



Synthesis and Absolute Configuration of (-)-Normalindine

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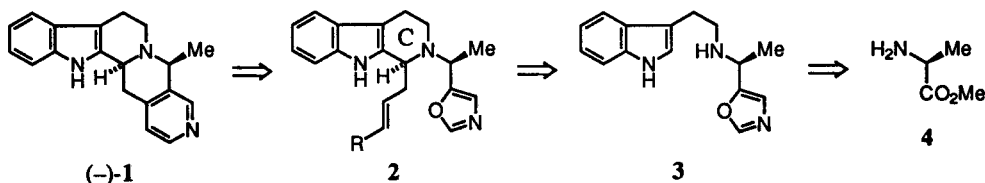
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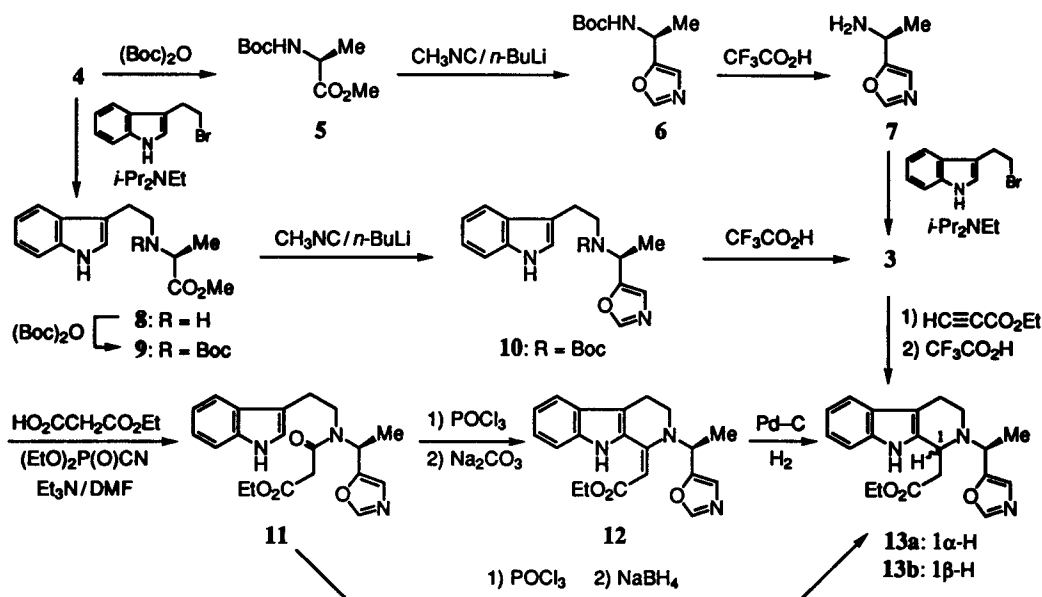
Abstract: The first chiral synthesis of the *Strychnos* and *Ophiorrhiza* alkaloid (-)-normalindine has been accomplished through a route starting from L-alanine methyl ester and exploiting intramolecular oxazole-olefin Diels-Alder reaction. As a result, the absolute stereochemistry of normalindine has been defined as represented by formula (-)-1. © 1997 Elsevier Science Ltd.

(-)-Normalindine (**1**), a member of the alkaloids containing the indolo[2',3':3,4]pyrido[1,2-*b*]naphthyridine ring system,¹ was first isolated by Massiot *et al.* in 1987 from the root bark of *Strychnos johnsonii* (Loganiaceae).² The structure and relative stereochemical assignment, based on its spectral properties, were subsequently confirmed by two racemic syntheses of **1**.³ Thereafter Arbain *et al.* also reported the isolation of this alkaloid from the leaves of *Ophiorrhiza filistipula* (Rubiaceae) and inferred its absolute configuration to be (-)-**1** on the basis of CD spectral evidence.⁴ With a view to verifying the correctness of this inference, we accomplished a chiral synthesis of the target compound (-)-**1** in the present work.



From the retrosynthetic perspective, we envisioned an efficient construction of the naphthyridine skeleton of (-)-**1** by adopting the intramolecular Diels-Alder reaction of the oxazole derivative **2**,^{5,6} which in turn would be obtained from **3** via the formation of ring C and the subsequent introduction of an appropriate dienophile. Furthermore, the requisite enantiomer of **3** would be secured by elaboration of L-alanine methyl ester (**4**).

