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Intramolecular Dearomative Oxidative Coupling of Indoles: A Unified Strategy for the Total Synthesis of Indoline Alkaloids

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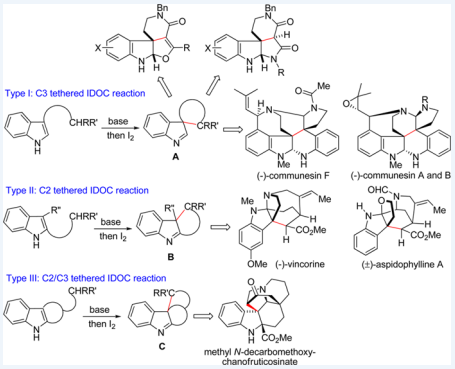
CONSPECTUS: Indole alkaloids, one of the largest classes of alkaloids, serve as an important and rich source of pharmaceuticals and have inspired synthetic chemists to develop novel chemical transformations and synthetic strategies. Many biologically active natural products contain challenging indoline scaffolds, which feature a C3 all-carbon quaternary stereocenter that is often surrounded by a complicated polycyclic ring system. The creation of this quaternary stereocenter creates an inherent synthetic challenge because the substituents on the carbon center cause high steric repulsion. In addition, the presence of nitrogen atoms within the surrounding polycyclic rings can lead to synthetic difficulties.



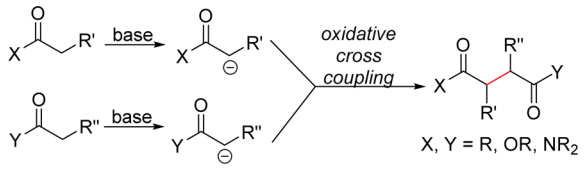
Oxidative coupling between two sp^3-hybridized carbon anions provides a unique and powerful method for building C−C single bonds, especially for generating a C−C bond that joins one or two vicinal quaternary stereocenters. Although chemists have known of this transformation for a long time, they have only applied this reaction in total synthesis of complex natural products during the past decade. The progress of this class of reaction depends on the use of indole moieties as coupling partners.

In this Account, we summarize our recent efforts to develop iodine-mediated intramolecular dearomative oxidative coupling (IDOC) reactions of indoles as part of a unified strategy for the total synthesis of three classes of indoline alkaloids. We categorized these IDOC reactions into three types based on their mode of connection to the indole moiety. In type I, the carboanion nucleophile was tethered to the indole at the C3 position. This reaction enabled the assembly of skeleton **A**, which features a spiro ring at the C3 position of the indole. We demonstrated the efficiency of this method by quickly assembling two classes of tetracyclic compounds and completing the total synthesis of (−)-communesins F, A, and B. For the type II IDOC reactions, the carboanion nucleophile residing at the C2 position of the indole formed a quaternary center at the C3 position of indole to produce skeleton **B**. We applied this IDOC reaction to synthesize two akuammiline alkaloids, vincorine and aspidophylline A. Type III IDOC reactions employed substrates with a preinstalled ring at the C2 and C3 positions of the indole. These transformations proceeded smoothly to afford polycyclic ring system **C**, which we used in the first enantioselective total synthesis of Kopsia alkaloid methyl *N*-decarbomethoxychanofruticosinate. These results further demonstrate how new chemical strategies and reactions facilitate both the first total syntheses of natural products and the discovery of more efficient synthetic routes.

1. INTRODUCTION

The oxidative cross coupling reaction between two sp^3-hybridized carbanions remains an area of intense interest in organic chemistry, particularly from the viewpoint of efficiency and practicability in total synthesis (Scheme 1).[1,2] This is not only because the carboanions, in most cases adjacent to an electron withdrawing group, are likely the most widely used species in organic chemistry but also because this transformation could be treated as a formal functional group umpolung and therefore greatly simplify synthetic manipulations. However, the major challenge of these transformations is avoiding formation of homocoupling products. This is why early studies in this area focused on oxidative dimerization of enolates of carbonyl compounds by using different oxidants.[1,2] The cross-coupling reaction between two different enolates was first reported by Saegusua in 1975.[3] But in their studies, a minimum 3-fold excess of one ketone enolate was required to ensure satisfactory yields, which partly explains that for a long period of time this methodology found nearly no application in chemical synthesis.

Scheme 1. General Process of Oxidative C(sp^3)−C(sp^3) Cross Coupling



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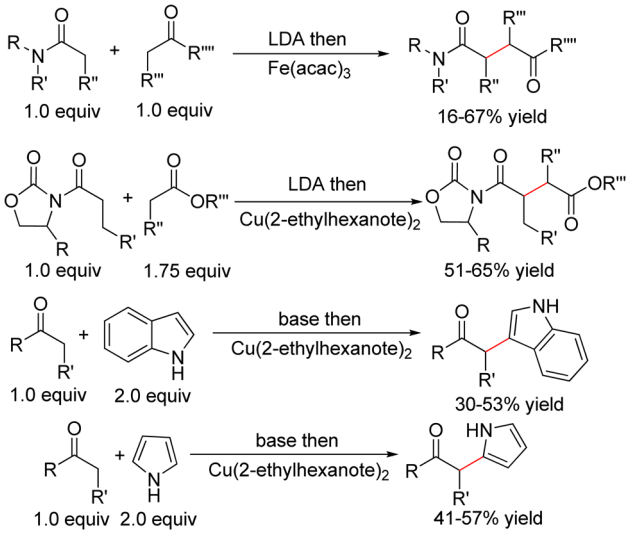
A noteworthy breakthrough in this field was achieved by the Baran group in 2006.[4,5] Using specific transition metal salts (such as Cu(2-ethylhexanote)$_2$ and Fe(acac)$_3$) as an oxidant, they successfully improved the yields of the cross coupling products to an acceptable level (40%−70% yield in most cases) even when a 1:1 ratio of reaction partners was employed (Scheme 2). Another

Scheme 2. Oxidative Cross Coupling Reactions Developed by the Baran Group



significant achievement was the discovery that these reaction conditions could be utilized for direct oxidative coupling of indoles and pyrroles with carbonyl compounds.[6] This reaction exhibited high levels of chemoselectivity (no C−N coupling) and regioselectivity (coupling occurs exclusively at C-3 of indole or C-2 of pyrrole) and therefore opened a window for applying C−C oxidative coupling reactions to the total synthesis of indole alkaloids.[7,8] Additionally, intramolecular oxidative coupling of two enolate units has been successively applied in Cohen's total synthesis of hirsutene,[9] Baran's total synthesis of stephacidin A,[10] Overman's total synthesis of actinophyllic acid,[11] and Thomson's total synthesis of metacycloprodigiosin.[12]

