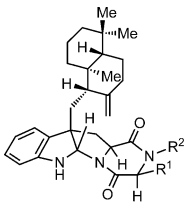
# Communications

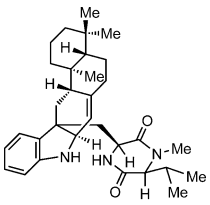
**Natural Product Synthesis**

Y. Sun, R. Li, W. Zhang, A. Li* ——— ■■■■–■■■■

Total Synthesis of Indotertine A and Drimentines A, F, and G



$R^1$ = *i*Bu, $R^2$ = H; drimentine A
$R^1$ = *i*Pr, $R^2$ = H; drimentine G
$R^1$ = *i*Pr, $R^2$ = Me; drimentine F



indotertine A

**Oh my darling, Drimentine**: The first total synthesis of the pyrroloindoline alkaloids drimentines A, F, and G, and their congener, indotertine A, is reported. An intermolecular radical conjugate addition was key in the synthesis of the drimentine alkaloids, and a biologically inspired iminium–olefin cyclization converted drimentine F into indotertine A.

Natural Product Synthesis

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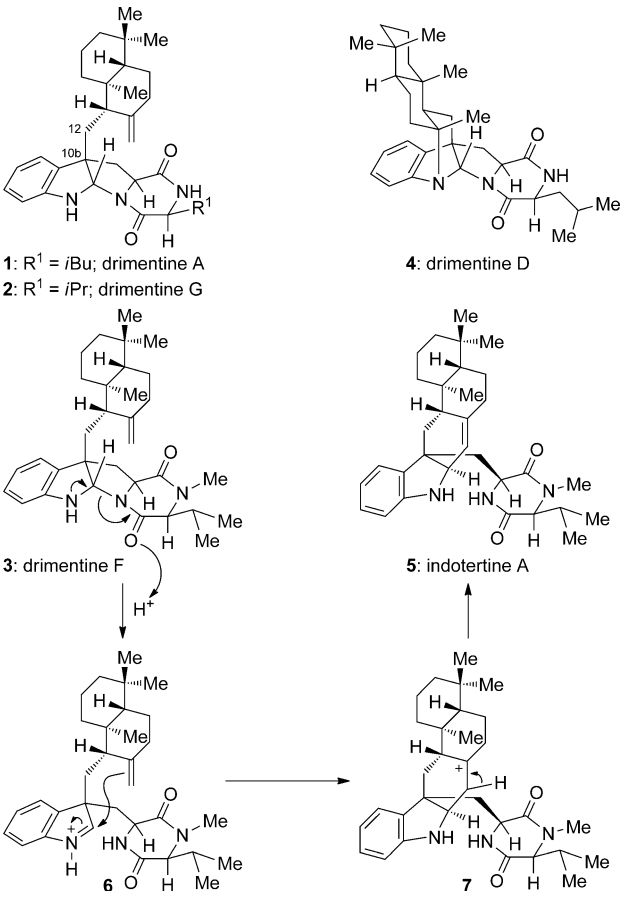
# Total Synthesis of Indotertine A and Drimentines A, F, and G**

*Yu Sun, Ruofan Li, Wenhao Zhang, and Ang Li**

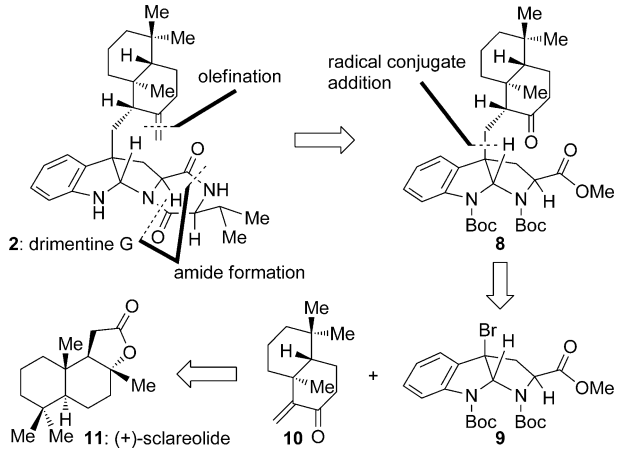
*Dedicated to Professor Guo-Qiang Lin on the occasion of his 70th birthday*

