Tetrahedron Letters, Vol 32, No 31, pp 3895-3898, 1991
Printed in Great Britain

0040-4039/91 $3 00 +
Pergamon Press plc

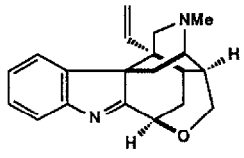
ASYMMETRIC SYNTHESIS OF INDOLE ALKALOIDS FROM (L)-TRYPTOPHAN: FORMAL SYNTHESES OF (-)-KOUMINE, (-)-TABERPSYCHINE & (-)-KOUMIDINE

Patrick D. Bailey and Neil R. McLay

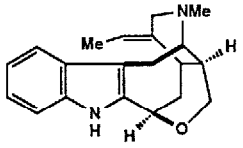
Department of Chemistry, University of York,
Heslington, York YO1 5DD, U.K.
EMAIL PDB4@UK.AC.YORK.VAXA

Summary. The reaction of (L)-tryptophan methyl ester with methyl 4-oxobutanoate under conditions of kinetic control gave a high yield of the *cis*-1,3-disubstituted tetrahydro-β-carboline (6); a simple five step procedure allowed this to be transformed into the optically pure (e.e. > 95%) bridged ketone (-)-(17), whose (+) isomer has previously been used in the syntheses of (+)-koumine (1), (+)-taberpsychine (2) & (+)-koumidine (3).

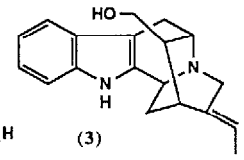
Despite the large amount of work published on the synthesis of indole alkaloids, very few groups have developed general asymmetric strategies for the preparation of these molecules. Interestingly, although (L)-tryptophan is a common biosynthetic precursor, most indole alkaloids originate from a decarboxylative pathway in which the absolute stereochemistry of the α-carbon of the amino acid is lost (temporarily, at least).[1] Nevertheless, for those alkaloids that contain the tryptophan skeleton, the stereochemistry of that moiety is invariably the same as that of the (L)-amino acid. (L)-Tryptophan would therefore seem to be the ideal starting material for the synthesis of such structures [e.g. compounds (1)-(4)].



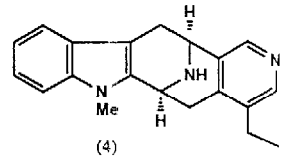
(1)



(2)



(3)



(4)

The Pictet-Spengler reaction is undoubtedly one of the most direct routes to the polycyclic systems of most indole alkaloids. But, disappointingly, the reaction of tryptophan esters with aldehydes has often led to poor *cis/trans* selectivity and racemisation.[2] In contrast, when the nitrogen is benzylated, excellent *trans* selectivity is observed,[3] and the products are optically pure.[4] This relative stereochemistry is rarely (if ever) found in indole alkaloids, but suitably functionalised aldehydes can be converted to optically pure bridged compounds *via* an elegant epimerisation α to the ester group, and the products are attractively functionalised for further modification of target alkaloids.[5] However, starting from (L)-tryptophan, this strategy leads to the

formation of antipodes of the natural products. Using a less stereo-selective variant of this tactic, Magnus was able to obtain optically pure bridged tetrahydro-β-carbolines of either absolute stereochemistry starting from (L)-tryptophan, but the undesired enantiomer still predominated, and was used in subsequent syntheses of (+)-koumine (1), (+)-taberpsychine (2) and (+)-koumidine (3).[6]