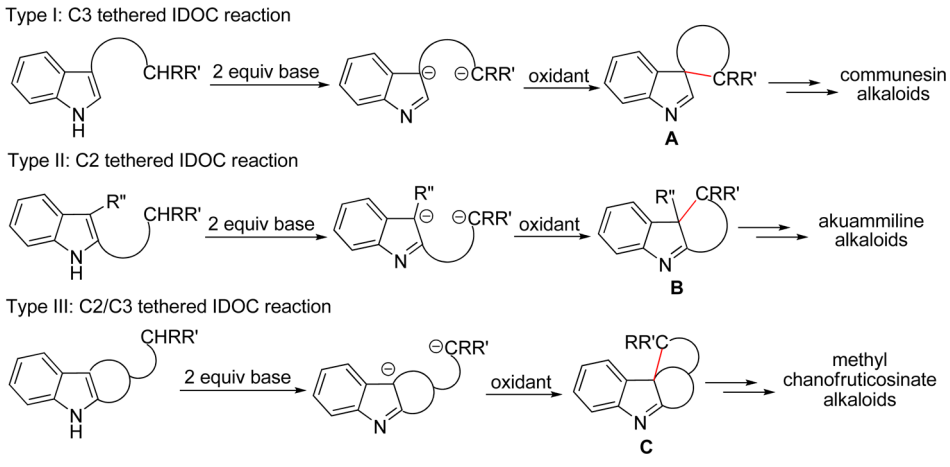
During the past years, we have focused on exploring different types of intramolecular dearomative oxidative coupling (IDOC) reactions of indoles and pursuing their applications in the total synthesis of indole alkaloids. As shown in Scheme 3, we initially envisioned that indoles with a substituent at the C3 position could undergo a type I IDOC reaction to afford 3,3-disubstituted indolines **A**. This particular spiro ring system has been found in many indoline alkaloids such as perophoramidine[13] and communesin family natural products.[14] Later, we designed the type II IDOC reaction by connecting the indole's C3 position with a carbonyl unit present on the C2 side chain of the indole. This gave the possibility to produce tricyclic indolines **B**, which constitute the core backbone of more than 30 akuammiline alkaloids.[15] Quite recently, we discovered that the type III IDOC reaction for tricyclic substrates with a preinstalled ring at the indole's C2 and C3 positions also worked well, leading to formation of polycyclic indoline intermediates **C**. These cage-like architectures could be utilized in the synthesis of the methyl chanofruticosinates family of alkaloids.[16] In this Account, we summarize our investigation progress.

2. TYPE I IDOC REACTION AND ITS APPLICATION IN THE TOTAL SYNTHESIS OF COMMUNESIN ALKALOIDS

2.1. Construction of Polycyclic Spiroindolines

In order to investigate whether our idea was workable, we chose conveniently available β-ketoamides **1** as the substrate to investigate the type I IDOC reaction. As depicted in Scheme 4, we speculated that deprotonation of **1** with 2 equiv of base should give dianion **2** and its resonance **2′**, which might be oxidized by a suitable oxidant to deliver diradical **3**. Following an intramolecular recombination of the resultant diradical species, spiroindoline **4** was produced, which might undergo tautomerization and subsequent nucleophilic attack to form tetracyclic compound **5**.[17] Initially, we tried to utilize Fe(III) or Cu(II) salts that were employed by the Baran group as the oxidants for this transformation (Table 1, entries 1−3) but found that no oxidative coupling occurred. After some experimentation, we were pleased that mild oxidant I_2 gave the desired product **5a** in 74% yield (entry 4). Interestingly, besides the oxidant, the base and solvent in the deprotonation step were also found to be crucial to this transformation (entries 4−10). This might be due to the chelation of counterions, which would stabilize the anion intermediate and in turn decrease the redox potential.[18] Thus, the optimal conditions for this transformation are LiHMDS as the base, THF as the solvent, and iodine as the oxidant.

Scheme 3. Three Types of Intramolecular Dearomative Oxidative Coupling Reaction of Indoles



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Scheme 4. IDOC Reaction of β-Ketoamides 1

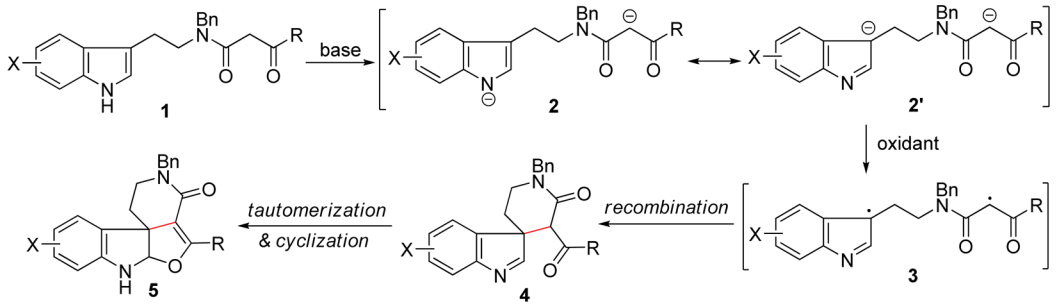
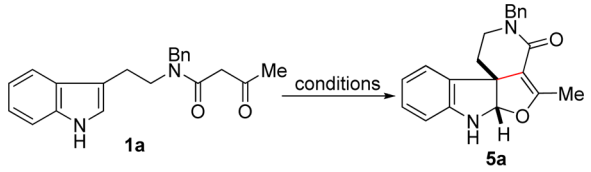


Table 1. Condition Screening for IDOC Reaction of 1a[a]



entry	base	oxidant	solvent	yield[b] (%)
1	LHMDS	Cu(2-ethylhexate)$_2$	THF	*c*
2	LHMDS	Cu(OTf)$_2$	THF	*c*
3	LHMDS	Fe(acac)$_3$	THF	*c*
4	LHMDS	iodine	THF	74
5	LDA	iodine	THF	46
6	NaHMDS	iodine	THF	72
7	KHMDS	iodine	THF	36
8	LHMDS	iodine	Et_2O	15
9	LHMDS	iodine	toluene	18
10	LHMDS	iodine	DME	40

