Polycycle Synthesis

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# Highly Efficient Formal [2+2+2] Strategy for the Rapid Construction of Polycyclic Spiroindolines: A Concise Synthesis of 11-Demethoxy-16-*epi*-myrtoidine

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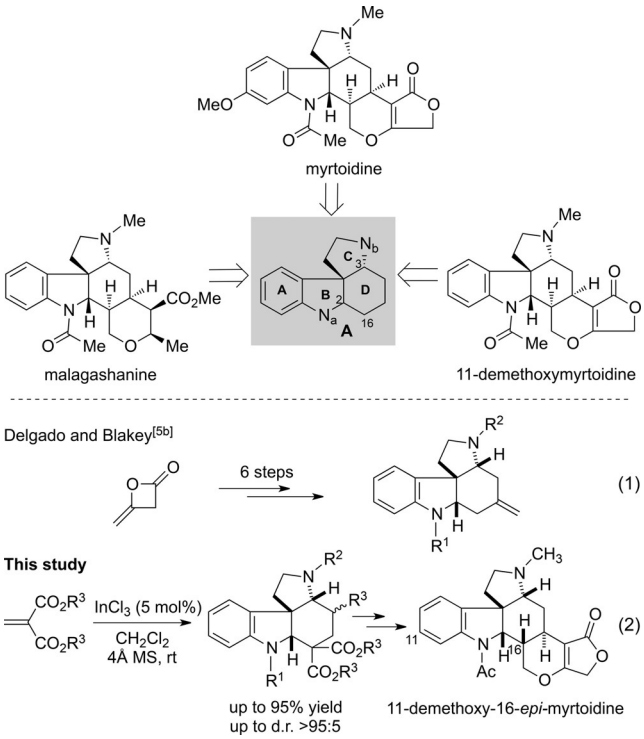
***Abstract:*** *A novel formal [2+2+2] strategy for the stereoselective elaboration of polycyclic indole alkaloids is described. Upon treatment with the catalyst $InCl_3$ (5 mol %), tryptamine-derived enamides reacted readily with methylene malonate, thus enabling rapid and gram-scale access to versatile tetracyclic spiroindolines with excellent diastereoselectivity (21 examples, up to 95 % yield, up to d.r. > 95:5). This strategy provides a concise approach to alkaloids isolated from Strychnos myrtoides, as demonstrated by a short synthesis of 11-demethoxy-16-epi-myrtoidine.*

From the perspective of green chemistry, synthetic efficiency is of the utmost importance in modern organic synthesis. One recent trend is the development of new reactions for the rapid construction of the molecular core of complex compounds from readily available materials, with improvements in atom economy, step economy, and selectivity.[1,2] Polycyclic spiroindolines are the basic skeletons of large families of biologically useful alkaloids, such as *Strychnos*, *Aspidosperma*, and *Vinca* alkaloids.[3] Although continuous efforts have been devoted to the development of versatile methods for the construction of the polycyclic spiroindoline skeleton,[4,5] one-step protocols for the highly stereoselective assembly of this backbone from simple materials are limited. Furthermore, effective access to the core structure of the newly discovered myrtoidine alkaloids, in which the C and D rings are fused with an unusual relative configuration (Scheme 1, motif **A**)[6]—a structure that is contained in a diverse range of bioactive natural products, such as malagashanine, myrtoidine, and 11-demethoxymyrtoidine—is extremely limited. The only known example was reported by Delgado and Blakey, who have developed an elegant intramolecular annulation reaction starting from diketene [Scheme 1, Eq. (1)].[5b]

Recently, we developed a direct and efficient method for the highly stereoselective construction of tetracyclic spiroindoline skeletons through intramolecular [3+2] annulations of cyclopropane-1,1-dicarboxylates with indoles.[7] Büchi and co-workers reported an efficient intramolecular tandem annulation of a tryptamine-derived vinylogous amide in the total synthesis of (±)-vindoline in the 1970s.[8] In line with our interest in developing concise syntheses of polycyclic indoline motifs, we have now discovered that simple tryptamine-derived enamides can react with methylene malonate in a tandem fashion to provide one-step and gram-scale access to the core skeleton of the malagashanine alkaloids [Scheme 1, Eq. (2)]. In this reaction, three continuous stereogenic carbon centers, together with two quaternary stereocenters, were created by a formal [2+2+2] process with excellent diastereoselectivity under mild reaction conditions. Furthermore, we successfully applied this reaction to the synthesis of 11-demethoxy-16-*epi*-myrtoidine.