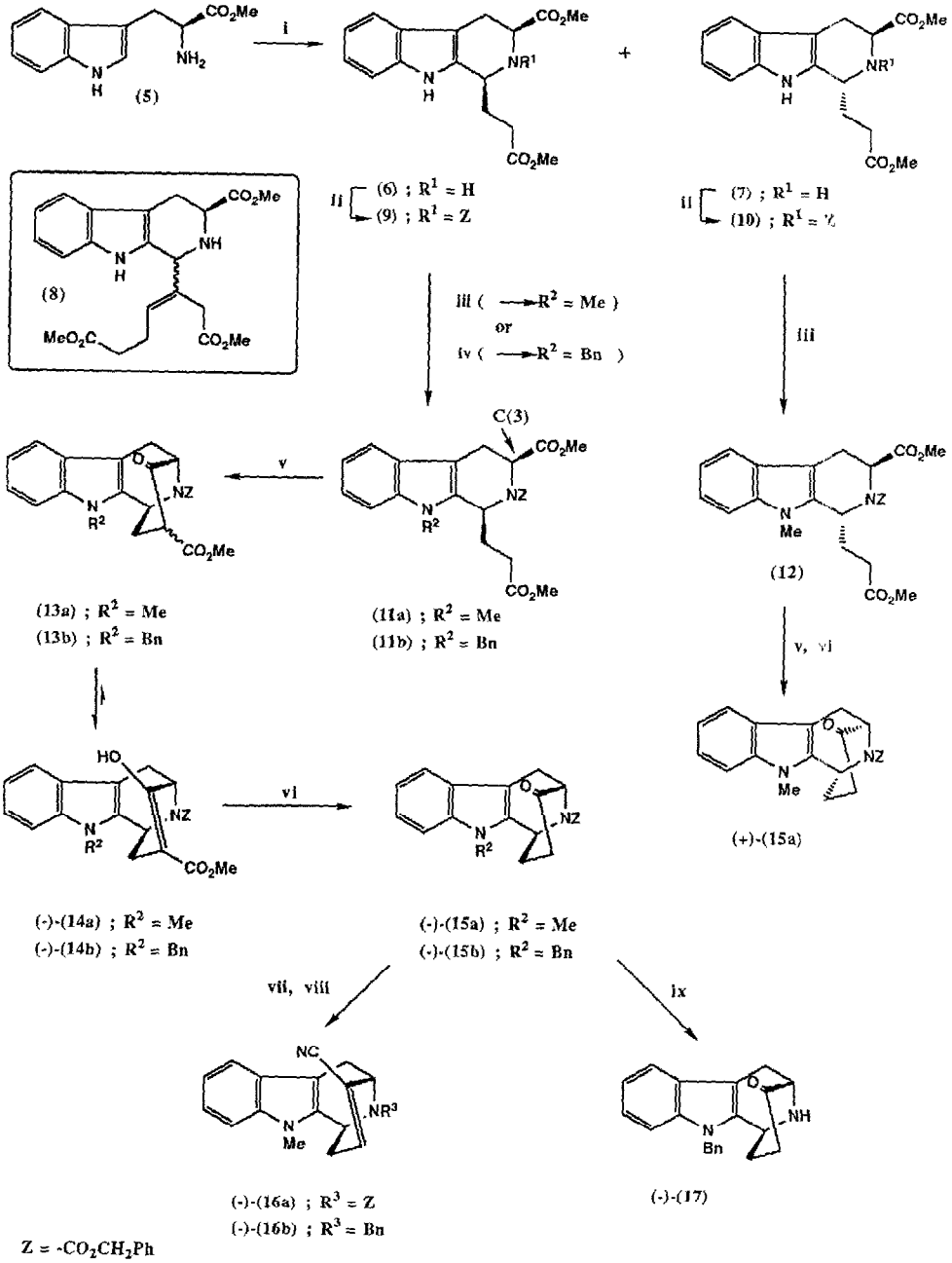
In 1987, we published results showing that *cis*-1,3-disubstituted tetrahydro-β-carbolines of high optical purity could be obtained by carrying out the Pictet-Spengler reaction under conditions of kinetic control.[7] This opened up the possibility that indolic natural products of the correct absolute stereochemistry might be accessible from (L)-tryptophan. In this paper, we describe our syntheses of advanced intermediates (-)-(15a) and (-)-(16), as the antipode of (16) has been transformed into (+)-koumine (1), (+)-taberpsychine (2) and (+)-koumidine (3), our work constitutes a formal synthesis of these alkaloids with the natural configuration (laevorotatory)

Starting from (L)-tryptophan methyl ester (5), condensation with methyl 4-oxobutanoate under acidic conditions at 0°C led to formation of the desired diesters (6) and (7), as well as the unwanted adduct (8) Suppression of this latter reaction was achieved by rapid formation of the imine (Dean-Stark apparatus, no acid), followed by Pictet-Spengler cyclisation under kinetic control[7] (CH_2Cl_2/ 0°C/ excess TFA); this tactic yielded the tetrahydro-β-carbolines (6/7) in 61% overall yield, with the *cis* isomer predominating by a ratio of 4:1. After protection of the N(2)-nitrogen using benzyl chloroformate (77%), separation of the *cis* and *trans* isomers (9) and (10) was readily accomplished by flash chromatography[8]. Subsequent N^{in}-methylation was smoothly achieved using NaH/ MeI (82%), giving the protected diesters (11a) and (12)

Interestingly, treatment of the *cis* isomer (11a) with sodium hydride under rigorously aprotic conditions led simply to epimerisation at C(3). However, when a proton source was present or added (e.g catalytic MeOH or H_2O), Dieckmann cyclisation readily took place (70%), yielding the β-keto ester (13a) in its enolic form (-)-(14a). Ester hydrolysis and *in situ* decarboxylation were effected by heating (14a) at 130°C in DMF containing H_2O (2 eq.) and NaCl (1.2 eq.),[9] giving the bridged ketone (-)-(15a) in 73% yield

