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AN ASYMMETRIC SYNTHESIS OF (+)-OCOTEINE

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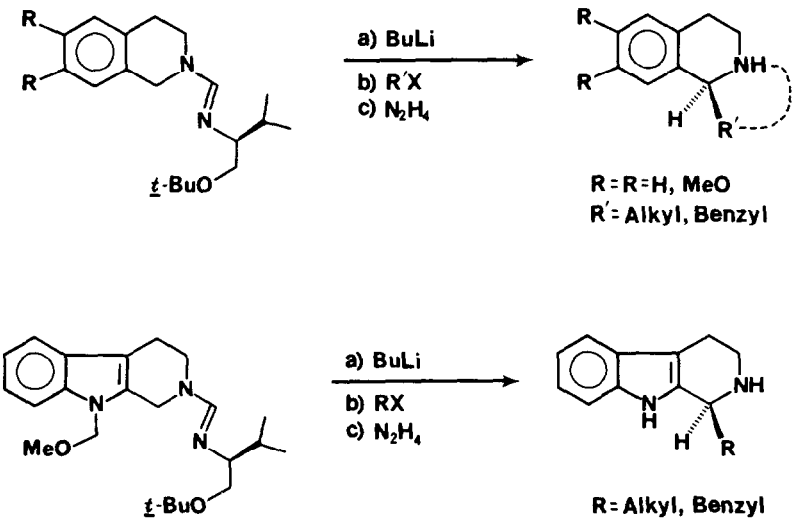
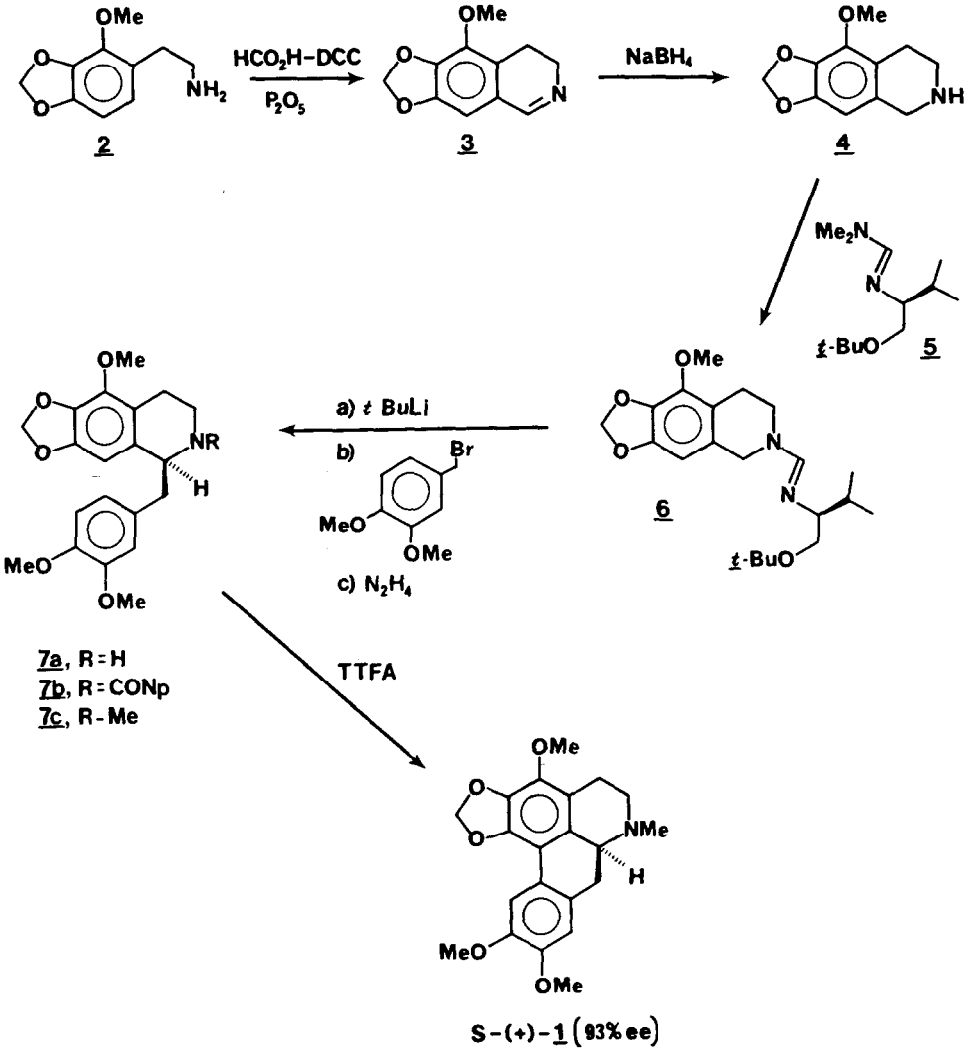
Summary: Using chiral formamidines, the synthesis of the title compound was accomplished in 93% ee.