The pyrroloindoline alkaloids attract wide interest from the fields of chemistry, biosynthesis, and biology.[1] From a structural perspective, they can be divided into several classes that vary in the substituent on C3a of the pyrroloindoline core, including heteroatoms, arenes, aliphatic groups, and another pyrroloindoline motif. Accordingly, a series of strategies have been developed for the synthesis of the above pyrroloindoline classes.[2–6] Notably, a structurally complex aliphatic side chain linked to the C3a position is rather rare. The drimentine alkaloids (**1**–**4**, Scheme 1), which exhibit anticancer, antibacterial, antifungal, and anthelmintic properties, possess the latter substitution mode.[7] A stereocontrolled method to form the C10b–C12 bond of the drimentine scaffold is highly desired for the synthesis of these compounds. Indotertine A (**5**, Scheme 1) with an unprecedented, but biosynthetically relevant, skeleton was recently discovered.[7b] The biosynthetic relationship between **3** and **5** is postulated in Scheme 1. Acidic activation of the germinal diamine moiety of **3** may generate an iminium species **6**, which could undergo an iminium–olefin cyclization[8,9] followed by a proton elimination of the cationic intermediate **7**. Herein, we report the first total synthesis of drimentines A, G, and F (**1**–**3**), exploiting a photocatalyzed radical conjugate addition to address the problem of the C10b–C12 bond formation; a synthesis of indotertine A (**5**), guided by the above biosynthetic hypothesis, is also described.

We first undertook a retrosynthetic analysis of drimentine G (Scheme 2). Disassembly of the diketopiperazine motif at the amide bonds followed by cleavage of the exocyclic C=C bond simplifies this molecule to core structure **8**. Disconnection of the C10b–C12 bond leads to a pair of precursors (**9** and **10**) for an intermolecular radical conjugate addition. The former is readily available from bis(Boc-L-tryptophan) methyl ester (Boc = *tert*-butoxycarbonyl), whereas the latter could be derived from commercially available (+)-sclareolide (**11**).




***Scheme 1.*** Representative drimentine alkaloids and the postulated biosynthetic relationship between drimentine F and indotertine A.




***Scheme 2.*** Retrosynthetic analysis of drimentine G.

[*] Y. Sun,[+] R. Li,[+] W. Zhang, Prof. Dr. A. Li
State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032 (China)
E-mail: ali@sioc.ac.cn

[+] These authors contributed equally to this work.

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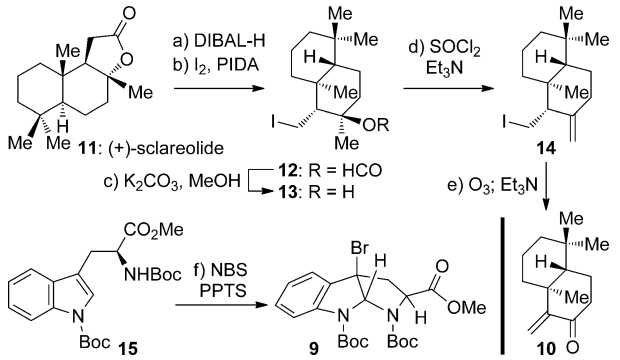
The intermolecular radical C–C bond formation is a powerful tool in organic synthesis,[10] and recent advances in this field are encouraging.[11] A C3a-bromopyrroloindoline, such as **9** (Scheme 2), can readily generate benzylic radicals with retention of the original stereochemistry. These have found good use in some intermolecular transformations,[5a,b,6a] including conjugate additions,[5a,b] albeit with rather limited scope of acceptors. Visible-light photoredox catalysis, pioneered by the groups of MacMillan, Yoon, and Stephenson, has emerged as a powerful, yet controllable, method to promote radical reactions.[12,13] In an inspiring synthesis of gliocladin C, Stephenson et al. developed the direct coupling of a pyrroloindoline radical with a substituted indole, employing $[Ru(bpy)_3Cl_2]$ (bpy = bipyridine) as a photocatalyst.[14] The conjugate addition of functionalized radicals (such as α-amino and α-alkoxy alkyl radicals) by photoredox catalysis has attracted remarkable attention,[15] whereas similar types of reactions with non-functionalized radicals remain rather rare in the literature, despite the seminal report by Okada et al. two decades ago.[16,17]

