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AN ENANTIOSELECTIVE ACCESS TO THE (-)-TUBOTAIWINE SKELETON

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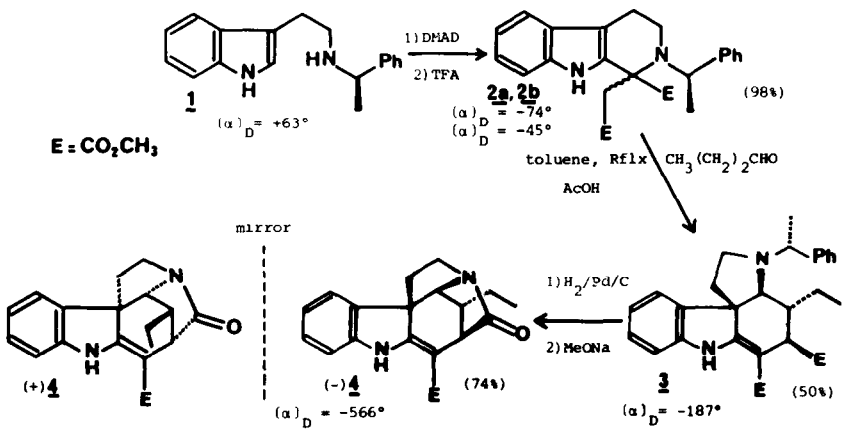
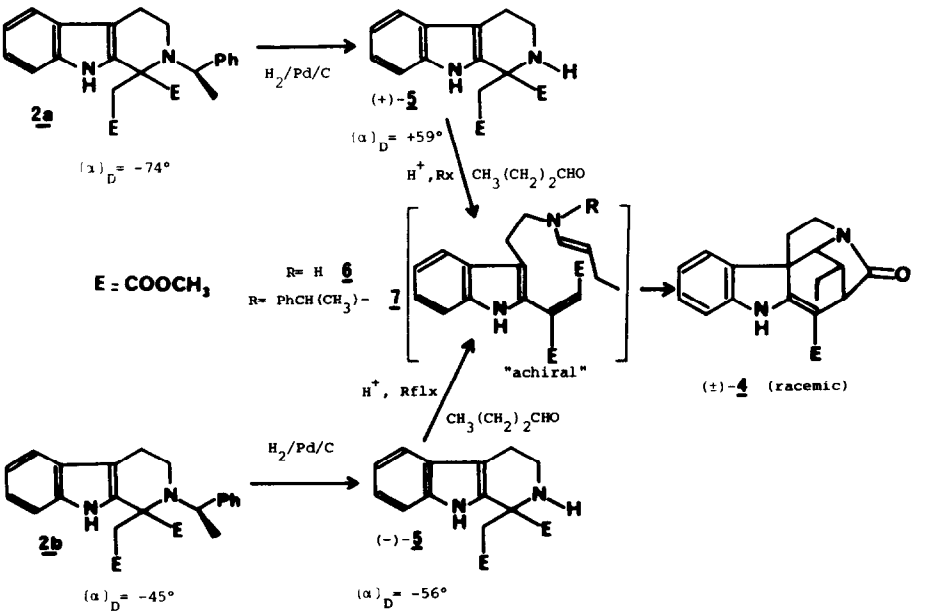
Summary: An efficient induction of chirality is obtained when using α-phenylethylamine as a chiral starting material to produce in few steps the skeleton of anilinoacrylic indole alkaloids. Ring enlargement is described to produce the complete five-ring system of tubotaiwine[2].

In a preceeding communication[3] we have described an enantioselective route to the skeleton of the *Strychnos* alkaloids which starts from L-tryptophan to yield the (+)-series of the anilinoacrylate alkaloids. The (-)-series (strychnine configuration) is, in principle, attainable by this route but at a three-fold cost because of the relative unavailability of D-tryptophan. In this article we wish to describe a more flexible route to both series which also features a shortcut in the removal of the chirality inducer.



