



Original article

Formal synthesis of (+)-tashiromine and study toward the total synthesis of (+)-stemoamide



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ABSTRACT

An efficient formal synthesis of (+)-tashiromine was achieved by employing an intermolecular asymmetric Mannich-type reaction as the key step. Concurrently, a novel approach toward the total synthesis of (+)-stemoamide through dyotropic rearrangement of 3,4-*cis*- β -lactone was also explored.

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1. Introduction

The *Stemona* alkaloids represent a group of natural products isolated from the plants named *Stemonaceae*. Over 120 structurally diverse compounds have been identified so far, and many of them display unique molecular architectures and biological profiles [1,2]. As one representative member of *Stemona* alkaloids, stemoamide (**1**, Scheme 1) was isolated from *Stemona tuberosa* Lour, a Chinese traditional medicine that has been used for the treatment of respiratory diseases, such as asthma, bronchitis, and tuberculosis [3]. Owing to its novel chemical structure and prominent biological activities, stemoamide has stimulated extensive synthetic efforts [4]. However, although much progress has been achieved in this field, most of the synthetic routes toward stemoamide take long linear sequences and result in racemic synthesis. Therefore, the development of more efficient and asymmetric approach for the synthesis of stemoamide remains a considerable synthetic challenge.

Recently, we have developed a novel approach for the syntheses of enantiopure, trisubstituted γ -butyrolactones via the dyotropic rearrangement of 3,4-*cis*- β -lactones [5]. As the proof-of-concept case, the total syntheses of a number of xanthanolides natural products (e.g., 11 α ,13-dihydroxanthatin) were achieved (Scheme 1A). From the structural point of view, both xanthanolides and

stemoamide feature a characteristic trisubstituted γ -butyrolactone moiety that is *trans*-fused with a seven-membered ring. Such structural similarity led us to assume that the 5-7-5 tricyclic core of stemoamide could also be made from the chiral β -lactone **2** through a dyotropic rearrangement, as depicted in Scheme 1B. We envisioned that the concerted nature of dyotropic rearrangement in conjunction with the rationally arranged stereochemistry of **2** (the migrating C4–C8 bond and C9–O2 bond positioned in the anti-periplanar relationship) could ensure the proposed transformation to occur in the desired manner. To validate the assumption, the asymmetric synthesis of β -lactone **2** is required, which might be achieved through an asymmetric ketene-aldehyde [2+2] cycloaddition from the aldehyde **3**. In turn, **3** could be derived from the alcohol **4** via oxidation.

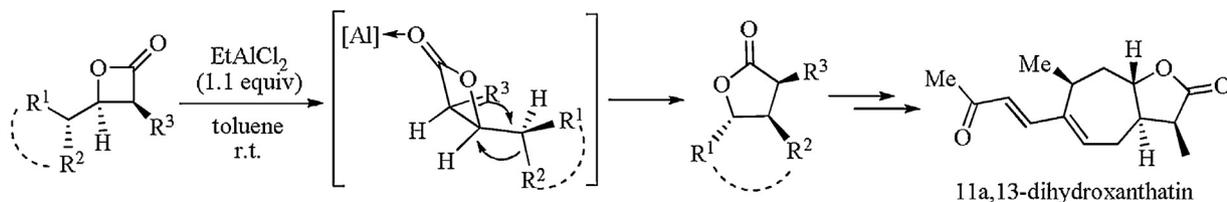
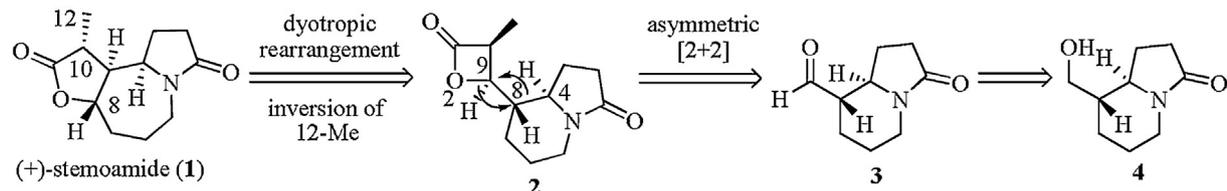
2. Experimental

The procedure for preparation of all the intermediates in Scheme 2 and Scheme 3 are included in the Supporting information, and some selected examples (for compounds **9**, **4** and **2**) are listed as below:

