Synthetic Approaches to the Alkaloids of the Ancistrocladaceae: (−)-*O*-Methylancistrocladine and (+)-*O*-Methylhamatine

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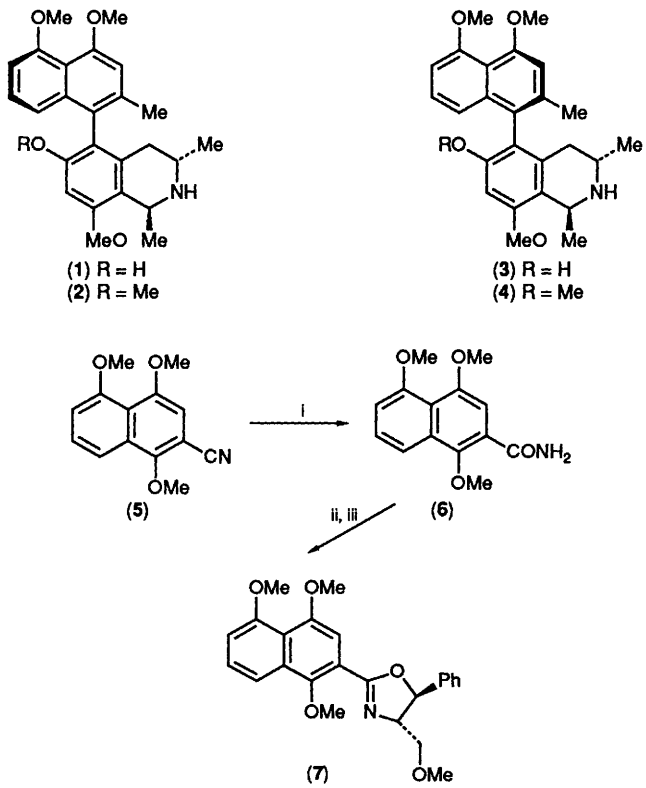
An asymmetric total synthesis of the naphthylisoquinoline alkaloid (−)-*O*-methylancistrocladine (**2**) is described; the synthetic method also provides routes to the atropisomer *O*-methylhamatine (**4**) and the enantiomers of these alkaloids.

In continuation of our studies on the total synthesis of the unusual naphthylisoquinoline alkaloids of the Ancistrocladaceae[1] we now report the asymmetric total synthesis of (−)-*O*-methylancistrocladine (**2**), an alkaloid of *Ancistrocladus congolensis* Léonard and *A. heyneanus* Wall.,[2] and also a derivative of ancistrocladine (**1**), an alkaloid of *A. heyneanus* Wall.,[3] as well as the synthesis of its atropisomer (+)-*O*-methylhamatine (**4**), a derivative of hamatine (**3**), an alkaloid of *A. hamatus* Gilg.[4]

By the use of a chiral dihydro-oxazole in the biaryl synthesis which we have described previously,[1] we have secured a diastereoisomeric excess of one atropisomer and these atropisomers were easily separated by chromatography. For this synthetic purpose the nitrile[1] (**5**) (Scheme 1) was partially hydrolysed to the amide (**6**)† (100%), m.p. 147—148 °C, which by the use of (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxypropan-1-ol,[5] was converted into the oily dihydro-oxazole (**7**) (81%), $[\alpha]_D^{23}$ +97.8° (THF, *c* 4.90). The Grignard reagent (**10**) (Scheme 2), required for the biaryl synthesis, was obtained from the 1,3-dioxane (**9**),† m.p. 105—106 °C, by protection (100%) of the known aldehyde (**8**),[6] and subsequent treatment with magnesium in tetrahydrofuran (THF).