As our point of departure, the *N*-protected amino ester **5**,⁷ derived from **4**, was converted into the oxazole **6** [mp 46.5–47.5 °C; $[\alpha]_D^{28} -85.1^\circ$ (*c* 1.00, MeOH)]⁸ in 76% yield by treatment with α -lithiated methyl isocyanide at -78 °C (THF, 30 min) followed by warming to 0 °C and quenching with AcOH according to the method of Schöllkopf.⁹ The enantiomeric purity of **6** thus obtained was determined to be 98% ee by chiral HPLC analysis. After deprotection of **6** (CF₃CO₂H, CH₂Cl₂, room temperature, 1 h, 97% yield), *N*-alkylation of the resulting primary amine **7** [$[\alpha]_D^{28} -13.0^\circ$ (*c* 1.01, MeOH)] with 2-(3-indolyl)ethyl bromide (*i*-Pr₂NEt, boiling THF, 7 days) was effected in a manner similar to that employed by Waldmann's group,¹⁰ providing the desired amino oxazole **3** [$[\alpha]_D^{22} -39.5^\circ$ (*c* 1.00, CHCl₃)] in 55% yield. Alternatively, **3** possessing a parallel

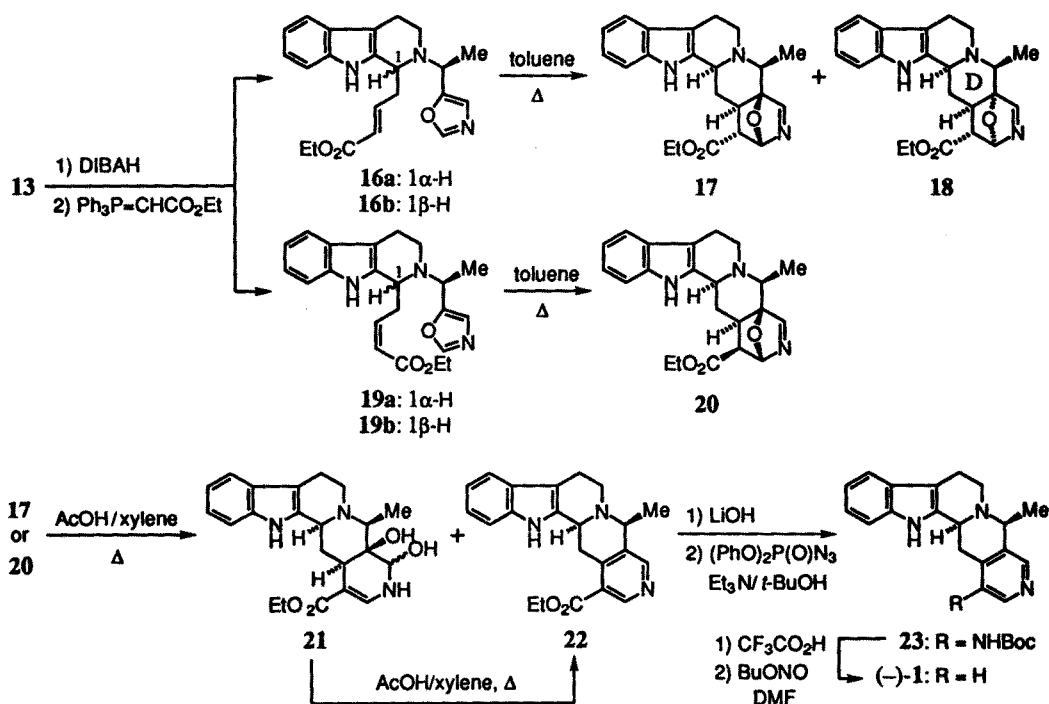


optical purity was also obtained from 4 in 46% overall yield through 8 [[α]_D²⁴ -23.1° (*c* 1.01, CHCl₃); 66%],¹⁰ 9 [mp 136.5–137 °C; [α]_D²¹ -21.7° (*c* 1.01, CHCl₃); 94%], and 10 [mp 116–117 °C; [α]_D¹⁷ -29.2° (*c* 1.00, CHCl₃); 76%].

For the construction of ring C in the intermediate 2, the amino oxazole 3 was first converted into the amide 11 [[α]_D²⁸ -38.8° (*c* 1.00, CHCl₃)] in 98% yield by condensation with monoethyl malonate using the coupling reagent diethyl phosphorocyanidate¹¹ (Et₃N, DMF, room temperature, 2 h). The Bischler–Napieralski cyclization (POCl₃, boiling CH₃CN, 4 h) of 11 and reduction of the resulting iminium salt 14 with NaBH₄ (MeOH, 0 °C, 1.5 h) afforded the amino ester 13 as a 2 : 1 diastereoisomeric mixture in 31% yield. The hydrogen at the newly generated stereogenic center [C(1)] in the major isomer 13a was assigned the α configuration on the basis of the argument of Polniaszek:¹² the hydride attack would take place preferentially at the sterically less hindered face of a conformer of the iminium ion 14 with minimized allylic 1,3-strain.¹³ Catalytic hydrogenation of 12 [[α]_D²⁸ -24.0° (*c* 0.50, CHCl₃)],¹⁴ obtained from 14 in 46% yield (from 11) by basification, with Pd-C and hydrogen (AcOEt, 1 atm, room temperature, 5 h) increased the diastereoselectivity to give a 3 : 1 mixture (93%) of 13a and 13b. On the other hand, application of the modified Pictet–Spengler cyclization¹⁵ to 3 [(i) ethyl propiolate, CHCl₃, room temperature, 40 h; (ii) CF₃CO₂H] gave a 1 : 2 mixture of 13a and 13b in 78% yield. By analogy with a consideration proposed by Waldmann *et al.*¹⁰ for related systems, this cyclization is presumed to have proceeded *via* the major conformer 15 of the iminium ion.

