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Total syntheses of (±)-folicanthine and (±)-chimonanthine via a double intramolecular carbamoylketene–alkene [2+2] cycloaddition

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ABSTRACT

Total syntheses of the dimeric pyrrolidinoindoline alkaloids folicanthine and chimonanthine have been accomplished in racemic forms employing a double intramolecular carbamoylketene–alkene [2+2] cycloaddition as the key step.

Folicanthine (**1**)[1] and chimonanthine (**2**)[2] are representatives of the dimeric pyrrolidinoindoline alkaloids[3] that have been isolated from the leaves of *Calycanthus floridus* L. and from the deciduous shrub *Chimonanthus fragrans*, respectively. Because of their fascinating structural array and biological profile,[4] these alkaloids are considered attractive targets for total synthesis. To date, a number of syntheses of the racemic[5] and optically active forms[6] have been reported. Interestingly, it was found that chimonanthine (**2**) could be converted into the isomeric alkaloid calycanthine (**3**) and folicanthine (**1**) by acidic treatment and reductive N-methylation, respectively[6c,d] (Fig. 1).

Previously, we developed an efficient intramolecular carbamoylketene–alkene [2+2] cycloaddition reaction (**4** → **5**) and demonstrated that the methodology could be successfully applied to the syntheses of the physovenine intermediate **6**,[7a] esermethole (**7**),[7b] and debromoflustramines B (**8**) and E (**9**).[7c] In an attempt to probe the further applicability of the cycloaddition, we chose both alkaloids **1** and **2** as the synthetic targets. Here we describe the total syntheses of (±)-folicanthine (**1**) and (±)-chimonanthine (**2**), employing a novel type of double intramolecular carbamoylketene–alkene [2+2] cycloaddition as the key step (Scheme 1).

Our retrosynthetic analysis is shown in Scheme 2. We thought that folicanthine (**1**) and chimonanthine (**2**) might be derived from **10** via a regio-selective ring expansion followed by appropriate functional group transformations. The bis-cyclobutanone **10** could be assembled by a double intramolecular [2+2] cycloaddition of the dienyl ketene **11**, which could be derived from 2,3-diaryl-1,3-butadiene **12**. The symmetrical diene can be prepared by palladium-catalyzed coupling of 2-nitrophenylboronic acid (**13**)[8] with the carbonate of butynediol **14**[9] (Scheme 2).

Based on the procedure reported by Grigg,[10a] we examined the preparation of the starting 2,2′-(buta-1,3-diene-2,3-diyl)bis(nitrobenzene) (**12**) shown in Table 1. Treatment of a mixture of **13** and **14** with a 10 mol % of $Pd(PPh_3)_4$ in THF at 70 °C provided the requisite diene **12** in 52% yield (entry 1). The reaction at the higher temperature of 100 °C in dioxane resulted in a slightly improved yield of 58% (entry 2). When the reaction was conducted with $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol %) in the presence of a ligand (40 mol %) in THF at 70 °C, the yields increased gradually depending upon the ligand (entries 3–5). The best result was obtained with dppe, which provided **12** in 68% yield (entry 5).

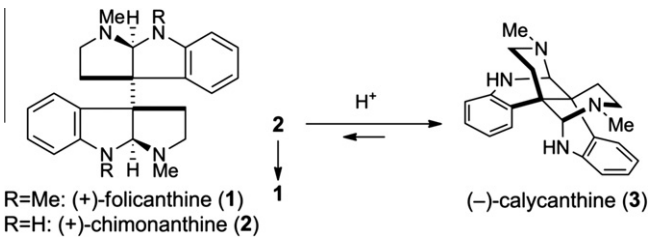

Figure 1. Dimeric pyrrolidinoindoline alkaloids.

