Supplementary Information

Goniomitine: An Overview on the Chemistry of This Indole Alkaloid

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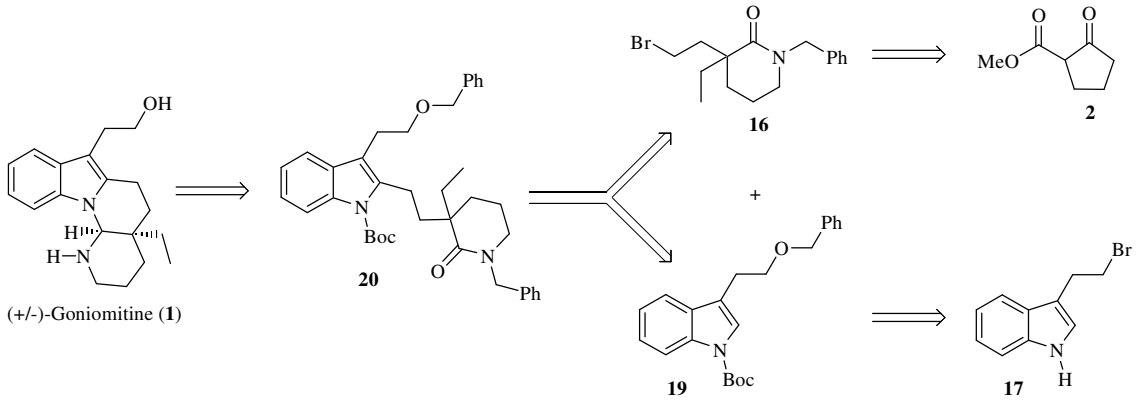
This supplementary material displays the proposals of synthesis of the indole alkaloids (+/-)-goniomitine, the natural (-)-goniomitine, and the unnatural (+)-goniomitine. The idealized strategies and synthetic routes for the preparation of these alkaloids and stereisomers are described.

*1. Proposal of Synthesis of (+/-)-Goniomitine (**1**).* The convergent synthesis of (+/-)-goniomitine (**1**) was idealized by the retrosynthetic analysis depicted in Scheme S1.

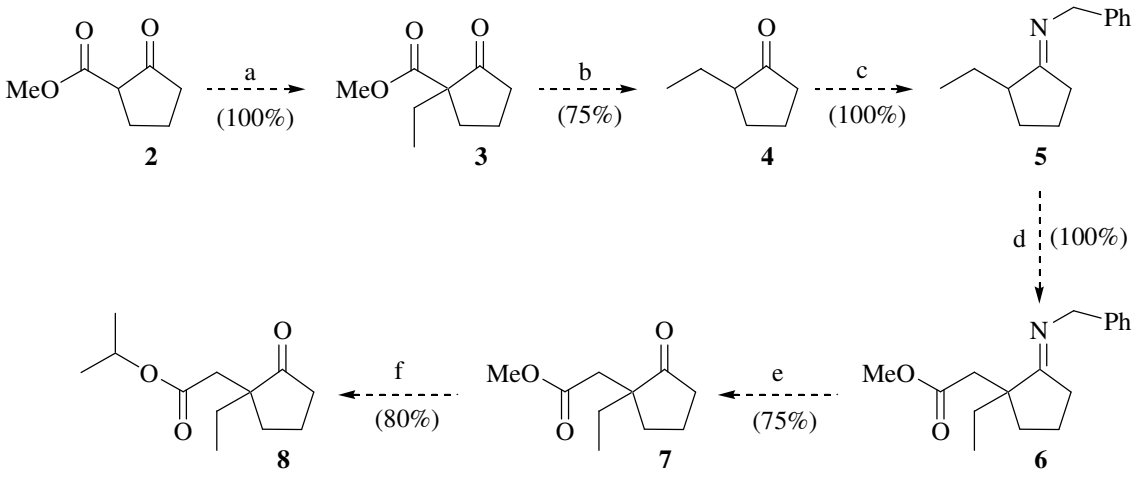


Scheme S1. Proposal of retrosynthetic analysis for the convergent synthesis of (+/-)-goniomitine (**1**).

The synthetic routes and conditions presented herein are based on previous experience of the author of this supplementary material on the synthesis of indole alkaloids [1-3].

