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Synthesis and Absolute Configuration of (–)-Normalindine

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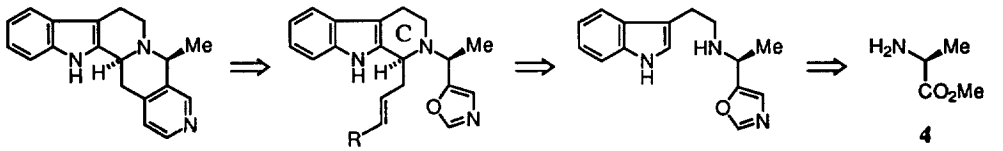
Abstract: The first chiral synthesis of the *Strychnos* and *Ophiorrhiza* alkaloid (–)-normalindine has been accomplished through a route starting from L-alanine methyl ester and exploiting intramolecular oxazole–olefin Diels–Alder reaction. As a result, the absolute stereochemistry of normalindine has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

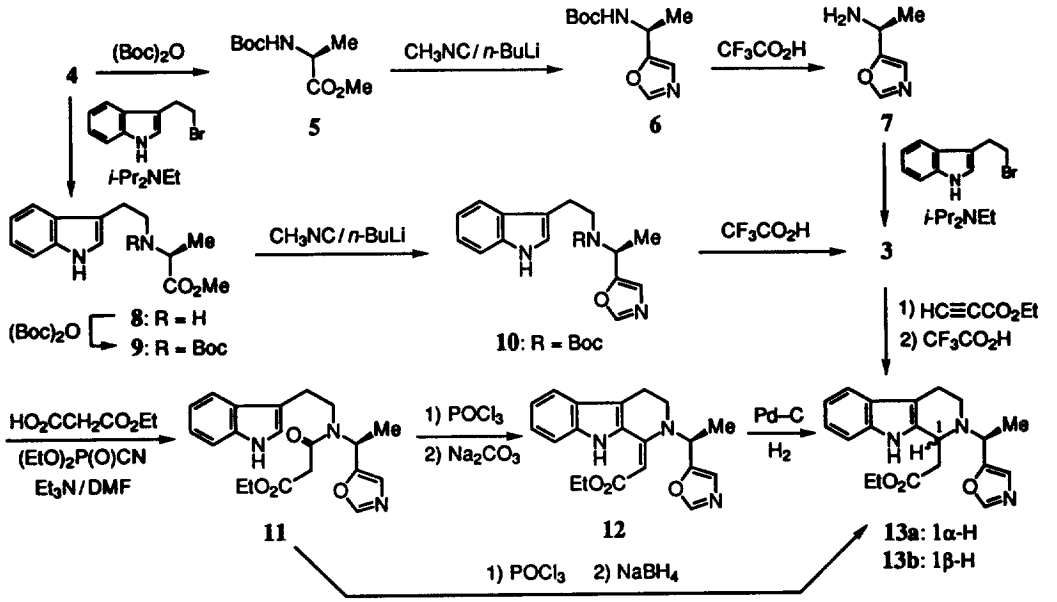
(–)-Normalindine (**1**), a member of the alkaloids containing the indolo[2',3':3,4]pyrido[1,2-*b*]naphthyridine ring system,[1] was first isolated by Massiot *et al.* in 1987 from the root bark of *Strychnos johnsonii* (Loganiaceae).[2] The structure and relative stereochemical assignment, based on 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.



(–)-**1** **2** **3** **4**

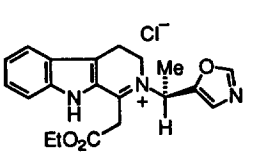
From the retrosynthetic perspective, we envisioned an efficient construction of the naphthyridine skeleton of (–)-**1** by adopting the intramolecular Diels–Alder reaction of the oxazole derivative **2**,[5,6] which in turn would be obtained from **3** *via* the formation of ring C and the subsequent 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° (*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** (CF_3CO_2H, CH_2Cl_2, room temperature, 1 h, 97% yield), *N*-alkylation of the resulting primary amine **7** [$[\alpha]_D^{28}$ –13.0° (*c* 1.01, MeOH)] with 2-(3-indolyl)ethyl bromide (*i*-Pr_2NEt, 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° (*c* 1.00, $CHCl_3$)] in 55% yield. Alternatively, **3** possessing a parallel



optical purity was also obtained from **4** in 46% overall yield through **8** [$[\alpha]_D^{24}$ –23.1° (*c* 1.01, $CHCl_3$); 66%],[10] **9** [mp 136.5–137 °C; $[\alpha]_D^{21}$ –21.7° (*c* 1.01, $CHCl_3$); 94%], and **10** [mp 116–117 °C; $[\alpha]_D^{17}$ –29.2° (*c* 1.00, $CHCl_3$); 76%].