With the above retrosynthetic analysis and literature precedents in mind, we started the synthesis of drimentine G by preparing precursors **9** and **10** (Scheme 3). Sclareolide (**11**) was converted into iodoformate **12** using the two-step method

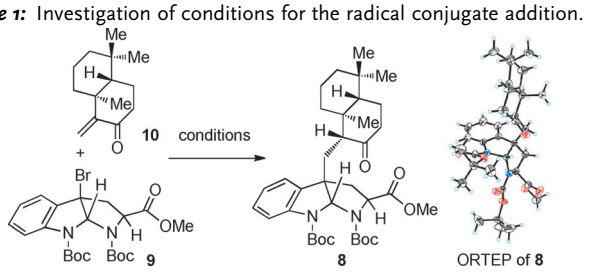



***Scheme 3.*** Multigram synthesis of the precursors for the radical conjugate addition. Reagents and conditions: a) DIBAL-H (1.2 equiv), $CH_2Cl_2$, −78 °C, 1 h; b) $I_2$ (1.2 equiv), PIDA (1.4 equiv), *hν*, benzene, 90 °C, 5 min; c) $K_2CO_3$ (1.5 equiv), MeOH, 22 °C, 2 h, 78% for the 3 steps; d) $SOCl_2$ (1.5 equiv), $Et_3N$ (3.0 equiv), $CH_2Cl_2$, −90 °C, 5 min, 86%; e) $O_3$, $CH_2Cl_2$, −78 °C, 5 min, then $Et_3N$ (20 equiv), 60 °C, 2 h, 82%; f) NBS (1.0 equiv), PPTS (1.0 equiv), $CH_2Cl_2$, 22 °C, 15 min, 96%. DIBAL-H = diisobutylaluminum hydride, NBS = *N*-bromosuccinimide, PIDA = phenyliodonium diacetate, PPTS = pyridinium *p*-toluenesulfonate.

developed by Baran et al. (DIBAL-H reduction followed by Suárez cleavage).[18] Compound **11** was then further hydrolyzed to give alcohol **13** (78% yield from **11**). Treatment of **13** with $SOCl_2/Et_3N$ furnished exocyclic olefin **14** in 86% yield, the C=C bond of which was cleaved by ozonolysis. The resulting iodoenone smoothly underwent β-elimination promoted by $Et_3N$ to give **10** on a multigram scale. Meanwhile, **9** was obtained through bromocyclization of L-tryptophan derivative **15** in 96% yield on a decagram scale.[19]

Having prepared a large quantity of both substrates, we investigated the radical conjugate addition (Table 1). Initially,

