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Catalytic [2+2+2] Tandem Cyclization with Alkyl Substituted Methylene Malonate Enabling Concise Total Synthesis of Four Malagasy Alkaloids

Yu-Jing Cheng[1], Liu-Peng Zhao[1], Lijia Wang[1,2]* & Yong Tang[1]*

[1]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032,* [2]*Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, Shanghai Frontiers Science Center of Molecule Intelligent Syntheses, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062*

**Corresponding authors: ljwang@chem.ecnu.edu.cn; tangy@sioc.ac.cn*

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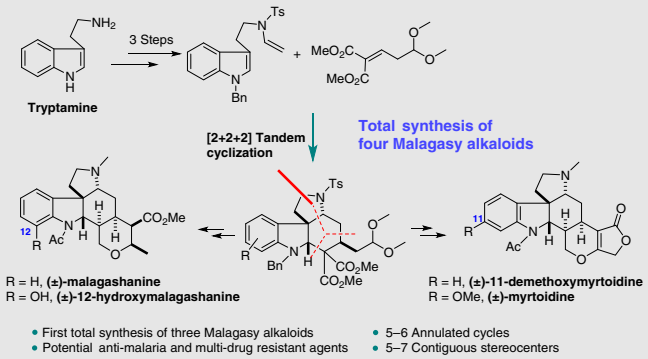
Myrtoidine and malagashanine, highly complex indole alkaloids, are effective adjuvants in developing cures for plasmodium malaria and potent multi-drug resistant agents. Despite nearly 30 years of progress, myrtoidine and the related family of Malagasy alkaloids still present formidable challenges for synthetic chemists. Here, we developed a diastereoselective [2+2+2] tandem cyclization reaction with alkyl-substituted methylene malonate, enabling highly efficient collective total synthesis of four Malagasy alkaloids from commercially available tryptamines within 10–13 steps. The synthetic strategy included rapid and highly stereoselective assembly of the tetracyclic indoline core containing 5–7 contiguous stereogenic carbon centers, rarely seen in indole alkaloids. Among the four natural products, (±)-myrtoidine, (±)-11-demethoxymyrtoidine, and (±)-12-hydroxymalagashanine were synthesized for the first time, and the work on (±)-malagashanine represented the shortest synthetic route so far. Our current study should enable further explorations of chemical and biological spaces based on myrtoidine, malagashanine, and related natural products.



Keywords: tandem cyclization, [2+2+2], methylene malonate, indole alkaloids, myrtoidine, malagashanine

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Introduction

Throughout every milestone in the development of synthetic chemistry, the continuous pursuit of a more accurate and efficient synthesis of target molecules is the driving force of the advancement and progress of this research area. In 2016, we reported a diastereoselective [2+2+2] tandem cyclization reaction of tryptamine derivative with methylene malonate and constructed the tetracyclic spiroindoline skeleton (rings A–D) successfully in one step, which is the core structure of many important biologically active indole alkaloids.[1] Our methodology provided a promising opportunity for the concise synthesis of various indole alkaloids from simple starting materials. Among those indole alkaloids, the Malagasy family of alkaloids **1**–**4** are a series of polycyclic indoline molecules with a unique stereochemical core structure (Figure 1).[2-4] Unlike most monoterpene indole alkaloids with a characteristic tetracyclic indoline skeleton, such as strychnine and aspidospermidine,[5-11] the *trans*-fused rings C/D (Figure 1) of the Malagasy alkaloids bring greater rigidity and distorted ring tension to the entire molecular structure, making the stereoselective construction of the C3 site very challenging. Although there are several efficient methods for constructing the tetracyclic indoline skeletons,[12-26] only a few achieved the unique C3-stereoselectivity.[27-29] Considering their sophisticated structure and great potential as lead compounds in multi-drug resistant diseases, the Malagasy alkaloids have been attractive synthetic targets.[30-32] Our previous attempts of using the [2+2+2] reaction for the total synthesis of Malagasy alkaloids were unsuccessful;[33-35] instead, 11-demethoxy-16-*epi*-myrtoidine was obtained.[1] In the past 6 years, further attempts on the stereoselective construction of rings E and F by altering the total synthesis routes have been made, but unfortunately, hundreds of trials have been unsuccessful (see Supporting Information Schemes S1–S4 for details). To learn from the failure, we recognized that it is imperative to customize an advanced methodology for the target molecules of Malagasy alkaloids. Herein, we report a newly designed [2+2+2] tandem cyclization with a substituted methylene malonate substrate.[36-41] Using this new methodology, we constructed four stereogenic centers with desired stereochemistry in one step and successfully applied the method to the first total synthesis of (±)-myrtoidine (**4**), (±)-11-demethoxymyrtoidine (**3**), (±)-12-hydroxymalagashanine (**2**), and the shortest total synthesis of (±)-malagashanine (**1**) so far.