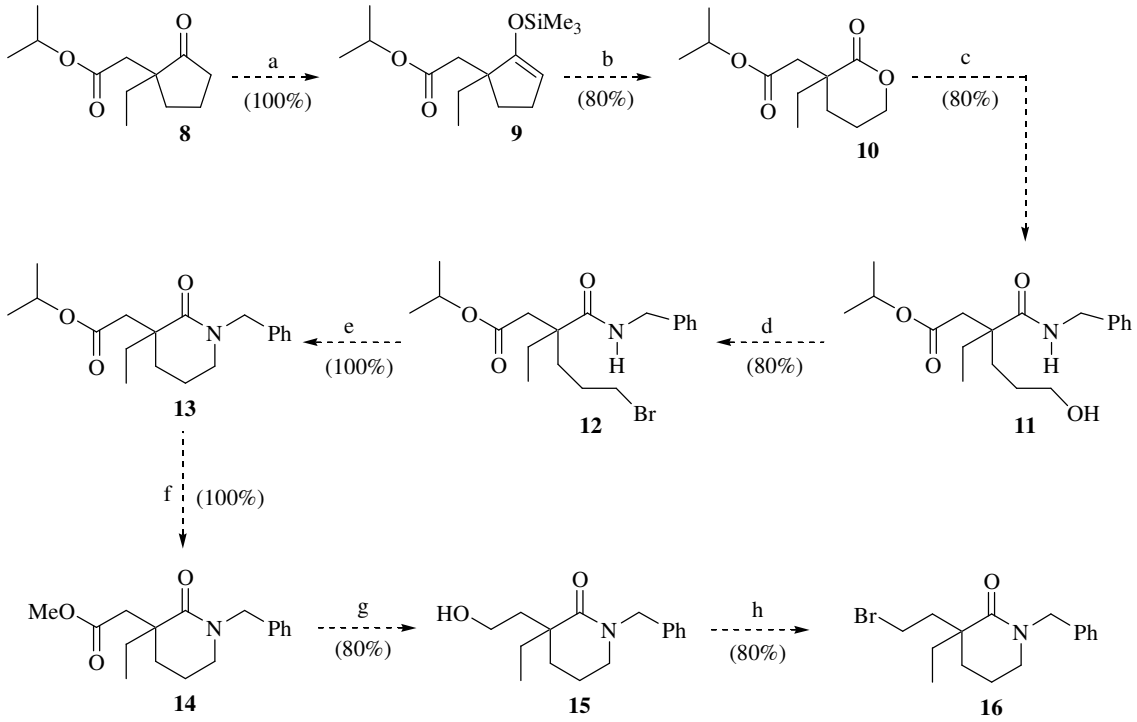
The sequences of reactions proposed for the total synthesis of (+/-)-goniomitine (**1**) are described in the following subitems.

