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Syntheses of *cis*- and *trans*-Jamtine and Their *N*-Oxides via a Benzyl Configuration-Inversion Approach

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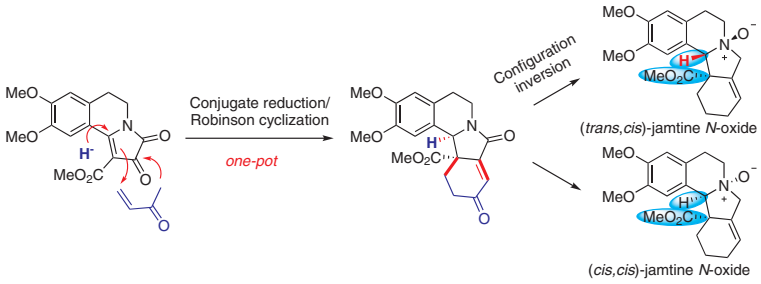

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Abstract A novel synthesis of the tetrahydroisoquinoline alkaloid jamtine and its epimer is reported. The synthetic strategy hinges on a one-pot conjugate reduction/Robinson cyclization sequence and an efficient benzyl configuration inversion by an oxidation/reduction approach. The *N*-oxide derivatives of the jamtine isomers were also synthesized and identified by X-ray crystallographic analysis. Additionally, a density functional theory calculation for the four possible *N*-oxide structures was exploited to gain further insight into the structure of the natural product in comparison to those of the synthetic *N*-oxides, because the NMR data of the synthetic derivatives did not match those reported for natural jamtine *N*-oxide.

Key words natural products, jamtine, total synthesis, one-pot reaction, conjugate reduction, Robinson cyclization

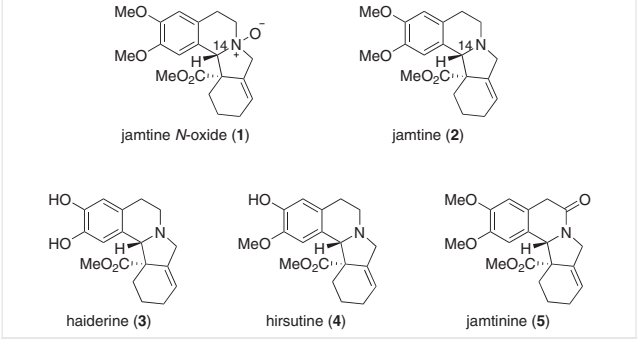


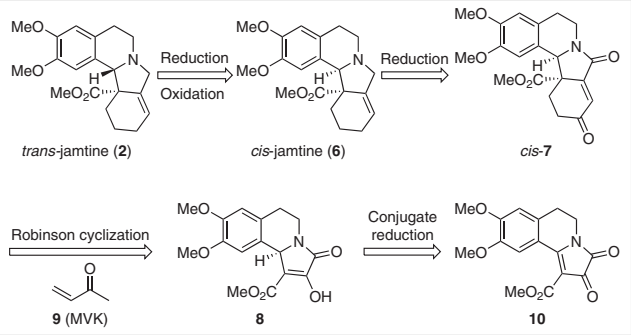
Figure 1 Jamtine *N*-oxide (**1**) and related tetrahydroisoquinoline alkaloids

Tetrahydroisoquinoline alkaloids are an important class of biologically and pharmacologically active candidates for use as antibiotics and antitumor agents.[1] Jamtine *N*-oxide (**1**), as a novel tetrahydroisoquinoline alkaloid, was isolated from the leaves of the climbing shrub *Cocculus hirsutus* from Pakistan,[2] the extracts of which have been used as a folk medicine to treat rheumatism and diarrhea.[3] Moreover, a previously reported in vitro study revealed that an aqueous extract of the leaves of *C. hirsutus* exhibited significant antihyperglycemic activity in mice.[4] Although jamtine (**2**), in the form of the free amine, has not been isolated previously, it is envisaged also to be a natural metabolite as the biogenic precursor of jamtine *N*-oxide, based on the fact that other related free amines such as haiderine (**3**),[5] hirsutine (**4**),[6] and jamtinine (**5**)[7] have been reported to be isolated from the same plant species (Figure 1).