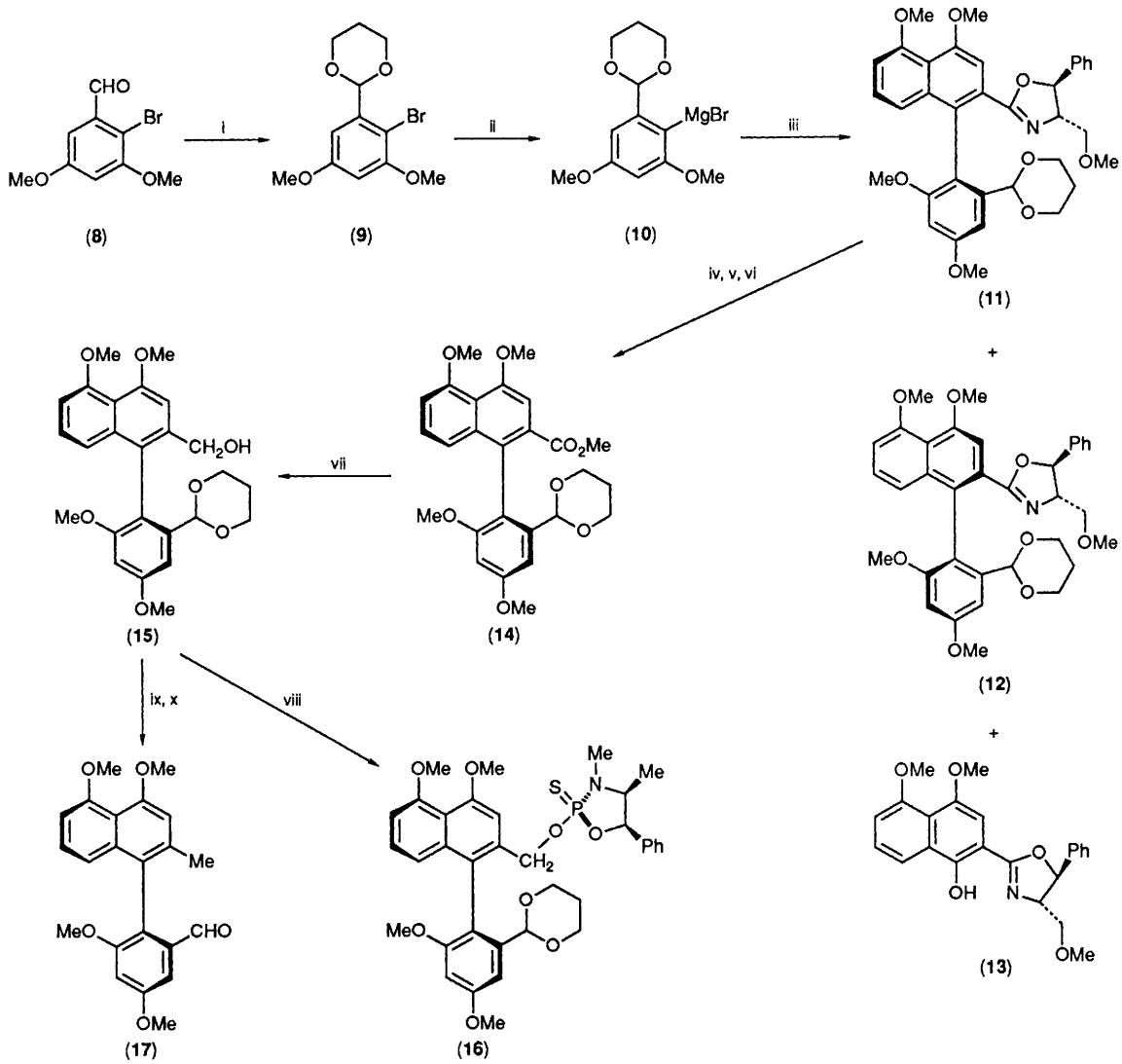
When the Grignard reagent (**10**) was allowed to react with the dihydro-oxazole (**7**) a readily separable mixture of the biaryls (**11**)† (45%), m.p. 172—173 °C, $[\alpha]_D^{23}$ +138.0° (THF, *c* 1.30), R_F 0.44 (EtOAc), and (**12**)† (20%), m.p. 160—161 °C, $[\alpha]_D^{23}$ +116.9° (THF, *c* 1.20), R_F 0.31 (EtOAc), was obtained as well as a small amount of the demethylated product (**13**) which could be recycled by methylation.

In order to establish the absolute configuration of the biaryl linkage the major diastereoisomer (**11**) was converted into the degradation product (**20**) of ancistrocladine (**1**). Thus compound (**11**) was converted into the oily ester (**14**) (91%), $[\alpha]_D^{23}$ +12.9° (THF, *c* 1.50), and thence by reduction into the primary alcohol (**15**)† (92%), m.p. 176—177 °C, $[\alpha]_D^{23}$ −71.9° (THF, *c* 2.76). That no racemization had occurred during these processes was demonstrated by the conversion of the alcohol (**15**) into the oxazaphospholidine-2-thione (**16**).[7] This compound, on comparison of its proton-decoupled ^{31}P NMR



Scheme 1. *Reagents and conditions*: i, KOH, Bu^{t}OH, reflux, 1.5 h; ii, Et_3OBF_4, $ClCH_2CH_2Cl$, Ar, 25 °C, 24 h; iii, (1*S*,2*S*)-(+)-1-phenyl-2-amino-3-methoxypropan-1-ol, $ClCH_2CH_2Cl$, Ar, reflux, 48 h.