*1.1. Proposal of Synthesis of the Cyclopentanone **8***



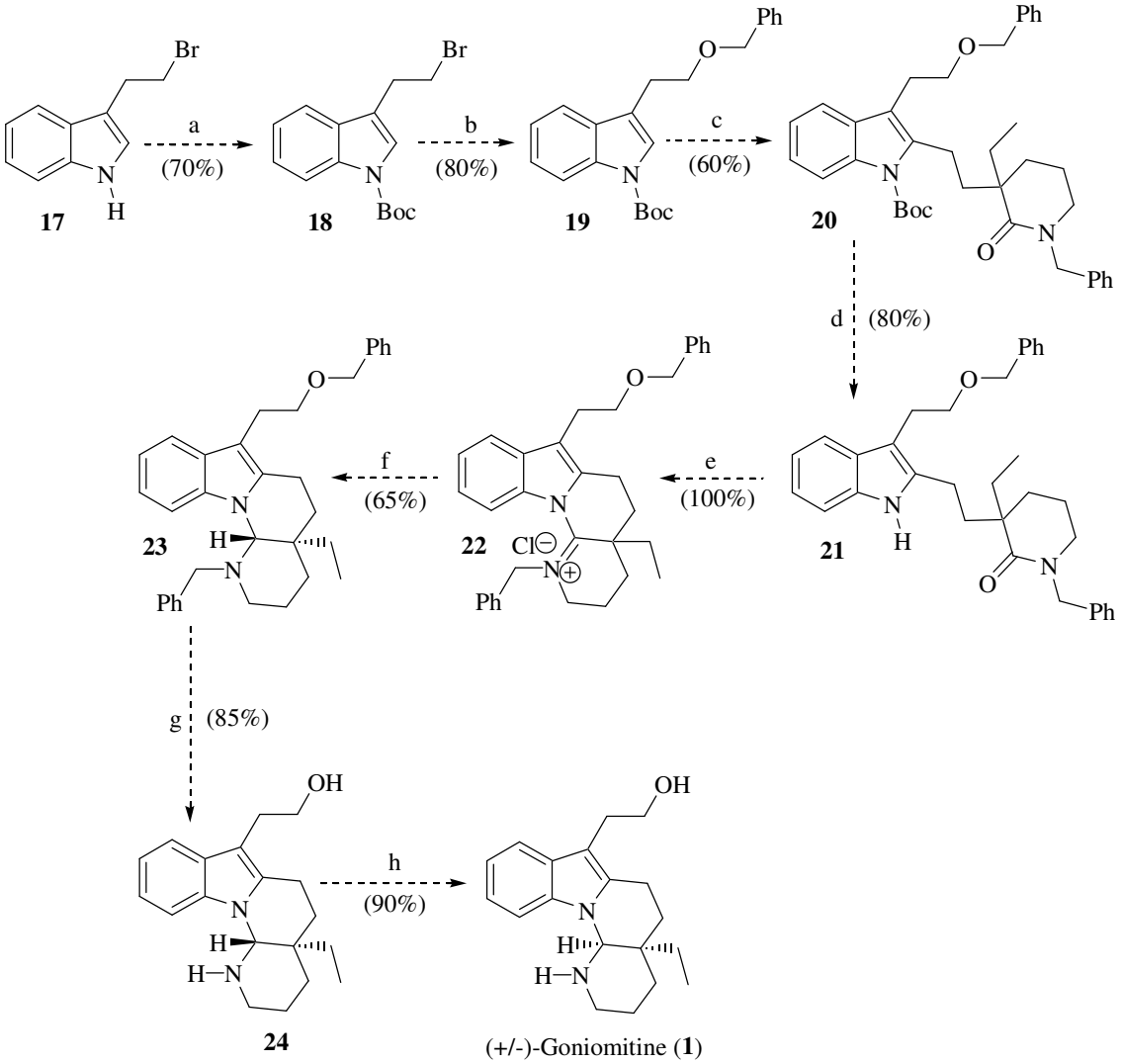
Scheme S2. Simulated conditions: (a) (i) Na_2CO_3 (4.0 equiv), acetone (1 mol L^{-1}), r.t. (30 min), (ii) CH_3CH_2I (2.0 equiv), reflux (6 h); (b) conc. HCl (2 mol L^{-1}), H_2O (10 mol L^{-1}), reflux (3.5 h); (c) Benzylamine (1.1 equiv), TsOH (0.02 equiv), toluene (0.5 mol L^{-1}), reflux (Dean-Stark, 5 h); (d) $BrCH_2CO_2Me$ (1.1 equiv), *t*-BuOH (3.3 mol L^{-1}), r.t. (24 h); (e) 10% AcOH-H_2O, THF (0.6 mol L^{-1}), r.t. (24 h); (f) *i*-PrONa (1.1 equiv), *i*-PrOH (0.3 mol L^{-1}), r.t. (15 min).

*1.2. Proposal of Synthesis of the Bromolactam **16***



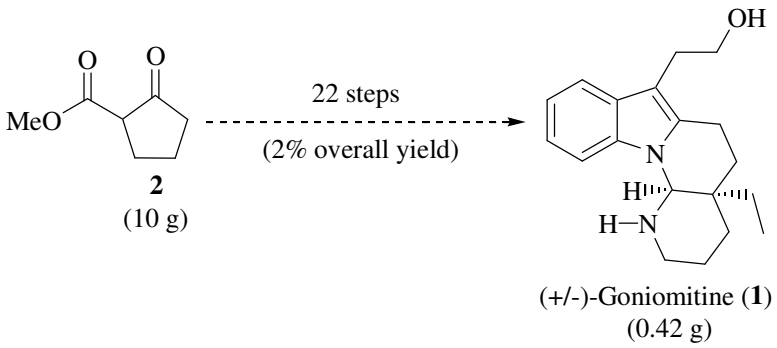
Scheme S3. Simulated conditions: (a) NaI (2.0 equiv), TMSCl (1.3 equiv), Et_3N (2.0 equiv), MeCN (1.13 mol L^{-1}), r.t. (30 min); (b) (i) O_3, 15% MeOH-CH_2Cl_2 (-78°C, 30 min), (ii) $NaBH_4$ (2.0 equiv), r.t. (3 h), (iii) 10% HCl-H_2O (pH 3), (iv) conc. HCl (cat.), CH_2Cl_2 (r.t., 3 h); (c) Benzylamine (1.2 equiv), CH_2Cl_2 (1 mol L^{-1}), 135°C (3 h); (d) CBr_4 (3.0 equiv), Ph_3P (1.5 equiv), CH_2Cl_2 (0.06 mol L^{-1}), r.t. (2 h); (e) KH (1.5 equiv), 18-crown-6 (0.6 equiv), THF (0.01 mol L^{-1}), r.t. (10 min); (f) MeONa (1.1 equiv), MeOH (0.02 mol L^{-1}), r.t. (1 h); (g) $LiAl(t\text{-}BuO)_3H$ (2.0 equiv), THF (0.1 mol L^{-1}), r.t. (4 h); (h) CBr_4 (3.0 equiv), Ph_3P (1.5 equiv), CH_2Cl_2 (0.06 mol L^{-1}), r.t. (2 h).