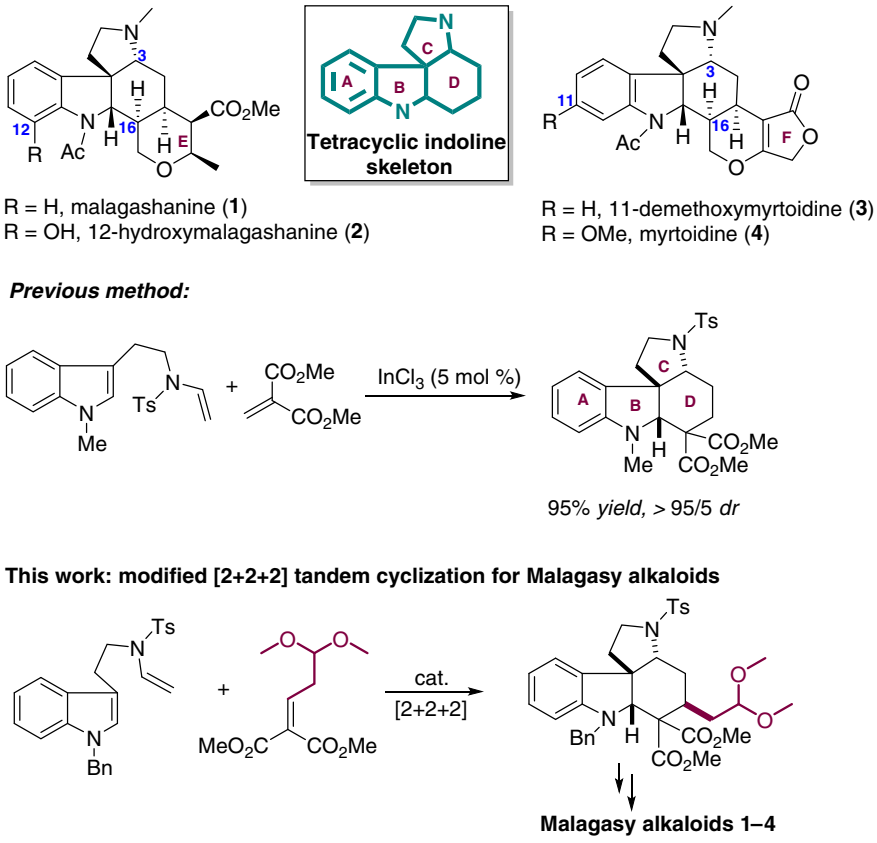

Figure 1 | *Malagasy alkaloids synthesis and [2+2+2] tandem cyclization.*

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Results and Discussion

Optimization and substrate scope

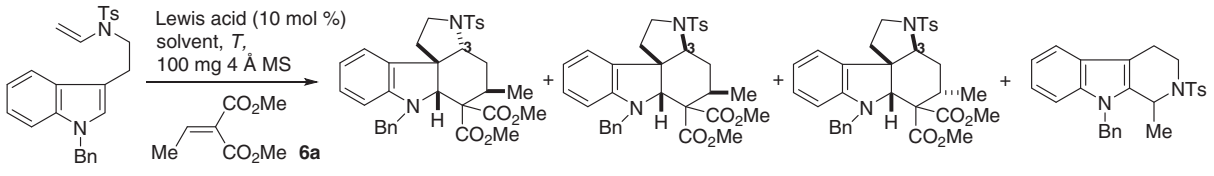
We first started with the preparation of vinyl sulfonamide **5** in three steps from tryptamine, which showed good reactivity with methylene malonate, affording the tetracyclic spiroindoline skeleton of Malagasy alkaloids. The challenge lied in replacing methylene malonate with substituted methylene malonate **6a**, which was less reactive than the former. Moreover, the reaction showed an unexpected decrease in diastereoselectivity. As shown in Table 1, starting from **5a** with β-ethylidenemalonate **6a**, we first employed $InCl_3$ as Lewis acid in dichloromethane (DCM) for the [2+2+2] tandem cyclization reaction at room temperature, which was the optimal reaction conditions for a previous similar reaction[1]; however, 87% yield with only 75:25 dr at C3 was obtained (entry 1, Table 1). When the reaction temperature was lowered to 0 °C, a sharp decrease of the [2+2+2] reaction product yield was observed with $InCl_3$, and quantitative conversion of **5a** to the intramolecular cyclization product **8a** was observed instead (entry 2). To minimize the intramolecular cyclization reaction and increase the desired ***trans*-7a** product, extensive screening of Lewis acids and solvents was conducted (entries 3–7, see Supporting Information Tables S9 and S10 for details). We found that by lowering the reaction temperature to 0 °C with catalytic $InBr_3$, the desired tetracyclic spiroindoline was forged in 86% yield with excellent diastereoselectivity (>95:5 dr) after 1 h (entry 8), although it delivered poor diastereoselectivity at room temperature (entry 5). Remarkably, the relative configurations of the resulting four stereogenic centers were in accord with the target natrual products, as confirmed by single-crystal X-ray diffraction studies (see Supporting Information Table S11 for details).