***Table 1:*** Investigation of conditions for the radical conjugate addition.




| Entry | Conditions | Yield [%][f] |
|---|---|---|
| 1 | AIBN, $Bu_3SnH$, or $(TMS)_3SiH$, toluene[a,b] | 0 |
| 2 | $Et_3B$, $O_2$, $Bu_3SnH$, THF[a,c] | 0 |
| 3 | $[Co(PPh_3)Cl]$, acetone[a,c] | 0 |
| 4 | $Bu_3SnH$ (syringe pump), benzene[b,d] | 58 |
| 5 | $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (2.5%), blue LED, $Et_3N$[a,c,e] | 51 |
| 6 | blue LED, $Et_3N$[a,c,e] | 12 |
| 7 | $[Ir(ppy)_2(dtbbpy)]PF_6$ (2.5%), blue LED, $Et_3N$[a,c,e] | 89 (87)[h] |
| 8 | $[Ir(ppy)_2(dtbbpy)]PF_6$ (2.5%), blue LED, $Et_3N$ **10**/**9** = 1:1.5[c,e] | 91 (86)[g,h] |

[a] 4.0 equiv of **10**. [b] 80 °C. [c] 22 °C. [d] 10.0 equiv of **10**. [e] 2.0 equiv of $Et_3N$ in DMF (0.5 M in **9** or **10**). [f] Based on **9**. [g] Based on **10**. [h] Yields in parentheses obtained from gram-scale reactions. AIBN = azobisisobutyronitrile, bpy = bipyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, ppy = 2-phenylpyridine, TMS = trimethylsilyl.

a large excess of enone **10** (4.0 equiv) was employed to accelerate the desired intermolecular reaction. The conventional radical conditions (AIBN, $Bu_3SnH$ or $(TMS)_3SiH$) led to rapid and complete debromination of **9** (entry 1), as did alternative initiation conditions, such as $Et_3B/O_2$ (entry 2). The reductive initiator $[Co(PPh_3)_3Cl]$ merely resulted in instantaneous homodimerization of the radical (entry 3), despite the high concentration of **10** (ca. 1.0 M). In all of the above cases, **10** was fully recovered. As these results illustrate, the pyrroloindoline radical was readily generated under various conditions; however, side reactions rapidly quenched the radical species before the desired conjugate addition occurred. At this point, we carefully examined the method employed by Crich et al. (slowly adding $Bu_3SnH$).[5a] Although the reported conditions only gave debromo-**9**, we were pleased to find that, with a much higher dilution (ca. 0.005 M in benzene) and a slower addition rate (syringe pump, 8 h) of $Bu_3SnH$, and in the presence of larger excess of **10** (10 equiv), the desired product **8** was obtained in 58% yield (entry 4). However, the use of a large excess of toxic $Bu_3SnH$ and the synthetically more precious **10** makes this reaction less satisfactory. Thus, we moved on to photoredox catalysis. Upon visible-light irradiation (blue LED, $\lambda_{max} = 454$ nm), treatment with the photocatalyst $[Ru(bpy)_3Cl_2]$ at 22 °C for 16 h produced **8** in 51% yield (entry 5). A control experiment in the absence of the photocatalyst provided only a small amount of **8** (entry 6). The efficiency of the conjugate addition was significantly improved by replacing $[Ru(bpy)_3Cl_2]$ with $[Ir(ppy)_2(dtbbpy)PF_6]$[20,13b–e] (89% yield, entry 7). Reactions with a reversed ratio of the two substrates were also investigated (entry 8). As shown, 1.5 equiv of **9** ensured optimal efficiency (91% yield), and the reaction scaled reliably (entries 7 and 8). The structure of **8** was