*1.3. Proposal of Final Steps for the Synthesis of (+/-)-Goniomitine (**1**)*



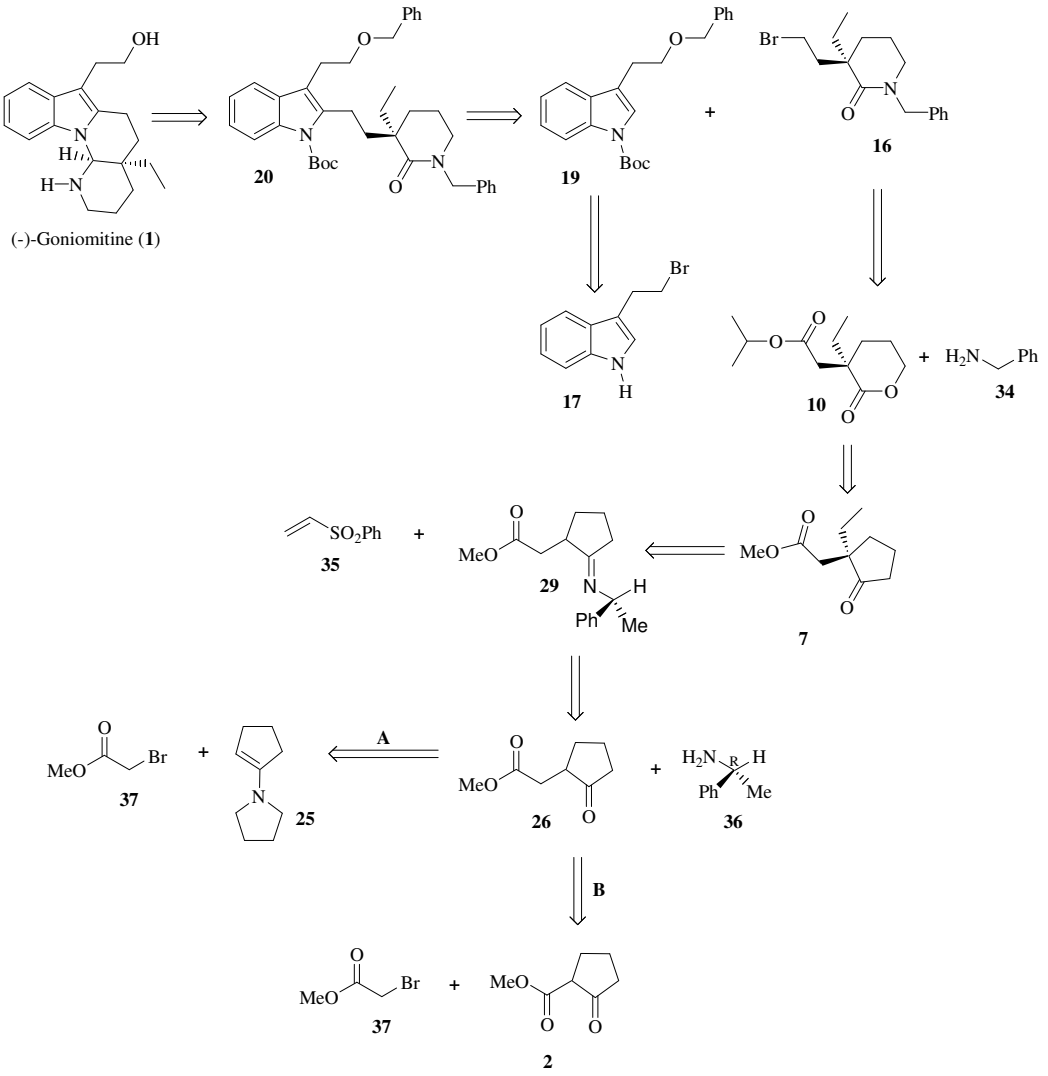
Scheme S4. Simulated conditions: (a) (i) NaH (1.2 equiv), THF (0.5 mol L^{-1}), 0°C (15 min), (ii) $(Boc)_2O$ (1.2 equiv), 0°C (30 min); (b) $C_6H_5CH_2ONa$ (1.2 equiv), MeCN (0.21 mol L^{-1}), 0°C (1 h); (c) (i) *n*-BuLi (1.1 equiv), -78°C (30 min), (ii) Compound **16** (1.0 equiv), THF (0.1 mol L^{-1}), [-78°C (30 min), r.t. (1 h)]; (d) TFA (1.1 equiv), CH_2Cl_2 (0.1 mol L^{-1}), r.t. (1 h); (e) $POCl_3$ (0.1 mol L^{-1}), reflux (5 h); (f) $LiAl(t\text{-}BuO)_3H$ (1.3 equiv), THF (0.1 mol L^{-1}), 0°C (4 h); (g) H_2 (50 psi), 20% $Pd(OH)_2$ (0.1 equiv), 40% EtOH-AcOH (0.1 mol L^{-1}), r.t. (3 h); (h) 10% HCl-MeOH (0.08 mol L^{-1}) reflux (30 min).