The aforementioned observation stimulated us to explore the substrate scope (Table 2). By introducing substituents on the phenyl ring of indole, such as fluoro- and methyl-groups, good yields with excellent diastereoselectivity were obtained. Aiming to synthesize Malagasy alkaloids, the olefin substrate **6b** bearing a pendant acetal side-chain was developed. The grand challenges were feasibility and efficiency since the newly designed olefin substrate (**6b**) bore more labile and bulky functional groups. To our delight, employing **6b**, the core structure **7d** for the total synthesis of Malagasy alkaloids was constructed in 82% yield with 92:8 dr on a gram scale. However, 11-methoxy substituted substrate led to the undesired intramolecular cyclization product, 11-bromo product **7e** was obtained in 70% yield with 91:9 dr. Introducing methoxy substituent at the C12 position, the [2+2+2] reaction served well to yield the corresponding products **7f** in high efficiency (76% yield) with increased catalyst loading.

Total synthesis of (±)-malagashanine (1) and (±)-11-demethoxymyrtoidine (3)

The limited natural sources of Malagasy alkaloids, together with their great potential as lead compounds in multi-drug resistant diseases, stimulated us to develop

Table 1 | *Optimization of the [2+2+2] Tandem Cyclization Reaction*[a]



Entry	Lewis Acid	Solvent	*T* (°C)	Yield (%)[b]	dr[c] (***trans*:*cis***)
1	$InCl_3$	DCM	25	87	75:25
2[d]	$InCl_3$	DCM	0	Trace	—
3	$FeCl_2$	DCM	25	Trace	—
4	$CuBr_2$	DCM	25	Trace	—
5	$InBr_3$	DCM	25	82	64:36
6	$InBr_3$	Toluene	25	53	77:23
7	$InBr_3$	THF	25	Trace	—
8	$InBr_3$	DCM	0	86	>95:5

[a] Conditions: **5a** (0.2 mmol), **6a** (0.6 mmol), Lewis acid (0.02 mmol), solvent (2.0 mL), 100 mg 4 Å MS, 1 h.
[b] Isolated yield of **7a** after flash chromatography.
[c] Determined by ^{1}H NMR analysis of the crude product, dr = ***trans*-7a**:(***cis*-7a**+***cis*-7a'**).
[d] >95% yield of **8a** was detected by crude ^{1}H NMR analysis.

