperatures were unsuccessful; at higher temperatures (Table 2, entries 1, 2), the substrate polymerized, whereas at lower temperatures (Table 2, entry 3), no reaction occurred. Reduction of the CuI amount had a somewhat positive effect on the reaction course (Table 2, entries 4−6). Further improvement was achieved by switching to CuBr (Table 2, entry 9). Dilution of the reaction mixture allowed for additional improvement of the reaction yields (Table 2, entries 10, 11). Taking into account that the yield for each pyrrolization in the transformation of **3d** to **4d** is about 70% and that the cycloisomerization yields for propyne derivatives are normally 10−20% lower than that of their higher homologues,[8] we considered 50−52% yield for the double pyrrolization to be a rather satisfactory result.

The optimized conditions were applied to the double cycloisomerization of the differently substituted bis-alkynylpyrimidines (Table 3). It was found that the double cycloisomerization of bis-alkynylpyrimidines generally allowed for the assembly of tricyclic aromatic compounds in moderate to good yields. Double cycloisomerization of **3a** provided low yield of nonsubstituted bis-pyrrolopyrimidine **4a** (Table 3, entry 1). Notably, introduction of additional alkyl substituents into bis-alkynylpyrimidines had a positive effect on the yields of the resulting bis-pyrrolopyrimidines, ranging from moderate yields for mono-, di-, and trisubstituted heterocycles (Table 3, entries 2−8) to good yields for tetra-alkyl-substituted heterocycles (Table 3, entries 9, 12, 13). For reasons which are not completely understood, the introduction of a methoxy substituent (R^3 or R^4) led to substantial decrease in the reaction yields (Table 3, entries 10, 11).

Apparently, the double cycloisomerization of bis-alkynylpyrimidines proceeds via an alternative sequence of single cycloisomerization steps. As depicted in Scheme 3, the first pyrrolization of bis-alkynylpyrimidine **3g** can proceed in three possible ways (Scheme 3, paths A−C). Among them, paths A and B, after the first cycloisomerization, will produce pyrrolopyrimidines **5** and **6**, which, after the second pyrrolization, will give rise to the desired product **4g**. In contrast to these cases, path C leads to the dead-end intermediate **7**. Under standard reaction conditions (1 equiv of CuBr in dilute Et_3N−DMA at 150°C), no other low-molecular-weight compounds, besides **4g**, 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 copper loading (30 mol %), GC−MS analysis revealed the presence of one isomeric compound along with starting material **3g** and product **4g**. This intermediate had quite a different R_f value from those of starting material **3g** or product **4g**, and thus it was easily separated by column chromatography and its structure assigned as **5** on the basis of extensive 2D NMR studies, including COSY, heteronuclear multiple-quantum coherence (HMQC), and heteronuclear multiple-bond correlation (HMBC). The structure of intermediate **5** was additionally proven by an independent synthesis, depicted in Scheme 4. Thus, known dichloropyrimidine **8** (Scheme 4) was first coupled with 1 equiv of hexyne under mild Sonogashira reaction conditions to give mono-alkynylated pyrimidine **9**, which was cycloisomerized into mono-pyrrolopyrimidine **10**. The subsequent high-temperature Sonogashira coupling of **10** with another molecule of hexyne produced **5**, which was identical to the isolated intermediate in all respects.

(8) For lower thermal stability of the terminal allenic intermediates, see ref 1 and: Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95.

SCHEME 3. Possible Pathways toward Bis-pyrrolopyrimidine 4g



SCHEME 4. Synthesis of Mono-pyrrolopyrimidine Intermediate 5

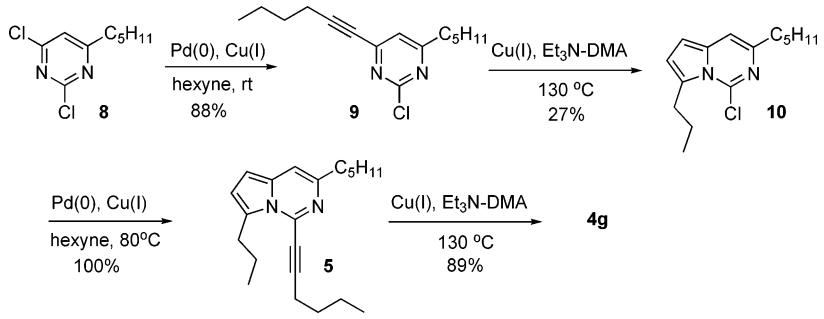
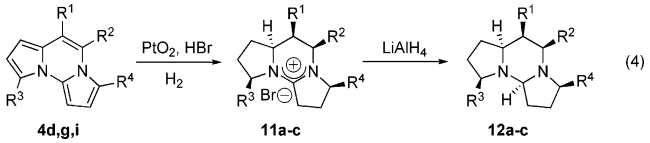


TABLE 4. Exhaustive Reduction of Bis-pyrrolopyrimidines



(4)

entry	R^1	R^2	R^3	R^4	yield of **12**[a] (%)	dr[b] (%)
1	H	C_5H_{11}	H	H (**4d**)	64 (**a**)	100:0
2	H	C_5H_{11}	C_3H_7	C_3H_7 (**4g**)	87 (**b**)[c]	88:12
3	CH_3	CH_3	C_2H_5	C_2H_5 (**4i**)	41 (**c**)	88:12

[a] Isolated yield over two steps. [b] Diastereomeric ratios were determined by ^{1}H NMR and GC−MS analyses of the crude reaction mixture. [c] NMR yield using CH_2Br_2 as an internal standard.