*1.4. Estimation of Overall Yield for the Synthesis of (+/-)-Goniomitine (**1**).* Using the supposed yields presented in the simulated routes for the synthesis of (+/-)-goniomitine (**1**) (Schemes S2-S4), this target alkaloid may be obtained in 22 steps with 2% overall yield. Thus, using as starting material 2-carboxymethyl-cyclopentanone (**2**) (10 g), it is expected to obtain (+/-)-goniomitine (**1**) (0.42 g) (Scheme S5).



Scheme S5. Estimated overall yield for the synthesis of (+/-)-goniomitine (**1**).

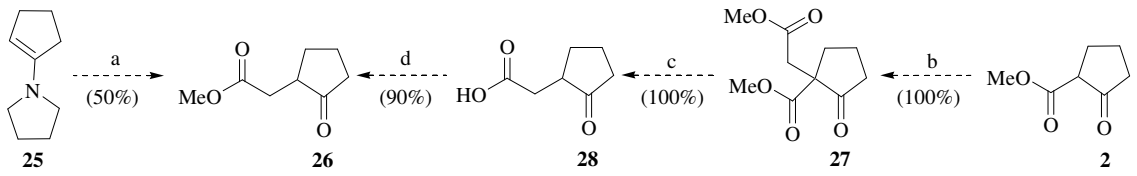
*2. Proposal of Synthesis of the Natural (-)-Goniomitine (**1**).* The convergent synthesis of (-)-goniomitine (**1**) was idealized by the retrosynthetic analysis depicted in Scheme S6.



Scheme S6. Proposal of retrosynthetic analysis for the convergent synthesis of (-)-goniomitine (**1**).

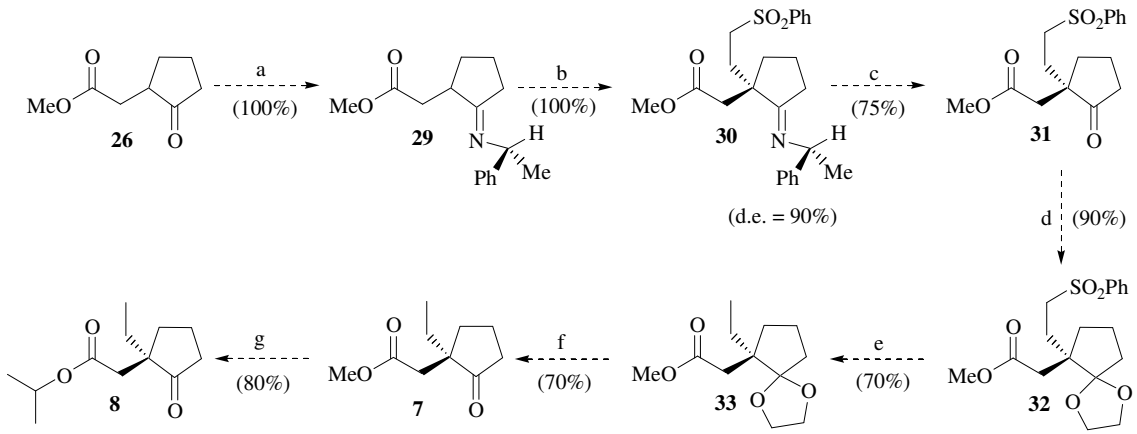
The sequences of reactions proposed for the total synthesis of (-)-goniomitine (**1**) are described in the following subitems.