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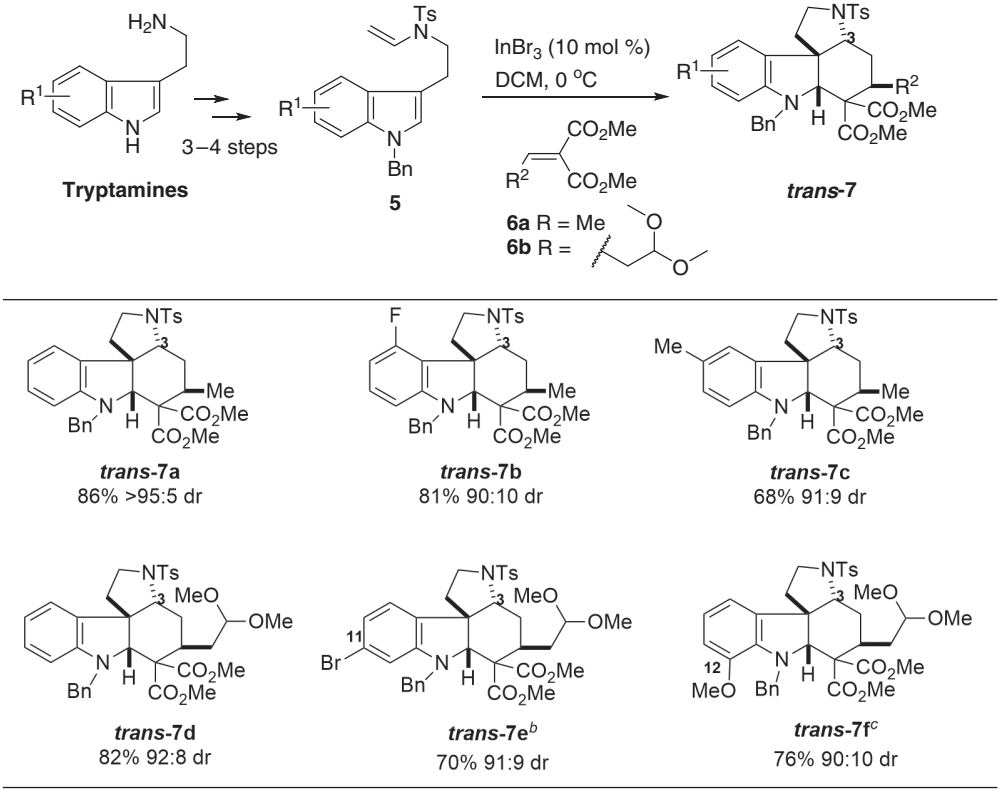
Table 2 | *Substrate Scope for the [2+2+2] Tandem Cyclization Reaction*[a]



[a] Isolated yield after flash chromatography; dr was determined by ^{1}H NMR analysis of the crude product.
[b] 30 mol % of InI_3 was used.
[c] 50 mol % of $InBr_3$ was used.

efficient synthetic routes for this family of natural products. Our synthetic routes for (±)-malagashanine (**1**) and (±)-11-demethoxymyrtoidine (**3**) are shown in Scheme 1. Highly stereoselective mono-decarboxylation of ***trans*-7d** followed by in situ treatment with diisobutyl aluminum hydride (DIBAL-H) led to the corresponding alcohol, which was further converted to lactone **9** via a one-pot transformation. The reaction included deacetylation initiated by trifluoroacetic acid (TFA), intramolecular acetylation of the newly generated aldehyde with alcohol, followed by an in situ Dess–Martin periodinane (DMP) oxidation in 36% overall yield with >99/1 dr. The relative configuration of **9** was determined by single-crystal X-ray crystallography of the mono-decarboxylation product **int-7d** (see Supporting Information Table S12 for details). **9** was deprotonated by lithium bis(trimethylsilyl)amide (LHMDS) and treated with Mander's reagent,[42] then an exocyclic olefin product was generated in situ with Tebbe's reagent,[43] which was isomerized in situ to form the internal olefin **10** after quenching the reaction mixture with NaOH aqueous solution and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Switching the *N*-indole protecting group from Bn- to Ac- by hydrogenation and acetylation led to a late-stage common intermediate **11** in 95% yield. The *N*-Ts group of **11** was removed by sodium/naphthalene at low temperature, and then formalin and formic acid solution were added in situ, followed by sodium triacetoxyborohydride for reductive amination. Gratifyingly, this approach was very efficient for the methylation of the exposed nitrogen atom. Finally, the *cis*-hydrogenation was conducted using the crude quaternary olefin with Raney nickel, following Blakey's procedure,[34] completing the total synthesis of (±)-malagashanine (**1**) successfully in 10 steps with an overall 9.1% yield, counting from the commercially available tryptamine (Scheme 1).