***Scheme 1.*** Polycyclic spiroindoline alkaloids.

Our initial hypothesis is shown in Scheme 2: The attack of a tryptamine-derived enamide on an electron-deficient olefin in a Michael addition manner to form an iminium intermediate **I** would be followed by double Mannich reactions to afford the desired tetracyclic spiroindoline core. We began

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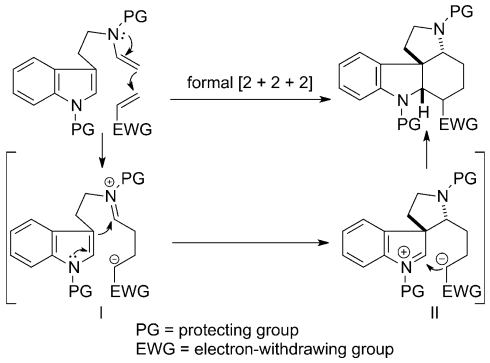
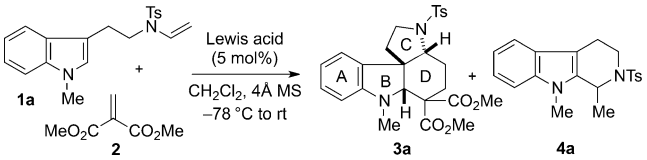



***Scheme 2.*** Proposed rapid construction of the tetracyclic spiroindoline core.

our study by using a readily available tryptamine derivative **1a** and methylene malonate **2** as starting materials. The desired transformation proved quite challenging owing to the competing intramolecular Pictet–Spengler reaction.[9] When the reaction was carried out in the absence of a catalyst, no reaction had taken place after 48 h (Table 1, entry 1). The reaction was also not promoted by 4 Å molecular sieves (entry 2). With $CuBr_2$ (5 mol%), **1a** was consumed very fast and underwent the intramolecular Pictet–Spengler reaction[9] to give the indole-fused heterocyclic product **4a** in 97% yield after 1 h (Table 1, entry 3). When the copper salt was assembled with a bisoxazoline ligand **L**, the reactivity diminished dramatically, and product **4a** was obtained in 72% yield after 23 h (entry 4).

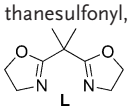
Although $NiCl_2$ could not promote this reaction, when $FeCl_2$ was used as a catalyst, a tandem cyclization reaction provided the desired polycyclic spiroindoline scaffold **3a** in 25% yield with d.r. 89:11 (Table 1, entries 5 and 6). Encouraged by this result, we tested $FeCl_3$ as the catalyst and found that the reaction proceeded very fast to afford **3a** in 73% yield with d.r. > 95:5 after 40 min (Table 1, entry 7). However, when a complex derived from **L** and $FeCl_3$ was employed, the reaction became sluggish, and only a trace amount of **3a** was detected (entry 8). This result suggested that the Lewis acidity of the catalyst may play an important role in this tandem cyclization reaction and drove us to examine some stronger Lewis acids. With $Y(OTf)_3$, the reaction was complete within 5.5 h and delivered a mixture of **3a** and **4a** with poor selectivity (Table 1, entry 9). When $AlI_3$ was used as the catalyst, the reaction proceeded even faster, but gave the undesired product **4a** in > 99% yield (entry 10). Although the reaction was slow with $InF_3$ as the catalyst (entry 11), $InCl_3$ promoted the reaction very efficiently to afford the desired product in 91% yield with d.r. 95:5 after 6 h (Table 1, entry 12). We found that both $InBr_3$ and $InI_3$ could promote this reaction even faster to give the product in 80 and 85% yield, respectively, with d.r. > 95:5 (Table 1, entries 13 and 14). Since $InCl_3$ is much cheaper than both $InBr_3$ and $InI_3$, we preferred to use the former for further optimization of the reaction conditions. To facilitate the reaction procedure, we carried out the reaction at room temperature. The reaction also proceeded well under these conditions, without loss of specificity, reactivity, or diastereoselectivity (Table 1, entry 15).