*2.1. Proposal of Synthesis of the Cyclopentanone **26***



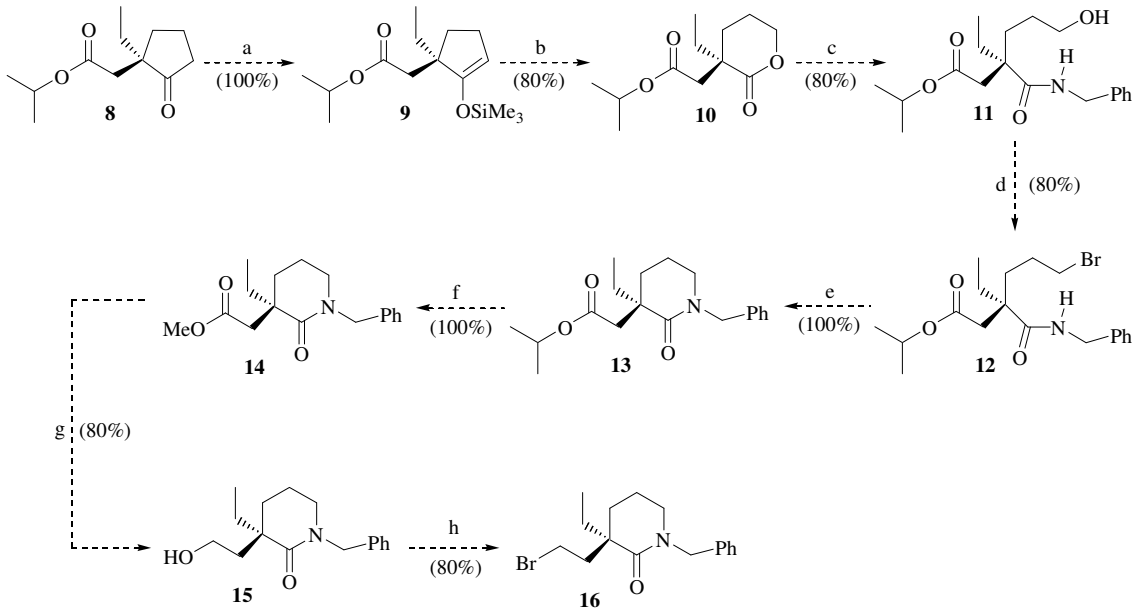
Scheme S7. Simulated conditions: *Procedure 1*. (a) (i) $BrCH_2CO_2Me$ (1.1 equiv), *t*-BuOH (3.3 mol L^{-1}), r.t. (12 h), (ii) 20% AcOH-H_2O, r.t. (4 h). *Procedure 2*. (b) (i) Na_2CO_3 (4.0 equiv), acetone (0.2 mol L^{-1}), r.t. (30 min), (ii) $BrCH_2CO_2Me$ (2.0 equiv), reflux (6 h); (c) conc. HCl (2 mol L^{-1}), H_2O (10 mol L^{-1}), reflux (3.5 h); (d) DCC (1.1 equiv), DMAP (0.1 equiv), MeOH (5.5 equiv), CH_2Cl_2 (0.08 mol L^{-1}), r.t. (15 h).