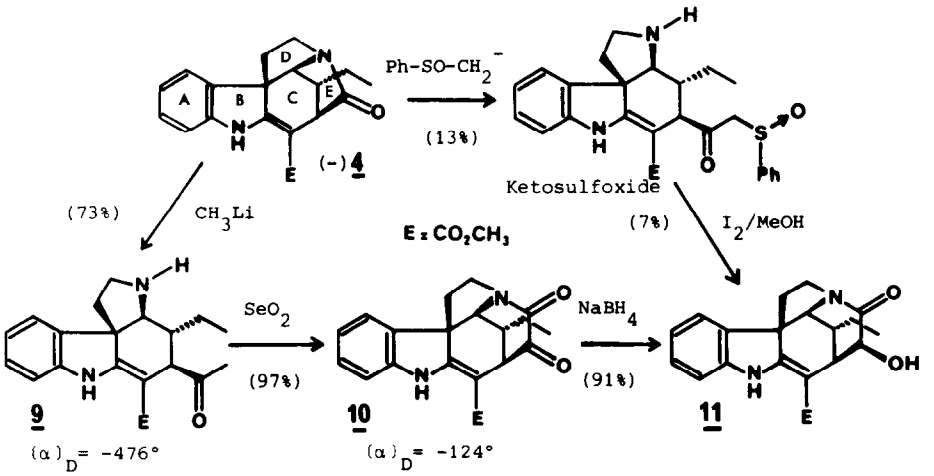
SCHEME 1

The chiral tryptamine **1** ($[\alpha]_D(CHCl_3, C=1) = +63°$), prepared from d-α-phenylethylamine and either tryptophyl bromide or methylindole-3-acetate followed by $LiAlH_4$ reduction, leads to a mixture (55:45) of diastereoisomers **2a**[4] and **2b**[5] when submitted to the previously reported procedure [3,6]. When this crude mixture is treated with butyraldehyde at refluxing toluene, a single anilinoacrylate **3**[7] is obtained ($[\alpha]_D(CHCl_3, C=1) = -187°$). This presents two advantages over the tryptophan route[3] : better diastereoselectivity and shortened reaction time (12 hours *vs* 3 days). To fully establish the absolute and relative configurations of the four newly created asymmetric centers, **3** was transformed into lactam (-)-**4**[8] ($[\alpha]_D(CHCl_3, C=0.5) = -566°$). This compound is the enantiomer of the lactam (+)-**4** ($[\alpha]_D(CHCl_3, C=1) = +573°$), obtained from L-tryptophan[3]. Absolute configuration of (-)-**4** is the one depicted in scheme **1**. Although the chiral auxiliary is lost during the hydrogenation step, its low cost renders this route acceptable. In an effort to understand the mechanism of the transformation of **2** to **3**, **2a** and **2b** were separated, debenzylated to (+)-**5** and (-)-**5** which were both separately treated with butyraldehyde. In each case racemic lactam (+,-)-**4** is obtained, which proves the existence of an achiral intermediate such as **6** which we have postulated earlier[9]. In the "phenylethylamine" case, the intermediate would be **7** (see scheme 2). Although it is difficult to rationalize the high asymmetric induction, analoguous transfer of chirality has been observed by Kuehne in experiments leading to the *Aspidosperma* series[10].



SCHEME 2

In a first series of experiments, expansion of ring E of **4** was brought about by phenylmethylsulfoxide anion addition followed by Pummerer-type rearrangement[11] (see scheme **3**). This sequence led to alcohol **11** in a disappointingly poor overall yield. As an alternative it was found that CH_3Li addition led to ketone **9** ($[\alpha]_D(CHCl_3, C=0.5) = -476°$) (73% yield) which was converted to amide **10**[12] ($[\alpha]_D(CHCl_3, C=0.5) = -124°$) by selenium dioxide oxidation. This last step is similar to the one used by Woodward in his strychnine synthesis[12]. Ketone **10** was converted into **11**[14] ($NaBH_4$, 91% yield) thus proving the structure of the Pummerer rearrangement product.



SCHEME 3

The pentacyclic (-)-**10** is obtained in 6 steps and *ca.* 35% overall yield from optically active tryptamine **1**. Work is in progress to elaborate this intermediate into natural products of the tubotaiwine series[2] and to extend the scope of the Diels-Alder reaction to desethyl analogues which would ultimately lead to the akuammicine-strychnine series[15]. Enantiomeric flexibility of this approach is made possible by the availability of both forms of α-phenylethylamine.

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4- **2a**: mp 130°C; $[\alpha]_D(CHCl_3, C=1) = -74°$; analysis: obsd. (calc. for $C_{24}H_{26}N_2O_4$)= C 71.01 (70.91), H 6.52 (6.45), N 6.86 (6.89); ^1H nmr ($CDCl_3$, 300MHz)= 4.60(q, 6.5Hz, 1H), 3.74 and

3.70(2s, 2xOCH_3), 3.50(d, 17.4Hz, 1H), 2.78(d, 17.4Hz, 1H), 1.35(d, 6.5Hz, 3H) ppm; ^{13}C nmr (75MHz)= 173.9, 172.4, 145.1, 135.8, 133.1, 128.2(2xC+2xC), 126.4(2xC), 122, 119.1, 118.4, 111.2, 109.7, 62.9, 52.9, 52.4 and 52.2(2xOCH_3), 42.5, 40.2, 21.8, 15.6 ppm.

5- **2b**: $[\alpha]_D$($CHCl_3$, C=1)= -45°; more polar than **2a** (Silica, CH_2Cl_2); ^1H nmr ($CDCl_3$,300MHz)= 4.45(q, 7.2Hz,1H), 3.71 and 3.38(2s, 2xOCH_3), 3.50(d, 15.8Hz, 1H), 3.16(d, 15.8HZ, 1H), 3.06(m, 2H), 2.84(m,1H), 2.69(m,1H), 1.56(d, 7.2Hz, 3H) ppm; ^{13}C nmr (75MHz)= 173.1(2xC), 143.8, 135.9, 132.5, 128.0(2xC), 127.2(2xC), 126.5, 126.3, 122.1, 119.2, 118.4, 111.2, 110.5, 64.9, 55.0, 52.4, 52.1, 40 0, 39.4, 22.1, 19.7 ppm.