When **5** was subjected to the cycloisomerization conditions, it was smoothly converted into **4g** in 89% yield (Scheme 4).

Next, we drew our attention to the exhaustive reduction of bis-pyrrolopyrimidines (Table 4). Direct, complete hydrogenation of heteroaromatic compound **4d** to **12a** proved not to be straightforward. It is well-known that catalytic hydrogenation of pyrimidine derivatives in acidic media is *cis*-diastereoselective and stops at the stage of formation of stable amidinium derivatives.[9] Accordingly, catalytic hydrogenation of **4d** over PtO_2 under acidic conditions gave stable amidinium salt **11a** as a single *cis*-isomer.[10] The total synthesis of (±)-tetraponerine T6 was completed by a highly diastereoselective reduction of crude **11a** with $LiAlH_4$ to give **12a** (T6) as the sole stereoisomer in 64% yield over two steps.

Exhaustive hydrogenation/reduction of trisubstituted bis-pyrrolopyrimidine **4g** and the tetrasubstituted analogue **4i** proceeded with high diastereoselectivity, producing all-*cis*-multisubstituted tetraponerine analogues **12b**−**c** in 88:12 diastereomeric ratios with a minor unidentified diastereomer. Notably, tetraponerine **12a** and its tetrasubstituted analogue **12c** are very stable compounds. In contrast, **12b**, possessing slightly longer side chains, appeared to be extremely unstable and was characterized as crude. Diastereomeric purity of each compound was determined by ^{1}H NMR and GC−MS analyses of the crude reaction mixtures.

The highly diastereoselective installation of the last stereogenic center at C-2 via the reduction of **11a**, which we believe is both sterically and stereoelectronically controlled, deserves a special note.[11] Our molecular mechanics force field (MMFF) calculations predicted that

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

(10) ^{13}C NMR analysis of the crude material revealed that **11d** was formed as a single diastereomer. The relative configuration of its stereogenic centers was assigned by NOE experiment after the subsequent reduction step.

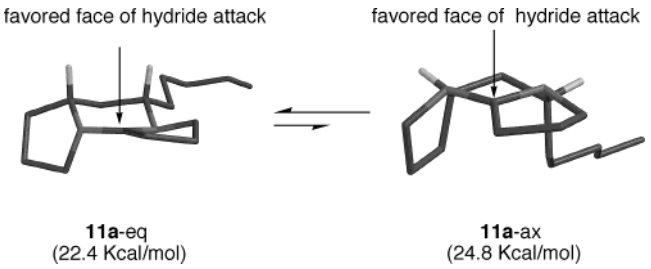


FIGURE 1. Two major conformations of amidinium ion **11a**.

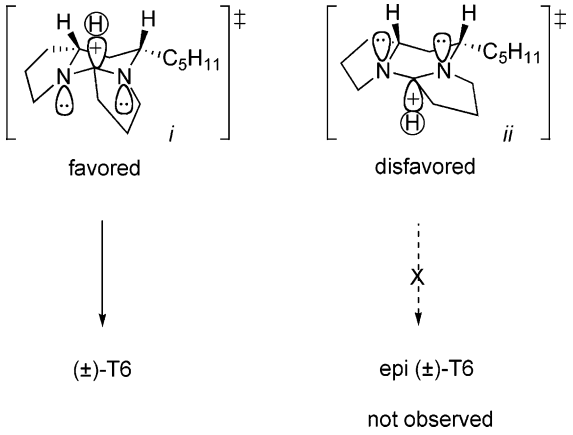


FIGURE 2. Proposed transition states for the nucleophilic attack of hydride at amidinium ion **11a**.

delivery of the hydride can be sterically controlled, favoring β-face attack at the most stable amidinium ion conformer with alkyl substituents occupying the equatorial position (**11a**-eq), as well as at another conformer **11a**-ax (Figure 1). Stereoelectronic reasons can also account for the delivery of hydride to the C-2 of the amidinium ion. The nucleophilic attack by the 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 2). The relative configurations of (±)-tetraponerine T6 and its analogues were confirmed by NOESY and ^{1}H NOE experiments.

Conclusions

In summary, the Cu(I)-assisted double pyrrolization of bis-alkynylpyrimidine to the 5−6−5 heteroaromatic core was demonstrated. A highly selective hydrogenation/reduction of the resulting bis-pyrrolopyrimidine allowed for the short, efficient, and highly diastereoselective total synthesis of (±)-tetraponerine T6 and its analogues. Considering that the assembly of a 5−6−5 tricyclic skeleton by this double pyrrolization−reduction functionalization protocol allows for the quick installation of up to 6 stereo centers in a highly diastereoselective manner, this method can serve as a new, short, and efficient approach toward selected polycyclic alkaloid structures.