To construct ring F, increasing the oxidation level to the methyl group of **11** became a priority. Direct allylic oxidation with Davis reagent[44–46] failed to produce the desired allyl alcohol, while the unsuccessful exocyclic olefin (an aforementioned intermediate generated with Tebbe's reagent) epoxidation disappointed us for the plan of epoxide ring-opening (see Supporting Information Schemes S5 and S6 for details). To our delight, when Riley oxidation[47,48] was tried, ring F was closed spontaneously to give **19** in 50% yield via intramolecular lactonization with an in situ generated oxidative product at 140 °C. However, further deprotection of the *N*-Ts group was unsuccessful due to the poor tolerance of the newly formed lactone

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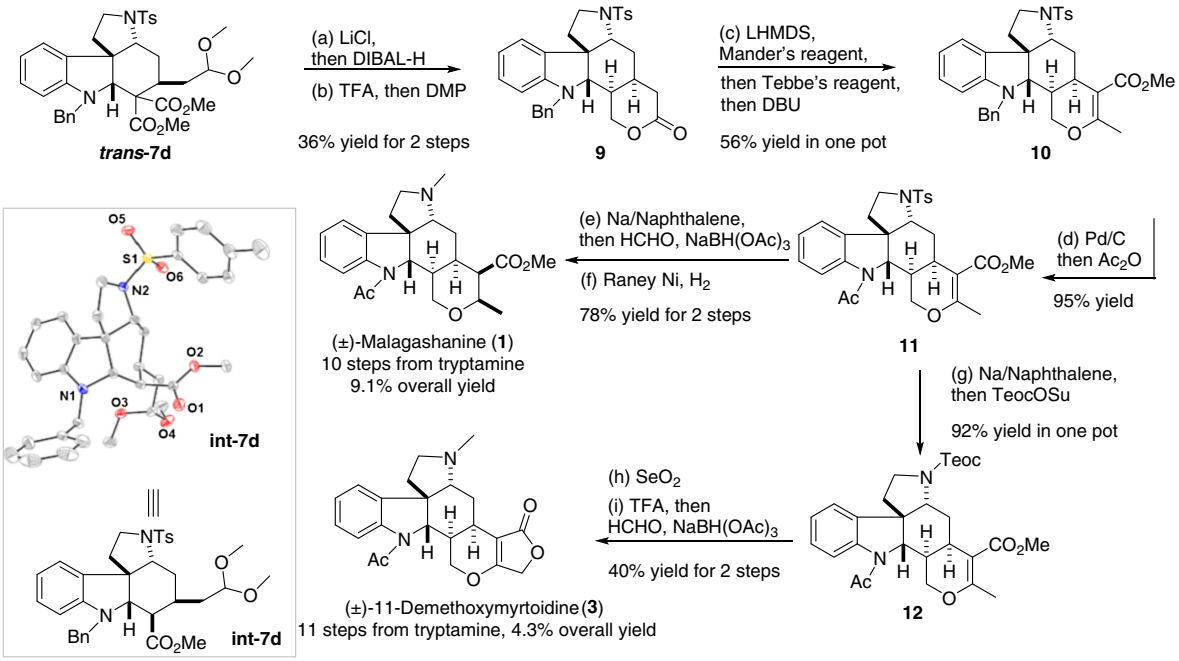
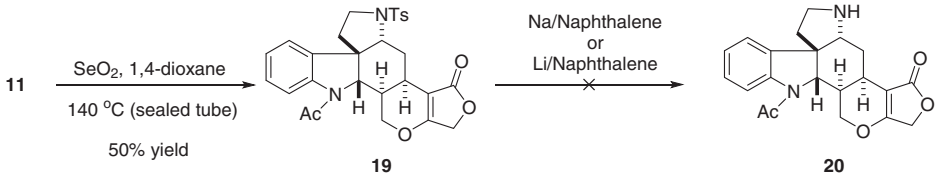


