Synthesis of the *S*-Enantiomer of Paniculidine A: Absolute *R*-Configuration of the Natural Paniculidines A and B

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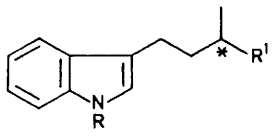
The absolute *R*-configuration of both the title monochiral indole alkaloids has been established.

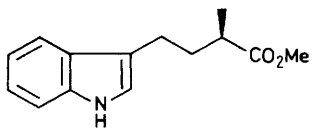
Monochiral prenylindoles paniculidine A (**1**) and paniculidine B (**2**) were recently isolated from the root bark of *Murraya paniculata* (Linn.) Jack [1] and were synthesized in racemic form.[1,2] Both alkaloids were shown to possess the same [1] but yet unknown absolute configuration. Here we report the preparation of chiral paniculidine A starting from the readily available (4*R*)-5-acetoxy-4-methylpentanoic acid (**3**).[3] The synthetic alkaloid was found to be the *S*-enantiomer of the natural compound. Hence, the natural paniculidines (**1**) and (**2**) belong to the *R*-series.

Coupling of the appropriate chiral C_4-building block with a α-formylindole fragment was chosen for the construction of the target molecule (see Scheme). For this purpose the acetoxy acid (**3**) was transformed into the homallylic acetate *R*-(**4**) using a procedure previously developed by us.[4] Its oxidative degradation using $KMnO_4$ on silica gel [5] gave the respective acetoxy

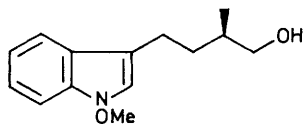


(**1**) R=H, R^1=CO_2Me

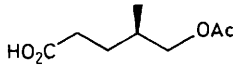
(**2**) R=OMe, R^1=CH_2OH



R - (**1**)

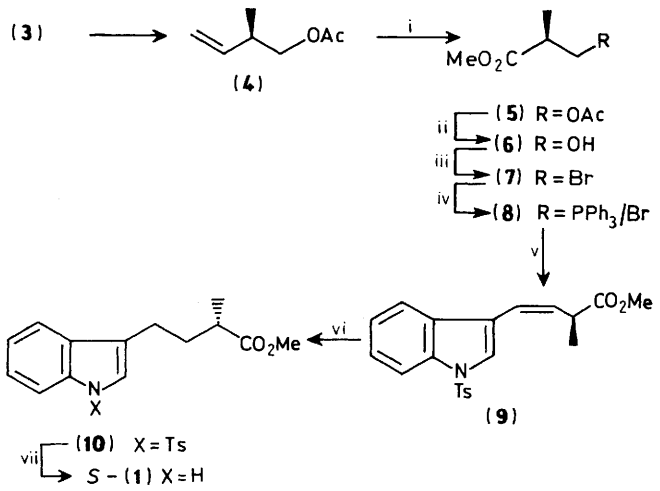


R - (**2**)



(**3**)

acid which was further converted, without any additional purification, into the known acetoxy ester (**5**).[6] Selective saponification of the latter furnished the known alcohol (**6**)[7] which, in turn, was smoothly transformed into the bromide (**7**): b.p. 56 °C/2 mmHg; n_D^{20} 1.4550; $[\alpha]_D^{23}$ + 16.7° (*c* 1.78, $CHCl_3$). The chiral phosphonium bromide (**8**) was obtained in virtually



Scheme. *Reagents and conditions:* i, (a) $KMnO_4/SiO_2$, C_6H_6, 25 °C, (b) CH_2N_2, Et_2O, 25 °C (87% overall); ii, K_2CO_3MeOH, 0—5 °C (75%); iii, CBr_4, Py, Ph_3P, THF, 25 °C (77%); iv, Ph_3P, THF, 80 °C, 14 kBar (100%); v, LDA, *N*-tosyl-3-formylindole, THF–HMPA, −78 °C (60%); vi, H_2, 5% Pd–C, EtOH, 25 °C (100%); vii, $C_{10}H_8$/Na, DME, −60 °C (100%).

quantitative yield from (**7**) with the use of a high-pressure technique (*cf.* ref. 8); (**8**), m.p. 70—72 °C; $[\alpha]_D^{24}$ + 27.3° (*c* 1.78, $CHCl_3$). The Wittig reaction of *N*-tosyl-3-formylindole[9] with the phosphorane generated from (**8**) gave smoothly the disubstituted *cis*-olefin (**9**) (>98% *Z*, ^{1}H n.m.r. data) as a colourless oil: $[\alpha]_D^{25}$ + 82.7° (*c* 1.64, $CHCl_3$); δ($CDCl_3$) 1.33 (d, *J* 7 Hz, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 3.64 (m, 1 H, CH), 3.78 (s, 3 H, CH_3O), 5.82 (dd, *J* 9 and 10 Hz, 1 H, HCCMe), 6.52 (d, *J* 10 Hz, HC=CCMe), 7.75 (s, 1 H, HCN), aromatic H: 7.2—7.4 (m, 4 H), indole H: 7.5—8.0 (m, 4 H). Catalytic hydrogenation of (**9**) yielded quantitatively the amido ester (**10**) as a colourless oil: $[\alpha]_D^{27}$ + 8.7° (*c* 1.64, $CHCl_3$).

Finally, reductive cleavage of the N–S bond in (**10**) using sodium naphthalenide gave quantitatively (*ca.* 30% isolated yield for the above seven stages) the target compound as a colourless oil: $[\alpha]_D^{25}$ + 31.3° (*c* 0.45, $CHCl_3$). For comparison,[1] the specific optical rotation of paniculidine A is $[\alpha]_D^{24}$ − 31.9° (*c* 0.1, $CHCl_3$). Spectral properties (i.r., ^{1}H n.m.r., u.v.) of the compound prepared were found to be very close to those reported for the natural product.[1]

Hence, the compound thus synthesized from *R*-(**4**), without affecting its chiral centre, is represented by formula *S*-(**1**). Accordingly, the absolute *R*-configuration of the natural paniculidine A and paniculidine B is represented by formula *R*-(**1**) and *R*-(**2**), respectively.

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