Experimental Section

All manipulations were conducted under argon atmosphere using a combination of glovebox and standard Schlenk techniques. Anhydrous Et_3N and DMA were purchased from Aldrich and stored over calcium hydride. Anhydrous THF and benzene were distilled over sodium/benzophenone. 6-Pentyl-1*H*-pyrimidine-2,4-dione was prepared according to the known procedures.[12]

Representative Procedure for Syntheses of Dibromopyrimidines (1, $R_1 = CH_3$, $R_2 = CH_3$). 5,6-Dimethyl-2,4-(1*H*,3*H*)-pyrimidinedione (2.08 g, 14.84 mmol), potassium carbonate (6.15 g, 44.50 mmol), and phosphorus oxybromide (12.76 g, 44.50 mmol) were heated to reflux in dry acetonitrile (100 mL) for 72 h. The mixture was cooled to room temperature, poured into ice, and neutralized (solid potassium carbonate). The aqueous phase was thoroughly extracted with CH_2Cl_2. The combined organic extracts were washed (brine), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 10% EtOAc/hexanes to give 2,4-dibromo-5,6-dimethyl-pyrimidine as a solid with mp 125 °C (3.28 g, 83%).

Representative Procedure for Mono-Sonogashira Reaction 2j. The mixture of 2,4-dibromo-5,6-dimethyl-pyrimidine (580 mg, 2.18 mmol), CuI (17 mg, 0.09 mmol), and $Pd(PPh_3)_2Cl_2$ (31 mg, 0.04 mmol) was stirred at room temperature, and then pent-4-ynyl-bezene (280 μL, 2.43 mmol) was added to the mixture and stirred for 12 h. The mixture was quenched (aqueous NH_4Cl). The phases were separated, and the aqueous phase was thoroughly extracted with hexanes. The combined organic extracts were washed (brine), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 5−10% EtOAc/hexanes to give **2j** as an oil (574 mg, 80%).

2j. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.30−7.18 (5H, m), 2.77 (2H, t, J = 7.6 Hz), 2.50 (2H, t, J = 7.1 Hz), 2.48 (3H, s), 2.32 (3H, s), 1.97 (2H, quint, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 168.9, 152.0, 148.9, 141.0, 129.4, 128.5 (×4), 126.1, 100.7, 77.7, 34.9, 29.6, 22.5, 19.0, 15.0. MS *m*/*z* (relative intensity): 329 (M^+, 14), 300 (27), 224 (100), 91 (89).

2k. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.32 (2H, s), 3.39 (3H, s), 2.44 (3H, s), 2.29 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 169.4, 150.8, 148.9, 129.7, 94.5, 82.0, 60.1, 58.1, 22.5, 14.9. MS *m*/*z* (relative intensity): 255 (M^+, 1), 224 (100), 143 (48), 77 (62).

Representative Procedure for Syntheses of Di-prop-1-ynyl-pyrimidine (3c). Using a high-pressure tube, propyne (10 mL) was condensed in a mixture of 2,4-dibromo-5-methyl-pyrimidine (2.50 g, 9.92 mmol), CuI (76 mg, 0.4 mmol), $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol), and Et_3N (50 mL) at −78 °C. The mixture was slowly warmed and stirred at 50 °C for 3 h. Then, the mixture was cooled to room temperature and quenched (aqueous NH_4Cl). The phases were separated, and the aqueous phase was thoroughly extracted with hexanes. The combined organic extracts were washed (brine), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 20% EtOAc/hexanes to give **3c** as a solid (1.69 g, >99%).

Representative Procedure for Sequential Sonogashira Reaction (3m). The mixture of 2,4-dibromo-5,6-dimethyl-pyrimidine (380 mg, 1.43 mmol), CuI (11 mg, 0.06 mmol), and $Pd(PPh_3)_2Cl_2$ (20 mg, 0.03 mmol) was stirred at room temper-

(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. 1* **1982**, *12*, 2801. (c) Kirby, A. J. *Stereoelectronic effects*; Oxford Chemistry Primer 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) (a) Yanai, M.; Naito, T. *J. Pharm. Soc. Jpn.* **1941**, *61*, 99. (b) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. (c) Botta, M.; Cavalieri, M.; Ceci, D.; Angelis, F. D.; Finizia, G.; Nicoletti, R. *Tetrahedron* **1984**, *40*, 3313. (d) Danel, K.; Larsen, E.; Pedersen, E. B. *Synthesis* **1995**, 934.

ature, and then *n*-hexyne (173 μL, 1.5 mmol) was added to the mixture and stirred for 12 h. The reaction progress was monitored by TLC and GC−MS analyses. Pent-4-ynyl-benzene (430 μL, 2.83 mmol) was added to the mixture and stirred for 12 h at 45 °C. The mixture was cooled to room temperature and quenched (aqueous NH_4Cl). The phases were separated, and the aqueous phase was thoroughly extracted with hexanes. The combined organic extracts were washed (brine), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 2−10% EtOAc/hexanes to give **3m** as an oil (355 mg, 75%).

3a. Mp 58 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.49 (1H, d, J = 5.1 Hz), 7.08 (1H, d, J = 5.1 Hz), 2.00 (3H, s), 1.99 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.5, 153.5, 151.8, 121.6, 93.2, 86.9, 79.4, 78.2, 4.8, 4.6. MS *m*/*z* (relative intensity): 156 (M^+, 100), 128 (5), 91 (14), 64 (52).