Scheme 1 | *Total synthesis of (±)-malagashanine (**1**) and (±)-11-demethoxymyrtoidine (**3**). Reagent and conditions: (a) LiCl (6.0 equiv), H_2O (6.0 equiv), DMF, 135 °C, 10 h; then DIBAL-H (4.0 equiv), DCM, –78 °C, 2 h; (b) TFA (50.0 equiv), DCM, 0 °C, 24 h; then DMP (1.0 equiv), $NaHCO_3$ (4.0 equiv), DCM, rt, 2 h, 36% for 2 steps; (c) LHMDS (1.1 equiv), $NCCO_2Me$ (1.1 equiv), tetrahydrofuran (THF), –78 °C, 8 h; then Tebbe's reagent (1.5 equiv), pyridine (4.0 equiv), THF, –20 °C to rt, 12 h; then 10 wt % NaOH aqueous (1.0 equiv), DBU (10.0 equiv), THF/toluene, –20 to 60 °C, 2 h, 50%; (d) Pd/C (1.0 equiv), H_2 (1 atm), THF, rt, 24 h; then Ac_2O (20.0 equiv), pyridine (40.0 equiv), THF, rt, 10 h, 95%; (e) Na (6.0 equiv), Naphthalene (6.0 equiv), THF, –78 °C, 1 h; then HOAc (10.0 equiv), 37 wt % formalin (4.0 equiv), $NaBH(OAc)_3$ (4.0 equiv), DCM, rt, 2 h; (f) Raney Ni (excess), H_2 (110 atm), MeOH, rt, 5 d, 78% for 2 steps; (g) Na (6.0 equiv), Naphthalene (6.0 equiv), THF, –78 °C, 1 h; then HOAc (6.0 equiv), TeocOSu (4.0 equiv), Et_3N (10.0 equiv), DCM, rt, 12 h, 92%; (h) SeO_2 (2.0 equiv), 1,4-dioxane, 140 °C, 10 h (sealed tube); (i) TFA (20.0 equiv), DCM, rt, 1 h; then 37 wt % formalin (4.0 equiv), $NaBH(OAc)_3$ (4.0 equiv), DCM, rt, 12 h, 40% for 2 steps.*



Scheme 2 | *A failed attempt of Malagasy alkaloids synthesis from 11 to 20.*

ring in the Na/naphthalene system (Scheme 2). Switching the *N*-Ts group to the *N*-Teoc group by a single electron reduction with Na/naphthalene, followed by in situ treatment with TeocOSu, gave **12** in 92% yield. Using SeO_2 as an oxidant, the construction of ring F proceeded smoothly. After removing the protecting group, the target natural product (±)-11-demethoxymyrtoidine (**3**) was obtained via reductive methylamination with formalin and $NaBH(OAc)_3$. The first total synthesis of (±)-12-hydroxymalagashanine was completed with an overall yield of 4.3% in 11 steps, counting from commercially available tryptamine (Scheme 1).

Total synthesis of (±)-12-hydroxymalagashanine (2)

Encouraged by these results, we continued to explore the total synthesis of (±)-12-hydroxymalagashanine (**2**, Scheme 3). Following a similar approach, ***trans*-7f** was converted readily to the acetal product **13** in 91% yield

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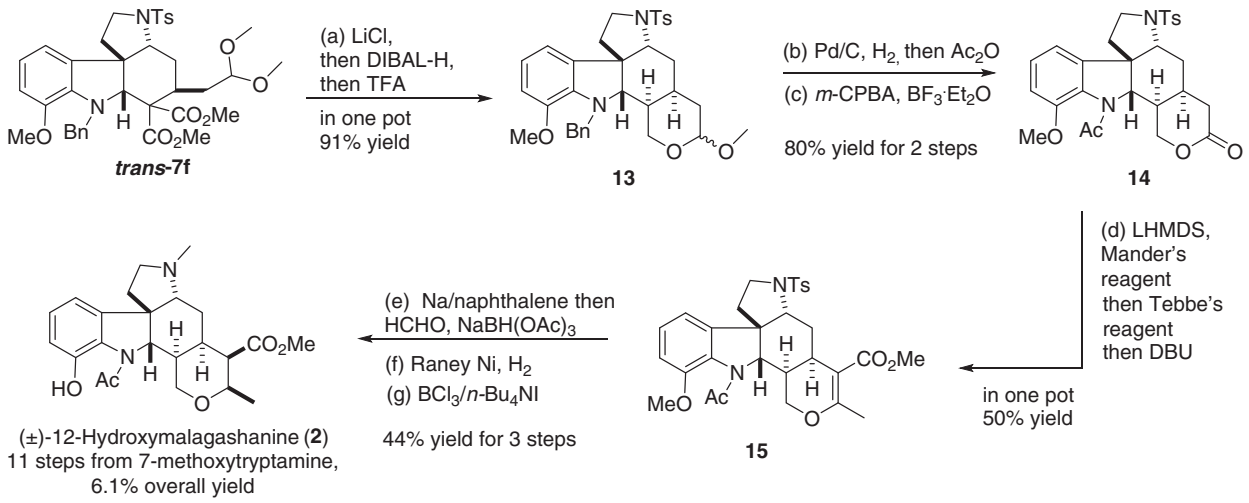