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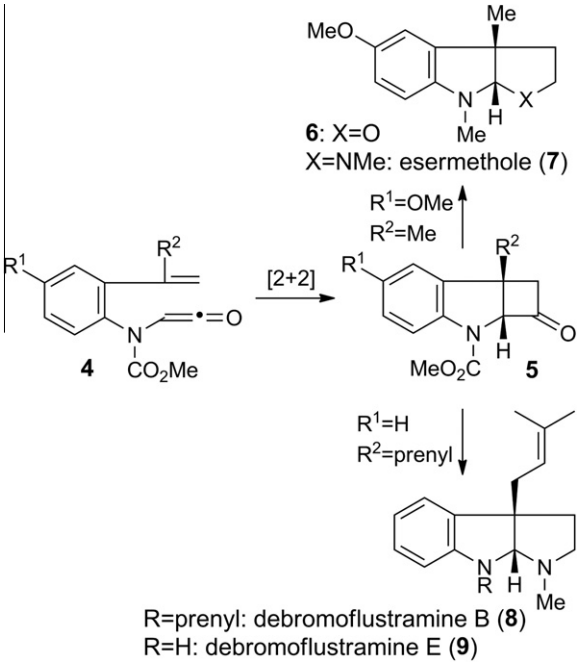
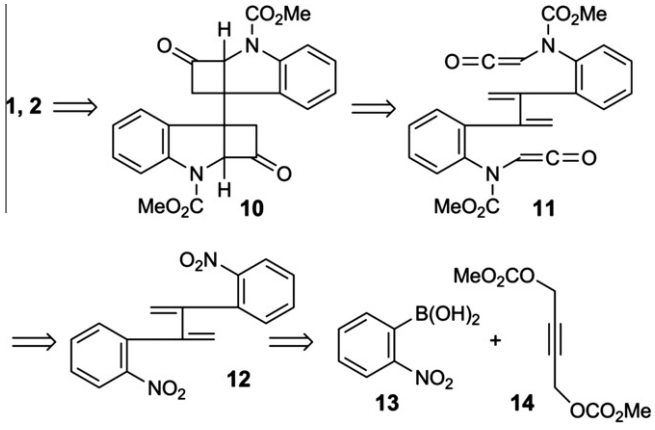


Scheme 1. Syntheses of pyrrolidinoindoline alkaloids.



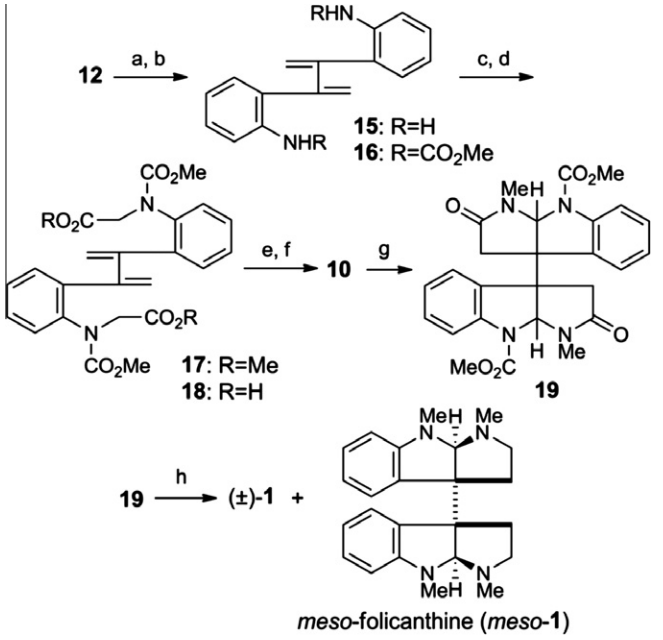
Scheme 2. Retrosynthetic analysis.

Table 1
Pd-catalyzed preparation of diarylated diene **12**

13 (1 equiv.) + **14** (1 equiv.) —conditions→ **12**

Entry	Pd species (10 mol %)	Ligand (40 mol %)	Solvent	Temp (°C)	Yield (%)
1	$Pd(PPh_3)_4$	—	THF	70	52
2	$Pd(PPh_3)_4$	—	1,4-Dioxane	100	58
3	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	THF	70	53
4	$Pd_2(dba)_3{\cdot}CHCl_3$	dppm	THF	70	61
5	$Pd_2(dba)_3{\cdot}CHCl_3$	dppe	THF	70	68