*2.2. Proposal of Synthesis of the Chiral Cyclopentanone **8***



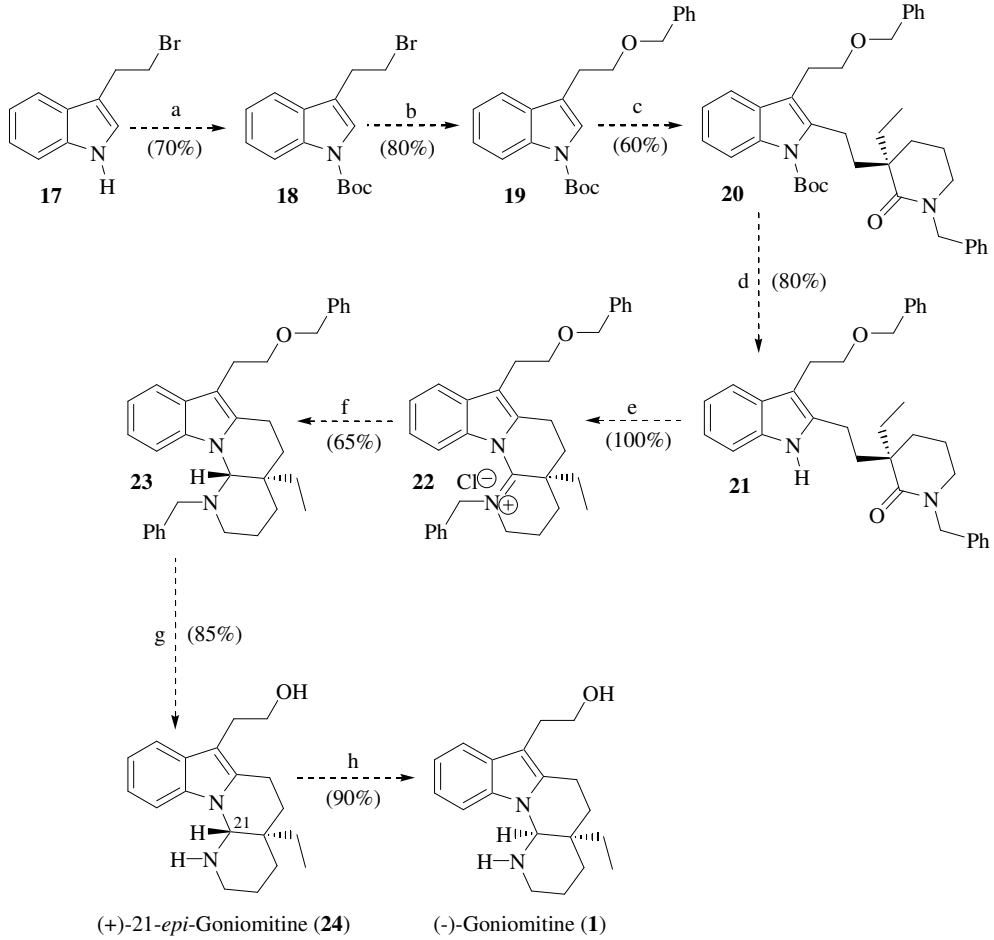
Scheme S8. Simulated conditions: (a) *R*-(+)-α-methylbenzylamine (1.1 equiv), toluene (0.37 mol L^{-1}), reflux (Dean-Stark, 24 h); (b) Phenyl vinyl sulfone (1.1 equiv), toluene (1.6 mol L^{-1}), 80°C (24 h); (c) 10% AcOH-H_2O, THF (0.6 mol L^{-1}), r.t. (36 h); (d) $HOCH_2CH_2OH$ (2.0 equiv), TsOH (0.4 equiv), toluene (0.26 mol L^{-1}), reflux (Dean-Stark, 24 h); (e) 6% Na(Hg), MeOH (0.1 mol L^{-1}), r.t. (1 h); (f) conc. HCl (cat.), THF (0.2 mol L^{-1}), r.t. (1.5 h); (g) *i*-PrONa (1.1 equiv), *i*-PrOH (0.3 mol L^{-1}), r.t. (15 min).

*2.3. Proposal of Synthesis of the Chiral Bromolactam **16***



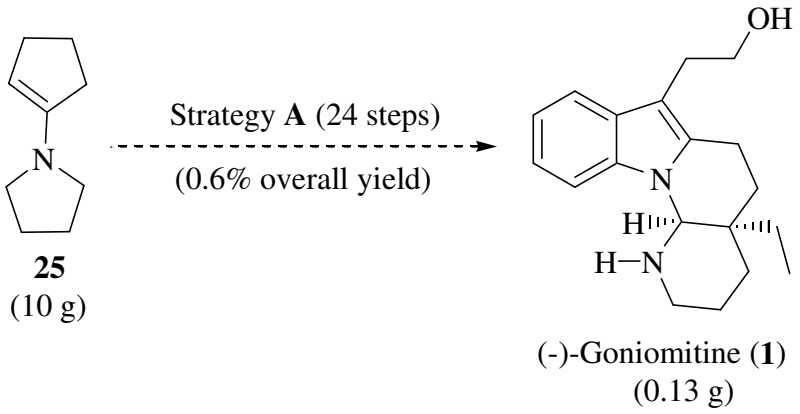
Scheme S9. Simulated conditions: see Scheme S3.

*2.4. Proposal of Final Steps for the Synthesis of (-)-Goniomitine (**1**)*



Scheme S10. Simulated conditions: see Scheme S4.

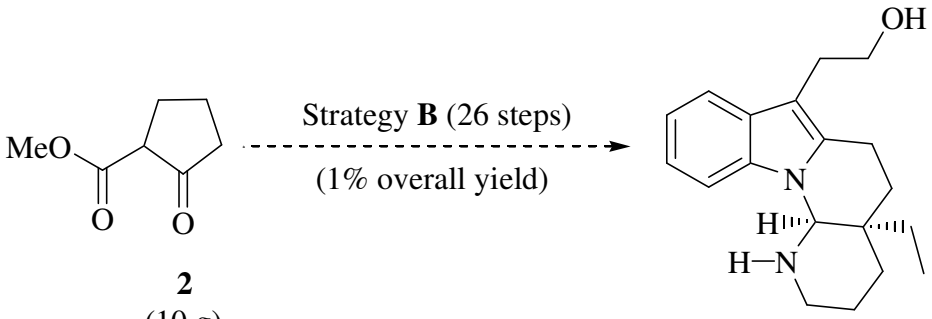
*2.5. Estimation of Overall Yield for the Synthesis of (-)-Goniomitine (**1**).* Using the supposed yields presented in the simulated routes for the synthesis of (-)-goniomitine (**1**) (Schemes S7-S10), this target alkaloid may be obtained in 24 steps with 0.6% overall yield (strategy **A**, Scheme S11), or it may be obtained in 26 steps with 1% overall yield (strategy **B**, Scheme S12).