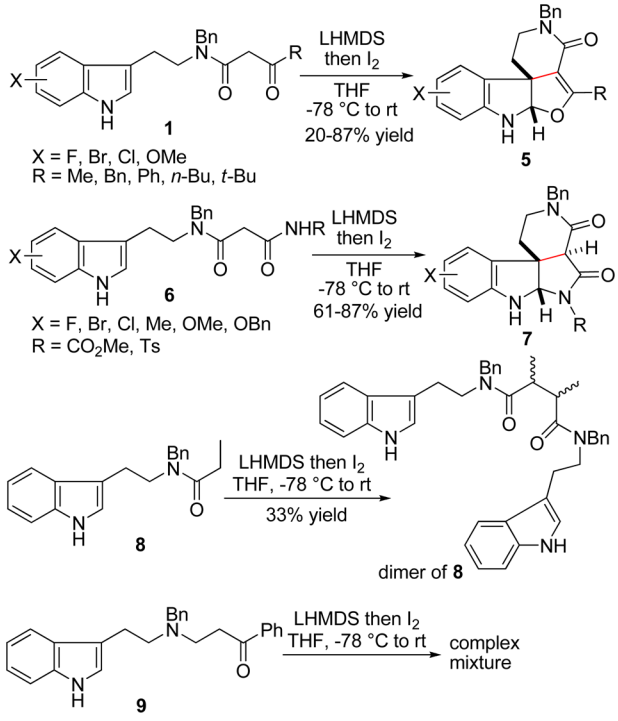
[a]Standard conditions: **1** (0.2 mmol), base (0.44 mmol), concentration (0.067 M), −78 °C, 30 min, then addition of oxidant (0.22 mmol), −78 °C, then rt, 30 min. [b]Isolated yield. [c]No oxidative coupling occurred.

These optimized reaction conditions were also applicable to other β-keto amides that possessed different substituents at the aromatic ring as well as the ketone part (Scheme 5). Furthermore, we found that this method could be extended to malonamides **6**, which provided polycyclic pyrroloindolines **7** under the same conditions.[19] Noteworthy is that using electron-withdrawing N-substituents like CO_2Me and Ts could give satisfactory results, while substrates with *N*-alkyl groups provided the corresponding products in low yields. It is expected that this transformation undergoes a similar reaction process as shown in Scheme 4. Interestingly, when comparably simple amide **8** was utilized, only the simple dimerization product (through enolate) was isolated in 33% yield, while reaction of ketone **9** under the same conditions gave a complex mixture. These results indicated that for simple indole substrates, existence of an activated enolate moiety is essential for successful intramolecular oxidative coupling.

2.2. Total Synthesis of Communesin F

The success in IDOC reaction of simple indole derivatives prompted us to explore its applications in the total synthesis of natural products. The communesin family of alkaloids (communesins A−H, Scheme 6) were isolated from a marine fungal strain of the *Penicillium* species.[14,20] Their significant cytotoxicity and insecticidal activity, as well as unique structures, have attracted great attention from the synthetic community.[20−25] Initially, we selected communesin F (**10**), a simple

Scheme 5. Iodine-Mediated Type I IDOC Reaction of Indoles



member, as our target molecule to test the type I IDOC reaction. As outlined in Scheme 6, we expected that the G ring and the A ring in communesin F could be installed at the late stage from diol **11**, which could be obtained from pentacyclic compound **12** via two carbon-chain elongation reactions. The aminal part of **12** could be created by intramolecular attack of aniline to imine, and therefore spiroindoline **13** was designed as our intermediate synthetic target, which was expected to be obtained through type I IDOC reaction of amide **14**.[24]

To evaluate these possibilities, we synthesized amides **15** with different substituents and examined their reactivity under our previously established reaction conditions (Scheme 7). We found that electronic effects of the substituents played an essential role in oxidative coupling. The substrate where X was an electron-donating group (NHBoc) completely prohibited the coupling reaction compared with 38% yield when X was H. The electron-withdrawing nitro group could dramatically increase the reactivity, and the desired oxidative coupling product was obtained in 83% yield.[24] The differences in reactivity indicated again that the pK_a values of the activated methylene units might have a crucial influence on the oxidative coupling step.

Encouraged by the model reaction, we next investigated a chiral auxiliary induced asymmetric type I IDOC reaction, aiming

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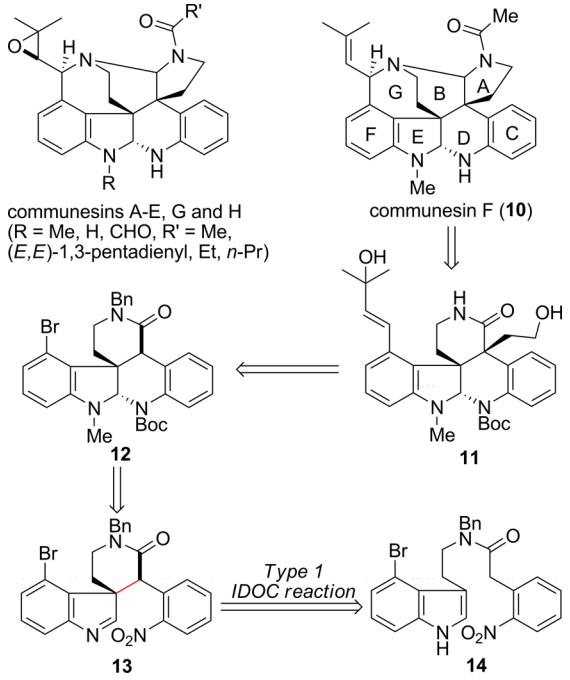
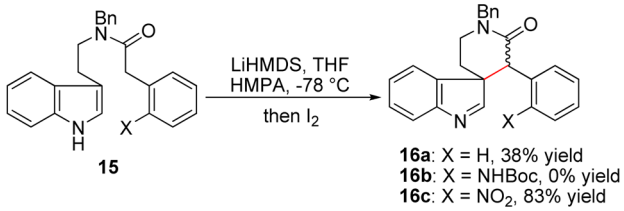
Scheme 6. Structures of Communesin Alkaloids and Retrosynthetic Analysis of Communesin F



