

The Enantiocontrolled Total Synthesis of Natural (–)-Goniomitine

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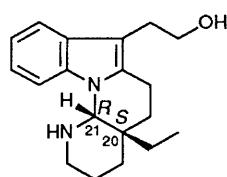
The first enantiocontrolled total synthesis of (–)-goniomitine, a new structural type of indole alkaloid of the *Aspidosperma* family isolated from the root bark of *Gonioma malagasy*, has been completed starting from a chiral cyclopentadienone synthon and establishes the absolute stereochemistry as 20*R*, 21*S*.

(–)-Goniomitine is a variant of *Aspidosperma* indole alkaloid, of a new structural type, isolated from the root bark of *Gonioma malagasy* by Husson and coworkers.^{1,2} Its structure was proposed as shown in **1**, having the 20*S*,21*R* configuration on the basis of its NMR spectra, though its absolute structure was deduced only tentatively by correlation with other *Aspidosperma* alkaloids found in the same plant. We report herein the first enantiocontrolled synthesis of the natural form of (–)-goniomitine [(20*R*,21*S*)-**1**] starting from a chiral cyclopentadienone synthon [(–)-**2**] which confirmed the validity of the proposed relative structure and clarified the absolute structure to be enantiomeric to that originally proposed having the 20*S*,21*R* configuration.

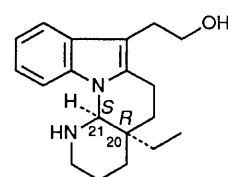
Treatment of the (–)-dienone **2**, prepared from dicyclopentadiene employing kinetic resolution by lipase,^{3,4} with zinc in acetic acid gave the enone† **3**, $[\alpha]_{\text{D}}^{30} -268.1^\circ$ (*c* 1.03, CHCl₃), in 92% yield. Sequential alkylation with ethyl iodide and allyl bromide allowed stereoselective introduction of the incoming groups in turn from the convex face of the stereochemically biased molecule to give the dialkyl enone **5**, $[\alpha]_{\text{D}}^{30} -172.8^\circ$ (*c* 1.13, CHCl₃), stereoselectively, in 58% overall yield *via* **4**, $[\alpha]_{\text{D}}^{30} -273.5^\circ$ (*c* 1.28, CHCl₃). Thermolysis of **5** in refluxing *o*-dichlorobenzene induced a retro-Diels–Alder reaction to yield the α,β -unsaturated ketone **6**, $[\alpha]_{\text{D}}^{30} -18.2^\circ$ (*c* 1.01, CHCl₃), the conjugated double bond of which was reduced with a complex^{4d,5} generated from lithium aluminium hydride and copper(I) iodide to give the cyclopentanone **7**, $[\alpha]_{\text{D}}^{28} -22.7^\circ$ (*c* 0.99, CHCl₃), in 91% overall yield. Treatment of **7** with propane-1,3-diyl dithiotosylate^{6,7} in the presence of potassium *tert*-butoxide furnished the α -diketone monothioether^{4b,8} **8**, $[\alpha]_{\text{D}}^{29} -47.6^\circ$ (*c* 1.07, CHCl₃), in 79.5% yield, which on exposure to potassium hydroxide in *tert*-butyl alcohol⁹ brought about ring cleavage to afford the dithiane ester **10**, $[\alpha]_{\text{D}}^{31} -39.5^\circ$ (*c* 1.10, CHCl₃), in 75% yield by