† New compounds gave satisfactory elemental analyses and spectra in accord with the assigned structures.



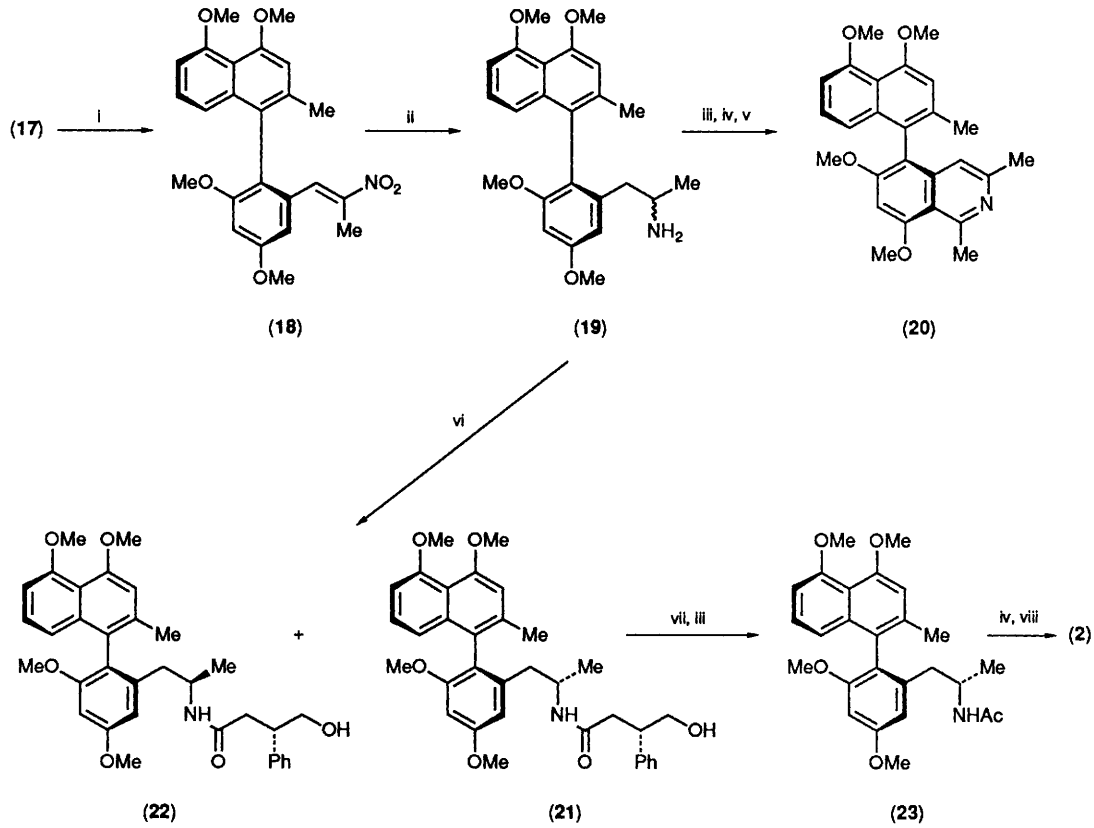
Scheme 2. *Reagents and conditions*: i, $HO(CH_2)_3OH$, PhH, *p*-$MeC_6H_4SO_3H$, reflux, 2 h; ii, Mg, THF; iii, (**7**), THF, reflux, Ar, 5 h; iv, MeI, $MeNO_2$, 60 °C, 24 h; v, KOH, Me_2SO, H_2O, 100 °C, 20 h; vi, MeI, dimethylformamide, K_2CO_3, 25 °C, 1.5 h; vii, $LiAlH_4$, THF, 25 °C, 0.5 h; viii, NaH, THF, 60 °C, 1 h, (2*R*,4*S*,5*R*)-(−)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione, reflux, 12 h; ix, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C, 20 min; x, $LiAlH_4$, THF, reflux, 2 h, H^+.

spectrum‡ with that of the similar derivative obtained from the racemic alcohol (**15**), exhibited only one signal thereby establishing the optical purity of the alcohol (**15**).

