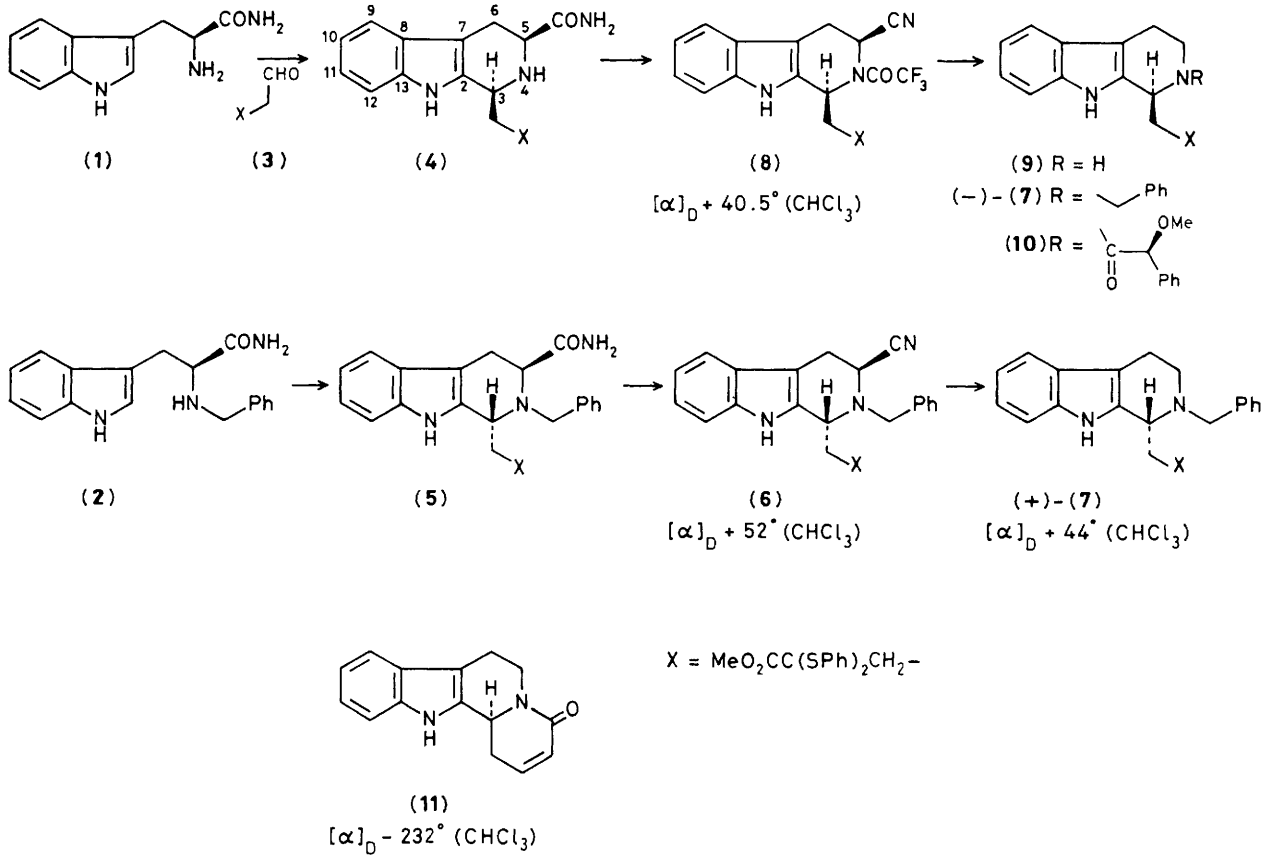
Synthesis of the Two Enantiomers of a Tetrahydro-β-carboline from L-(−)-Tryptophan

Georges Massiot* and Tshilundu Mulamba

Faculté de Pharmacie, ERA au CNRS no. 319, 51 rue Cognacq-Jay, 51096 Reims Cedex, France

Pictet–Spengler condensations of methyl 4-formyl-2,2-bis(phenylthio)butyrate with tryptophanamide and N^b-benzyltryptophanamide are stereospecific; dehydration of the adducts [$(CF_3CO)_2O$] followed by cyanide elimination ($NaBH_4$) yields tetrahydro-β-carbolines of opposite absolute configurations, in high optical purities as demonstrated by n.m.r. examination of their methoxy-mandelamides.

Tryptophan is frequently used instead of tryptamine in the synthesis of optically active β-carbolines. Associated with this approach are two problems, namely the control of the *cis/trans* ratio arising from Pictet–Spengler reactions, and



the removal of the superfluous carbon atom. Many solutions to the second problem have been proposed,[1-4] and the use of N^b-benzyltryptophan methyl ester allows the selective preparation of isomers which have the newly introduced chain *trans* to the tryptophan carbonyl groups.[5] We now report an approach whose salient features are the simple removal of the extra carbon atom and the preparation as required of either enantiomer of a tetrahydro-β-carboline from the same L-(−)-tryptophan.

Although insoluble in normal solvents, the carboxamides (**1**) and (**2**), available from L-(−)-tryptophan, are valuable partners in Pictet–Spengler reactions. Their condensation with methyl 4-formyl-2,2-bis(phenylthio)butyrate (**3**)[6] was accomplished in two steps: imine formation with water removal by azeotroping with benzene, then protonation by CF_3CO_2H in CH_2Cl_2 at room temperature to yield the esters (**4**) (70%) and (**5**) (75%).