esterification of the resulting acid **9**. After hydrolysis of the dithiane group,¹⁰ the resulting aldehyde **11** was transformed¹¹ into the acetylene **13**, $[\alpha]_{\text{D}}^{29} -6.65^\circ$ (*c* 1.04, CHCl₃), *via* the dibromoalkene **12**, $[\alpha]_{\text{D}}^{30} -6.1^\circ$ (*c* 0.95, CHCl₃), in 82% overall yield. Treatment of **13** with *N*-ethoxycarbonyl-2-iodoaniline **14** in the presence of dichlorobis(triphenylphosphine)palladium(II)¹² gave the cross-coupling product **15**, $[\alpha]_{\text{D}}^{30} -8.45^\circ$ (*c* 0.82, CHCl₃), in 81% yield, which was exposed to sodium ethoxide¹³ to form the indole lactam **16**, $[\alpha]_{\text{D}}^{26} -57.6^\circ$ (*c* 0.79, CHCl₃), in 70% yield accompanied by the ester‡ **17**, $[\alpha]_{\text{D}}^{28} -9.69^\circ$ (*c* 0.88, CHCl₃), in 11% yield (Scheme 1).

Sequential hydroboration and oxidation converted **16** into the primary alcohol **18** which on Mitsunobu reaction¹⁴ followed by deacylation and spontaneous ring-transformation furnished the lactam **21**, m.p. 208–209 °C, $[\alpha]_{\text{D}}^{30} -34.4^\circ$ (*c* 0.48, MeOH), in 65% overall yield *via* the phthalimide **19**, $[\alpha]_{\text{D}}^{29} -30.8^\circ$ (*c* 0.92, CHCl₃), and the primary amine **20**. The β -substituent on the indole ring was next introduced by sequential Mannich reaction,¹⁵ quaternization, and nucleophilic substitution to give the cyanide **24**, m.p. 161–162 °C, $[\alpha]_{\text{D}}^{29} -30.8^\circ$ (*c* 1.26, MeOH), in 78% overall yield, *via* **22** and **23**.