Scheme 3 | *Total synthesis of (±)-12-hydroxymalagashanine (**2**). Reagent and conditions: (a) LiCl (6.0 equiv), H_2O (6.0 equiv), DMF, 135 °C, 10 h; then DIBAL-H (4.0 equiv), DCM, –78 °C, 2 h; then MeOH (excess), TFA (50.0 equiv), 0 °C, DCM, 12 h, 91%; (b) Pd/C (1.0 equiv), H_2 (1 atm), THF, rt, 24 h; then Ac_2O (20.0 equiv), pyridine (40.0 equiv), THF, rt, 10 h; (c) m-CPBA (3.0 equiv), $BF_3{\cdot}Et_2O$ (2.0 equiv), DCM, 0 °C, 24 h, 80% for 2 steps; (d) LHMDS (1.1 equiv), $NCCO_2Me$ (1.1 equiv), THF, –78 °C, 8 h; then Tebbe's reagent (1.5 equiv), pyridine (4.0 equiv), THF, –20 °C to rt, 12 h; then 10 wt % NaOH aqueous (1.0 equiv), DBU (10.0 equiv), THF/toluene, –20 to 60 °C, 2 h, 50%; (e) Na (6.0 equiv), naphthalene (6.0 equiv), THF, –78 °C, 1 h; then HOAc (10.0 equiv), 37 wt % formalin (4.0 equiv), $NaBH(OAc)_3$ (4.0 equiv), DCM, rt, 2 h; (f) Raney Ni (excess), H_2, MeOH, 110 bar, rt, 5 d; (g) BCl_3 (6.0 equiv)/n-Bu_4NI (1.3 equiv), DCM, –78 °C (1 h) to rt (4 h), 44% for 3 steps.*

with >99/1 dr. However, a further transformation of **13** to the corresponding lactone by DMP failed. Other oxidation conditions such as Swern oxidation, pyridinium chlorochromate (PCC) oxidation, *m*-chloroperbenzoic acid (*m*-CPBA)/$BF_3{\cdot}Et_2O$ oxidation, and so on, were attempted with no luck. This problem was finally solved by changing the indole *N*-Bn group to a smaller *N*-Ac group, which resulted in successful oxidation with *m*-CPBA/$BF_3{\cdot}Et_2O$ to afford lactone **14** in two steps and 80% yield. Similar methods were employed to transform **14** to the corresponding (±)-12-methoxymalagashanine, which, upon treatment with BCl_3/*n*-Bu_4NI,[49] was converted to the desired natural product **2**. The first total synthesis of (±)-12-hydroxymalagashanine was completed with an overall 6.1% yield in 11 steps, counting from commercially available 7-methoxytryptamine (Scheme 3).

Total synthesis of (±)-myrtoidine (4)

In the wake of the success of the total synthesis of **1-3**, studies on the total synthesis of (±)-myrtoidine (**4**), the last member of the Malagasy alkaloids, were addressed. Following the same strategy, ***trans*-7e** was transformed to **16** smoothly in 92% yield as a single diastereomer, and then the bromo-substituent was converted to MeO- group by Ullmann ether synthesis.[50–52] Although attempts on DMP oxidation of the corresponding acetal exhibited poor efficiency even in the presence of pyridine buffer,[53,54] tetra-*N*-propylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) proved to be a suitable oxidation system, giving lactone **17** smoothly.[55] Following a similar protocol in the synthesis of **3**, **18** was obtained from **17** in 3 steps and 33% yield. Finally, **4** was synthesized by a tandem Riley oxidation/*N*-Teoc group conversion to the *N*-Me group. The first total synthesis of (±)-myrtoidine was completed in 13 steps, with an overall 3.3% yield, counting from commercially available 6-bromotryptamine (Scheme 4).