***Table 1:*** Reaction optimization.




| No.[a] | Lewis acid | $t$ | Yield [%][b] | | d.r.[b] |
|---|---|---|---|---|---|
| | | | **3a** | **4a** | |
| 1 | – | 48 h | NR | 0 | – |
| 2[c] | – | 48 h | NR | 0 | – |
| 3 | $CuBr_2$ | 1 h | 0 | 97 | – |
| 4 | $Cu(SbF_6)_2$ + **L** | 23 h | 0 | 72 | – |
| 5 | $NiCl_2$ | 17 h | trace | 0 | nd |
| 6 | $FeCl_2$ | 16.5 h | 25 | 0 | 89:11 |
| 7 | $FeCl_3$ | 40 min | 73 | trace | > 95:5 |
| 8 | $FeCl_3$ + **L** | 21 h | trace | 0 | nd |
| 9 | $Y(OTf)_3$ | 5.5 h | 20 | 32 | 94:6 |
| 10 | $AlI_3$ | 25 min | 0 | > 99 | – |
| 11 | $InF_3$ | 17 h | trace | 0 | nd |
| 12 | $InCl_3$ | 6 h | 91 | 0 | 95:5 |
| 13 | $InBr_3$ | 20 min | 84 (80[d]) | 0 | > 95:5 |
| 14 | $InI_3$ | 15 min | 85 (85[d]) | 0 | > 95:5 |
| 15[e] | $InCl_3$ | 5 h | 90[d] | 0 | 95:5 |

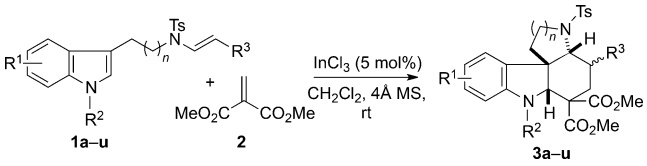
[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.9 mmol), 4 Å MS (molecular sieves, 200 mg), and the Lewis acid (5 mol%) were mixed in $CH_2Cl_2$ (4 mL) at −78 °C, and the reaction mixture was then stirred at room temperature. [b] The yields of **3a** and **4a**, and the diastereomeric ratio of **3a**, were determined by $^1$H NMR analysis of the crude material with $CH_2Br_2$ as an internal standard; the diastereomeric ratio is defined by the relative configuration of ring C; the structure of **3a** was identified by X-ray diffraction.[10] [c] The reaction was carried out without 4 Å MS. [d] Yield of the isolated product. [e] The reaction was carried out at room temperature. nd = not determined, NR = no reaction, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

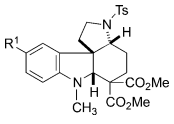
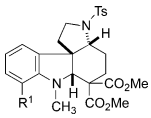
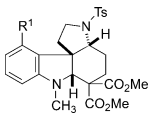
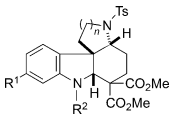
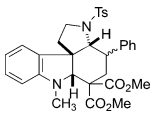



We next explored the generality of the transformation under the optimal reaction conditions. A broad range of tryptamine derivatives were found to be suitable for this tandem reaction (Table 2). Tryptamine derivatives **1b–g** with various functional groups, such as Me, $TBSOCH_2$, MeO, and halo groups, at the 5-position were converted into the corresponding products in up to 92% yield with up to d.r. > 95:5. Regardless of the electronic nature of the aromatic ring, products **3h–k** were obtained in high yield (85–90%) with excellent diastereoselectivity (d.r. 92:8 or 95:5). When a halo group was present at the 7-position (substrates **1l** and **1m**), the corresponding products were obtained in 91 and 93% yield with d.r. 75:25. Tryptamine derivatives **1n–r** bearing different halo groups at the 4- or 6-position were also tolerated by the current reaction system, and were transformed into products **3n–r** in 86–95% yield with d.r. 86:14–90:10. Furthermore, spiroindoline **3s** containing a six-membered C ring could be assembled in 92% yield with d.r. 80:20. When the nitrogen atom of the indole moiety was protected with a benzyl group, the tetracyclic spiroindoline **3t** was obtained in 91% yield with d.r. 91:1, thus facilitating further transformation. However, when the 6-position of