Scheme 7. Oxidative Coupling Reaction of Amides 15



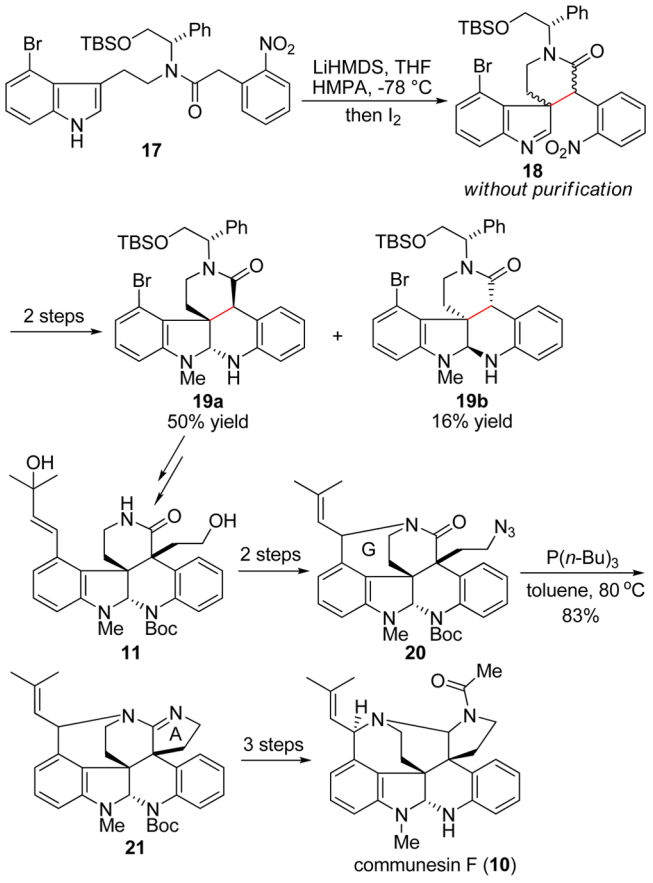
to achieve the first enantioselective synthesis of communesin F. We expected TBS protected (*S*)-phenylglycinol to be an ideal choice for generating an optically pure oxidative coupling precursor, considering the fact that the precursor should have similar reactivity compared with our model substrate, and more importantly, it could readily be removed via Ennis' method.[26] Actually, when **17** was subjected to the iodine-mediated IDOC reaction, we observed a moderate diastereoselectivity (dr = 3.1:1), and isolated the desired isomer **19a** in 50% yield after two more steps (Scheme 8).

The highly efficient access to intermediate **19a** allowed us to rapidly complete the total synthesis of (−)-communesin F.[24] After removal of the chiral auxiliary and introduction of the two carbon chains with a base-mediated allylation/olefin oxidative cleavage/reduction process and a Heck reaction to obtain the desired diol **11**, the G ring formation via *N*-alkylative cyclization accompanied by mesylation and azidation produced **20**. The last remaining A ring was installed by an intramolecular Staudinger reaction and finally provided the first enantioselective synthesis of (−)-communesin F in 19 steps (longest linear sequence from 4-bromotryptophol) and 6% overall yield.

2.3. Total Synthesis of Communesin A and B

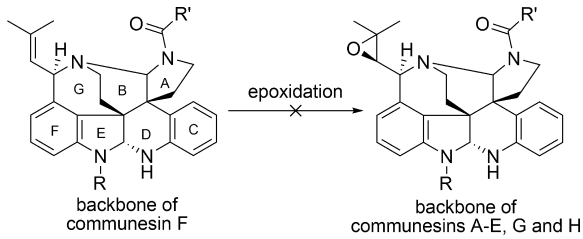
The insight gained from the structural similarity of communesin F and other family members led us to expand our synthetic studies from communesin F and its simple analogues toward other relatives of the communesin alkaloids via a late stage

Scheme 8. Asymmetric Total Synthesis of Communesin F



epoxidation of the olefin moiety (Scheme 9). However, plenty of effort toward this purpose proved to be unsuccessful. We

Scheme 9. Late Stage Epoxidation To Synthesize Other Communesin Alkaloids



speculated that the problem was a result of the sensitivity of the aminal nitrogen atoms to oxidants and therefore decided to mask the epoxide as an oxidation-state-equivalent ketal early on in the synthesis. Obviously, this modification forced us to significantly alter our synthetic strategy. Accordingly, a modified IDOC reaction was developed (Scheme 10). We conceived that the ketal moiety could be transformed into the epoxide under mild conditions, and thus bridged amide **23** was envisioned to undergo IDOC reaction.[25]

To this purpose, enantiomerically enriched triol **25** was prepared from allyl alcohol **24** via a Sharpless asymmetric dihydroxylation reaction (Scheme 11). After six more steps to obtain sulfonamide **26**, a Mitsunobu reaction was employed to deliver azepine **27**. Desulfonation of **27** followed by acylation provided the bridged amide **23** that was used for testing another type I IDOC reaction. This reaction was initially conducted

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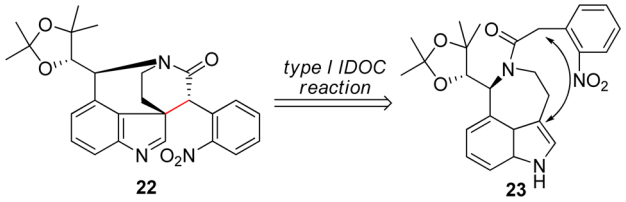
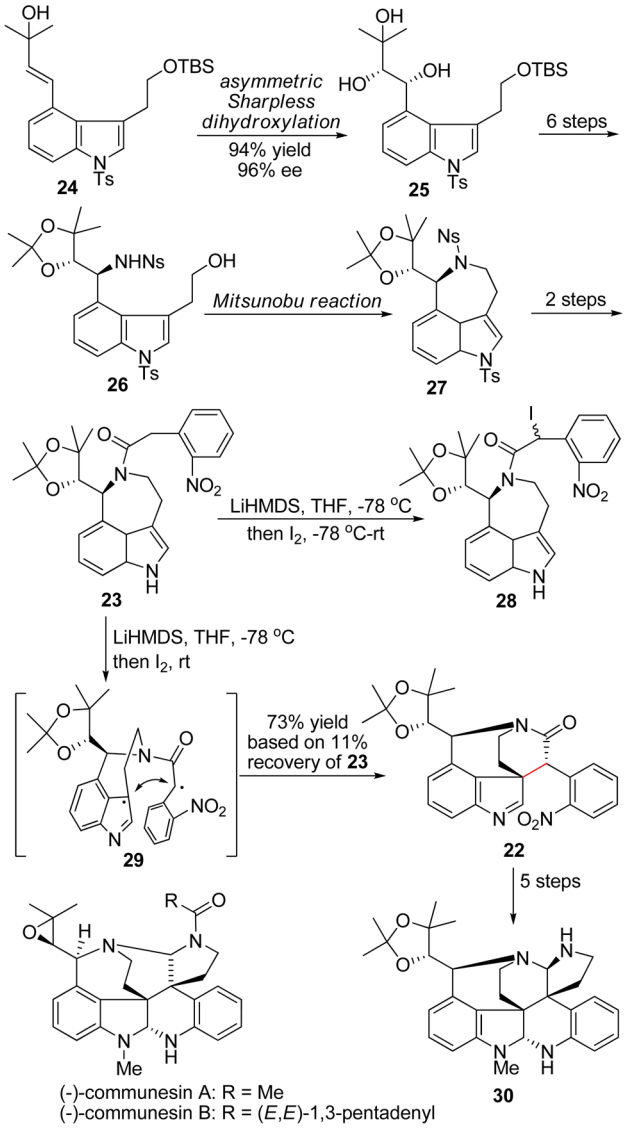
Scheme 10. Designed Key Intermediates for Synthesizing Communesin A and B