We next focused our attention on the introduction of an olefinic dienophile, required for the subsequent intramolecular oxazole–olefin Diels–Alder reaction, into the amino ester 13. Thus, reduction of the above 3 : 1 mixture of 13a and 13b with diisobutylaluminum hydride (CH₂Cl₂, -78 °C, 20 min) provided the correspond-

ing aldehyde (**13**: CHO for CO₂Et), but initial attempts at methylenation of the aldehyde to give the olefin **2** (R = H) were all unsuccessful. However, the Wittig reaction of the aldehyde with ethyl (triphenylphosphoranylidene)acetate (CH₂Cl₂, room temperature, 3 h) proceeded smoothly, affording a 3 : 1 mixture of the (*E*)-esters **16a** [*J* = 15.5 Hz (olefinic protons)] and **16b** (*J* = 15.5 Hz) and a 3 : 1 mixture of the (*Z*)-esters **19a** (*J* = 11.5 Hz) and **19b** (*J* = 11.5 Hz) in 59% and 26% overall yields (from **13**), respectively.



With the oxazole–olefin derivatives **16** and **19** in hand, we set out to explore their intramolecular Diels–Alder reactions. Best results were obtained when the 3 : 1 mixture of the (*E*)-isomers **16a** and **16b** was heated in boiling toluene for 24 h, producing the adducts **17** [mp 208–211 °C (dec), [α]_D²⁰ +136° (*c* 0.49, CHCl₃)] and **18** [mp 181–182 °C (dec), [α]_D²⁰ –52.3° (*c* 0.51, CHCl₃)] in 53% and 5% yields, respectively. None of adducts arising from the minor diastereoisomer **16b** were obtained. In a similar fashion, the 3 : 1 mixture of the (*Z*)-isomers **19a** and **19b** provided the adduct **20** [mp 208–210 °C (dec), [α]_D²⁵ –4.3° (*c* 0.50, CHCl₃)] in 40% yield. The stereochemistries of **17**, **18**, and **20** were assigned on the basis of the appearance of absorption bands due to a *trans*-quinolizidine ring¹⁶ in their IR spectra and the results of detailed NOE experiments.

On treatment with AcOH–xylene (1 : 5, reflux, 8 h), **17** was converted into the aromatic ester **22** [mp 198–200 °C (dec), [α]_D²⁴ –268° (*c* 0.35, CHCl₃)] and the diol **21** in 18% and 64% yields, respectively. Similar treatment of **21** gave **22** in 13% yield together with unaltered **21** (62%). A parallel result was also obtained with **20**.¹⁷ Alkaline hydrolysis (LiOH, THF–MeOH–H₂O, room temperature, 1.5 h) of **22** followed by the modified Curtius rearrangement utilizing diphenyl phosphoroazidate¹⁸ (Et₃N, boiling *t*-BuOH, 5 h) afforded the carbamate **23** [mp 183–185 °C (dec), [α]_D²¹ –205° (*c* 0.11, CHCl₃)] in 64% yield. Finally, treatment of **23** with CF₃CO₂H (CH₂Cl₂, room temperature, 5 h) and subsequent reductive deamination of the resulting arylamine

with butyl nitrite in DMF¹⁹ (70 °C, 30 min) provided the target compound [(-)-1] [mp 122–126 °C, $[\alpha]_D^{22}$ –212° (c 0.29, CHCl₃)] in 40% yield. The UV (MeOH), IR (KBr), ¹H NMR (CDCl₃), and mass spectra and TLC mobility (three solvent systems) of the synthetic (-)-1 were found to be virtually identical with those of natural normalindine [mp 131–136 °C, $[\alpha]_D$ –210° (c 0.1, CHCl₃)].⁴

In conclusion, the synthesis of the *Strychnos* and *Ophiorrhiza* alkaloid normalindine has been achieved in chiral form. The present results have not only established the stereoformula (-)-1 to be a complete expression for normalindine but also, to our knowledge, represent the first example for the chiral synthesis of the indolopyridonaphthyridine alkaloids, featuring the application of intramolecular oxazole–olefin Diels–Alder reaction to a chiral compound.

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