Towards Total Synthesis of Communesins and Perophoramidine: Unexpected Cascade Reaction of Michael–Mannich–Mannich Additions

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Dedicated to Professors Lixin Dai and Prof. Xiyan Lu of the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences

Abstract: A new type of chiral amidinobenzodiene **5** was prepared from isatin in ten steps. While attempting to prepare the core structure from **5** and tryptamine derivative **17** via a hetero Diels–Alder reaction for the total synthesis of communesin and perophoramidine, we observed an unexpected three-step, one-pot cascade reaction of Michael–Manich–Manich additions. The cascade reaction between **5** and **17** yielded diasteromers **21a** and **21b** with a complex polycyclic skeleton of 2,3,4,5-diindolinohexahydropyrrole in 76% yield and a ratio of 3:1. The stereochemistry of **21a** was confirmed by X-ray crystal-structural analysis.

Key words: communesin, perophoramidine, cascade reaction, Michael addition, Mannich addition

Since communesins A and B were isolated from a *Penicillium* mold by Numata in 1993,[1] six additional members (C–H) of this indole alkaloid family have been identified during the past two decades (Figure 1).[2] Among communesins, communesin B is the most active in vitro cytotoxicity against the lymphocytic leukemia cell line P388 (ED_{50}: 0.45 μg/mL). In 2002, perophoramidine, a biosynthetically related alkaloid and with opposite stereochemistry at the two adjacent quaternary stereocenters related to communesin B, was isolated by Ireland from the marine ascidian *Perophora Namei* (Figure 1). This compound showed low cytotoxicity against the colon carcinoma cell line HCT116 (IC_{50} of 60 μg/mL).[3]

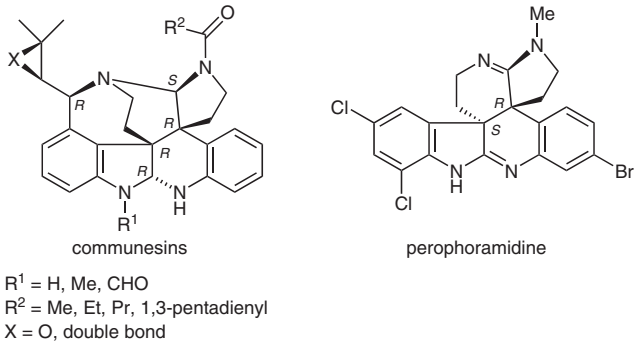

Figure 1 Structures of communesins and perophoramidine (communesin B: R^1 = Me, R^2 = 1,3-pentadienyl, X = O; communesin F: R^1 = R^2 = Me, X = double bond)

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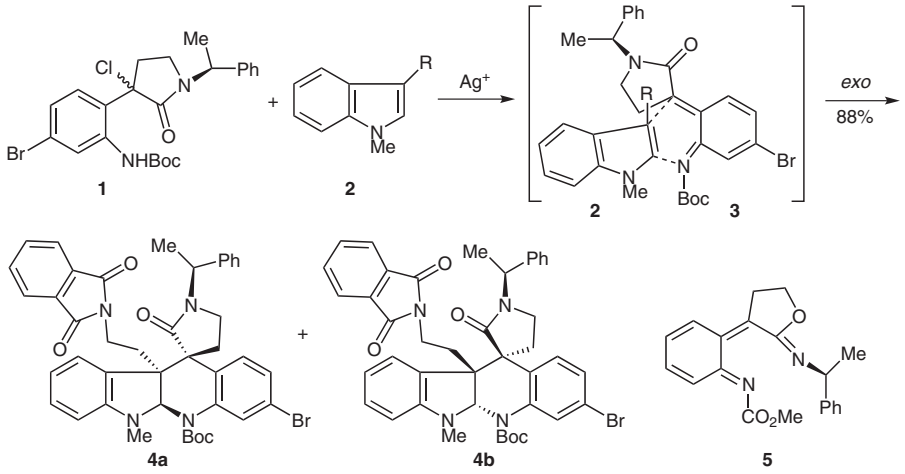
The intriguing structure and interesting biological activity of communesins and perophoramidine have attracted intense interest among synthetic chemists wishing to recreate the core structure.[4] Their efforts have led to two total syntheses of racemic (dehalo)perophoramidine[5] and two total syntheses of racemic communesin F.[6] Recently, the absolute configuration of these alkaloids has been determined by asymmetric total syntheses of (–)-communesin F from Ma's group[7] and an asymmetric total synthesis of (+)-perophoramidine by our group.[8]