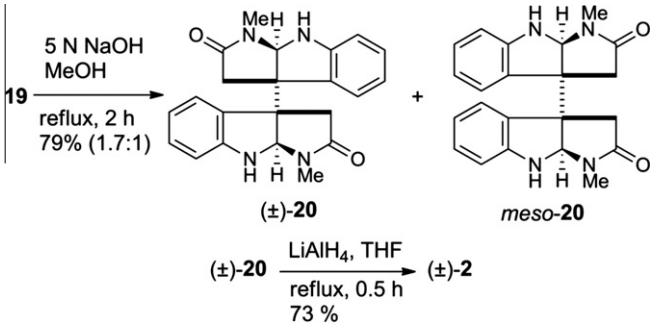
With the symmetrical diene **12** in hand, we then turned our attention to the key double [2+2] cycloaddition. Initially, diene **12** was converted into bis-carboxylic acid **18**, which is a precursor of ketene **11**, by sequential reduction of the nitro group, carbomethoxylation, alkylation with methyl bromoacetate, and alkaline hydrolysis in 63% yield for the four steps. Treatment of **18** with oxalyl chloride in benzene provided the acid chloride, to which triethylamine was added in one pot at 90 °C to give an inseparable mixture of (±)-**10** and the *meso*-**10**[11] in 89% yield. The mixture was then treated with *N*-methylhydroxylamine hydrochloride, $NaHCO_3$, and 3A molecular sieves in ethanol at 50 °C to afford the corresponding nitrone,[12] which, without purification, was immediately reacted with *p*-TsCl and 4-dimethylaminopyridine (4-DMAP) in refluxing chloroform to furnish the bis-lactam **19**[13] in 62% yield as an inseparable mixture. Thus, we were able to install the bis-hexahydropyrrolo[2,3-*b*]indole backbone by a double carbamoylketene–alkene [2+2] cycloaddition. Reduction of **19** with lithium aluminum hydride ($LiAlH_4$) in refluxing THF for 1.5 h provided a mixture of (±)-folicanthine (**1**)[14] and *meso*-folicanthine (*meso*-**1**),[15] which was separated by preparative TLC, in 36% and 28% yields, respectively. The spectroscopic properties of the synthetic **1** and *meso*-**1** were identical with those reported in the literature[5f,16] (Scheme 3).



Scheme 3. Synthesis of (±)-folicanthine (**1**). Reagents and conditions: (a) Zn, AcOH, rt, 1 h, 73%; (b) $ClCO_2Me$, K_2CO_3, THF, H_2O, rt, 10 min, 86%; (c) $BrCH_2CO_2Me$, NaH, DMF, rt, 1.5 h, quant.; (d) $LiOH{\cdot}H_2O$, THF, H_2O, rt, 1 h, quant.; (e) $(COCl)_2$, benzene, rt, 1 h then 85 °C, 30 min; (f) Et_3N, benzene, 90 °C, 1 h, 89% (2 steps); (g) $MeNHOH{\cdot}HCl$, $NaHCO_3$, MS 3A, EtOH, 50 °C, 4 h then *p*-TsCl, 4-DMAP, $CHCl_3$, 70 °C, 3 h, 62% (2 steps); (h) $LiAlH_4$, THF, reflux, 1.5 h, 36% for **1**, 28% for *meso*-**1**.

For the synthesis of chimonanthine (**2**), **19** was hydrolyzed under alkaline conditions to give a 1.7:1 mixture (from ^1H NMR) of (±)-**20**[17] and the *meso*-**20**[18] in 79% yield.[19] When placed in chloroform, the (±)-**20** dissolved smoothly whereas the *meso*-**20** remained an insoluble solid. Thus, we were able to separate the mixture without using chromatography. The (±)-**20** was exposed to $LiAlH_4$ in refluxing THF for 0.5 h to give (±)-chimonanthine (**2**)[20] in 73% yield, the spectral properties of which were identical with those reported in the literature.[6d] It should be noted that attempted reduction of the *meso*-**20** with $LiAlH_4$ did not give *meso*-chimonanthine at all, but instead a mixture of unidentified products (Scheme 4).

In summary, the total syntheses of (±)-folicanthine (**1**) and (±)-chimonanthine (**2**) have been accomplished employing a novel and efficient double intramolecular carbamoylketene–alkene [2+2] cycloaddition as the key step, thus opening a fascinating entry to the dimeric pyrrolidino[2,3-*b*]indolines. The synthetic method developed here is general and efficient and could also be applied



Scheme 4. Synthesis of (±)-chimonanthine.

to the synthesis of other related dimeric alkaloids with more complicated molecular structures.