Because epimerisation at C(3) was so readily achieved, it was also possible to effect Dieckmann cyclisation on the *trans* diester (12) (c.f. ref. 5), yielding the antipode of the enolic keto ester, which was hydrolysed and decarboxylated as before to give (+)-(15a) This compound has the opposite configuration to that of naturally occurring indole alkaloids, but it conveniently allowed us to show that both enantiomers [(-)-(15a) and (+)-(15a)] were optically pure within our detection limits (e.e. > 95%, as determined by chiral HPLC). This confirmed that the initial Pictet-Spengler reaction had taken place without any racemisation, in accordance with our previous observations [7]

Elaboration of the bridged ketone (-)-(15a) to the advanced intermediate (-)-(16a) was unexpectedly difficult. Numerous attempts to achieve dehydration of the corresponding



Scheme. Reagents: i, $MeO_2CCH_2CH_2CHO$/ PhH azeotrope/ 15 min then TFA/ CH_2Cl_2/ 0°C (60% overall), ii, $PhCH_2OCOCl$/ $NaHCO_3$/ CH_2Cl_2/ RT (90%), iii, MeI/ NaH/ DMF/ 0°C (82%); iv, $PhCH_2Br$/ NaH/ DMF/ 0°C (70%), v, NaH (2.2eq), MeOH (0.1eq)/ DMF/ RT (71%); vi, NaCl (1.2eq)/ H_2O (2eq)/ DMF, 130°C (68%), vii, $(CF_3SO_2)_2NPh$/ NaH/ THF/ RT /68%); viii, LiCN/ PhH/ $Pd(PPh_3)_4$ (cat.)/ 12-crown-4 (cat.)/ RT (5/%), ix, H_2/ 10% Pd-C/ MeOH (77%)

cyanohydrin were unsuccessful, but the desired transformation was eventually accomplished *via* the enol triflate using Pd(0) catalysed displacement by cyanide.[10] Compound (-)-(16a) possesses an α,β-unsaturated nitrile for Michael addition of a C_4 fragment, giving access to the full carbon skeleton of N^{in}-methylated alkaloids of the ajmaline-sarpagine group. This overall route is more efficient than that to the N(2)-benzyl derivative (-)-(16b) described by us in 1988 [11]

Finally, we were able to prepare the N^{in}-benzyl ketone (-)-(17), which is the antipode of the advanced intermediate used by Magnus *et al* in their syntheses of (+)-koumine, (+)-taberpsychine and (+)-koumidine.[6] Thus, treatment of (9) with NaH/ $PhCH_2Br$ gave the N^{in}-benzylated derivative (11b) (70%), which was subjected to Dieckmann cyclisation (71%) and hydrolytic decarboxylation (68%) as before, generating (-)-(15b); catalytic hydrogenation (65%) gave the N^{in}-benzyl ketone (-)-(17)

In summary, we have shown that our kinetically controlled Pictet-Spengler reaction can be used to prepare optically pure 1,3-disubstituted tetrahydro-β-carbolines that are suitably functionalised for the synthesis of indole alkaloids. Of particular importance is the fact that (L)-tryptophan gives access to compounds with the same absolute stereochemistry as that of the natural products

We thank Dr. G.K. Barlow, Mrs. B. Chamberlain, Dr. T.A. Dransfield and Mr. B.R Glennie for NMR and mass spectra.

REFERENCES AND NOTES

1) E.E. van Tamelen and L.K. Oliver, **J. Bioorg. Chem.**, 1976, 309.
2) For example, see J. Sandrin, D Soerens, L. Hutchins, E. Richfield, F. Ungemach and J.M Cook, **Heterocycles**, 1976, **4**, 1101; see ref. 7 below for a discussion of the racemisation
3) F. Ungemach, M. DiPierro, R. Weber and J.M. Cook, **J. Org. Chem.**, 1981, **46**, 164.
4) For example, see L.H Zhang and J.M Cook, **J. Amer. Chem. Soc.**, 1990, **112**, 4088, and ref. 4 therein.
5) a) M. Shimizu, M Ishikawa, Y. Komoda, T. Nakajima, K. Yamaguchi and N. Yoneda, **Chem. Pharm. Bull.**, 1984, **32**, 463; b) L. Zhang and J.M. Cook, **Heterocycles**, 1988, **27**, 2795.
6) P. Magnus, B. Mugrage, M.R. DeLuca and G.A. Cain, **J. Amer. Chem. Soc.**, 1990, **112**, 5220.
7) P.D. Bailey, S.P. Hollinshead and N.R. McLay, **Tetrahedron Lett.**, 1987, **28**, 5177
8) W.C. Still, M. Kahn and A. Mitra, **J. Org. Chem.**, 1978, **43**, 2923.
9) A.P. Krapcho, **Synthesis**, 1982, 805.
10) E. Piers and F.F. Fleming, **J. Chem. Soc., Chem. Commun.**, 1989, 756.
11) P.D. Bailey and S.P. Hollinshead, **J. Chem. Soc., Perkin Trans. 1**, 1988, 739

(Received in UK 8 May 1991)