25
(10 g)

(-)-Goniomitine (**1**)
(0.13 g)

Scheme S11. Estimated overall yield for the synthesis of (-)-goniomitine (**1**), starting from 1-pyrrolidino-1-cyclopentene (**25**).

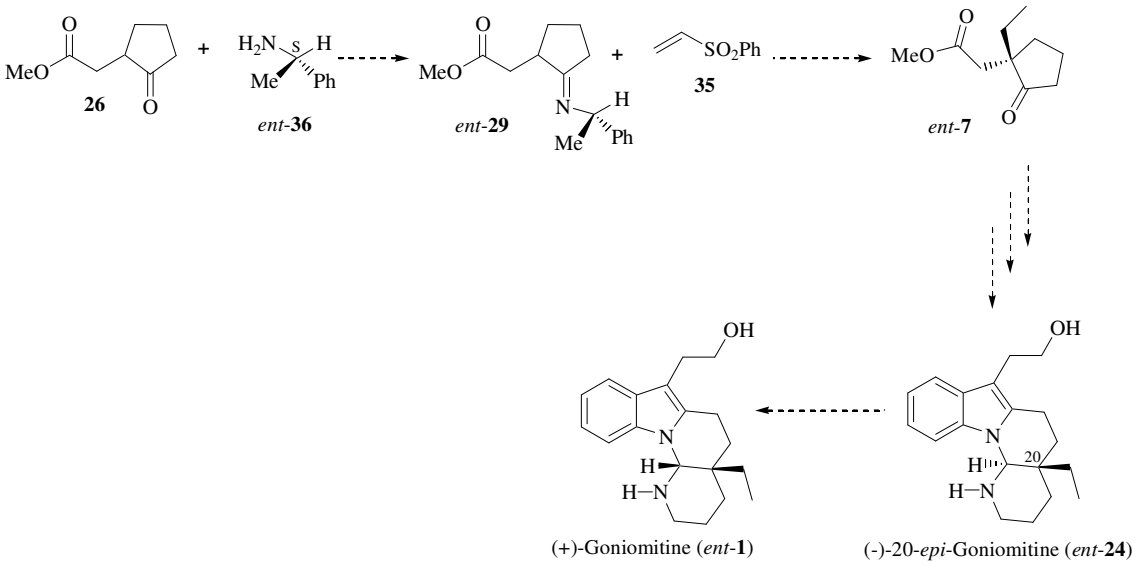


2
(10 g)

(-)-Goniomitine (**1**)
(0.2 g)

Scheme S12. Estimated overall yield for the synthesis of (-)-goniomitine (**1**), starting from 2-carboxymethyl-cyclopentanone (**2**).

*3. Proposal of Synthesis of the Unnatural (+)-Goniomitine (ent-**1**).* The synthesis of (+)-goniomitine (*ent*-**1**) was idealized starting from the enantiomer of the chiral imine **29** (*ent*-**29**), which may be synthesized in the reaction of the cyclopentanone **26** with the chiral amine *S*-(+)-α-methylbenzylamine (*ent*-**36**), using the same simulated conditions described for the synthesis of (-)-goniomitine (**1**) (see Scheme S13).



Scheme S13. Synthetic route proposed for the synthesis of (+)-goniomitine (*ent*-**1**).

References

[1] J. C. F. Alves, A. B. C. Simas, P. R. R. Costa, and J. d'Angelo, "Stereocontrolled elaboration of quaternary carbon centers involving the asymmetric Michael-type alkylation of chiral imines: an efficient enantioselective access to (+)-vincamine," *Tetrahedron: Asymmetry*, vol. 8, no. 12, pp. 1963-1966, 1997.

[2] J. C. F. Alves, A. B. C. Simas, and P. R. R. Costa, "Formal enantioselective synthesis of (+)-vincamine. The first enantioselective route to (+)-3,14-epivincamine and its enantiomer," *Tetrahedron: Asymmetry*, vol. 10, no. 2, pp. 297-306, 1999.

[3] J. C. F. Alves, *Formal enantioselective synthesis of (+)-vincamine and derivatives*, Ph.D. thesis, NPPN, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, 2000.