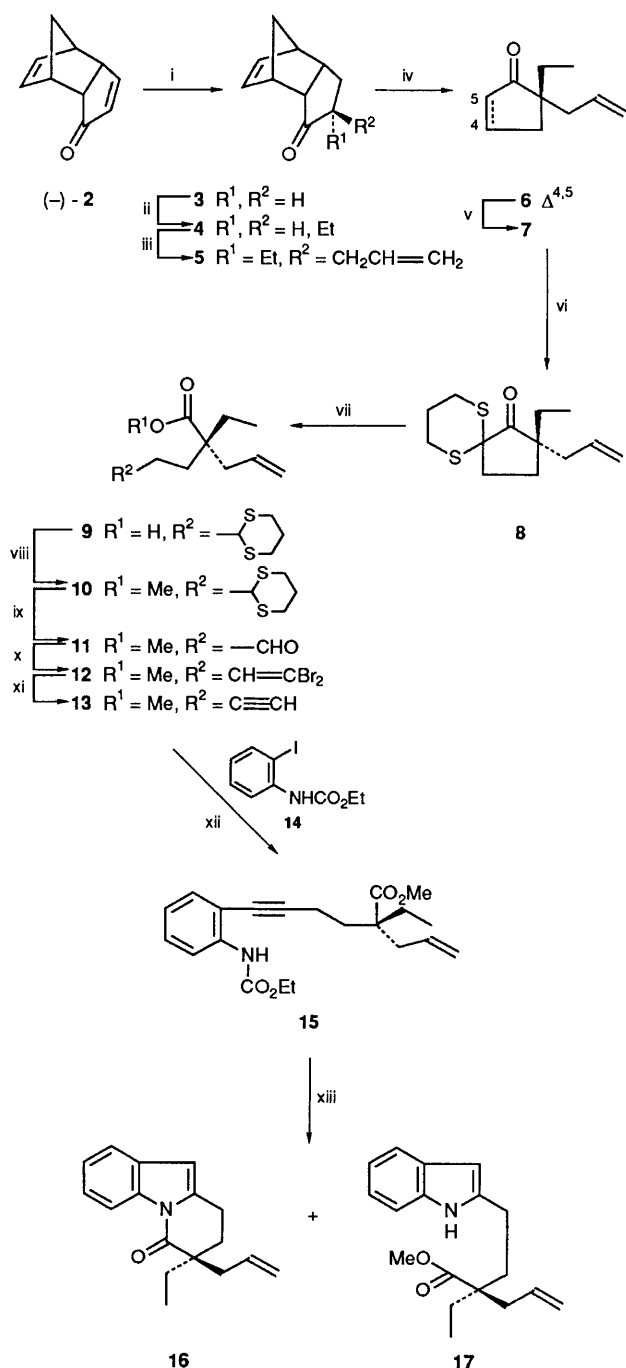
(20*S*, 21*R*) - **1**



(20*R*, 21*S*) - **1**

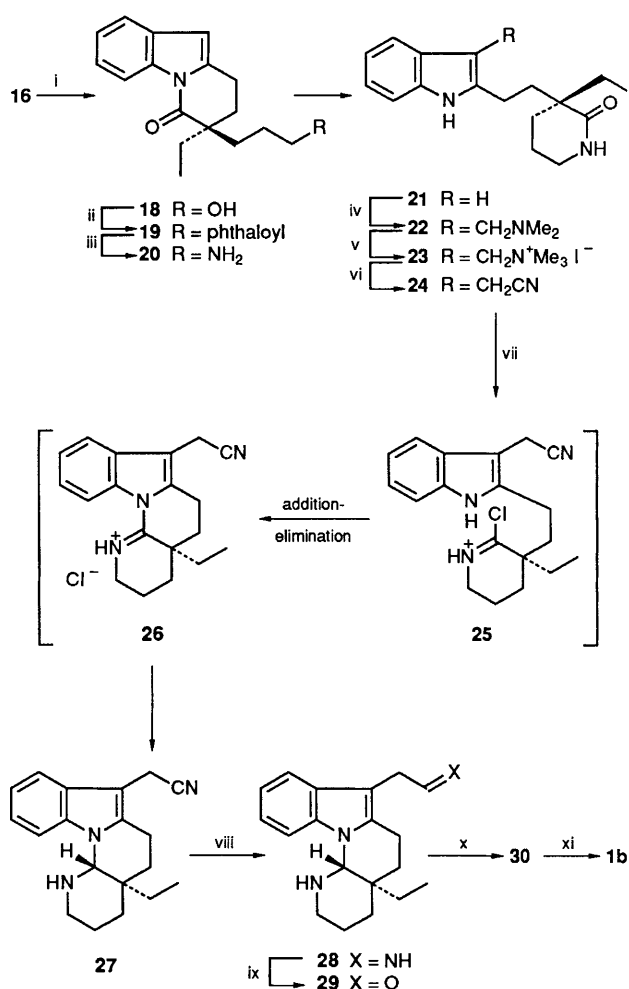
† All new compounds gave the expected analytical (combustion and/or high resolution mass) and spectral (IR, NMR and mass) data.

‡ The ester **17** could also be transformed into the lactam **21** in 44% overall yield *via* sequential hydroboration–oxidation, Mitsunobu reaction and deacylation.



Scheme 1 Reagents and conditions: i, Zn (5.0 equiv.), AcOH-EtOH (1 : 3), reflux, 4 h; ii, EtI (2.0 equiv.), Bu^tOK (1.2 equiv.), THF, -70 to -30 °C, 15 min; iii, allyl bromide (2.0 equiv.), Bu^tOK (1.2 equiv.), THF, -30 °C, 5 min; iv, *o*-dichlorobenzene, reflux, 24 h; v, LiAlH₄ (1.0 equiv.), CuI (0.5 equiv.), HMPA-THF (1 : 4), -75 °C, 15 min; vi, propane-1,3-diylthiosylate (1.5 equiv.), Bu^tOK (3.0 equiv.), Bu^tOH-THF (1 : 4), 0 °C; vii, KOH (5.0 equiv.), Bu^tOH, 70 °C, 12 h; viii, CH₂N₂, Et₂O; ix, MeI (*ca.* 1.0 equiv.), CaCO₃ (5.0 equiv.), 10% aq. MeCN, reflux, 1 h; x, Ph₃P (4.0 equiv.), CBr₄ (2.0 equiv.), NEt₃ (3.0 equiv.), CH₂Cl₂, 0 °C, 5 min; xi, LDA (3.0 equiv.), THF, -78 °C, 10 min; xii, **14** (1.1 equiv.), PdCl₂(PPh₃)₂ (2.0%), CuI (5.0%), NEt₃, reflux, 30 min; xiii, NaOEt (10 equiv.), NEt₃ (5.0%), EtOH, reflux, 3 h; HMPA = hexamethylphosphoric triamide; LDA = lithium diisopropylamide