Synthesis of compound 9: To a solution of compound **7** (50 mg, 0.14 mmol, 1.0 equiv.) in DCM (2.5 mL) at 0 °C was added TiCl₄ (0.03 mL, 0.27 mmol, 2.0 equiv.), and the reaction mixture was stirred for 5 min. After cooling to –30 °C, the reaction mixture was treated with a solution of diisopropylethylamine (DIPEA) (0.026 mL, 0.15 mmol, 1.2 eq.) in CH₂Cl₂ (1 mL), and then stirred for 40 min. The reaction mixture was further cooled to –78 °C, and

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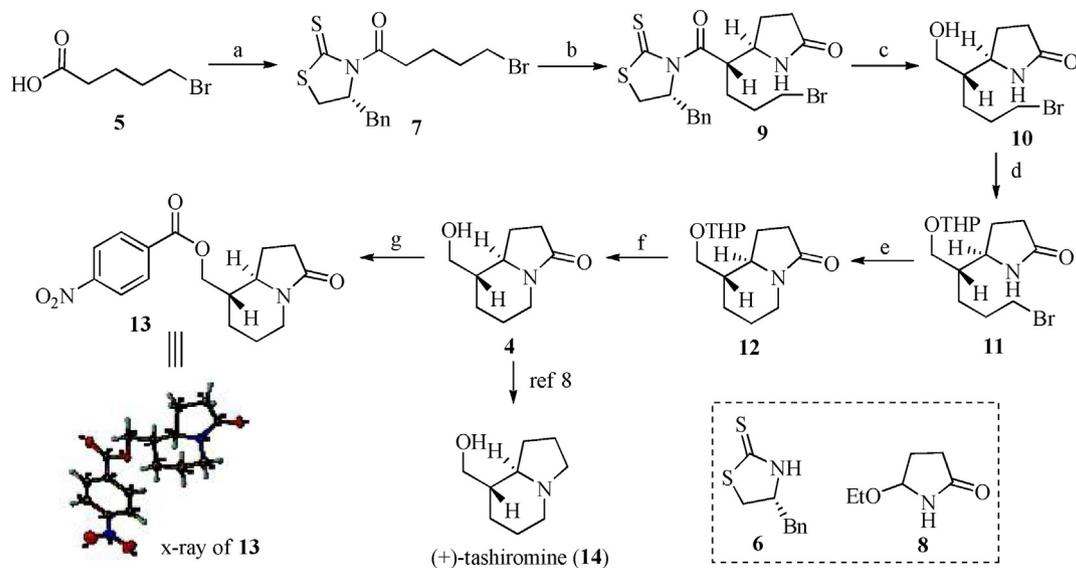
1A: Dyotropic rearrangement of 3,4-*cis*- β -lactone (previous work)1B: Proposed synthetic strategy towards stemoamide *via* dyotropic rearrangementScheme 1. Dyotropic rearrangement of 3,4-*cis*- β -lactone and synthetic strategy toward stemoamide.

a solution of compound **8** in CH_2Cl_2 (0.5 mL) was added. After 10 min, the reaction mixture was allowed to warm to 0°C and kept stirring for 6 h before it was quenched with saturated NH_4Cl . The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (DCM/EtOAc, 3:1) to afford compound **9** as yellow oil (60 mg, 91%). $[\alpha]_{\text{D}}^{25} -216.1$ (c 1.4, CH_2Cl_2); $R_f = 0.62$ (silica gel, DCM/EtOAc, 3:2); IR (film, cm^{-1}): ν_{max} 2121, 1691, 1502, 1257, 1165, 829; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.26–7.34 (m, 5H), 6.18 (s, 1H), 5.36–5.41 (m, 1H), 4.93 (m, 1H), 4.05 (dd, 1H, $J = 12.0, 6.4$ Hz), 3.34–3.38 (m, 3H), 3.20 (d, 1H, $J = 12.8$ Hz), 3.02–3.07 (m, 1H), 2.95 (d, 1H, $J = 12.0$ Hz), 2.24–2.38 (m, 3H), 1.98–2.06 (m, 1H), 1.67–1.90 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 202.6, 177.9, 175.3, 136.1, 129.5, 129.0, 127.5, 68.8, 55.2, 46.1, 37.1, 32.8, 32.5, 30.3, 29.8, 26.9, 24.3; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{25}\text{BrN}_2\text{O}_2\text{S}_2$: 457.0437, found: 457.0437.