For the construction of ring C in the intermediate **2**, the amino oxazole **3** was first converted into the amide **11** [$[\alpha]_D^{28}$ –38.8° (*c* 1.00, $CHCl_3$)] in 98% yield by condensation with monoethyl malonate using the coupling reagent diethyl phosphorocyanidate[11] (Et_3N, DMF, room temperature, 2 h). The Bischler–Napieralski cyclization ($POCl_3$, boiling CH_3CN, 4 h) of **11** and reduction of the resulting iminium salt **14** with $NaBH_4$ (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** [$[\alpha]_D^{28}$ –24.0° (*c* 0.50, $CHCl_3$)],[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 cyclization[15] to **3** [(i) ethyl propiolate, $CHCl_3$, room temperature, 40 h; (ii) CF_3CO_2H] 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.



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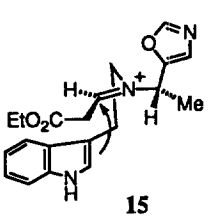

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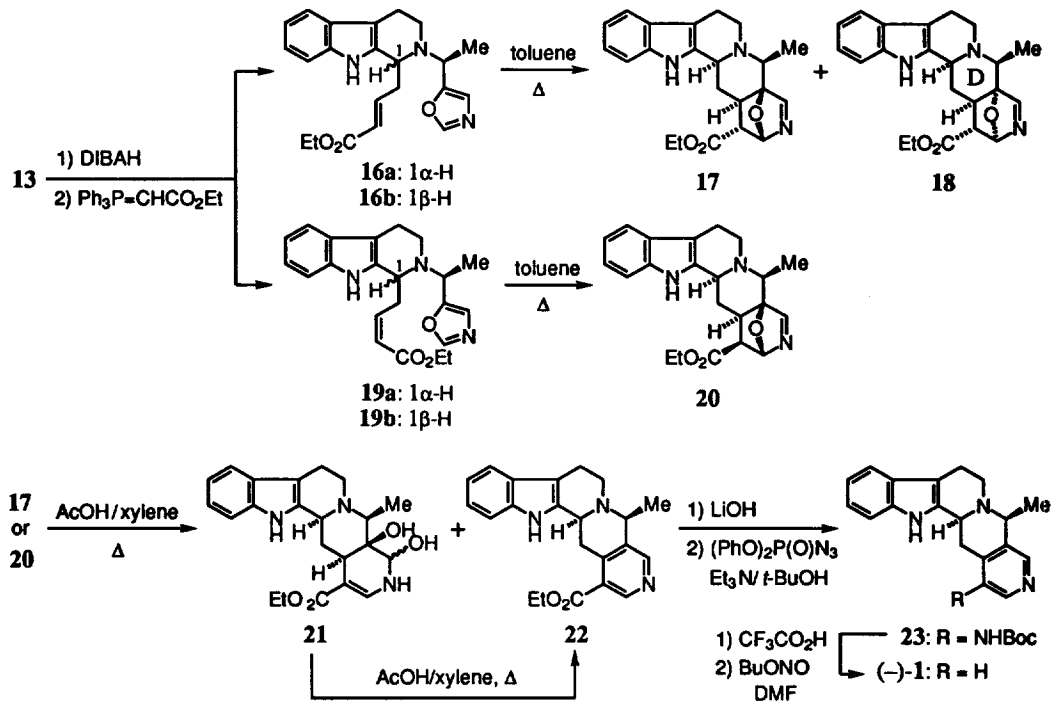
We next focused our attention on the introduction of an olefinic dienophile, required for the subsequent intramolecular oxazole–olefin Diels–Alder reaction, into the amino ester **13**. Thus, reduction of the above 3 : 1 mixture of **13a** and **13b** with diisobutylaluminum hydride (CH_2Cl_2, –78 °C, 20 min) provided the correspond-

ing aldehyde (**13**: CHO for CO_2Et), 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 (CH_2Cl_2, 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), $[\alpha]_D^{20}$ +136° (*c* 0.49, $CHCl_3$)] and **18** [mp 181–182 °C (dec), $[\alpha]_D^{20}$ –52.3° (*c* 0.51, $CHCl_3$)] 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), $[\alpha]_D^{25}$ –4.3° (*c* 0.50, $CHCl_3$)] 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 ring[16] 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), $[\alpha]_D^{24}$ –268° (*c* 0.35, $CHCl_3$)] 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–H_2O, room temperature, 1.5 h) of **22** followed by the modified Curtius rearrangement utilizing diphenyl phosphoroazidate[18] (Et_3N, boiling *t*-BuOH, 5 h) afforded the carbamate **23** [mp 183–185 °C (dec), $[\alpha]_D^{21}$ –205° (*c* 0.11, $CHCl_3$)] in 64% yield. Finally, treatment of **23** with CF_3CO_2H (CH_2Cl_2, room temperature, 5 h) and subsequent reductive deamination of the resulting arylamine

with butyl nitrite in DMF[19] (70 °C, 30 min) provided the target compound [(–)-**1**] [mp 122–126 °C, $[\alpha]_D^{22}$ –212° (*c* 0.29, $CHCl_3$)] in 40% yield. The UV (MeOH), IR (KBr), ^1H NMR ($CDCl_3$), 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, $CHCl_3$)].[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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