Construction of the cyclic aminal portion could be accomplished in a two-step sequence in the same reaction flask. Thus, treatment of **24** with phosphoryl chloride in refluxing toluene, followed by sodium borohydride at 0 °C, yielded the tetracyclic amine **27**, m.p. 121.5–123 °C, $[\alpha]_D^{28} +104.1^\circ$ (*c* 1.26,

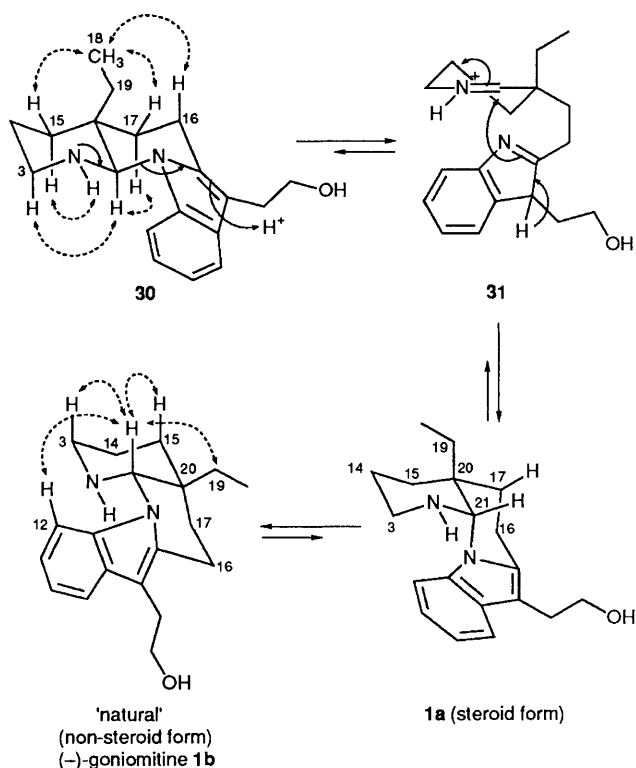


Scheme 2 Reagents and conditions: i, dicyclohexylborane (1.5 equiv.), THF, 0 °C, 30 min then 10% NaOH (1.0 equiv.), 30% H₂O₂ (3.0 equiv.), 0 °C, 30 min; ii, phthalimide (1.3 equiv.), Ph₃P (1.3 equiv.), (PrⁱO₂CN)₂ (1.3 equiv.), THF, 0 °C, 10 min; iii, NH₂NH₂·H₂O (4.0 equiv.), EtOH, reflux, 2 h; iv, Me₂N⁺=CH₂(Cl⁻) (1.5 equiv.), CH₂Cl₂, room temp., 30 min; v, MeI, MeOH, room temp., 10 min; vi, NaCN (1.3 equiv.), DMF, 100 °C, 10 min; vii, POCl₃ (6.0 equiv.), toluene, reflux 2 h then NaBH₄, MeOH, 0 °C; viii, DIBAL (1.5 equiv.), CH₂Cl₂, -75 °C, 10 min; ix, dil. H₂SO₄; x, NaBH₄; xi, 30% HCl-MeOH (1 : 10), reflux, 30 min

CHCl₃), in 84% yield as a single epimer. Although the stereochemistry of the ring juncture of the aminal portion could not be determined at this stage, the later transformation clarified it to be *trans*. We presumed that the cyclization occurred at the chloroiminium stage **25** to give the iminium intermediate **26**, by spontaneous addition-elimination reaction, which was reduced stereoselectively from the less hindered face to give **27** with the *trans*-configuration.