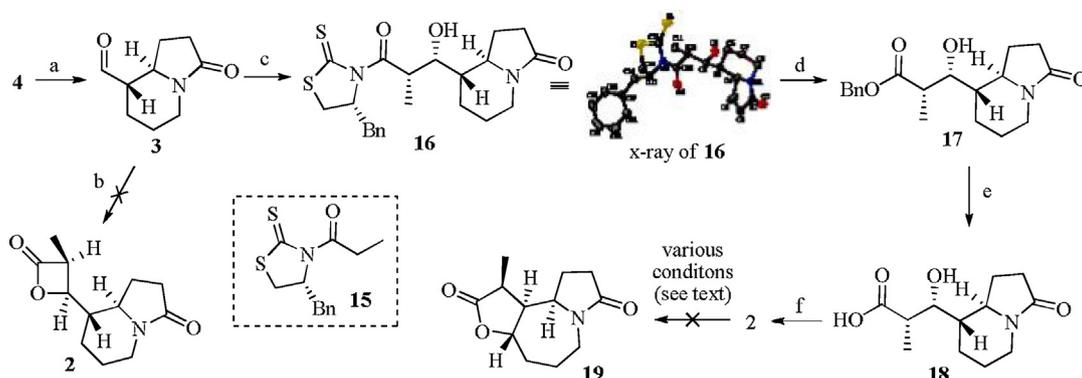
Synthesis of compound **4**: A solution of compound **12** (253 mg, 1 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (25 mg, 0.1 mmol,

0.1 equiv.) in methanol (4 mL) was stirred at room temperature for 3 h. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (DCM/EtOAc, 1:1) to afford compound **4** as colorless oil (150 mg, 90%). $[\alpha]_{\text{D}}^{25} +85.0$ (c 1.3, acetone); $R_f = 0.33$ (silica gel, DCM/MeOH, 20:1); IR (film, cm^{-1}): ν_{max} 3386, 2920, 1661, 1460, 1369, 1050, 731; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.13 (dd, 1H, $J = 12.8, 4.4$ Hz), 3.57–3.69 (m, 2H), 3.24–3.28 (m, 1H), 2.53–2.60 (m, 1H), 2.28–2.39 (m, 3H), 1.92–1.96 (m, 1H), 1.67–1.76 (m, 4H), 1.29–1.43 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 173.9, 59.2, 46.1, 40.0, 30.6, 27.1, 24.6, 24.1; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{15}\text{NO}_2$: 170.1176, found: 170.1177.

Synthesis of compound **2**: A suspension of compound **16** (20 mg, 0.09 mmol, 1.0 equiv.) in DCM (2 mL) was treated with Et_3N (0.04 mL, 0.27 mmol, 3 equiv) and BOP-Cl (33 mg, 0.13 mmol, 1.5 equiv.) at 23°C . After stirring for 2 h, the resulting reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were dried and concentrated *in vacuo*. The residue was submitted to chromatograph (DCM/MeOH, 20:1) to afford the pure product **2** as white



Scheme 2. Reagents and conditions: (a) $(\text{COCl})_2$, DMF, DCM, r.t., then **6**, Et_3N , r.t., 80%; (b) TiCl_4 , DIPEA, then **8**, DCM -78°C ; (c) NaBH_4 , MeOH, r.t., 60% for two steps; (d) 3,4-dihydro-2-pyran, *p*-toluenesulfonic acid pyridine salt, DCM, r.t.; (e) NaH , THF, r.t., 89% for two steps; (f) *p*-toluenesulfonic acid, MeOH, r.t., 90%; (g) 4-nitrobenzoyl chloride, Et_3N , DCM, r.t., 80%.



Scheme 3. Reagents and conditions: (a) DMP, DCM, r.t., 80%; (b) TMSQ, LiClO₄, propionyl chloride, DCM, -40 °C; (c) TiCl₄, DIPEA, NMP, **15**, DCM, -78 °C, 35%; (d) BnOH, DMAP, DCM, 60%; (e) H₂, Pd/C, MeOH, r.t.; (f) BOP-Cl, Et₃N, DCM, r.t., 50%.