Conclusion

We have designed and developed a highly diastereoselective catalytic [2+2+2] tandem cyclization reaction with alkyl-substituted methylene malonate, which enabled the collective total synthesis of Malagasy alkaloids **1-4** in high efficiency from simple starting materials and concise routes. This work further demonstrated the power of the [2+2+2] tandem cyclization in the context of total synthesis with four Malagasy alkaloids obtained from tryptamine in 10–13 steps. The [2+2+2] reaction for constructing the consecutive stereogenic centers, although always challenging, could serve as a source of inspiration for an innovative strategy for monoterpene indole alkaloids. In addition, the approach for building the E and F rings opens up a new avenue toward synthesizing lactones-fused tetrahydropyran structure. Further, the

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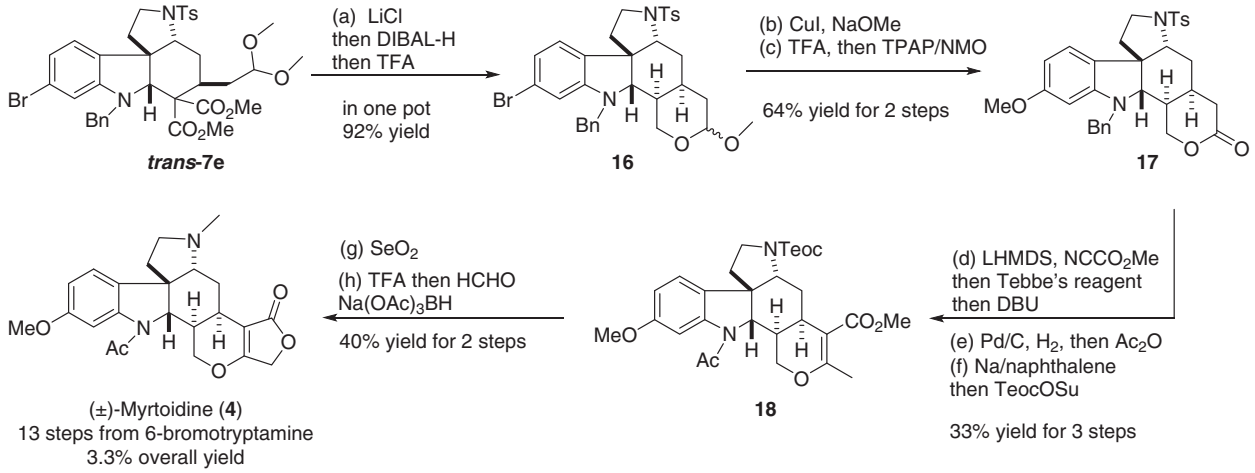

Scheme 4 | *Total synthesis of (±)-myrtoidine (**4**). Reagent and conditions: (a) LiCl (6.0 equiv), H_2O (6.0 equiv), DMF, 135 °C, 10 h; then DIBAL-H (4.0 equiv), DCM, –78 °C, 2 h; then MeOH (excess), TFA (50.0 equiv), 0 °C, DCM, 12 h, 92%; (b) CuI (4.0 equiv), NaOMe (10.0 equiv), MeOH/DMF, 120 °C, 12 h; (c) TFA (50.0 equiv), DCM, 0 °C, 24 h; then TPAP (0.1 equiv), NMO (2.0 equiv), DCM, rt, 2 h, 64% for 2 steps; (d) LHMDS (1.1 equiv), $NCCO_2Me$ (1.1 equiv), THF, –78 °C, 8 h; then Tebbe's reagent (1.5 equiv), pyridine (4.0 equiv), THF, –20 °C ~rt, 12 h; then 10 wt % NaOH aqueous (1.0 equiv), DBU (10.0 equiv), THF/toluene, –20 to 60 °C, 2 h; (e) Pd/C (1.0 equiv), H_2 (1 atm), THF, rt, 24 h; then Ac_2O (20.0 equiv), pyridine (40.0 equiv), THF, rt, 10 h; (f) Na (6.0 equiv), naphthalene (6.0 equiv), THF, –78 °C, 1 h; then HOAc (6.0 equiv), TeocOSu (4.0 equiv), Et_3N (10.0 equiv), DCM, rt, 12 h, 33% for 3 steps; (g) SeO_2 (2.0 equiv), 1,4-dioxane, 140 °C, 10 h (sealed tube); (h) TFA (20.0 equiv), DCM, rt, 1 h; then 37 wt % formalin (4.0 equiv), $NaBH(OAc)_3$ (4.0 equiv), DCM, rt, 12 h, 40% for 2 steps.*

application of this strategy in the total synthesis of other monoterpene indole alkaloids is underway and will be reported in due course.

Supporting Information

Supporting Information is available and includes experimental procedures, substrates preparation procedures, optimization details, characterizations and analytical data of products, X-ray structures, and NMR spectra.

Conflict of Interest

There is no conflict of interest to report.

Funding Information

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