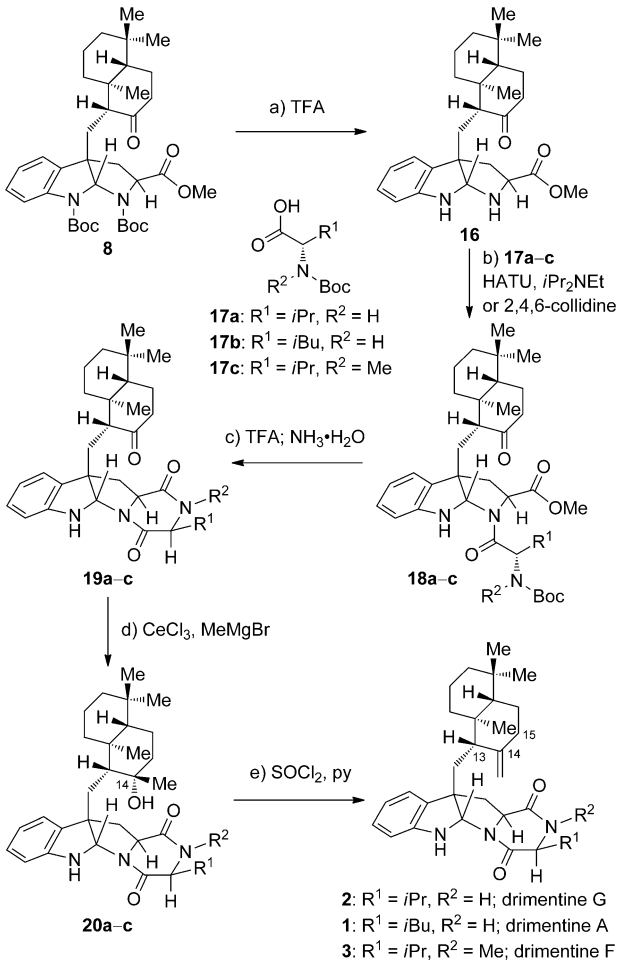
  

confirmed by X-ray crystallographic analysis (m.p. 210–212 °C, EtOAc/petroleum ether 1:1).[21]

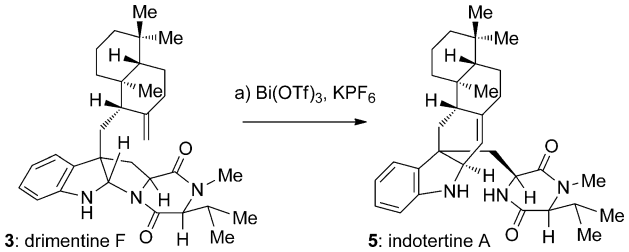
The postulated mechanism for this conjugate addition reaction is as follows: The pyrroloindoline radical can be generated through $Ir^{II}$ reduction of the indoline moiety (a SET process) followed by mesolytic cleavage of the C–Br bond. It then attacks **10** to form an α-carbonyl radical, which is quenched by hydrogen transfer from a $Et_3N$ radical cation[22] or an electron transfer from the $Ir^{II}$ species[15c–e] (to generate an enolate), followed by protolysis. The success of this reaction is presumably due to the low concentration of the reductive species and the slow rate of side reactions such as the formation of debromo-**9**.[23] Interestingly, **9** plays a protecting role for **10** in the reaction, by preferentially reacting with the $Ir^{II}$ species. We observed significant reductive dimerization and hetero [4+2] cycloaddition reactions of **10** in the absence of **9**.[22,24]