As expected from Cook's findings[5] the ester (**5**) is the diastereoisomerically pure *trans*-isomer as demonstrated by ^{13}C n.m.r. spectroscopy.[7] Most surprisingly, however, the condensation (**1**) → (**4**) yields within the limits of n.m.r. detection a single isomer of opposite configuration at C-3† (alkaloid numbering). Compound (**5**) was uneventfully trimmed of its extra carbon atom by the sequence amide (**5**) → nitrile (**6**) [$(CF_3CO)_2O$]‡[8] → amine (+)-(**7**) ($NaBH_4$, 70% overall yield), $[\alpha]_D$ +44° ($CHCl_3$).

In an analogous fashion the secondary amine (**4**) was converted into the trifluoroacetamidonitrile (**8**) and thence into the amine (**9**), $[\alpha]_D$ −27° ($CHCl_3$), using KBH_4 in boiling MeOH. For correlation purposes, (**9**) was benzylated ($PhCH_2Br$, $NaHCO_3$, MeCN, heat, 60%) to give the mirror image (−)-(**7**) (31% overall yield), $[\alpha]_D$ −41° ($CHCl_3$). The stereointegrity of (**9**) was demonstrated by its conversion into the mandelamide (**10**) (*O*-methylmandelic acid,[9] EEDQ[10]) and by comparison with the amides (**10a,b**) obtained from racemic (**9**).[6] Although apparently homogeneous on t.l.c., the mixture (**10a,b**) showed in its ^1H n.m.r. spectrum two three-proton singlets for the OCH_3 ethers (δ 3.40 and 3.44) and two one-proton singlets for the mandelic protons (δ 5.01 and 5.06). The mandelamide derived from (−)-(**9**) shows only one set of these signals (CH_3 at δ 3.44, CH at δ 5.01). We thus estimate the optical purity of (−)-(**9**) to be at least 95% (optical purity of *O*-methylmandelic acid is 99%).

To illustrate the usefulness of the sequence (−)-(**9**) has been converted in three steps:[6] (a) PhSH, NaH: reductive desulphenylation and lactam formation; (b) *m*-chloroperbenzoic acid: sulphoxide formation; (c) toluene, reflux:

† ^{13}C n.m.r. spectrum of (**4**) (selected values): δ 176.4 (s, CO_2CH_3), 170.0 (s, $CONH_2$), 136.4 (d), 136.1 (d), 135.3 (s), 130.9 (s), 130.8 (s), 129.9 (d), 128.9 (d), 127.2 (s), 121.7 (d), 119.5 (d), 118.2 (d), 111.2 (d), 108.7 (s), 107.9 (s), 69.2 (s, C-16), 57.5 (d), 52.9 (d + q), 31 (t), 29.5 (t), and 25.4 (t) p.p.m.

‡ ^{13}C n.m.r. of spectrum (**6**) (selected values): δ 169.9 (s, CO), 137.2 (s, C-13), 136.6 (s, C-2), 136.2 (d), 135.7 (d), 132.5 (s), 131.1 (s), 130.9 (s), 129.6 (d), 128.7 (d), 126.7 (s), 121.8 (d), 119.5 (d), 117.9 (d), 117.4 (s, CN), 111.4 (d, C-12), 106.6 (s, C-7), 68.7 (s, C-16), 55.3 (d), 54.7 (t, $CH_2C_6H_5$), 52.7 (q, OCH_3), 48.2 (d), 29.8 (t), 26.7 (t), and 25.1 (t) p.p.m.

elimination, into the optically active unsaturated lactam (**11**), $[\alpha]_D$ −232°, an intermediate for the synthesis of anthirine.[11] We are currently investigating the use of this reaction sequence in the synthesis of pentacyclic alkaloids of the heteroyohimbine type.

We thank Mr. Merle, I.C.I.-Pharma, for kindly performing the n.m.r. experiments with the mandelamides, the government of Zaire for support (to T. M.), and Professor Jean Lévy for fruitful discussions.

Received, 27th June 1983; Com. 858

References

1 S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, 1976, 61; S. Yamada and H. Akimoto, *ibid.*, 1969, 3105.
2 J. E. Johansen, B. D. Christie, and H. Rapoport, *J. Org. Chem.*, 1981, **46**, 4914.
3 S. Takano, T. Nishimura, and K. Ogasawara, *Heterocycles*, 1977, **6**, 1167.
4 J. M. Bobbitt and J. P. Willes, *J. Org. Chem.*, 1980, **45**, 1978.
5 F. Ungemach, M. Dipierro, R. Weber, and J. P. Cook, *J. Org. Chem.*, 1981, **46**, 164, and references 7—12 cited therein.
6 G. Massiot, T. Mulamba, and J. Lévy, *Bull. Soc. Chim. Fr., Part II*, 1982, 241.
7 F. Ungemach, D. Soerens, R. Weber, M. Dipierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silberton, *J. Am. Chem. Soc.*, 1980, **102**, 6976.
8 F. Campagna, A. Carotti, and G. Casini, *Tetrahedron Lett.*, 1977, 1813.
9 B. M. Trost, D. O.'Krongly, and J. L. Belletire, *J. Am. Chem. Soc.*, 1980, **102**, 7596; B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, 1981, **22**, 4929.
10 EEDQ = *N*-ethoxycarbonyl-2-ethoxy-1,3-dihydroquinoline: B. Belleau, R. Martel, G. Lacasse, M. Ménard, N. L. Weinberg, and Y. G. Perron, *J. Am. Chem. Soc.*, 1968, **90**, 823.
11 J. Ficini, A. Guingant, and J. d'Angelo, *J. Am. Chem. Soc.*, 1979, **101**, 1318.