Mesylation and subsequent reduction of the alcohol (**15**) with acidic work-up provided the intermediate (**17**)† (95%), m.p. 152—154 °C, $[\alpha]_D^{23}$ +8.0° (THF, *c* 3.15). Henry reaction now gave the nitrostyrene (**18**)† (81%), m.p. 192—193 °C, $[\alpha]_D^{23}$ −145.8° (THF, *c* 3.90) which on reduction gave the amine (**19**) (88%) as a mixture of diastereoisomers (Scheme 3). Subsequent acetylation, Bischler–Napieralski ring-closure, and dehydrogenation of the resultant 3,4-dihydroisoquinoline gave the naphthylisoquinoline (**20**)† (14%), m.p. 238—240 °C, $[\alpha]_D^{23}$ +64.0° ($CHCl_3$, *c* 0.04) [lit.,[3,4] m.p. 240—242 °C, $[\alpha]_D$ +58.87, 53.01° ($CHCl_3$)], previously obtained by degradation of ancistrocladine;[3] hence the absolute configuration of the major diastereoisomer (**15**) is as shown.

An efficient resolution[8] of the diastereoisomeric amines (**19**) was achieved by their conversion into the chromatographically separable oily hydroxy-amides (**21**) (34%), $[\alpha]_D^{23}$ −7.2° (THF, *c* 1.24), R_F 0.40 (EtOAc), and (**22**) (34%), $[\alpha]_D^{23}$ −12.0° (THF, *c* 1.02), R_F 0.48 (EtOAc). Hydrolysis and subsequent acetylation of compound (**21**) furnished the *N*-acetyl compound (**23**)† (71%), m.p. 72—75 °C, $[\alpha]_D^{23}$ −43.9° (THF, *c* 1.42). This compound, on cyclization and stereoselective reduction[9] (90% *trans*) of the resultant 3,4-dihydroisoquinoline, gave (−)-*O*-methylancistrocladine (**2**) (84%), best characterized as its hydrochloride,† m.p. 271—273 °C (decomp.), $[\alpha]_D^{23}$ −40.0° ($CHCl_3$, *c* 0.42), which was identical in all respects with a sample prepared from authentic ancistrocladine (**1**), kindly provided by Dr. T. R. Govindachari.

‡ (**16**): ^{31}P NMR ($CDCl_3$, relative to 85% H_3PO_4 capillary), δ 84.28.



Scheme 3. *Reagents and conditions*: i, $EtNO_2$, NH_4OAc, AcOH, 80 °C, 4 h; ii, $LiAlH_4$, THF, reflux, 2 h; iii, C_5H_5N, Ac_2O, 25 °C, 1 h; iv, $POCl_3$, MeCN, reflux, 30 min; v, W2 Raney nickel, $C_{10}H_8$, reflux, Ar, 4 h; vi, 2-hydroxypyridine, (*S*)-(+)-4,5-dihydro-4-phenylfuran-2(3*H*)-one, PhMe, reflux, Ar, 24 h; vii, 1 M H_2SO_4, dioxane, reflux, Ar, 7 h; viii, $LiAlH_4$, Bu^i_3Al, THF, −78 to 25 °C, 3 h.

The epimeric amide (**22**) was converted into (−)-*O*-methylhamatine, and application of the same methodology to the minor diastereoisomer (**12**) gave (+)-*O*-methylhamatine (**4**)[4] and (+)-*O*-methylancistrocladine.

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References

1 M. A. Rizzacasa and M. V. Sargent, *J. Chem. Soc., Chem. Commun.*, 1989, 301.
2 J. P. Foucher, J. L. Pousset, A. Cavé, A. Bouquet, and R. Paris, *Plant. méd. et Phytothér.*, 1975, **9**, 87; H. K. Desai, D. H. Gawad, T. R. Govindachari, B. S. Joshi, P. C. Parthasarathy, K. S. Ramachandran, K. R. Ravindranath, A. R. Sidhaye, and N. Viswanathan, *Ind. J. Chem.*, 1976, **14B**, 473.
3 T. R. Govindachari and P. C. Parthasarathy, *Tetrahedron*, 1971, **27**, 1013; T. R. Govindachari, K. Nagarajan, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, G. Kartha, S. L. Chen, and K. Nakanishi, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1413.
4 T. R. Govindachari, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, K. S. Ramachandran, and E. Lee, *Ind. J. Chem.*, 1975, **13**, 641.
5 A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, 1976, **98**, 567.
6 G. Lock and G. Nottes, *Monatsh. Chem.*, 1936, **68**, 51.
7 C. R. Johnson, R. C. Elliott, and T. D. Penning, *J. Am. Chem. Soc.*, 1984, **106**, 5019.
8 G. Helmchen and G. Nill, *Angew. Chem.*, 1979, **91**, 66.
9 Y. Matsumura, K. Maruoka, and H. Yamomoto, *Tetrahedron Lett.*, 1982, 1929.

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