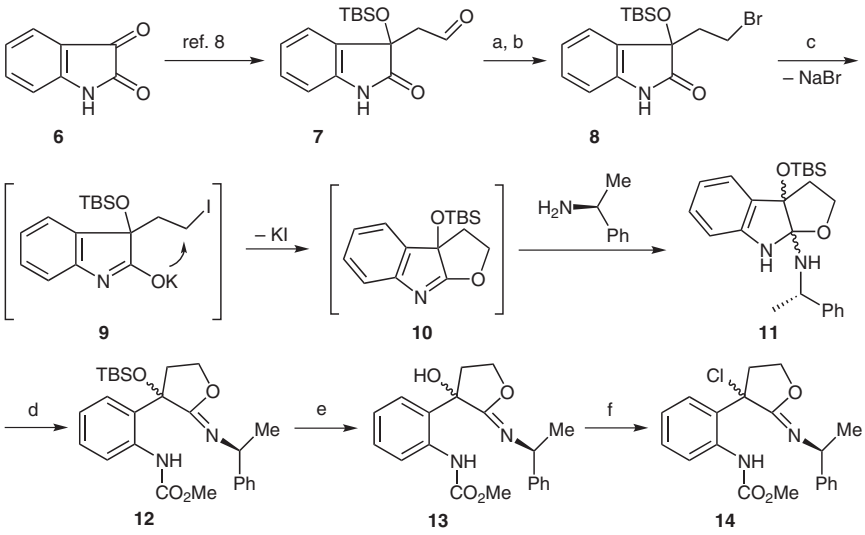
In our total synthesis of (+)-perophoramidine,[8] we carried out an asymmetric intermolecular hetero Diels–Alder reaction between the in situ generated *trans*,*trans*-benzodiene **3** and indole **2** to assemble the chiral core structures **4a** and **4b**. In this reaction, the chirality of adducts **4a** and **4b** was induced by a chiral auxiliary pre-installed on the amide nitrogen (Scheme 1).

During our further explorations of the efficiency and scope of this type of in situ generated benzodiene on asymmetric hetero Diels–Alder reaction, we observed an unexpected cascade reaction of Michael–Mannich–Mannich additions to yield a new chiral skeleton when a chiral auxiliary attached to the carbon of a benzodiene **5** rather than to the nitrogen of the benzodiene **3** (Scheme 1). In this letter, we report the unusual cascade reaction.

Preparation of chloroimidate **14**, a precursor of benzodiene **5**, is shown in Scheme 2. By adapting our previous procedure,[8] aldehyde **7** was prepared in 65% yield in three steps from isatin (**6**). After reduction of the aldehyde group in **7**, the resulting hydroxyl group was converted to bromide to give compound **8** in 84% yield. Treatment of **8** with NaI, K_2CO_3, and (*S*)-α-methylbenzylamine in DMF for 10 hours at 90 °C led to the formation of a mixture of diastereomers **11** in 83% yield. The reaction most likely proceeded through a three-step reaction of iodo exchange (**9**), ring closure (**10**), and nucleophilic attack of the imidate group by (*S*)-α-methylbenzylamine. Selective protection of the indole nitrogen with $MeCO_2Cl$ under weak basic conditions resulted in ring opening of the indoline to give imidate **12** in 87% yield. Removal of TBS in **12** with TBAF provided alcohol **13**. Chlorination of **13** with $SOCl_2$ in pyridine at 0 °C afforded chloride **14** in 90% yield. Because of its instability under chromatography conditions, chloride **14** was used directly in the next step without purification.