3b. Mp 68 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.88 (1H, s), 2.29 (3H, s), 1.90 (3H, s), 1.89 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 167.8, 152.9, 151.3, 121.1, 92.2, 86.3, 79.3, 78.2, 24.2, 4.7, 4.5. MS *m*/*z* (relative intensity): 170 (M^+, 100), 78 (14), 64 (38).

3c. Mp 143 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.44 (1H, s), 2.31 (3H, s), 2.12 (3H, s), 2.04 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.8, 151.4, 151.1, 130.8, 96.6, 85.9, 79.3, 77.0, 16.6, 5.0, 4.7. MS *m*/*z* (relative intensity): 170 (M^+, 100), 78 (33), 66 (33).

3d. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.99 (1H, s), 2.63 (2H, t, J = 7.8 Hz), 2.03 (3H, s), 2.02 (3H, s), 1.64 (2H, quint, J = 7.7 Hz), 1.28−1.25 (4H, m), 0.83 (3H, t, 3.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 171.8, 153.1, 151.4, 120.5, 92.0, 86.1, 79.5, 78.3, 38.0, 31.7, 28.9, 22.7, 14.2, 4.7, 4.6. MS *m*/*z* (relative intensity): 226 (M^+, 2), 197 (8), 183 (17), 170 (100). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.57; H, 7.98; N, 12.29.

3e. Mp 122 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.36 (3H, s), 2.23 (3H, s), 2.02 (3H, s), 1.95 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.1, 151.2, 150.6, 129.0, 93.8, 83.8, 81.0, 78.2, 22.5, 15.1, 4.1, 3.8. MS *m*/*z* (relative intensity): 184 (M^+, 100), 142 (14), 78 (52).

3f. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.15 (1H, d, J = 5.1 Hz), 7.11 (1H, d, J = 5.1 Hz), 2.37−2.33 (4H, m), 1.61−1.55 (4H, m), 0.99−0.94 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.0, 153.2, 151.5, 121.3, 97.0, 90.6, 79.9, 78.7, 21.4 (×2), 21.3, 21.2, 13.6, 13.5. MS *m*/*z* (relative intensity): 212 (M^+, 5), 184 (100), 164 (11).

3g. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.01 (1H, s), 2.65 (2H, t, J = 7.8 Hz), 2.40 (4H, t, J = 7.3 Hz), 1.66−1.64 (2H, m), 1.60−1.55 (4H, m), 1.42 (4H, sext, J = 7.5 Hz), 1.30−1.27 (4H, m), 0.90 (3H, t, J = 7.4 Hz), 0.88 (3H, t, J = 7.1 Hz), 0.85 (3H, t, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 171.8, 153.2, 151.6, 120.7, 96.5, 90.5, 80.4, 79.2, 38.1, 31.9, 30.4 (×2), 29.0, 22.8, 22.5, 22.4, 19.5, 19.4, 14.3, 14.0, 13.9. MS *m*/*z* (relative intensity): 310 (M^+, 2), 281 (10), 267 (16), 254 (100).

3h. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.44 (1H, s), 2.45 (2H, t, J = 7.0 Hz), 2.38 (2H, t, J = 7.0 Hz), 2.31 (3H, s), 1.66−1.61 (4H, m), 1.03 (3H, t, J = 7.3 Hz), 1.01 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.7, 151.6, 151.2, 130.8, 101.1, 90.0, 80.2, 77.9, 44.3, 22.0, 21.9, 21.6, 16.7, 14.1, 14.0. MS *m*/*z* (relative intensity): 226 (M^+, 8), 198 (100), 181 (9), 169 (9).

3i. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.41 (3H, s), 2.40 (2H, t, J = 7.1 Hz), 2.34 (2H, t, J = 7.1 Hz), 2.29 (3H, s), 1.62−1.57 (4H, m), 0.99 (3H, t, J = 7.4 Hz), 0.97 (3H, t, J = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.4, 150.7, 150.4, 129.1, 99.6, 89.3, 80.3, 78.3, 22.9, 22.0, 21.9 (×2), 21.6, 15.6, 14.1, 14.0. MS *m*/*z* (relative intensity): 240 (M^+, 8), 225 (9), 212 (100), 195 (8).

3j. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.29−7.17 (5H, m), 4.31 (2H, s), 3.43 (3H, s), 2.77 (2H, t, J = 7.5 Hz), 2.48 (2H, t, J = 7.1 Hz), 2.47 (3H, s), 2.37 (3H, s), 1.95 (2H, quint, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.3, 150.3, 149.2, 141.1, 129.6, 128.5 (×4), 126.1, 99.2, 84.9, 82.9, 78.1, 60.0, 57.9, 34.9, 29.7, 22.6, 19.0, 15.4. MS *m*/*z* (relative intensity): 318 (M^+, 23), 290 (14), 214 (100), 91 (93).

3k. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.21−7.08 (5H, m), 4.30 (2H, s), 3.38 (3H, s), 2.70 (2H, t, J = 7.5 Hz), 2.41 (3H, s), 2.38 (2H, t, J = 7.1 Hz), 2.30 (3H, s), 1.89 (2H, quint, J = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.6, 150.0, 149.1, 141.2, 129.2, 128.4 (×2), 128.3 (×2), 125.9, 92.7, 88.9, 82.7, 80.0, 60.1, 58.0, 34.8, 29.5, 22.6, 18.7, 15.3. MS *m*/*z* (relative intensity): 318 (M^+ − 1, 19), 214 (100), 91 (73).