Scheme 11. Total Synthesis of (−)-Communesin A and B

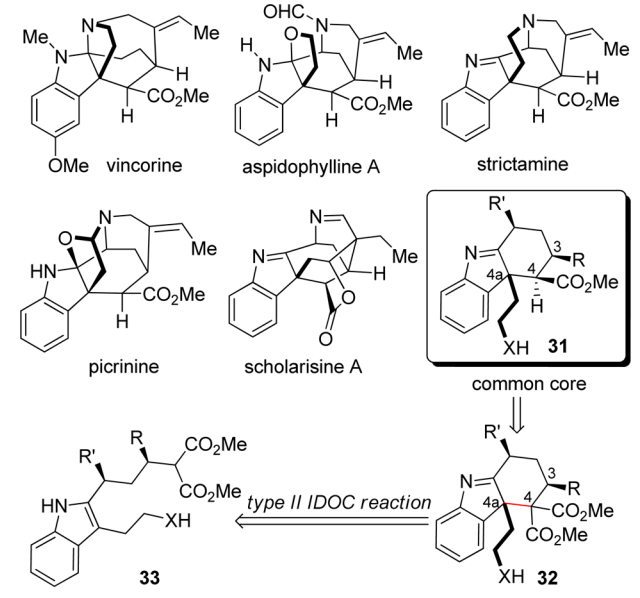


under our previous conditions (LiHMDS, THF at −78 °C, then I_2, from −78 °C to rt) but only gave simple iodination product **28** as a diastereomeric mixture. We conceived that the constrained azepine ring might restrict the approach of two radicals and thus decided to conduct the oxidative coupling at elevated temperatures. Actually, when iodine was added at room temperature, the desired spiro-fused, twisted-amide containing indoline **22** was isolated as a single isomer. The excellent stereoselectivity in this case could be rationalized by proposed transition state **29**, in which the rigid conformation was strengthened by the favorable stacking interaction between the electron-deficient arene and indole moiety, and two radicals combined from the opposite site of the bulky 1,3-dioxolane group to give **22** as a single isomer. With **22** in hand, the D ring and A ring were established successively using a similar strategy similar to the one employed in the total synthesis of communesin F to give aminal **30**. Finally, the epoxide moiety was constructed via a deprotection/mesylation/epoxidation reaction sequence, leading to the first asymmetric total synthesis of communesin A and B.[25]

3. APPLICATION OF TYPE II IDOC REACTION IN THE TOTAL SYNTHESIS OF AKUAMMILINE ALKALOIDS

Akuammiline alkaloids are a growing family of indole alkaloids that contains more than 30 members so far. These alkaloids have displayed comprehensive biological activities and have garnered numerous synthetic efforts during the past decade.[27−36] Although these alkaloids are structurally diversified, a common carbazole core **31** is present in all the akuammiline alkaloids. A synthetically straightforward way to access this carbazole ring system would allow a unified approach for assembling the akuammiline family of alkaloids. Our interest in synthesizing these alkaloids originated from the type II IDOC reaction of **33**, which might enable assembly of carbazole **32**, a precursor of the common core **31**, from simple malonate **33** in a single step (Scheme 12).[35]

Scheme 12. Structures of Akuammiline Alkaloids and Type II IDOC Reaction to Their Common Core



3.1. Total Synthesis of (−)-Vincorine

To examine our hypothesis, we selected vincorine as our synthetic target because it contains a relatively simple side chain (R′ = H).[35] As outlined in Scheme 13, *α,β*-unsaturated ester **35** was prepared from commercially available 5-methoxytrypamine **34** in six steps, which was subjected to an organocatalyzed Michael addition with a special aldehyde to afford malonate compound **36**. After olefin formation from **36**, aldehyde reduction, silyl protection, and selective removal of the N-1 Boc group, we obtained oxidative coupling precursor **37**.

To our delight, type II IDOC reaction of **37** proceeded smoothly under modified conditions (2 equiv of LiHMDS, 1.1 equiv of I_2, from −40 °C to rt) to provide aminal **40** as a single

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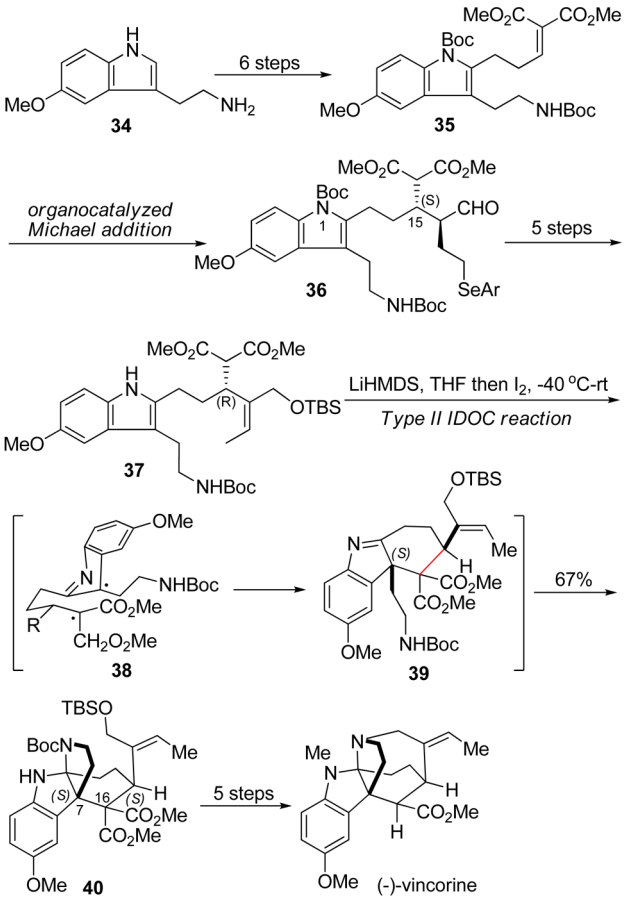
Scheme 13. Asymmetric Synthesis of (−)-Vincorine