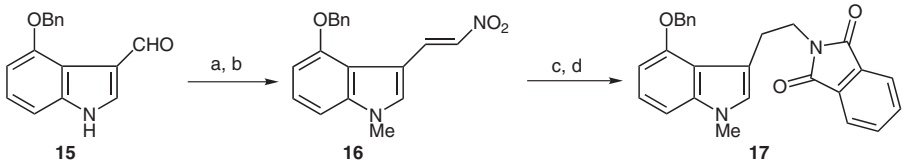
Scheme 1 Asymmetrically intermolecular Diels–Alder reaction



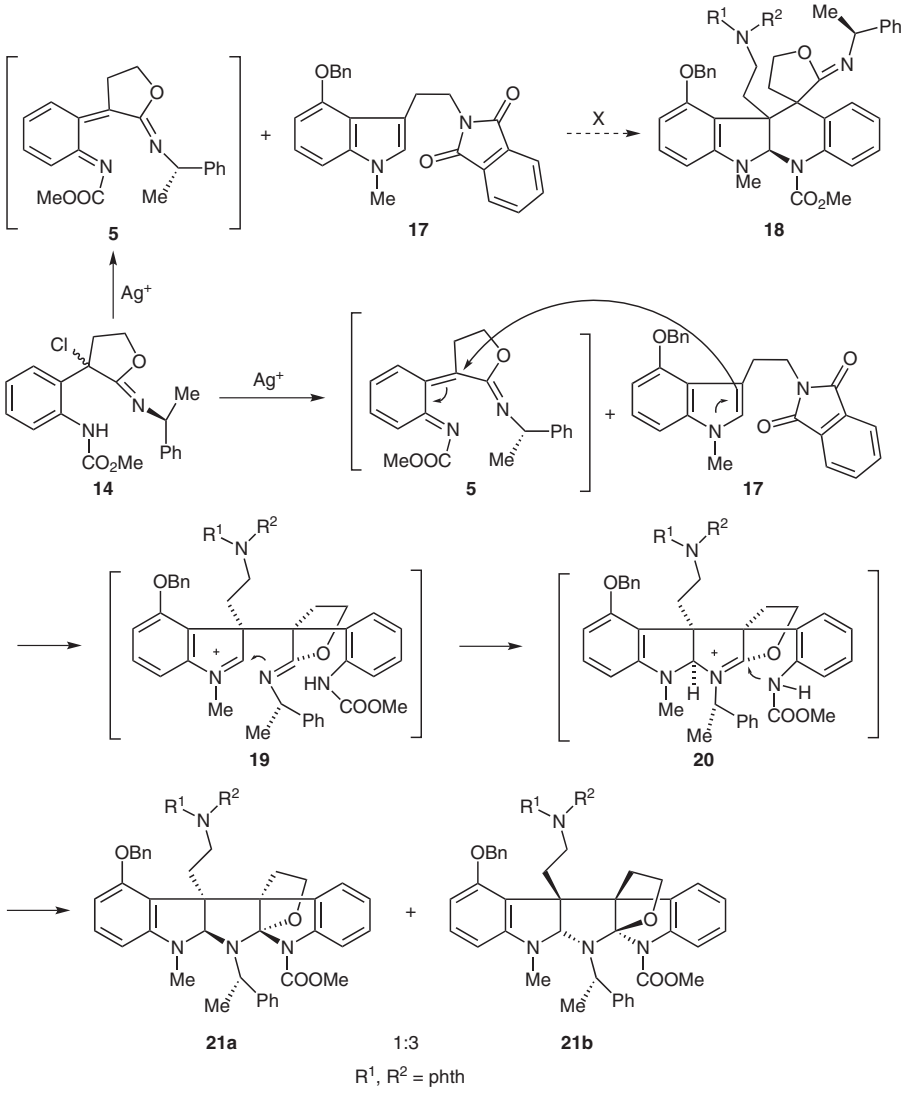
Scheme 2 *Reagents and conditions*: a) $NaBH_4$, THF, 0 °C, 1 h, 93%; b) Ph_3P, NBS, CH_2Cl_2, r.t., 12 h, 90%; c) NaI, K_2CO_3, (*S*)-α-methylbenzylamine, DMF, 90 °C, 10 h, 83%; d) $ClCO_2Me$, $NaHCO_3$, THF, r.t., 5 h, 87%; e) TBAF, THF, r.t., 12 h, 90%; f) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C, 15 min.