3l. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.24−7.12 (5H, m), 2.72 (2H, t, J = 7.5 Hz), 2.44 (2H, t, J = 7.1 Hz), 2.42 (3H, s), 2.37 (2H, t, J = 7.2 Hz), 2.30 (3H, s), 1.90 (2H, quint, J = 7.6 Hz), 1.55 (2H, quint, J = 7.3 Hz), 1.40 (2H, sext, J = 7.3 Hz), 0.86 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.1, 150.1, 149.9, 141.1, 128.8, 128.4 (×4), 126.0, 98.8, 89.4, 79.7, 78.2, 34.8, 30.0, 29.7, 22.5, 22.1, 18.9 (×2), 15.3, 13.6. MS *m*/*z* (relative intensity): 330 (M^+, 35), 301 (29), 226 (90), 91 (100).

3m. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.26−7.11 (5H, m), 2.72 (2H, t, J = 7.6 Hz), 2.44 (2H, t, J = 7.1 Hz), 2.42 (3H, s), 2.40 (2H, t, J = 7.1 Hz), 2.29 (3H, s), 1.91 (2H, quint, J = 7.5 Hz), 1.57 (2H, quint, J = 7.5 Hz), 1.44 (2H, sext, J = 7.6 Hz), 0.88 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.0, 150.3, 149.9, 141.3, 128.6, 128.4 (×4), 125.9, 99.4, 88.5, 80.2, 77.7, 34.9, 30.1, 29.7, 29.5, 22.6, 19.2, 18.7, 15.2, 13.5. MS *m*/*z* (relative intensity): 229 (M^+ − 1, 19), 239 (11), 226 (100), 91 (49).

Representative Procedure for Double Cycloisomerization Reaction (4l). Using a high-pressure tube, the mixture of compound **3l** (370 mg, 1.12 mmol) and CuBr (161 mg, 1.12 mmol) in Et_3N (6 mL) and DMA (40 mL) was stirred at 150 °C for 18 h. The reaction was protected from the light by covering the flask with aluminum foil. Then, the mixture was cooled to room temperature and quenched (aqueous NH_4Cl). The phases were separated, and the aqueous phase was thoroughly extracted with hexanes. The combined organic extracts were washed (brine), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 5% EtOAc/hexanes (1% Et_3N was used for deactivation of the silica gel) to give **4l** as a solid (278 mg, 75%).

4a. Mp 145 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.34−7.33 (1H, m), 7.23 (1H, d, J = 7.6 Hz), 6.86 (1H, dd, J = 3.1, 1.7 Hz), 2.42 (3H, s), 6.64 (1H, dd, J = 3.7, 2.8 Hz), 6.58 (1H, d, J = 7.6 Hz), 6.48 (1H, t, J = 3.3 Hz), 6.40 (1H, dd, J = 3.7, 1.3 Hz), 6.17−6.16 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 129.0, 126.1, 118.9, 113.2, 112.4, 112.1, 110.1, 103.6, 103.3, 88.1. MS *m*/*z* (relative intensity): 156 (M^+, 100), 129 (14), 102 (10). Anal. Calcd for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.94; H, 5.21; N, 17.91.

4b. Mp 45 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.34 (1H, d, J = 1.0 Hz), 6.91 (1H, dd, J = 3.1, 1.6 Hz), 6.65 (1H, dd, J = 3.5, 2.8 Hz), 6.55 (1H, t, J = 3.4 Hz), 6.43 (1H, s), 6.32 (1H, dd, J = 3.6, 1.1 Hz), 6.25 (1H, dd, J = 3.8, 1.6 Hz), 2.47 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 129.4, 126.9, 126.8, 112.3, 112.2, 110.0, 109.4, 101.9, 101.5, 88.5, 18.3. MS *m*/*z* (relative intensity): 170 (M^+, 100), 155 (24), 142 (10), 115 (7), 85 (10). Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.69; H, 5.95; N, 16.45.

4c. Mp 68 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.37 (1H, dd, J = 2.7, 1.4 Hz), 7.07 (1H, d, J = 1.2 Hz), 6.83 (1H, d, J = 1.4 Hz), 6.67 (1H, dd, J = 3.7, 2.8 Hz), 6.47 (1H, t, J = 3.1 Hz), 6.41 (1H, dd, J = 3.7, 1.4 Hz), 6.16 (1H, d, J = 3.6 Hz), 2.28 (3H. s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 128.5, 128.4, 116.6, 113.5, 112.2, 111.9, 111.5, 109.6, 102.2, 87.5, 15.4. MS *m*/*z* (relative intensity): 170 (M^+, 100), 155 (43), 142 (14), 115 (10), 85 (11). Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.38; H, 5.92; N, 16.46.