As part of a program to produce various alkaloids *via* asymmetric alkylation of chiral formamidines containing the tetrahydroisoquinoline[1] or β-carboline[2] moiety (Scheme 1) we

Scheme 1



undertook the task of assessing the feasibility of reaching the aporphine-class. The present report describes the asymmetric synthesis of (+)-ocoteine 1[3] which was obtained in 93% ee. The sequence leading to (+)-1 began by transforming the known 2-methoxy-3,4-methylenedioxy-β-phenethylamine 2[4] into the corresponding dihydroisoquinoline 3[5] via a standard Bischler-Napieralski reaction. Reduction with sodium borohydride gave the appropriately substituted tetrahydroisoquinoline 4.[6] In order to effect the asymmetric



alkylation, 4 was converted to 6 via the dimethylaminoformamidine of t-butylvalinol 5,[7] by heating in toluene containing a catalytic amount of camphor sulfonic acid. The formamidine 6 (60%, oil, $[\alpha]_D$ = 0.19°, THF) was metalated with 1.3 equiv of t-butyllithium (-100°, THF) for 20 min and then treated with 3,4-dimethoxybenzyl bromide (1.3 equiv, -100°). After 20 min, the mixture was quenched with excess methanol and worked up by extraction with $CHCl_3$. The crude product was immediately subjected to hydrazinolysis (EtOH-H_2O, 3:1; 8 equiv hydrazine, 3 equiv HOAc) by warming overnight at 50°. Extractive work-up gave 7a (83%) purified by flash chromatography (7% MeOH-$CHCl_3$). The extent of asymmetric alkylation was verified by transforming 7a to its α-naphthamide 7b (α-naphthoyl chloride, Et_3N, 25°, 15 h) and subjecting it to HPLC analyses using the Pirkle chiral covalent column[8] which showed an enantiomeric ratio of 96.5:3.5 with the S-enantiomer predominating.

N-methylation of 7a using formaldehyde-$NaBH_4$[4] gave the N-methyl derivative 7a[9] (mp 200° $[\alpha]_D$ -4.7°, THF) which underwent coupling to (+)-1 using thallium (III) trifluoroacetate according to Taylor and McKillop;[9] $[\alpha]_D^{25}$ +32.1° ± 0.7° (c 1.01 EtOH) mp (HI salt) 210-212°.[3] The (+)-syn of rotation further confirmed that the natural S-enantiomer was prepared and using the Pirkle HPLC column again demonstrated that, for tetrahydroisoquinolines 7b, the S-enantiomer elutes from the column after the R-enantiomer. The synthesis of (+)-1 is therefore another example of the potent methodology based on chiral formamidines to reach isoquinoline alkaloids in 90-99% ee. Furthermore, the correspondence of the specific rotations for natural and synthetic (+)-1 as well as the HPLC data on 7 indicates that the TTFA oxidative coupling proceeds with little or no racemization during the radical cation process.

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6. Mp 89-90°, 87% yield; NMR (270 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.86 (s, 2H) 3.99 (s, 3H), 3.89 (s, 2H), 3.09 (t, 2H, J = 6.01 Hz), 2.61 (t, 2H, J = 5.90 Hz), 2.25-2.08 (br.s, 1 H). ^{13}C-NMR (67.6 MHz) 147.71, 141.63, 134.66, 129.85, 120.28, 100.60, 59.39, 48.61, 43.92, 23.77. IR (CM^{-1} KBr) 3260-3100, 2924, 1620, 1489, 1393, 1046, 820. Anal $C_{11}H_{13}NO_3$.

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