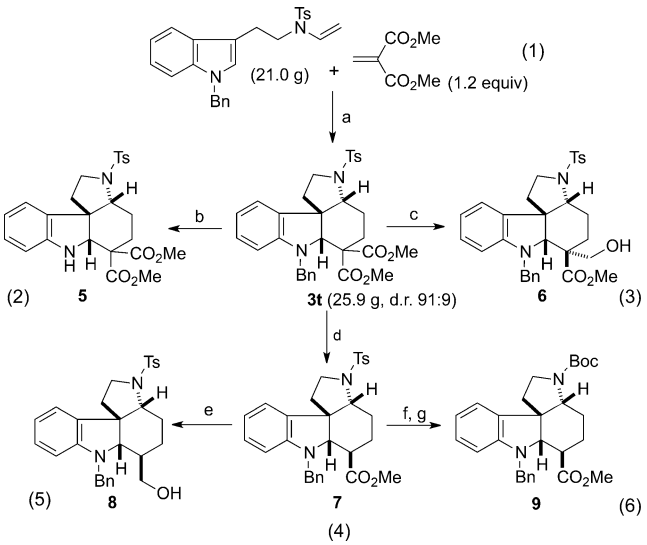
  

***Table 2:*** Reaction scope.




| No.[a] | Product ($R^1$) | | $t$ [h][b] | d.r.[c] | Yield [%][d] |
|---|---|---|---|---|---|
| 1 | | **3a** (H) | 5 | 95:5 | 90 |
| 2 |  | **3b** ($CH_3$) | 6 | >95:5 | 88 |
| 3 | | **3c** ($CH_2OTBS$) | 3 | >95:5 | 57 |
| 4 | | **3d** ($OCH_3$) | 18 | 94:6 | 88 |
| 5 | | **3e** (F) | 47.5 | 91:9 | 65 |
| 6 | | **3f** (Cl) | 10 | 90:10 | 90 |
| 7 | | **3g** (Br) | 9 | 89:11 | 92 |
| 8 | | **3h** ($CH_3$) | 4 | 95:5 | 89 |
| 9 |  | **3i** (Et) | 6 | 95:5 | 85 |
| 10 | | **3j** ($CH_2OTBS$) | 7.5 | 92:8 | 90 |
| 11 | | **3k** (OBn) | 16 | 92:8 | 87 |
| 12 | | **3l** (Cl) | 10 | 75:25 | 91 |
| 13 | | **3m** (Br) | 8 | 75:25 | 93 |
| 14 | | **3n** (F) | 7 | 90:10 | 95 |
| 15 |  | **3o** (Cl) | 6 | 88:12 | 95 |
| 16 | | **3p** (Br) | 7 | 87:13 | 92 |
| 17 | | **3q** (Cl) | 10 | 86:14 | 86 |
| 18 | | **3r** (Br) | 6 | 87:13 | 93 |
| 19[e] |  | **3s** (H) | 12.5 | 80:20 | 92 |
| 20[f] | | **3t** (H) | 5 | 91:9 | 91 |
| 21 | | (OMe) | 38 | – | 0 |
| 22 |  | **3u**+**3u′** | 36 | 50:50 | 55 |

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), 4 Å MS (200 mg), $InCl_3$ (5 mol%), $CH_2Cl_2$ (4 mL), room temperature; unless otherwise noted, $R^2=CH_3$, $R^3=H$, $n=1$. [b] The reaction times were not optimized. [c] The diastereomeric ratio was determined by $^1H$ NMR analysis of the crude product. [d] Yield of the isolated product. [e] $n=2$. [f] $R^2$ = Bn. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.