4d. Mp 53 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.29 (1H, dd, J = 2.4, 1.2 Hz), 6.93 (1H, dd, J = 3.1, 1.6 Hz), 6.59 (1H, dd, J = 3.6, 2.9 Hz), 6.50 (1H, t, J = 3.5 Hz), 6.41 (1H, s), 6.28 (1H, dd, J = 3.6, 1.3 Hz), 6.19 (1H, dd, J = 3.8, 1.6 Hz), 2.75 (2H, t, J = 7.6 Hz), 1.77 (2H, quint, J = 7.6 Hz), 1.47−1.38

(4H, m), 0.94 (3H, t, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 131.0, 129.4, 126.8, 112.2 (×2), 109.9, 109.3, 101.6, 100.7, 88.2, 32.0, 31.6, 26.9, 22.9, 14.4. MS *m/z* (relative intensity): 226 (M^+, 50), 197 (7), 183 (14), 170 (100). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.67; H, 8.03; N, 12.40.

4e. Mp 116 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.34 (1H, dd, J = 2.7, 1.4 Hz), 6.90 (1H, dd, J = 2.8, 1.5 Hz), 6.64 (1H, dd, J = 3.6, 3.0 Hz), 6.50 (1H, t, J = 3.4 Hz), 6.33 (1H, dd, J = 3.7, 1.3 Hz), 6.20 (1H, dd, J = 3.7, 1.2 Hz), 2.44 (3H, s), 2.30 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 129.0, 128.9, 123.0, 112.6, 112.0, 109.4, 109.3, 107.9, 100.9, 87.8, 14.1, 13.6. MS *m/z* (relative intensity): 184 (M^+, 100), 142 (14), 115 (7), 104 (10), 78 (52). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.41; H, 6.57; N, 15.20.

4f. ^{1}H NMR (500 MHz, C_6D_6, δ): 6.58 (1H, d, J = 7.6 Hz), 6.46 (1H, d, J = 3.7 Hz), 6.44 (1H, d, J = 3.7 Hz), 6.27 (1H, d, J = 5.0 Hz), 6.26 (1H, s), 6.23 (1H, d, J = 3.7 Hz), 3.00 (2H, q, J = 7.4 Hz), 2.37 (2H, q, J = 7.4 Hz), 1.29 (3H, t, J = 7.4 Hz), 1.18 (3H, t, J = 7.4 Hz). ^{13}C NMR (125 MHz, C_6D_6, δ): 131.2, 128.5, 125.9, 124.6, 114.6, 109.1, 105.8, 102.9, 102.5, 89.7, 22.0, 19.2, 13.3, 12.5. MS *m/z* (relative intensity): 212 (M^+, 43), 197 (100), 181 (16), 91 (21), 78 (52). HRMS (EI) calcd for $C_{14}H_{16}N_2$ (M^+) 212.1314, found 212.1314.

4g. Mp 60 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.28 (1H, d, J = 3.9 Hz), 6.25 (1H, s), 6.24 (1H, d, J = 3.7 Hz), 6.21 (1H, d, J = 3.9 Hz), 6.12 (1H, d, J = 3.7 Hz), 3.30 (2H, t, J = 7.5 Hz), 2.90 (2H, t, J = 7.4 Hz), 2.87 (2H, t, J = 7.7 Hz), 1.80 (2H, sext, J = 7.5 Hz), 1.72−1.63 (4H, m), 1.44−1.35 (4H, m), 1.08 (3H, t, J = 7.3 Hz), 1.03 (3H, t, J = 7.3 Hz), 0.93 (3H, t, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 131.5, 130.3, 128.8, 126.1, 125.6, 109.7, 109.1, 102.7, 99.6, 89.4, 32.8, 32.0, 31.3, 30.9, 28.8, 23.5, 22.5, 22.2, 14.0 (×2). MS *m/z* (relative intensity): 310 (M^+, 33), 281 (100), 209 (26), 195 (23). HRMS (EI) calcd for $C_{21}H_{30}N_2$ (M^+) 310.2409, found 310.2398.

4h. Mp 55 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.95 (1H, s), 6.35 (1H, d, J = 3.6 Hz), 6.32 (1H, d, J = 3.6 Hz), 6.25 (1H, d, J = 2.3 Hz), 6.18 (1H, s), 3.19 (2H, q, J = 3.4 Hz), 2.77 (2H, q, J = 7.4 Hz), 2.27 (3H, s), 1.44 (3H, t, J = 7.4 Hz), 1.38 (3H, t, J = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 131.5, 127.8, 127.7, 124.2, 112.4, 111.1, 108.1, 104.7, 100.2, 86.3, 21.7, 19.1, 15.1, 13.1, 12.3. MS *m/z* (relative intensity): 226 (M^+, 45), 211 (100), 195 (19), 98 (17). HRMS (EI) calcd for $C_{15}H_{18}N_2$ (M^+) 226.1470, found 226.1484.

4i. Mp 123 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.31 (1H, m), 6.24 (1H, s), 6.20 (1H, d, J = 3.5 Hz), 3.16−3.10 (4H, m), 2.61 (3H, s), 1.44 (3H, t, J = 7.3 Hz), 1.36 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 130.9, 129.8, 128.3, 127.3, 123.7, 108.4, 108.9, 107.7, 99.2, 88.7, 23.8, 22.1, 16.0, 14.2, 13.6, 13.1. MS *m/z* (relative intensity): 240 (M^+, 54), 225 (100), 210 (21), 105 (24). HRMS (EI) calcd for $C_{16}H_{20}N_2$ (M^+) 240.1627, found 240.1614.