On sequential reduction with diisobutylaluminium hydride (DIBAL), acid hydrolysis and reduction with sodium borohydride, **27** furnished the amino-alcohol **30**, m.p. 140–142 °C, $[\alpha]_D^{29} +110.7^\circ$ (*c* 0.97, CHCl₃), δ_H (500 MHz, CDCl₃) 0.89 (t, 3H, *J* 7.3 Hz), 1.23 (dt, 1H, *J* 3.1, 13.5 Hz), 1.34–1.43 (m, 3H), 1.58–1.73 (m, 4H), 1.85 (dd, 1H, *J* 7.3, 12.8 Hz), 1.91 (d, 1H, *J* 13.4 Hz), 4.62 (s, 1H), 7.02–7.06 (m, 2H), 7.44–7.48 (m, 1H) and 8.40–8.44 (m, 1H); δ_C (125.65 MHz, CDCl₃) 7.1, 16.2, 19.1, 22.1, 27.7, 30.3, 32.3, 36.1, 45.7, 62.6, 79.9, 106.8, 115.3, 117.1, 119.4, 120.4, 129.0, 135.2 and 137.6, in 49% overall yield, *via* **28** and **29**, which was not identical with the natural product **1**. Since the discordance indicated the product to be either an epimer or a conformer, it was refluxed in

§ Attempts to isolate **25** as well as its cyclization product **26** failed.



Scheme 3 Arrows on structures **30** and **1b** show NOEs

methanolic hydrochloric acid to yield the thermodynamically most stable isomer. As expected clean and complete isomerization occurred to afford the single product **1**, m.p. 149–150 °C, $[\alpha]_D^{27} -87.1^\circ$ (c 0.42, CHCl_3), in 82% yield, the physical¹ [m.p. 150 °C, $[\alpha]_D^{20} -80^\circ$ (c 0.9, CHCl_3)] and spectral data^{2,¶} of which were identical with those of (-)-goniomitine (**1**) (Scheme 2).

NOE experiments in $[\text{D}_5]\text{pyridine}$ revealed that the unnatural and the natural products are epimeric at the aminal centre. Namely, significant NOE between the C-21 aminal proton and axial protons on C-3, C-15 and C-17 and between the C-18 methyl group and equatorial protons on C-15 and C-17 as well as the C-16 axial proton in the former and a significant NOE between the C-21 aminal proton and one of the C-19 protons, axial protons on C-3 and C-15 and aromatic

¶ Spectral identification between natural goniomitine [(20*R*,21*S*)-**1**] and the synthetic (+)-enantiomer [(20*S*,21*R*)-**1**] which was first obtained from (+)-dienone [(+)-**2**] was kindly carried out by Professor H.-P. Husson.

C-12 proton in the latter clearly indicated the unnatural isomer to have a *trans*-junction and the natural isomer a *cis*-junction. Moreover, the NOE observed in the latter unambiguously supported the natural product existing in the thermodynamically more stable conformation shown as **1b**, disposing the indole moiety in the less congested equatorial position. Facile transformation of the *trans*-epimer **30** into the natural product **1b** may be rationalised by a sequence of equilibrium reactions, such as acid-promoted ring opening, recyclization of the iminium intermediate **30** in a stereoelectronically favoured direction, and conformational inversion of the kinetic product **1a** ('steroid form') into the thermodynamic product **1b** ('non-steroid form') (Scheme 3).

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