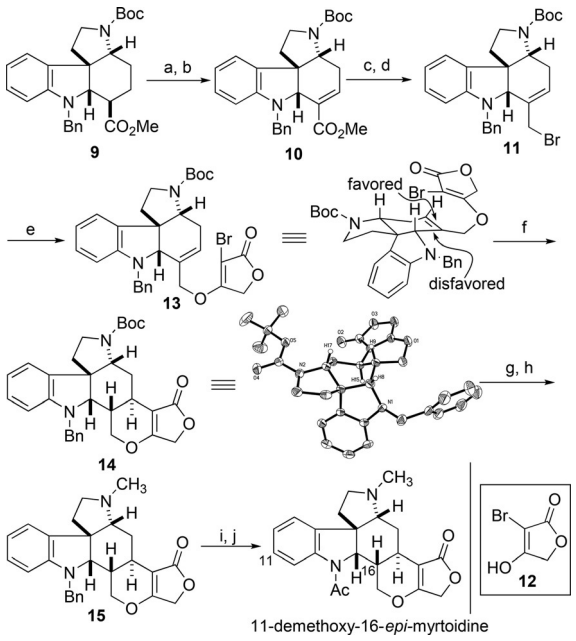

***Scheme 3.*** Gram-scale synthesis and product transformation. Reagents and conditions: a) $InCl_3$ (5 mol%), $CH_2Cl_2$, 4 Å MS, room temperature, 92%, d.r. 91:9; b) $Pd(OH)_2/C$, $H_2$, 92%; c) DIBAL-H, $CH_2Cl_2$, −78 °C, 62%; d) LiCl/$H_2O$, DMSO, 130 °C, 74%, d.r. 83:17; e) DIBAL-H, THF, 0 °C, 92%; f) Na/naphthalene, THF, −78 °C; g) $(Boc)_2O$, $Et_3N$, $CH_2Cl_2$, 62% for 2 steps. Boc = *tert*-butoxycarbonyl, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide.

indole was OMe, by employing this substrate, no desired product was detected; instead a mixture of by-products was observed (entry 21). Notably, the tryptamine-derived substrate **1u** bearing an internal-olefin substituent on the N atom was also suitable for this [2+2+2] tandem annulation reaction. The two diastereomers of the corresponding product, **3u** and **3u′**, with four continuous stereogenic carbon centers were formed in 55% combined yield (Table 2, entry 22).

The highly efficient tandem cyclization was carried out on a higher scale with **1t** (21.0 g) and 1.2 equivalents of **2**. In this case, we obtained 25.9 g of spiroindoline **3t** (92% yield) with d.r. 91:9, with the advantage that the pure major diastereomer(22.1 g) could be obtained readily by recrystallization of the reaction mixture [Scheme 3, Eq. (1); see the Supporting Information for details]. Furthermore, the protecting group on the indole nitrogen atom could be readily removed by $Pd(OH)_2/C$-catalyzed hydrogenation [Scheme 3, Eq. (2)]. Manipulation of the ester groups in the product **3t** could be performed without erosion of diastereoselectivity. With DIBAL-H, one of the two diastereotopic ester groups was reduced exclusively to give **6** [Scheme 3, Eq. (3)]. Also, one of the two ester groups could be decarboxylated stereoselectively, thus leading to product **7**, which accommodates four contiguous stereocenters, in 74% yield with d.r. 83:17 [Eq. (4)]. Compound **7** could be reduced with DIBAL-H to give **8** in 92% yield [Eq. (5)], and could be further deprotected/protected with Na/naphthalene and $(Boc)_2O$ to give **9** in 62% yield for two steps [Eq. (6)]. These transformations show the potential of the current reaction in organic synthesis.