Considerable efforts toward the total synthesis of jamtine *N*-oxide (**1**) or jamtine (**2**) have been reported by several groups, whose key synthetic strategies included tandem Pummerer/Pictet–Spengler cyclization, asymmetric desymmetrization of a *meso*-imide, and a Castagnoli condensation approach.[8] However, the NMR data for the synthetic jamtine *N*-oxide disagreed with those reported for the natural product. It is observed that all the synthetic jamtine derivatives possess a *trans*-configuration between the methyl ester and H-14 atom, as proposed at the time of their isolation. Actually, the relative configuration of these two groups could not be determined, even after a detailed analysis of the NOESY spectra of all related natural compounds.[2a,5–7] In a further exploration of the total synthesis and structural elucidation of jamtine isomers and their *N*-oxides, we set out to devise a flexible synthetic strategy to access both *cis*- and *trans*-jamtine and their *N*-oxides.

Alkaloid *N*-oxides are known to be readily available from the corresponding amines through appropriate oxidation. Thus, our retrosynthetic analysis began from the *cis*- and *trans*-jamtines, as outlined in Scheme 1. *trans*-Jamtine (**2**) might be derived by a consecutive benzyl oxidation/reduction sequence from *cis*-jamtine (**6**), which would in turn be obtained from the amide *cis*-**7** through reduction of the two carbonyl groups. The characteristic α,β-unsaturated

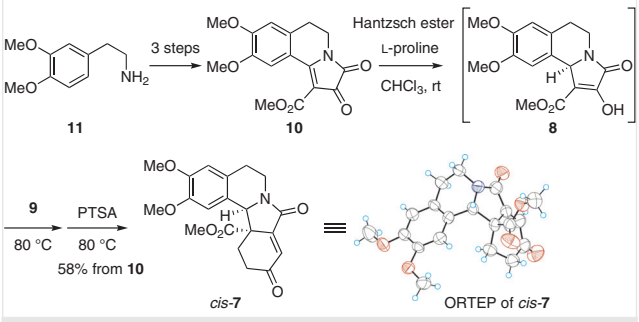
cyclohexenone group of **7** might be constructed through a Robinson cyclization between the 1,3-dicarbonyl compound **8** and methyl vinyl ketone (**9**; MVK), whereas **8** might be derived from the known precursor **10** through a conjugate reduction.



Scheme 1 Retrosynthetic analysis

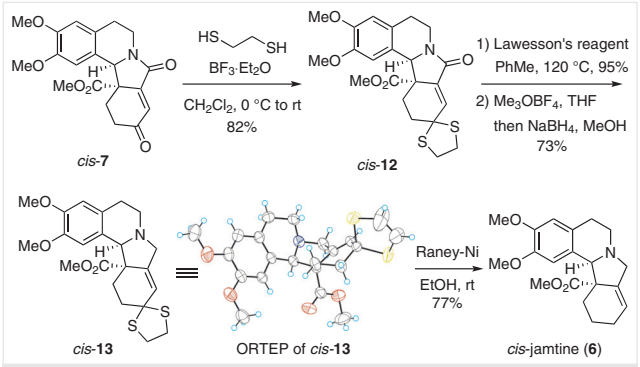
Our synthesis started from 2-(3,4-dimethoxyphenyl)ethylamine (**11**), which was converted into the known compound **10** in moderate yield over three steps by using dimethyl malonate and oxalyl chloride (Scheme 2).[9] Reduction of compound **10** with Hantzsch ester[10] in refluxing CH_2Cl_2 resulted in the formation of enol **8**; this reaction was effectively catalyzed by L-proline at r.t. with the reduction in the reaction time from 15 to 3 hours. Gratifyingly, we successfully conducted the conjugate reduction and subsequent Robinson cyclization[11] in one-pot under Hantzsch ester/L-proline/$CHCl_3$ conditions, followed with sequentially addition of MVK and PTSA, affording the cyclohexenone *cis*-**7**. Although chiral proline was used in this reaction, no enantiomeric excess of *cis*-**7** was observed. X-ray crystallographic analysis of this tetracyclic compound **7** unambiguously confirmed the *cis*-configuration between the ester group and H-14. The nearly planar structure of compound **8** rendered H-14 sterically significant in preventing approach of MVK from the same side.