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7- **3**: mp 180°C; M^+·460 ($C_{28}H_{32}N_2O_4$); ^1H nmr ($CDCl_3$, 300MHz)= 9.11(bs, 1H), 7.5-7.2(m,5H), 7.10(t, 6.4Hz,1H), 6.80(d, 6.4Hz, 1H), 6.60(t, 6.4Hz,1H), 6.20(d, 6.4Hz,1H), 4.04(q, 7.3Hz, 1H), 3.86(bs, 1H), 3.79 and 3.68(2s, 2xOCH_3), 3.01(bs, 1H), 2.91(t, 7.3Hz, 1H), 2.70(m, 1H), 2.50(m, 1H), 2.38(ddd, 4.8, 9.7 and 12.1Hz, 1H), 1.50(d, 7.3Hz, 3H), 1.45(dd, 4.8 and 12.1Hz, 1H), 1.00(m, 1H), 0.89(m, 4H) ppm; ^{13}C nmr (75MHz)= 175.3, 168.6, 167.5, 142.3, 140, 138.3, 128.4(2xC), 128, 127.4, 127.2, 121.1, 120.6, 109.2, 88.4, 67.5, 58.7, 55.2, 51.5, 50.9, 45.5, 42.6, 42.4, 42.1, 25.5, 20.5, 12.1 ppm.

8- (-)-**4**: mp 212°C; analysis: obsd. (calc. for $C_{19}H_{20}N_2O_3$)= C 70.19(70.35), H 6.25(6.21), N 8.58(8.64); ^1H nmr ($CDCl_3$, 300MHz)= 9.00(bs, 1H), 7.19(d, 7.5Hz, 1H), 7.16(t, 7.5Hz, 1H), 7.00(t, 7.5Hz, 1H), 6.85(d, 7.5Hz, 1H), 4.00(d, 4Hz, 1H), 3.80(bs, 1H), 3.78(s, 3H), 3.65(ddd, 4.3, 9.7 and 11.8Hz, 1H), 3.17(ddd, 6.9, 9.5 and 11.8Hz, 1H), 2.60(m, w1/2= 20Hz, 1H), 2.46(ddd, 6.9, 9.7 and 13.6Hz, 1H), 2.10(ddd, 4.3, 9.5 and 13.6Hz, 1H), 1.00(m, 2H), 0.75(t, 7.3Hz, 3H) ppm; ^{13}C nmr (75MHz)= 184.7, 167.3, 166.4, 144, 133.3, 128.2, 121.6, 121.1, 110.2, 64.3, 54.5, 51.5, 44.1, 42.5, 41.8, 40.0, 18.2, 11.8 ppm.

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b) B. M. TROST and C. MILLER, J. Amer. Chem. Soc., 1975, **96**, 7182.

12- **10**: ^1H nmr ($CDCl_3$, 300MHz)= 9.10(bs, 1H), 7.20(t, 7.5Hz, 1H), 7.19(d, 7.5Hz, 1H), 6.98(t, 7.5Hz, 1H), 6.89(d, 7.5Hz, 1H), 4.6O(dd, 7.4 and 11.6Hz, 1H), 4.30(dd, 2 and 3.1Hz, 1H), 3.95(t, 2Hz, 1H), 3.80(s, 3H), 3.20(dt, 6.2 and 11.6Hz, 1H), 2.70(m, 1H), 2.50(ddd, 7.4, 11.6 and 13.1Hz, 1H), 2.00(dd, 6.2 and 13.1Hz, 1H), 1.15(m, 2H), 0.85(t, 7.5Hz, 3H) ppm.

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14- **11**: ^1H nmr ($CDCl_3$, 300MHz)= 8.90(bs, 1H), 7.15(t, 7.5Hz, 1H), 7.12(d, 7.5Hz, 1H), 6.90(t, 7.5Hz, 1H), 6.80(d, 7.5Hz, 1H), 4.5(dd, 8 and 11.5Hz, 1H), 4.23(d, 5.5Hz, 1H), 4.16(bs, 1H), 3.80(s, 3H), 3.70(bd, 5.5Hz, 1H), 2.90(dt, 6.5 and 11.5Hz, 1H), 2.46-2.34(m, 2H), 1.84(dd, 6.5 and 12.8Hz, 1H), 1.00(m, 2H), 0.80(t, 7.2Hz, 3H) ppm; ^{13}C nmr (75MHz)= 177.3, 169.0, 168.7, 143.5, 134.1, 127.1, 121.2, 119.4, 109.9, 92.1, 70.0, 64.2, 55.3, 51.5, 45.9(2xC), 38.4, 36.6, 22.3, 11.5 ppm.

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