To the best of our knowledge, the myrtoidine alkaloid 11-demethoxymyrtoidine, which was isolated from the stem bark of *Strychnos mostueoides* in 1999,[6] has never been synthesized in the laboratory owing to the limitation of effective and facile strategies for the stereoselective construction of the unique C3–$N_b$ ring system (Scheme 1). With compound **9** in hand, we attempted the synthesis of 11-demethoxymyrtoidine. Thus, intermediate **9** was converted into the α,β-unsaturated ester **10** through a two-step protocol with PhSeBr and $H_2O_2$ oxidation (52% yield for two steps). The reduction of ester **10** to the corresponding alcohol by using DIBAL-H (85% yield), followed by an Appel reaction, gave the allyl bromide **11** (95% yield). The etherification of allyl bromide **11** with tetronic acid derivative **12** led to intermediate **13** in 60% yield. A radical cyclization reaction was then performed to give the product **14**. X-ray diffraction analysis of

compound **14** indicated that the D and E rings are *trans*-fused, which meant that the core skeleton of 11-demethoxy-16-*epi*-myrtoidine had been built up. This isomer is probably formed because the steric hindrance of the indoline ring causes both the radical addition and the hydrogen abstraction to take place preferentially at the upper side of the olefin (see Scheme 4). Then, after the simple replacement of the Boc group with a methyl group, intermediate **15** was obtained in 51% yield for two steps. Deprotection of the benzyl group, followed by an acetylation step, afforded 11-demethoxy-16-*epi*-myrtoidine in 48% yield for two steps.




***Scheme 4.*** Synthesis of 11-demethoxy-16-*epi*-myrtoidine. Reagents and conditions: a) LDA, PhSeBr, THF, −78 °C; b) pyridine, $H_2O_2$, $CH_2Cl_2$, 0 °C, 52% for 2 steps; c) DIBAL-H, $CH_2Cl_2$, −78 °C, 85%; d) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 95%; e) DIPEA, **12**, $CH_2Cl_2$, 50 °C, 60%; f) AIBN, $nBu_3SnH$, benzene, 75 °C, 24%; g) TMSOTf, 2,6-lutidine, $CH_2Cl_2$; h) $Et_3N$, $CH_3I$, THF, 51% for 2 steps; i) Pd/C, $H_2$, MeOH/EtOAc; j) $Ac_2O$, AcOH, 48% for 2 steps. AIBN = azobisisobutyronitrile, DIPEA = *N*,*N*-diisopropylethylamine, LDA = lithium diisopropylamide, TMS = trimethylsilyl.

In summary, we have developed a new practical protocol for the elaboration of polycyclic indole alkaloids with high efficiency. This protocol provides rapid and concise access to versatile tetracyclic spiroindolines from readily available starting materials with excellent diastereoselectivity by the use of $InCl_3$ as a catalyst (21 examples, up to 95% yield and up to d.r. > 95:5). This reaction is a remarkable method for the construction of important indole alkaloids, as it shows broad scope, occurs under mild conditions, can be readily scaled up to a gram scale, and provides products that can be transformed further in multiple ways. The current reaction enabled a concise synthesis of 11-demethoxy-16-*epi*-myrtoidine and could potentially be used for the rapid construction of other myrtoidine alkaloids.

## Experimental Section

Typical procedure: A solution of **1a** (106.3 mg, 0.3 mmol) in dry $CH_2Cl_2$ (1.0 mL) was added in one portion to a stirred suspension of $InCl_3$ (3.3 mg, 0.015 mmol) and 4 Å molecular sieves (200 mg) in dry $CH_2Cl_2$ (2.0 mL) at room temperature under an Ar atmosphere in a Schlenk tube, and then a solution of dimethyl 2-methylenemalonate (129.7 mg, 0.9 mmol) in dry $CH_2Cl_2$ (1.0 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature, and when the reaction was complete, the suspension was filtered through a glass funnel with a thin layer (ca. 20 mm) of silica gel (100–200 mesh) and eluted sequentially with $CH_2Cl_2$ (ca. 50 mL) and EtOAc (ca. 100 mL). The filtrate was concentrated under reduced pressure, and the diastereomeric ratio of the resulting crude product mixture was determined by $^1H$ NMR spectroscopy (d.r. 95:5). Purification by silica-gel column chromatography (*n*-hexane/ethyl acetate/$CH_2Cl_2$, *v*/*v*/*v* 7:1:1) gave **3a** (134.9 mg, 90% yield).

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**Keywords:** diastereoselectivity · indole alkaloids · polycyclic indolines · tandem reactions · tryptamine derivatives

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