The tryptamine derivative **17** with a 4-benzyloxy substituent was prepared from 3-(4-benzyloxyindolo)carboxaldehyde **15**[9] (Scheme 3). Methylation with MeI and condensation with nitromethane provided nitroolefin **16** in 81% yield in two steps. After simultaneous reduction of the double bond and nitro group in **16** with $LiAlH_4$, the resulting amine was protected with the phthalic group to give **17** with 62% yield in two steps.

We originally envisioned that benzodiene **5** might react with **17** through an intermolecular hetero Diels–Alder reaction to give a chiral intermediate **18** possessing the basic skeleton of communesins and perophoramidine (Scheme 4). Unfortunately, when the benzodiene **5**, generated in situ with 2 equivalents of $AgBF_4$, reacted with **17** at –78 °C in CH_2Cl_2 for 2 hours, the diastereomers **21a** and **21b**[10] instead of **18** were generated. These diastereomers, which have a complex polycyclic skeleton of 2,3,4,5-diindolinohexahydropyrrole, were produced in 76% yield and a ratio of 1:3. The formation of **21a** and **21b** was explained through a three-step, one-pot cascade reaction of Michael–Mannich–Mannich additions. We hypothesize that the attack of indole **17** on the benzodiene



Scheme 3 *Reagents and conditions*: a) MeI, K_2CO_3, THF, r.t., 10 h; b) NH_4OAc, $MeNO_2$, 100 °C, 30 min, 81% in 2 steps; c) $LiAlH_4$, THF, 0–60 °C, 3 h, 79%; d) phthalic anhydride, toluene, 90 °C, 12 h, 78%.



Scheme 4 *Reagents and conditions:* $AgBF_4$, CH_2Cl_2, –78 °C, 2 h, 76%.

5 gave indolinium **19**, which was susceptible to addition of the imidate group in **19** to afford the iminium intermediate **20**. A final Mannich addition of the amide group in **20** to the iminium moiety provided **21a** and **21b**. X-ray crystal-structural analysis of **21a**[11] firmly established the stereochemistry of **21a** and **21b**. Efforts to carry out an acid-catalyzed rearrangement to convert **21a** and **21b** to **18**, a potentially useful intermediate for the total synthesis of communesins and perophoramidine, failed because of the easy decomposition of **21a** and **21b** under a variety of acidic conditions.

In conclusion, two chiral compounds **21a** (Figure 2) and **21b** with a polycylic skeleton of 2,3,4,5-diindolinohexahydropyrrole were prepared through a three-step, one-pot cascade reaction of Michael–Mannich–Mannich additions involving tryptamine derivative **17** and benzodiene **5**. Although we failed to prepare **18** with a skeleton of communesins and perophoramidine from **21a** and **21b**, this work demonstrates the usefulness of the new benzodiene **5** for preparing a complex ring system.