solid (10 mg, 50%). $[\alpha]_D^{25} +22.1$ (c 0.6, CH₃Cl); $R_f = 0.30$ (silica gel, DCM/MeOH, 20:1); IR (film, cm⁻¹): ν_{\max} 2958, 1821, 1764, 1677, 1442, 1270, 1144, 1114, 759; ¹H NMR (400 MHz, CDCl₃): δ 4.48 (dd, 1H, $J = 6.4, 4.4$ Hz), 4.08–4.17 (m, 1H), 3.85–3.88 (m, 1H), 3.30–3.36 (m, 1H), 2.58–2.64 (m, 1H), 2.36–2.40 (m, 1H), 2.22–2.33 (m, 1H), 2.00–2.04 (m, 1H), 1.83–1.86 (m, 1H), 1.56–1.66 (m, 5H), 1.42–1.49 (m, 2H), 1.38 (d, 3H, $J = 7.6$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 173.7, 171.6, 74.8, 59.4, 47.9, 42.8, 40.0, 30.3, 29.8, 25.5, 24.8, 23.6; HRMS (ESI) m/z [M+Na]⁺ calcd. for C₁₂H₁₇NO₃: 224.1281, found: 224.1280.

3. Results and discussion

We initiated our study by preparing the enantiopure compound **4**. Although several racemic syntheses of **4** were documented [6,7], to date only one asymmetric synthesis of (+)-**4** has been achieved, which required 11 linear steps and resulted in 18% overall yield [8]. To keep our synthesis as concise as possible, we developed a new approach to access (+)-**4**, as described in Scheme 2. Thus, treatment of the acid **5** with oxalyl chloride provided the corresponding acid chloride, which was coupled with thiazolidinethione **6** in the presence of Et₃N to give compound **7** in 80% yield. The Lewis acid-promoted Mannich-type reaction between **7** and ethoxy-2-pyrrolidine **8** proceeded with high diastereoselectivity to afford compound **9** [9], which after treatment with NaBH₄/MeOH, gave the alcohol **10** in 60% yield for two steps. Protection of the hydroxyl group with THP followed by treatment of the resulting product **11** with NaH furnished the bicyclic compound **12** in good yield. Removal of the THP group of **12** with TsOH/MeOH led to the formation of (+)-**4** in an excellent yield (90%). The relative stereochemistry of **4** was unambiguously confirmed by the X-ray crystallographic study of its derivative **13**, while its absolute configuration was verified in the following experiments (see the X-ray of **16**). Compound (+)-**4** could be converted into (+)-tashiromine (**14**) in a single step according to the literature method [8], thus our work represents a formal synthesis of (+)-**14** via **7** linear steps in 30% overall yield.

With **4** in hand, we then moved forward to synthesize the chiral β -lactone **2**. At the outset, the asymmetric [2+2] cycloaddition was attempted using conditions reported by Nelson [10]. Although this protocol has been successfully applied in our previous work [5], we failed to get satisfactory results under the current scenario, and only observed the recovery of starting material. To circumvent this problem, we adopted a detour strategy. Thus, the asymmetric aldol reaction between **15** and **3** afforded **16** in 35% yield [11], which was converted into the benzyl ester **17** with the action of BnOH/DMAP. Hydrolysis of the benzyl ester through hydrogenation provided the acid **18** in high yield, which after treatment with BOP-Cl/Et₃N [12],

formed the 3,4-*cis*- β -lactone **2** in 50% yield. With the precursor **2** in hand, we next turned to examine the ambitious dyotropic rearrangement to synthesize the tricyclic compound **19**, which in principle, could be further converted into (+)-**1** by inversion of the stereochemistry of 12-Me. However, to our disappointment, we failed to observe the desired transformation using the standard conditions (Et₂AlCl, DCM, r.t.) [5]. Further efforts to improve the reaction by employing different Lewis acids (e.g. EtAlCl₂, TiCl₄ and MgBr₂) also turned out to be fruitless. Comparing this result with the previous one [5], we assumed that the failure of the dyotropic rearrangements of **2** could be attributed to the presence of the lactam ring which may coordinate to the Lewis acid and preclude the rearrangement from occurring.

4. Conclusion

In summary, we have completed a highly efficient asymmetric formal synthesis of (+)-tashiromine. Furthermore, the total synthesis (+)-stemoamide (**1**) via a novel dyotropic rearrangement of 3,4-*cis*- β -lactone was also explored. Albeit this route failed to attain the intended objective, the experimental results shed light on the substrate limitation of the dyotropic rearrangement of 3,4-*cis*- β -lactone, which prompted us to devise an alternative strategy to achieve the compounds. The relevant work is in progress and will be reported in due course.

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