4j. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.38−7.26 (5H, m), 6.28 (1H, d, J = 3.3 Hz), 6.16 (1H, d, J = 3.6 Hz), 6.10 (1H, s), 5.56 (1H, s), 3.86 (3H, s), 3.37 (2H, t, J = 7.9 Hz), 3.11 (2H, t, J = 7.9 Hz), 2.60 (3H, s), 2.19 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.7, 141.6, 128.5, 128.4 (×4), 126.0, 123.1, 122.7, 109.0, 107.5, 99.5, 85.6, 85.1, 58.6, 35.1, 30.6, 14.8, 13.1. MS *m/z* (relative intensity): 318 (M^+, 26), 227 (100), 212 (74), 183 (64), 91 (40). HRMS (EI) calcd for $C_{21}H_{22}N_2O$ (M^+) 318.1732, found 318.1738.

4k. Mp 122 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.36−7.25 (5H, m), 6.48 (1H, s), 6.24 (1H, s), 6.06 (1H, d, J = 2.4 Hz), 5.73 (1H, s), 3.98 (3H, s), 3.35 (2H, t, J = 8.1 Hz), 3.03 (2H, t, J = 8.1 Hz), 2.59 (3H, s), 2.17 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.2, 141.6, 128.3 (×4), 127.4, 126.0, 125.0, 122.7, 120.7, 108.6, 108.2, 97.0, 89.2, 87.4, 58.4, 36.5, 32.6, 16.0, 13.1. MS *m/z* (relative intensity): 318 (M^+, 23), 227 (90), 212 (100), 183 (96), 91 (40). HRMS (EI) calcd for $C_{21}H_{22}N_2O$ (M^+) 318.1732, found 318.1729.

4l. Mp 79 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.46−7.34 (5H, m), 6.42 (1H, d, J = 3.0 Hz), 6.41 (1H, s), 6.31 (1H, s), 6.29 (1H, d, J = 3.5 Hz), 3.50 (2H, d, J = 7.9 Hz), 3.21 (2H, d, J = 7.9 Hz), 3.10 (2H, d, J = 7.7 Hz), 2.67 (3H, s), 2.30 (3H, s), 1.82 (2H, sext, J = 7.6 Hz), 1.14 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 141.5 (×2), 129.5, 128.4 (×4), 125.9, 125.7, 123.7 (×2), 109.5, 108.8, 108.4, 99.3, 88.6, 35.1, 32.7, 30.7, 23.4, 15.8, 14.0, 13.6. MS *m/z* (relative intensity): 330 (M^+, 30), 239 (100), 209 (19), 91 (9). HRMS (EI) calcd for $C_{23}H_{26}N_2$ (M^+) 330.2096, found 330.2092.

4m. Mp 76 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.41−7.30 (5H, m), 6.37 (1H, d, J = 3.5 Hz), 6.33 (2H, s), 6.25 (1H, d, J = 3.4 Hz), 3.41 (2H, d, J = 7.8 Hz), 3.12−3.06 (4H, m), 2.65 (3H, s), 2.26 (3H, s), 1.89 (2H, sext, J = 7.5 Hz), 1.17 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 141.5 (×2), 129.3 (×2), 128.4 (×4), 126.0, 124.9, 123.4, 109.6, 108.9, 108.7, 99.4, 88.7, 36.5, 32.8, 31.0, 22.1, 16.1, 14.0, 13.7. MS *m/z* (relative intensity): 330 (M^+, 23), 239 (100), 209 (21), 91 (11). HRMS (EI) calcd for $C_{23}H_{26}N_2$ (M^+) 330.2096, found 330.2080.

Representative Procedure for Exhaustive Reduction of Bis-pyrrolopyrimidines (12a, T6). PtO_2 (23 mg) and HBr (235 μL, 2.1 mmol, 48% in H_2O) were added to the solution of **4d** (230 mg, 1.02 mmol) in MeOH (10 mL). The mixture was stirred under hydrogen pressure (50 psi) for 40 h. After this period, the mixture was filtered through Celite and concentrated under reduced pressure to give the amidinium salt **11a**.

Without further purification, crude **11a** was dissolved in anhydrous THF (10 mL). Molecular sieves (4Å)(300 mg) were added to the mixture, stirred for 30 min and cooled to 0 °C. $LiAlH_4$ (5.0 mL, 1.0 M in THF) was added to the mixture dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. After this period, saturated aqueous Na_2SO_4 was added to the mixture dropwise, and the white precipitate was filtered off through Celite. The filtrate was concentrated under reduce pressure and purified by silica gel chromatography with 5% EtOH/CH_2Cl_2 to give (±)-tetraponerine T6 (**12a**) as an oil (154 mg, 64%).

12a (T6). ^{1}H NMR (500 MHz, C_6D_6, δ): 3.14 (1H, m), 3.02 (1H, dt, J = 8.6, 2.4 Hz), 2.98 (1H, t, J = 5.2 Hz), 2.52 (1H, m), 2.44 (1H, m), 2.05−1.98 (2H, m), 1.90−1.34 (18H, m), 0.99 (3H, t, J = 7.2 Hz). ^{13}C NMR (125 MHz, C_6D_6, δ): 83.3, 64.1, 59.6, 49.1, 45.7, 34.7, 33.3, 32.6, 30.6, 29.2, 25.9, 23.1, 21.3, 21.0, 14.4. MS *m/z* (relative intensity): 235 ($M^+ - 1$, 100), 179 (87), 138 (81), 96 (81), 70 (52). HRMS (EI) calcd for $C_{15}H_{27}N_2$ ($M^+ - 1$) 235.2174, found 235.2163.