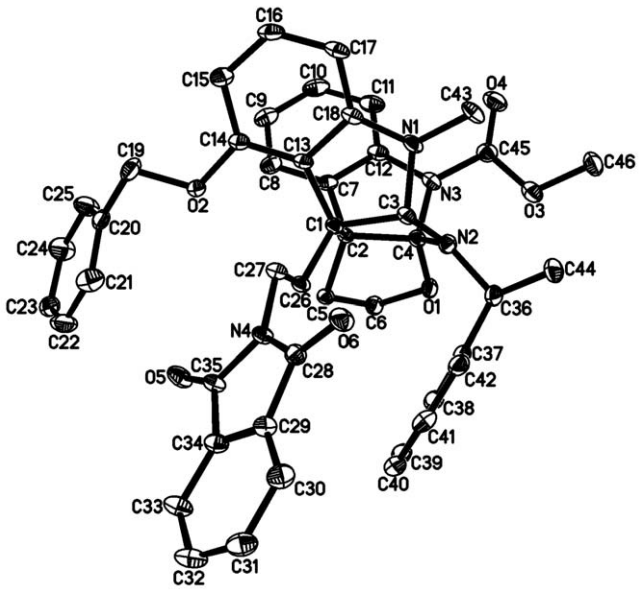


Figure 2 ORTEP diagram of **21a**

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(10) **Analytical Data**

Compound **21a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.32 (br, 1 H), 1.60–1.64 (m, 1 H), 1.74 (d, *J* = 7.6 Hz, 3 H), 2.04–2.12 (m, 1 H), 2.64–2.72 (m, 1 H), 2.69 (s, 3 H), 3.18–3.33 (m, 2 H), 3.72–3.79 (m, 1 H), 3.94 (s, 3 H), 4.25–4.29 (m, 1 H), 4.74–4.81 (m, 2 H), 5.16 (br, 1 H), 5.40 (s, 1 H), 5.62–5.67 (m, 2 H), 6.50 (t, *J* = 6.8 Hz, 1 H), 6.61 (t, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 6.8 Hz, 1 H), 6.92 (t, *J* = 7.6 Hz, 2 H), 7.17 (t, *J* = 7.6 Hz, 2 H), 7.31–7.34 (m, 1 H), 7.39–7.43 (m, 2 H), 7.53–7.56 (m, 5 H), 7.65–7.74 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.74, 29.32, 29.33, 30.55, 34.19, 34.20, 36.04, 52.09, 52.10, 54.70, 69.23, 72.65, 92.73, 99.60, 99.73, 112.95, 113.43, 121.13, 122.66, 122.67, 123.75, 124.77, 126.83, 127.48, 127.50, 127.51 127.78, 127.79, 127.85, 128.11, 128.17, 128.43, 128.44, 128.45, 128.46, 129.50, 130.86, 132.19, 133.42, 133.48, 137.03, 144.82, 151.73, 153.36, 154.89, 167.61. HRMS: *m/z* [M + H$^+$] calcd for $C_{46}H_{43}N_4O_6$: 747.3183; found: 747.3142. IR (KBr): 3463, 2950, 2875, 1712, 1608, 1446, 1393, 1208, 716 cm^{-1}. $[\alpha]_D^{20}$ +1.98 (*c* 1.0, $CHC1_3$).

Compound **21b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 3 H), 1.71 (d, *J* = 6.8 Hz, 3 H), 1.80–1.84 (m, 1 H), 2.05–2.12 (m, 1 H), 2.60–2.68 (m, 1 H), 2.87–2.94 (m, 1 H), 3.48–3.55 (m, 1 H), 3.73–3.79 (m, 1 H), 3.80–3.96 (m, 1 H), 3.96 (s, 3 H), 4.31–4.35 (m, 1 H), 5.15 (d, *J* = 11.6 Hz, 1 H), 5.29 (d, *J* = 11.6 Hz, 1 H), 5.30–5.36 (m, 2 H), 5.32 (br, 1 H), 5.49 (d, *J* = 7.6 Hz, 1 H), 6.07 (d, *J* = 8.4 Hz, 1 H), 6.55–6.57 (m, 1 H), 6.75 (t, *J* = 8.0 Hz, 1 H), 6.89–6.93 (m, 1 H), 6.93–6.97 (m, 1 H), 7.24–7.28 (m, 1 H), 7.33–7.43 (m, 6 H), 7.65–7.67 (m, 2 H), 7.72–7.74 (m, 2 H), 7.75–7.78 (m, 2 H), 7.85–7.89 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.05, 29.42, 29.66, 31.15, 35.40, 36.97, 52.39, 53.18, 54.40, 69.79, 72.49, 72.92, 93.04, 99.56, 100.00, 113.03, 113.25, 121.26, 123.13, 123.14, 124.53, 125.04, 127.08, 127.10, 127.71, 127.72, 127.86, 127.88, 128.12, 128.15, 128.35, 128.47, 129.14, 129.15, 129.88, 131.15, 132.27, 133.80, 133.82, 137.68, 141.41, 144.51, 151.69, 153.57, 155.46, 168.06. HRMS: *m/z* [M + H$^+$] calcd for $C_{46}H_{43}N_4O_6$: 747.3183; found: 747.3141. IR (KBr): 3464, 2951, 2868, 1709, 1606, 1445, 1389, 1189, 719 cm^{-1}. $[\alpha]_D^{20}$ –0.43 (*c* 1.0, $CHC1_3$).

(11) The crystallographic data of **21a** ($C_{46}H_{42}N_4O_6$) have been deposited with the Cambridge Crystallographic Data Centre; the entry CCDC 776462 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.