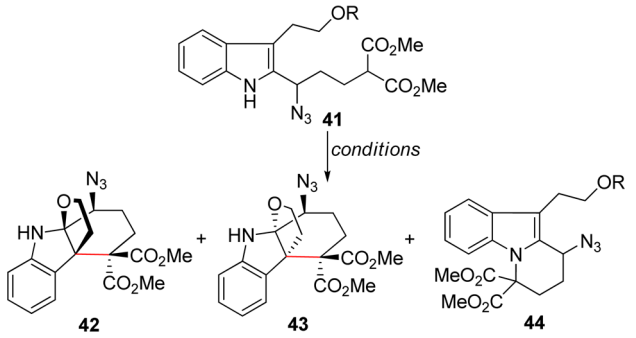
isomer in 67% yield. Obviously, this process went through an energetically favorable chairlike transition-state **38** to give cross-coupling product **39**, in which the resultant imine moiety was captured immediately by the carbamate unit to form tetracyclic compound **40**. Noteworthy is that other oxidants such as NIS, Cu(II), or Fe(III) salts proved to be less effective for this IDOC reaction. With the diester **40** in hand, we next established the last seven-member ring via *N*-alkylative cyclization, furnishing the first enantioselective synthesis of (−)-vincorine.[35]

3.2. Total Synthesis of Aspidophylline A

For synthesizing aspidophylline A, we designed malonate compounds **41** as the substrates for applying the type II IDOC reaction (Table 2), in which the azido group was expected to be used for generating the piperidine ring in the target molecule.[36] Using azide as the amine source was essential in our synthesis because replacing azide with different protected amines always caused lactam formation at a later stage. Interestingly, when TBS and MOM protected substrates were employed, only C−N coupling products **44** were isolated under our standard oxidative coupling conditions (entries 1−3). A similar phenomenon has been discovered by Zhu and co-workers in their recent attempt to synthesize strictamine by employing the IDOC strategy (Scheme 14).[37] It is noteworthy that direct C−N bond formation via deprotonation/oxidative coupling has been successively used by the Sarpong group in their total synthesis of lyconadin A (Scheme 15).[38]

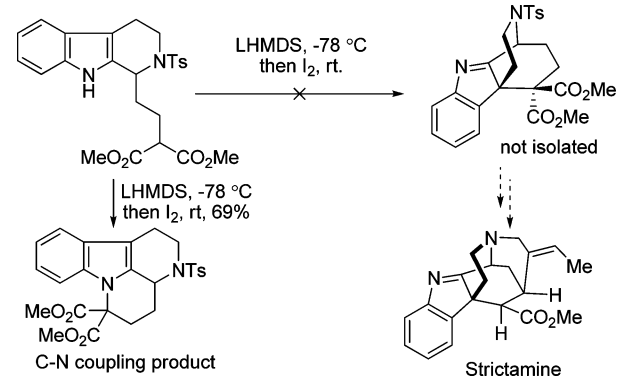
All the efforts to eliminate this side reaction via variation of reaction conditions failed. Fortunately, when substrate with a free hydroxyl group was subjected to IDOC reaction, the desired

Table 2. C−N Coupling versus C−C Coupling of Malonate Compounds 41

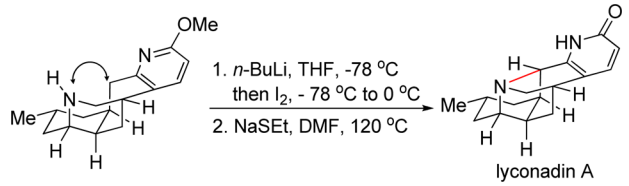


entry	R	conditions	product (yield, %)
1	TBS	LiHMDS, THF, −40 °C then I_2, −40 to 0 °C	**44a** (38)
2	TBS	LiHMDS, THF, HMPA, −40 °C then I_2, −40 to 0 °C	**44a** (73)
3	MOM	LiHMDS, THF, −40 °C then I_2, −40 to 0 °C	**44b** (40)
4	H	LiHMDS, THF, −40 °C then I_2, −40 to 0 °C	**42**/**43** (2:1, 54)
5	H	LiHMDS, THF, HMPA, −40 °C then I_2, −40 to 0 °C	**44c** (36)

Scheme 14. Zhu's Attempt To Synthesize Strictamine through IDOC Reaction



Scheme 15. Sarpong's Total Synthesis of Lyconadin A via Oxidative C−N Bond Formation



tetracyclic compound **42** and its diastereomer **43** were isolated in 54% yield. To our surprise, in the presence of HMPA, the formation of **42** and **43** was inhibited and C−N coupling product **44c** was isolated as the major product (entry 5).