Acknowledgments

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11. *Compound* ***10*** *(1:1 mixture of (±)-**10** and meso-**10**)*: IR (neat) 2955, 1794, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.38 (2H, dd, J = 2.8, 12.0 Hz), 3.40 (2H, dd, J = 2.8, 17.6 Hz), 3.77–3.92 (16H, m), 5.20–5.75 (4H, m), 6.73 (2H, d, J = 7.6 Hz), 6.90–6.99 (2H, m), 6.97 (2H, t, J = 7.6 Hz), 7.13 (2H, d, J = 7.6 Hz), 7.15–7.26 (2H, m), 7.33 (2H, t, J = 7.6 Hz), 7.70–7.95 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.5 (C × 4), 53.1 (CH_3 × 2), 53.3 (CH_3 × 2), 57.3 (CH_2 × 2), 57.5 (CH_2 × 2), 78.2 (CH × 2), 78.9 (CH × 2), 116.2 (CH × 4), 123.8 (CH × 2), 124.2 (CH × 4), 124.6 (CH × 2), 129.7 (CH × 2), 130.1 (CH × 2), 130.9 (C × 4), 143.8 (C × 4), 152.3 (C × 4), 200.9 (C × 2), 201.1 (C × 2); HRMS (ESI-TOF) m/z calcd for $C_{24}H_{21}N_2O_6$ $[M+H]^+$: 433.1400, found 433.1394.
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13. *Compound* ***19*** *(1:1 mixture of (±)-**19** and meso-**19**)*: IR (neat) 2956, 1704, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.66–3.08 (20H, m), 3.62–3.95 (12H, m), 5.15–5.95 (4H, m), 6.98–7.81 (16H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (CH_3 × 2), 27.3 (CH_3 × 2), 38.0 (CH_2 × 4), 39.2 (C × 4), 53.3 (CH_3 × 4), 79.9 (CH × 2), 80.5 (CH × 2), 117.3 (CH × 2), 117.6 (CH × 2), 124.1 (CH × 2), 124.3 (CH × 2), 124.8 (CH × 4), 130.0 (CH × 2), 130.2 (CH × 2), 131.8 (C × 4), 139.6 (C × 2), 140.5 (C × 2), 152.1 (C × 2), 154.2 (C × 2), 170.2 (C × 2), 170.5 (C × 2); HRMS (ESI-TOF) m/z calcd for $C_{26}H_{27}N_4O_6$ $[M+H]^+$: 491.1931, found 491.1908.
14. *Compound (±)-**1***: Mp 166–167 °C (hexane/AcOEt); IR (KBr) 1602, 1490, 1347, 1157, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92–1.98 (2H, m), 2.30–2.49 (4H, m), 2.41 (6H, s), 2.58–2.67 (2H, m), 3.00 (6H, s), 4.40 (2H, br), 6.46 (2H, d, J = 7.6 Hz), 6.47–6.51 (2H, m), 6.88–6.93 (2H, m), 6.97 (2H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.2 (CH_2 × 2), 35.4 (CH_3 × 2), 37.7 (CH_3 × 2), 52.5 (CH_2 × 2), 62.5 (CH × 2), 91.8 (C × 2), 105.7 (CH × 2), 116.5 (CH × 2), 123.6 (CH × 2), 128.0 (CH × 2), 132.6 (C × 2), 152.8 (C × 2); HRMS (ESI-TOF) m/z calcd for $C_{24}H_{30}N_4Na$ $[M+Na]^+$: 397.2368, found 397.2361.