Conversion of *cis*-**7** into *cis*-jamtine (**6**) was achieved in four steps (Scheme 3). The enone carbonyl group was selectively protected as a 1,3-dithiane, and the resulting amide

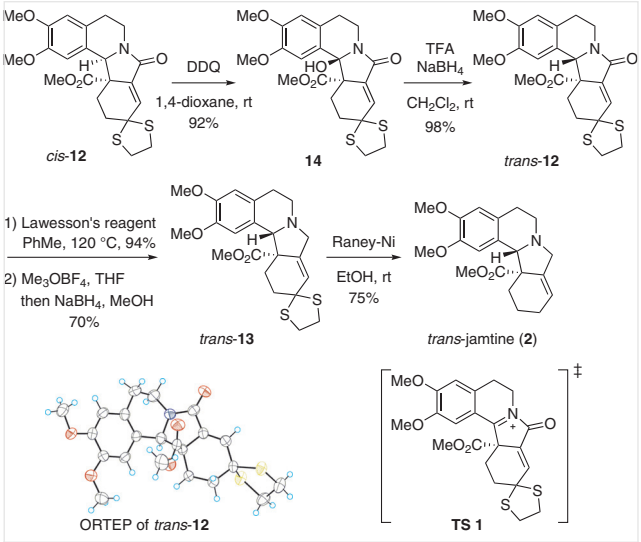


Scheme 2 One-pot synthesis of *cis*-**7** by conjugate reduction/Robinson cyclization

cis-**12** was almost quantitatively converted into a thioamide under Lawesson's conditions, followed by reduction to the free amine *cis*-**13** with Meerwein's salt and $NaBH_4$. Finally, desulfurization of *cis*-**13** with Raney-nickel resulted in the successful formation of *cis*-jamtine (**6**). The configuration of these compounds was confirmed by the X-ray crystallographic analysis of *cis*-**13**.



Scheme 3 Synthesis of *cis*-jamtine (**6**)

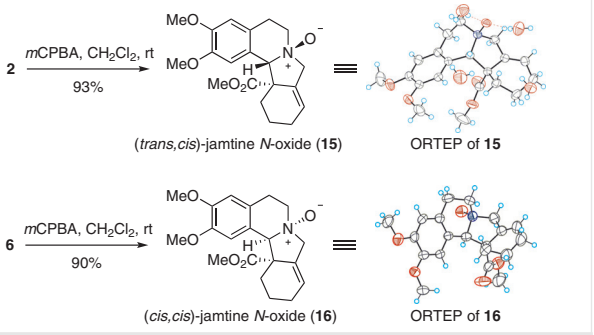


Scheme 4 Synthesis of *trans*-jamtine (**2**)

As hydroisoquinolines can be easily oxidized to imines,[12] the desired inversion of the configuration at H-14 of *cis*-**12** was conducted through an oxidation/reduction approach (Scheme 4). DDQ oxidation of *cis*-**12** delivered alcohol **14** in 92% yield; this was then reduced with $NaBH_4$/TFA to afford *trans*-**12** in quantitative yield. These two transformations might proceed via a common iminium intermediate (**TS 1**), in which both the nucleophilic OH and the negative H react separately with the iminium **TS 1** by approaching from the opposite side of the ester group to facilitate the formation of the *trans*-product. The structure of *trans*-**12** was further confirmed by X-ray crystallographic analy-

sis. Next, following the same procedures as used in the synthesis of *cis*-jamtine (**6**), *trans*-jamtine (**2**) was successfully generated from *trans*-**12** in 49% overall yield. The NMR data of *trans*-jamtine (**2**) was in full agreement with those of synthesized samples reported by other research groups.[8a–d]