We proposed the following mechanism to rationalize the above oxidative-coupling results (Scheme 16). Deprotonation of **41c** with three equiv of LiHMDS would rapidly produce chelated intermediate **45**. The tridendate lithium complex effectively stabilizes this transition state with the C3 of indole very close to the malonate moiety, and thus C−C bond formation predominately occurs during oxidative coupling. However,

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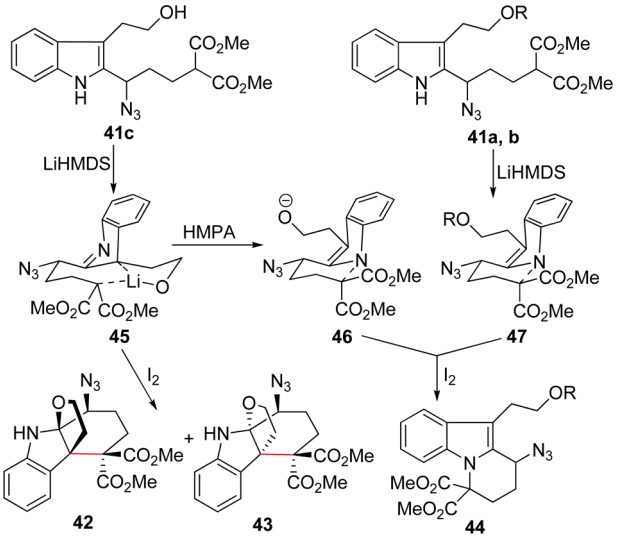
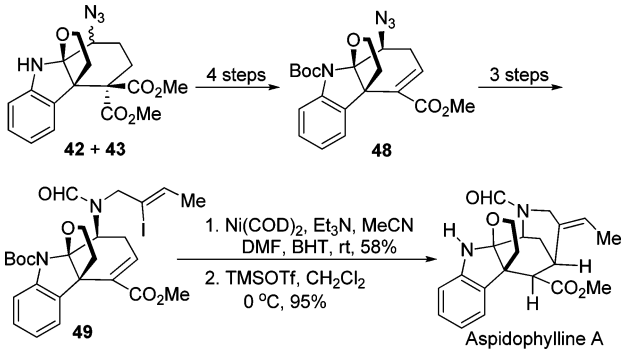
Scheme 16. Proposed Mechanism for Type II IDOC Reaction



when HMPA is added to coordinate with lithium ion, this chelated intermediate might decompose to give thermodynamically stable transition state **46**, which would prefer to give the C−N coupling product in the oxidation step. Similarly, while the hydroxyl group was protected with TBS or MOM, transition state **47** could be preferred, and therefore C−N coupling takes place exclusively. The present result implied that during our synthesis of vincorine a similar tridendate lithium complex might form via deprotonation of the carbamate part of the malonate compound **37**, and thereby facilitating the C−C bond formation.

Although the diastereoselectivity for the IDOC reaction of **41c** was only moderate, the quick assembly of the tetracyclic intermediate **42** greatly facilitated the late-stage transformations. Krapcho decarboxylation of the mixture of **42** and **43** followed by treatment with LDA/PhSeBr and hydrogen peroxide provided α,β-unsaturated ester **48** (Scheme 17), whose azide moiety was

Scheme 17. Synthesis of Aspidophylline A

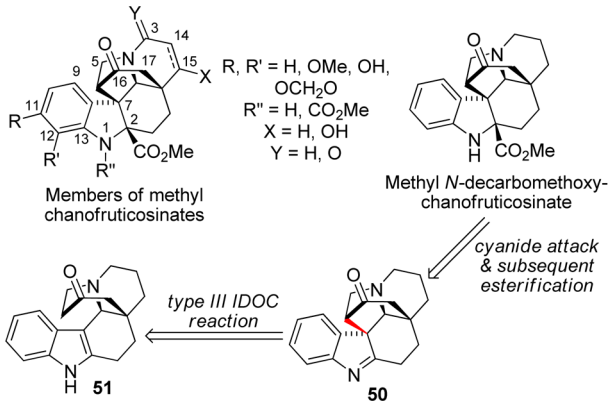


reduced to deliver vinyl iodide **49** after allylation and formylation. Ni-mediated Michael addition of **49** and subsequent cleavage of the Boc group led to the formation of aspidophylline A. In this synthesis only 14 steps were used from conveniently available starting materials.[36]

4. TOTAL SYNTHESIS OF (+)-METHYL *N*-DECARBOMETHOXYCHANOFRUTICOSINATE BY USING TYPE III IDOC REACTION

Methyl chanofruticosinates alkaloids have been isolated from a variety of *Kopsia* (Apocynaceae) species that are widely distributed in tropical Asia.[16] Preliminary studies revealed these alkaloids have a wide range of biological properties, which span from anticancer to antitussive.[39] Structurally, all methyl chanofruticosinate alkaloids contain a caged and strained hexacyclic ring system, but they are differentiated by the substituents at the 1, 3, 11, 12, 14, and 15 positions (Scheme 18). In order to develop a general route for synthesizing these

Scheme 18. Structures of Methyl Chanofruticosinate Alkaloids and Retrosynthetic Analysis of (+)-Methyl *N*-Decarbomethoxychanofruticosinate



alkaloids, we decided to investigate whether a type III IDOC reaction of ketone **51** was feasible. Obviously, success in oxidative coupling of **51** would give an ideal approach for assembling (+)-methyl *N*-decarbomethoxychanofruticosinate because this step not only establishes the caged and strained ring system but also delivers an imine moiety that is ready for installing the amino ester part in the target molecule via a simple cyanide attack (Scheme 18).[40]

We commenced our synthesis from the asymmetric preparation of **53** (Scheme 19). By the method introduced by Lupton and Shao, **53** was obtained within four steps from commercially available **52**.[41,42] After three more steps, ketone **54** was obtained, which was subjected to reductive cyclization with newly generated nickel boride and subsequent hydrogenation of the resultant imine to produce amine **55** in 88% yield. After acylation, desilylation, and Ley oxidation to give aldehyde **56**, SmI_2-mediated intramolecular Reformatsky-type reaction was carried out to provide lactam **57**. Reduction of the amide moiety in **57** followed by oxidation of the alcohol afforded oxidative coupling precursor **51**. We were pleased that type III IDOC reaction of **51** took place under typical conditions, leading to formation of imine **50** in 78% yield. Finally, total synthesis of (+)-methyl *N*-decarbomethoxychanofruticosinate was accomplished by cyanide attack of the imine **50** and subsequent hydration and esterification.[40]

As discussed previously, we had found the pK_a value of activated methylene units crucial to the coupling reaction, and ketones were detrimental to IDOC reaction of simple indole derivatives under our reaction conditions. The success in transformation of **51** to **50** therefore offers a special example for IDOC reactions. Similarly, Higuchi and co-workers found