With **8** in hand, we entered the final stage of drimentine G (**2**) synthesis (Scheme 4). Boc deprotection with trifluoroacetic acid (TFA) gave diamine **16** in 98% yield, which was mono-aminoacylated with Boc-L-valine **17a** to afford amide **18a**. Treatment of **18a** with TFA followed by basification with $NH_3{\cdot}H_2O$ furnished diketopiperazine **19a** in 86% yield over the three steps. A variety of ketone methylenation methods, such as Wittig, Julia, Tebbe, Petasis, Nysted, and Peterson (or ceric Peterson) reactions, failed to convert **19a** into **2**, presumably due to the sterically hindered nature of **19a**. To our delight, tertiary alcohol **20a** could be obtained as a single diastereomer on a 500 mg scale through the use of a methyl ceric reagent (generated in situ from anhydrous $CeCl_3$ and MeMgBr).[25] Conventional tertiary alcohol dehydration conditions ($MsCl/Et_3N$, Martin sulfurane, or Burgess reagent) did not provide any characterizable product; $BF_3{\cdot}OEt_2$ treatment instantaneously gave the thermodynamically more-favored trisubstituted olefin, the $\Delta^{14,15}$ isomer of **2**. The optimized conditions for dehydrating tertiary alcohol **13** ($SOCl_2/Et_3N$) unfortunately led to a 6:1 mixture of the $\Delta^{14,15}$ and $\Delta^{13,14}$ isomers of **2**. Finally, **20a** was subjected to $SOCl_2$ and pyridine at −90 °C,[26] producing drimentine G (**2**, 43% yield) together with its $\Delta^{14,15}$ and $\Delta^{13,14}$ isomers (ca. 5:5:1 ratio). Drimentines A and F were also synthesized through similar routes from **16** and the corresponding Boc-L-leucine **17b** and Boc-*N*-Me-L-valine **17c** (Scheme 4). Tertiary alcohols **20b** and **20c** were obtained in four steps (68% and 43% overall yield) through intermediates **18b**/**19b** and **18c**/**19c**, respectively. Dehydration reactions under the same conditions mentioned above furnished drimentine A (**1**, 35% yield) and drimentine F (**3**, 28% yield), respectively. The ratio of **1** and its $\Delta^{14,15}$ and $\Delta^{13,14}$ isomers was ca. 3:4:1, whereas, in the case of the elimination of **20c**, the $\Delta^{14,15}$ isomer was favored over **3** (ca. 2.4:1).

As shown in Scheme 5, treatment of drimentine F (**3**) with $Bi(OTf)_3/KPF_6$[27] smoothly rendered indotertine A (**5**, 78% yield), presumably through the path depicted in Scheme 1. The spectral and physical properties of the synthetic drimentines A, F, and G, and indotertine A were identical to those reported for the natural samples, which also verified their absolute configuration.[7b]




***Scheme 4.*** Completion of the total synthesis of drimentines A, F, and G. Reagents and conditions: a) $TFA/CH_2Cl_2$ (1:3), 22 °C, 2 h, 98%; b) **17a**/**b** (1.5 equiv), 2,4,6-collidine (3.0 equiv), HATU (1.5 equiv), $CH_2Cl_2$, 22 °C, 5 h; **17c** (2.0 equiv), $iPr_2NEt$ (3.0 eq), HATU (1.5 equiv), DMF, 22 °C, 8 h; c) $TFA/CH_2Cl_2$ (1:3), 22 °C, 2 h; then aq $NH_3{\cdot}H_2O$ (28 wt%)/MeOH (1:20), 22 °C, 10 min, 86% for **19a**, 93% for **19b**, 68% for **19c**, over the 3 steps, respectively; d) MeMgBr (4.0 equiv), $CeCl_3$ (5.0 equiv), THF, 0 °C, 30 min; then 22 °C, 30 min, 73% for **20a**; 73% for **20b**, 63% for **20c**; e) $SOCl_2$ (5.0 equiv), pyridine (10.0 equiv), $CH_2Cl_2$, −90 °C, 5 min, 43% for **2**, 35% for **1**, 28% for **3**. DMF = dimethylformamide, HATU = *o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, TFA = trifluoroacetic acid.




***Scheme 5.*** Conversion of drimentine F into indotertine A. Reagents and conditions: a) $Bi(OTf)_3$ (1.0 equiv), $KPF_6$ (1.0 equiv), 22 °C, 2 h, 78%. Tf = trifluoromethanesulfonate.

In conclusion, we have developed a concise route to accomplish the first total synthesis of drimentines A, F, and G, and indotertine A. The key intermediate for this synthesis was

assembled by an intermolecular radical conjugate addition. Photoredox catalysis played a determining role in the success of this transformation. A biologically inspired iminium–olefin cyclization was exploited to convert drimentine F into indotertine A. This synthesis is expected to facilitate the biological studies on these naturally scarce compounds.

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**Keywords:** conjugate addition · iminium-olefin cyclization · photoredox catalysis · pyrroloindoline alkaloids · total synthesis

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