With both *cis*- and *trans*-jamtines in hand, our attention then turned to the nitrogen oxidation to access the required jamtine *N*-oxides. Two jamtine *N*-oxides were synthesized readily by exposing the corresponding free amines to *m*CPBA at room temperature (Scheme 5), whereby the products **15** and **16** appeared as solids (not oils or gums as previously reported), and both were obtained as single diastereoisomers. The structures of the two stereoisomers were unambiguously confirmed as (*trans*,*cis*)-jamtine *N*-oxide (**15**) and (*cis*,*cis*)-jamtine *N*-oxide (**16**) by X-ray crystallography; the oxygen of the N–O bond and H-14 have a *cis* configuration. A complete comparison of the spectroscopic data of *N*-oxides **15** and **16** with those of the natural *N*-oxide revealed a considerable discrepancy (see Supporting Information), probably due to the diastereochemistry of the N–O bond.



Scheme 5 Syntheses of (*trans*,*cis*)- and (*cis*,*cis*)-jamtine *N*-oxides (**15** and **16**)

To gain further insight into the structures of jamtine *N*-oxides, we performed preliminary conformational research[13] on the four relative configurations of jamtine *N*-oxide including the synthetic (*trans*,*cis*)- and (*cis*,*cis*)-products **15** and **16** and their N–O epimers (*trans*,*trans*)-**17** and (*cis*,*trans*)-**18**, as shown in Figure 2. DFT calculations showed that both our synthetic isomers **15** and **16** exhibited lower free energies in a solvent model of CH_2Cl_2 or H_2O, whereas isomers **17** and **18** possessed higher free energies. However, whether or not the natural product is one of the N–O epimers **17** and **18** is yet to be determined by their total synthesis. Our late-stage oxidation facilitated a substrate-dependent diastereoselective formation of the *N*-oxide with a *cis*-configuration relative to H-14. However, an early installation of the *N*-oxide functionality or enzymatically mediated epimerization might be involved in the biosynthesis of the isomer **17** or **18**.

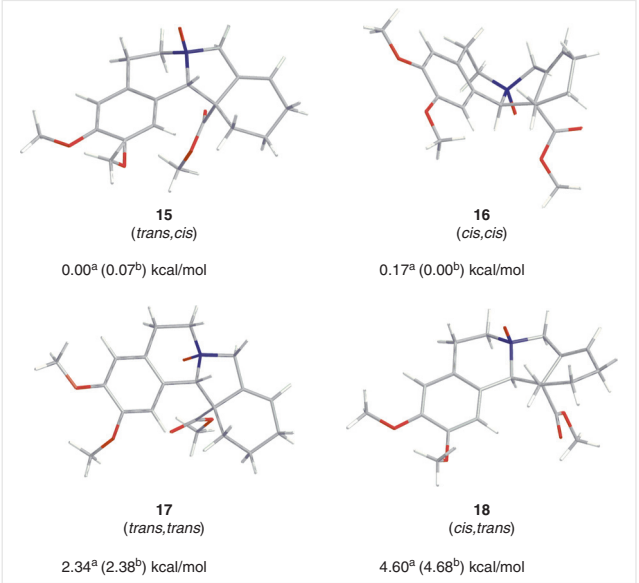


Figure 2 Relative free energies of the four relative configurations of jamtine *N*-oxide calculated in CH_2Cl_2 or H_2O solvent. [a] ΔE calculated in CH_2Cl_2. [b] ΔE calculated in H_2O.

In summary, we have accomplished syntheses of *cis*- and *trans*-jamtine[14] and their *N*-oxides. The assembly of the core of these four tetrahydroisoquinoline compounds relied on a one-pot conjugate reduction/Robinson cyclization sequence followed by an efficient benzyl configuration inversion (by an oxidation/reduction approach). The synthetic jamtine *N*-oxides **15** and **16** were confirmed to be the non-natural isomers. Development of an alternative oxidation methodology to access the natural *N*-oxide, as well as biological evaluations of our synthetic jamtine *N*-oxides, are currently underway and will be reported in due course.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610745.