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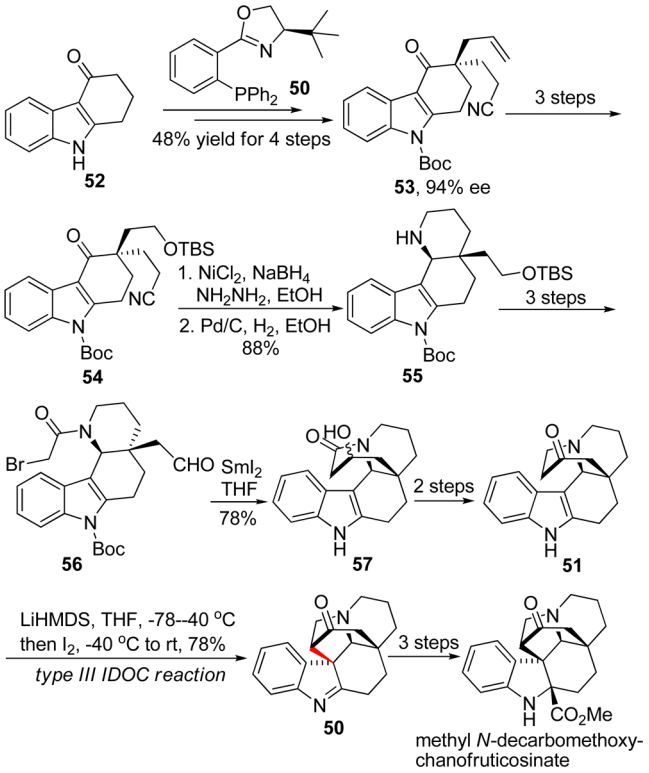
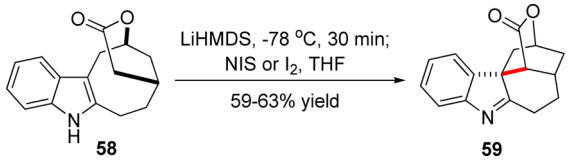
Scheme 19. Total Synthesis of (+)-Methyl *N*-Decarbomethoxychanofruticosinate



that oxidative coupling between unactivated enolates and indoles was possible during their model studies on the total synthesis of scholarisine A (Scheme 20).[43] This success could have resulted

Scheme 20. Higuchi's Type III IDOC Reaction

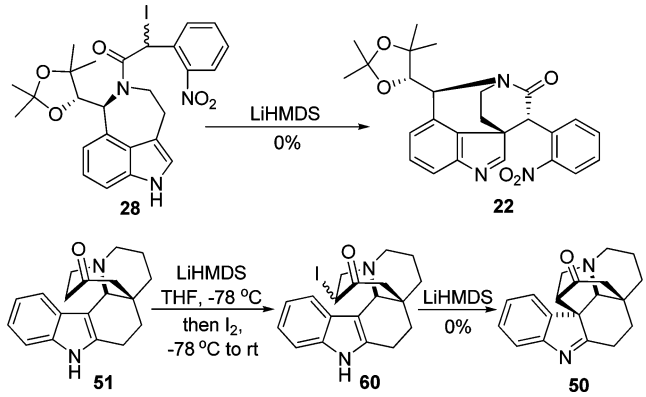


from the special geometry of the substrates; due to the proximity of two coupling reaction sites resulting from conformational restriction, even simple ketones and esters underwent the oxidative coupling process.

5. MECHANISTIC CONSIDERATIONS

The mechanism for iodine-mediated dimerization of ester enolates was initially proposed to proceed via an iodination/nucleophilic displacement process.[44] After systematic studies, Fox and Renaud realized that a radical pathway was more suitable for this reaction, particularly for those substrates that could form sterically hindered anion.[45] Although a detailed mechanistic investigation of our IDOC reaction awaits further exploration, some experimental results have shed light on mechanistic considerations. As mentioned before, during the synthesis of communesin A, we observed that when the oxidative step was conducted at −78 °C, only the simple iodinated product **28** was isolated. Similar results were noticed when ketone **51** was sequentially treated with LiHMDS and iodine at −78 °C (Scheme 21). Further treatment of iodination products **28** and **60** with base under various conditions failed to give any

Scheme 21. Cyclization of Iodination Products under Basic Conditions



cyclization products. These results indicated that the oxidative coupling step requires higher reaction temperatures compared with simple iodination; therefore a S_N2 mechanism for the present C−C bond formation could be ruled out. Accordingly, we tentatively proposed that IDOC reaction might go through a radical pathway as shown in Scheme 4. As discussed before, both electronic and steric effects of the carbonyl units could greatly influence the oxidative coupling step, indicating that formation of two radicals at the right rate and right place was the key for successful coupling.

6. SUMMARY AND OUTLOOK

In this Account, we have summarized our recent research progress in intramolecular dearomative oxidative coupling (IDOC) reactions of indoles. It was proven that the LiHMDS/I_2 system was compatible with all three types of IDOC reactions, although tuning reaction temperatures was needed due to the structural complexity for each substrate. It was possible to control the stereochemistry of the IDOC reaction by chiral auxiliaries or by substrate chirality induction. The efficiency and diversity of this transformation were illustrated during our total synthesis of several bioactive indoline alkaloids, including (−)-communesin A, B, and F, (−)-vincorine, aspidophylline A, and (+)-methyl *N*-decarbomethoxychanofruticosinate, which belong to three different alkaloid families. Along with applications of IDOC reaction in total synthesis of natural products, our future efforts will focus on insightful mechanistic studies as well as achieving a reagent controlled asymmetric version of IDOC reaction.

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Notes

The authors declare no competing financial interest.

Biographies

Weiwei Zi was born and raised in Hunan, China. He obtained his B.Sc. from Lanzhou University in 2006. He then moved to Shanghai Institute

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of Organic Chemistry to pursue his Ph.D. under the supervision of Prof. Dawei Ma. His Ph.D. thesis was focused on the total synthesis of alkaloids GB 13 and vincorine. He is currently a postdoctoral fellow in the laboratory of Prof. F. Dean Toste at the University of California, Berkeley.

Zhiwei Zuo was born in Hubei, China, and received his undergraduate degree in chemistry at Nanjing University. In 2007, he began his doctoral studies under the direction of Professor Dawei Ma at Shanghai Institute of Organic Chemistry, engaging in the development of concise synthesis of indole alkaloids. In 2013, he moved to Princeton University and began his postdoctoral studies with Professor David W. C. MacMillan.

Dawei Ma received his Ph.D. in 1989 from Shanghai Institute of Organic Chemistry and did his postdoctoral studies at the University of Pittsburgh and Mayo Clinic. He returned to SIOC in 1994 and was appointed as research professor in 1995. His research interests currently focus on the development of new synthetic methodologies, the total synthesis of complex natural products, and their SAR and action mode studies, as well as the discovery of small modulators for target proteins and special biological processes.

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