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ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-MONOMORINE I

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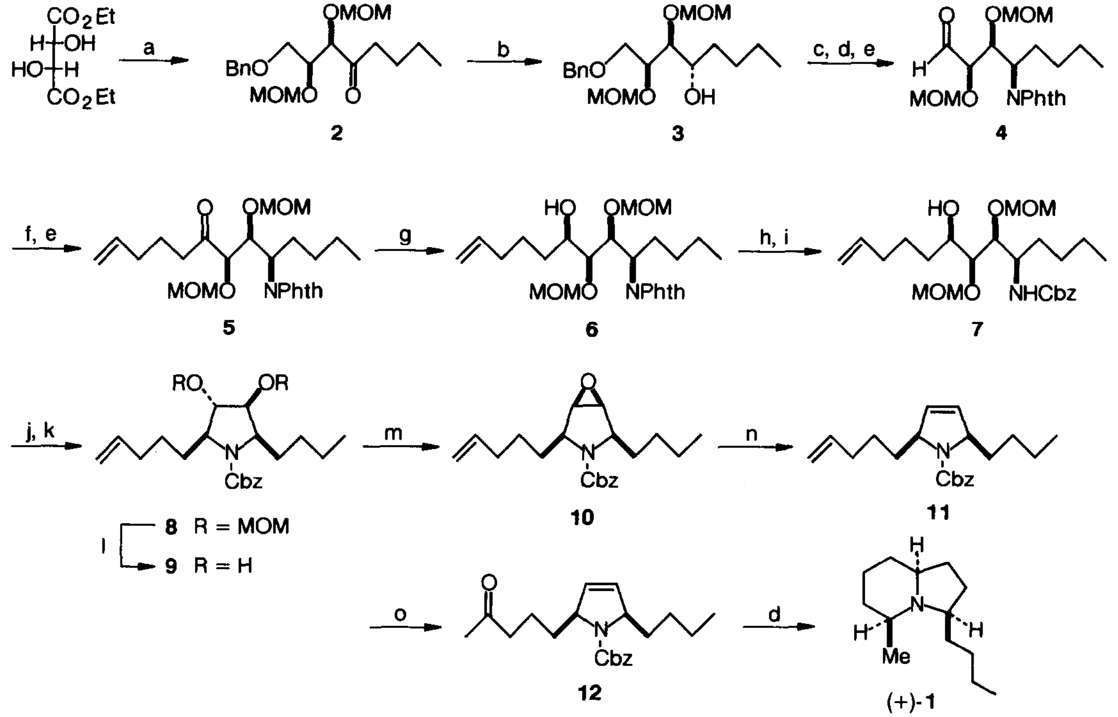
Abstract: Enantioselective total synthesis of (+)-monomorine I was achieved starting from diethyl L-tartrate via 1,2-asymmetric induction based on highly diastereoselective hydride addition to acyclic α,ß-dialkoxy ketones.

(+)-Monomorine I [(+)-1] has been isolated from the cosmopolitan ant Monomorium pharaonis (L.)[1] as a major component having attractant and trail-initiating activity.[2] The absolute configuration of (+)-1 has been established recently as 3R,5S,9S.[3] While several syntheses of monomorine I in racemic form[4] and a chiral synthesis of the nonnatural (-)-enantiomer[3] have been reported, synthesis of the natural (+)-enantiomer remains unexplored. In this communication we report the first asymmetric synthesis of (+)-1.

Our approach to (+)-monomorine I was initiated by 1,2-asymmetric induction based on hydride addition to acyclic α,ß-dialkoxy ketones in a predictable and controlled manner.[5,6] Thus the ketone **2** bearing the methoxymethyl (MOM) ethers at α and ß positions was initially prepared from diethyl L-tartrate in 6 steps according to published method.[7] Reduction of **2** with $Zn(BH_4)_2$ provided high anti selectivity of >99:1 (by 400-MHz ^1H NMR) yielding the alcohol **3** (95%),[8] $[\alpha]^{20}_D$ -25.7° (c 0.27, MeOH). Compound **3** was converted to the aldehyde **4**, $[\alpha]^{24}_D$ -11.1° (c 1.01, $CHCl_3$), by the Mitsunobu reaction with phthalimide followed by debenzylation (H_2, Pd/C) and Swern oxidation in 41% overall yield. Subsequent Grignard reaction and Swern oxidation afforded the ketone **5**, $[\alpha]^{20}_D$ -16.4° (c 0.28, MeOH), in 78% overall yield. On reduction of **5** with L-Selectride (THF, -78 °C) the alcohol **6** (83%),[8] $[\alpha]^{20}_D$ -28.5° (c 2.24, $CHCl_3$), was obtained with high syn selectivity (syn:anti = 98:2). Syn selectivity (syn:anti = 97:3) was also observed when LS-Selectride (THF, -78 °C) was used as the reducing agent, affording **6** (67%).[8]

The syn,syn,syn alcohol **6** thus prepared via twofold diastereoselective hydride addition was subjected to removal of the phthaloyl group followed by N-benzyloxycarbonylation to give **7** (80% from **6**). Compound **7** underwent mesylation and subsequent base-induced cyclization (t-BuOK, THF, r.t.) to exclusively afford the (2S,5R)-pyrrolidine **8**, $[\alpha]^{20}_D$ -15.6° (c 1.05, MeOH), with complete inversion of the C-6 configuration (R to S) in 83% yield. Cleavage of the MOM ether (concd. HCl, MeOH) and treatment of resulting **9** with triiodoimidazole and PPh_3 afforded the epoxide **10** (82% from **8**), which was deoxygenated[9] by treatment with PPh_3 and zinc in refluxing toluene to yield the 3-pyrroline derivative **11** (93%), $[\alpha]^{20}_D$ +8.6° (c 0.36, MeOH). Site selective oxidation of the terminal olefin via Wacker process (O_2, $PdCl_2$, $CuCl_2$) gave **12** (81%), $[\alpha]^{22}_D$ +7.2° (c 0.57, MeOH), which on hydrogenation over Pd/C in methanol exclusively provided (+)-monomorine I [(+)-1] (76%), $[\alpha]^{22}_D$ +34.3° (c 1.02, hexane).[10] This material had identical spectra (400-MHz ^1H and ^{13}C NMR and mass) with the corresponding spectra of both authentic (-)-1 and (±)-1.[4f]



(a) ref. 7; (b) $Zn(BH_4)_2$, Et_2O, -20 °C; (c) phthalimide, Ph_3P, $(NCO_2Et)_2$, THF, 0 °C → r.t.; (d) H_2, Pd/C, MeOH; (e) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, -78 °C; (f) $CH_2=CH(CH_2)_3MgBr$, THF, -78 °C; (g) LiBH(sec-Bu)$_3$, THF, -78 °C; (h) $(NH_2)_2 \cdot H_2O$, EtOH, refl; (i) $PhCH_2OCOCl$, aq. Na_2CO_3, CH_2Cl_2, 0 °C; (j) MsCl, Et_3N, CH_2Cl_2, 0 °C; (k) t-BuOK, THF, r.t.; (l) concd. HCl, MeOH, refl; (m) imidazole, triiodoimidazole, Ph_3P, toluene, refl; (n) Ph_3P, Zn, toluene, refl; (o) O_2, $PdCl_2$, $CuCl_2$, DMF-H_2O, 70 °C.

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10. For (-)-1: lit.^{3} $[\alpha]^{20}_D$ -35.8° (c 1.35, hexane).

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