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(13) The conformational research was carried out using DFT method in *Gaussian 09* software (for details see the Supporting Information).

(14) Methyl *cis*-2,3-Dimethoxy-5,8,10,11,12,12b-hexahydroisoindolo[1,2-*a*]isoquinoline-12a(6*H*)-carboxylate (cis-Jamtine) (6)
To a solution of **cis-**13 (355 mg, 0.82 mmol) in absolute EtOH (10 mL) was added excess Raney-Ni (W-2 type, newly reactivated), and the mixture was vigorously stirred at rt for 2 h. The mixture was then filtered through a plug of Celite that was washed with EtOAc. The filtrate was concentrated, and the residue was purified by chromatography [silica gel, CH_2Cl_2–MeOH (50:1)] to give a white solid; yield: 218 mg (77%); mp 95.2–98.0 °C.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.98 (s, 1 H), 6.56 (s, 1 H), 5.70 (s, 1 H), 4.36 (s, 1 H), 3.88 (s, 3 H), 3.90–3.82 (m, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.35 (d, J = 12.8 Hz, 1 H), 2.94–2.85 (m, 1 H), 2.73–2.57 (m, 3 H), 2.16 (dt, J = 12.8, 3.1 Hz, 1 H), 2.12–2.04 (m, 1 H), 2.04–1.94 (m, 1 H), 1.68–1.60 (m, 1 H), 1.44–1.33 (m, 1 H), 0.70 (td, J = 13.6, 3.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.8, 147.6, 147.0, 138.8, 126.9, 125.0, 121.8, 110.9, 110.6, 68.2, 61.5, 55.8, 55.7, 54.3, 52.2, 46.5, 29.9, 28.6, 23.5, 19.4. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{20}H_{26}NO_4$: 344.1856; found: 344.1854.
Methyl *trans*-2,3-Dimethoxy-5,8,10,11,12,12b-hexahydroisoindolo[1,2-*a*]isoquinoline-12a(6*H*)-carboxylate (trans-Jamtine) (2)
To a solution of **trans-**13 (180 mg, 0.42 mmol) in absolute EtOH (8 mL) was added excess Raney-Ni (W-2 type, newly reactivated), and the mixture was vigorously stirred at rt for 2 h. The mixture was then filtered through a plug of Celite that was washed with EtOAc. The filtrate was concentrated, and the residue was purified by chromatography [silica gel, CH_2Cl_2–MeOH (50:1)] to give a white solid; yield: 108 mg (75%); mp 104.0–106.3 °C.
^{1}H NMR (500 MHz, CDCl3): δ = 6.79 (s, 1 H), 6.56 (s, 1 H), 5.71 (s, 1 H), 3.98 (dq, J = 12.0, 2.8 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 1 H), 3.84 (s, 3 H), 3.42 (d, J = 11.2 Hz, 1 H), 3.29 (s, 3 H), 3.11 (dt, J = 11.9, 4.3 Hz, 1 H), 2.90 (ddd, J = 15.1, 10.1, 4.9 Hz, 1 H), 2.82 (dd, J = 8.9, 3.7 Hz, 1 H), 2.78–2.72 (m, 1 H), 2.52 (dt, J = 15.3, 3.3 Hz, 1 H), 2.14–2.08 (m, 2 H), 1.89–1.82 (m, 1 H), 1.56–1.51 (m, 2 H). ^{13}C NMR (125 MHz, CDCl3): δ = 173.3, 147.4, 146.6, 137.8, 128.4, 126.9, 121.1, 111.1, 110.0, 71.3, 57.1, 56.8, 56.0, 55.7, 51.4, 47.8, 31.9, 27.2, 24.3, 19.8. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{20}H_{26}NO_4$: 344.1856; found: 344.1855.