15. *meso-**1***: Mp 161–162 °C (hexane/AcOEt); IR (KBr) 2926, 1601, 1494, 743 cm^{-1}; ^{1}H NMR (C_5D_5N, 400 MHz) δ 1.68 (2H, dd, J = 4.6, 11.4 Hz), 2.09 (6H, s), 2.18–2.46 (12H, m), 4.17 (2H, br), 6.17 (2H, d, J = 7.6 Hz), 6.20–6.40 (2H, m), 6.50–7.05 (4H, m); ^{13}C NMR (C_5D_5N, 100 MHz, 90 °C) δ 37.0 (CH_2 × 2), 37.4 (CH_3 × 2), 37.7 (CH_3 × 2), 53.5 (CH_2 × 2), 64.6 (CH × 2), 91.9 (C × 2), 108.4 (CH × 2), 118.5 (CH × 2), 125.3 (CH × 2), 129.5 (CH × 2), 135.7 (C × 2), 155.2 (C × 2); HRMS (ESI-TOF) m/z calcd for $C_{24}H_{31}N_4$ $[M+H]^+$: 375.2549, found 375.2533.
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17. *Compound (±)-**20***: IR (neat) 3403, 1662, 1484 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.66 (6H, s), 2.78 (2H, d, J = 16.8 Hz), 3.11 (2H, d, J = 16.8 Hz), 4.70 (2H, s), 6.68 (2H, d, J = 7.6 Hz), 6.84 (2H, t, J = 7.6 Hz), 7.15 (2H, t, J = 7.6 Hz), 7.23 (2H, d, J = 7.6 Hz), 2H of –NH– were not observed clearly; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4 (CH_3 × 2), 39.3 (CH_2 × 2), 55.3 (C × 2), 80.4 (CH × 2), 111.1 (CH × 2), 120.6 (CH × 2), 125.1 (CH × 2), 129.8 (CH × 2), 130.8 (C × 2), 148.2 (C × 2), 171.4 (C × 2); HRMS (ESI-TOF) m/z calcd for $C_{22}H_{23}N_4O_2$ $[M+H]^+$: 375.1821, found 375.1830.
18. *meso-**20***: Mp 360 °C (decomp.) (MeOH/$CHCl_3$); IR (KBr) 3403, 1661, 1482 cm^{-1}; ^{1}H NMR (C_5D_5N, 400 MHz) δ 2.87 (6H, s), 3.10 (2H, d, J = 16.8 Hz), 3.37 (2H, d, J = 16.8 Hz), 5.52 (2H, d, J = 2.4 Hz), 6.68 (2H, d, J = 8.0 Hz), 6.72 (2H, br), 6.81 (2H, br), 7.14 (4H, t, J = 8.0 Hz); ^{13}C NMR (C_5D_5N, 100 MHz) δ 26.6 (CH_3 × 2), 41.5 (CH_2 × 2), 56.3 (C × 2), 79.9 (CH × 2), 110.7 (CH × 2), 119.3 (CH × 2), 125.1 (CH × 2), 129.8 (CH × 2), 132.0 (C × 2), 150.6 (C × 2), 171.4 (C × 2); HRMS (ESI-TOF) m/z calcd for $C_{22}H_{23}N_4O_2$ $[M+H]^+$: 375.1821, found 375.1829.
19. Treatment of a mixture (1.7:1) of **20** with $LiAlH_4$ in refluxing THF for 3 h provided (±)-**2** and the recovered *meso*-**20** in 29% and 6% yield, respectively.
20. *Compound (±)-**2***: Mp 168–172 °C (benzene); IR (KBr) 3297, 2932, 1605, 1486 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, 50 °C) δ 2.03–2.08 (2H, m), 2.31 (6H, s), 2.49–2.58 (6H, m), 4.44 (2H, br), 6.53 (2H, d, J = 7.5 Hz), 6.66 (2H, t, J = 7.5 Hz), 6.98 (2H, t, J = 7.5 Hz), 7.18 (2H, d, J = 7.5 Hz), 2H of –NH– were not observed clearly; ^{13}C NMR ($CDCl_3$, 125 MHz, 50 °C) δ 35.5 (CH_2 × 2), 37.0 (CH_3 × 2), 52.7 (CH_2 × 2), 63.3 (C × 2), 85.3 (CH × 2), 109.3 (CH × 2), 118.7 (CH × 2), 124.4 (CH × 2), 128.2 (CH × 2), 133.0 (C × 2), 150.7 (C × 2); HRMS (ESI-TOF) m/z calcd for $C_{22}H_{26}N_4Na$ $[M+Na]^+$: 369.2055, found 369.2054.