12b (Crude). ^{1}H NMR (500 MHz, C_6D_6, δ): 2.71 (2H, m), 2.44 (1H, m), 2.36−2.32 (1H, m), 2.0 (1H, m), 1.90−1.65 (9H, m), 1.54−1.25 (17H, m), 1.03−0.89 (9H, m). ^{13}C NMR (125 MHz, C_6D_6, δ): 87.7, 66.7, 62.5, 61.2, 58.6, 42.2, 39.3, 36.7, 35.5, 32.5, 30.3, 30.2, 29.8, 29.5, 28.7, 25.7, 22.9, 19.6, 14.5, 14.4, 14.1. MS *m/z* (relative intensity): 319 ($M^+ - 1$, 11), 263 (16), 152 (100), 82 (32). HRMS (EI) calcd for $C_{21}H_{39}N_2$ ($M^+ - 1$) 319.3113, found 319.3089.

12c. ^{1}H NMR (500 MHz, C_6D_6, δ): 2.63 (1H, dd, J = 10.0, 3.9 Hz), 2.58−2.54 (1H, m), 2.51 (1H, dq, J = 6.8, 2.6 Hz), 2.40−2.34 (1H, m), 2.21 (1H, ddd, J = 11.3, 5.0, 2.8 Hz), 1.83−1.45 (13H, m), 1.19 (3H, d, J = 4.2 Hz), 1.17 (3H, d, J = 4.3), 0.98 (3H, t, J = 7.5 Hz), 0.96 (3H, t, J = 7.5 Hz). ^{13}C NMR (125 MHz, C_6D_6, δ): 89.0, 71.3, 62.6, 62.0, 59.9, 38.1, 32.1, 30.6, 29.8, 29.1, 28.1, 26.3, 19.8, 10.2, 10.0, 8.0. MS *m/z* (relative intensity): 249 ($M^+ - 1$, 36), 125 (20), 96 (100), 82 (24). HRMS (EI) calcd for $C_{16}H_{29}N_2$ ($M^+ - 1$) 249.2331, found 249.2327.

5. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.93 (1H, s), 6.56 (1H, d, J = 3.8 Hz), 6.27 (1H, d, J = 3.8 Hz), 3.31 (2H, t, J = 7.6 Hz), 2.58 (2H, t, J = 7.6 Hz), 2.52 (2H, t, J = 7.3 Hz), 1.76 (2H, sext, J = 7.6 Hz), 1.68−1.66 (4H, m), 1.49 (2H, sext, J = 7.6 Hz), 1.34−1.32 (4H, m), 1.00 (3H, t, J = 7.3 Hz), 0.95 (3H, t, J = 7.4 Hz), 0.88 (3H, t, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.9, 134.0, 131.1, 126.3, 115.5, 110.1, 97.7, 95.3, 76.6, 36.5, 31.5, 30.5, 29.7, 28.9, 23.4, 22.6, 22.3, 19.6, 13.9, 13.6. MS *m/z* (relative intensity): 310 (M^+, 33), 281 (100), 254 (10), 182 (19).

9. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.06 (1H, s), 2.67 (2H, t, J = 9.6 Hz), 2.43 (2H, t, J = 8.8 Hz), 1.68 (2H, quint, J = 9.4

Hz), 2.59 (2H, quint, $J = 9.0$ Hz), 1.43 (2H, sext, $J = 9.6$ Hz), 1.33−1.28 (4H, m), 0.90 (3H, t, $J = 9.2$ Hz), 0.86 (3H, t, $J = 8.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 174.5, 160.9, 153.2, 120.5, 98.1, 78.2, 37.5, 31.4, 29.9, 28.4, 22.4, 22.0, 19.1, 13.9, 13.5. MS *m*/*z* (relative intensity): 263 ($M^+ - 1$, 1), 235 (11), 221 (23), 208 (100).

10. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.90 (1H, s), 6.58 (1H, d, $J = 3.8$ Hz), 6.31 (1H, d, $J = 3.8$ Hz), 3.22 (2H, t, $J = 7.6$ Hz), 2.56 (2H, t, $J = 7.5$ Hz), 1.76 (2H, sext, $J = 7.5$ Hz), 1.70−1.64 (2H, m), 1.37−1.30 (4H, m), 1.01 (3H, t, $J = 7.3$ Hz), 0.90 (3H, t, $J = 7.0$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 143.3, 136.4, 135.8, 127.4, 117.1, 109.7, 99.5, 36.4, 32.1, 31.8, 29.0, 24.4, 23.0, 14.5, 14.2. MS *m*/*z* (relative intensity): 264 (M^+, 14), 235 (100), 178 (14).

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Supporting Information Available: General information and copies of ^{1}H and ^{13}C NMR spectra for **4f**−**m**, **5**, **12a**, and **12c**. Copies of NOESY spectra for **12a** and **12c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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