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Total Synthesis of (*ent*)-Korupensamine D

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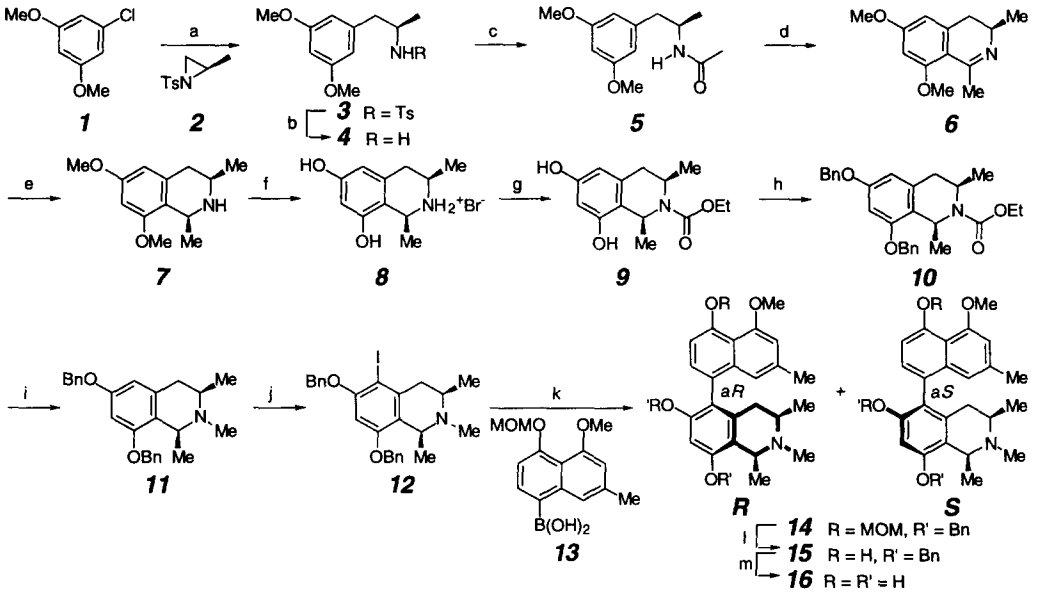
Abstract *The first total synthesis of the enantiomer of the natural product, korupensamine D (**16R**), is described. The key steps include a highly efficient preparation of the enantiomerically pure primary amine **4** via the ring opening of aziridine **2** with an arylcuprate reagent and the development of a one-pot selective functionalization of a hindered secondary amine in the presence of phenolic hydroxyl groups (i.e., **8** to **9**).*

Because of the promising anti-HIV profile of the michellamines, the preparation and evaluation of various analogs, including unnatural antipodes, is of considerable interest. The potential use of various korupensamines as starting materials for this purpose has prompted our efforts toward the synthesis of korupensamine D[1] (structure **4** in the preceding *Letter*), which differs from korupensamines A-C[1] (**1**-**3** in the preceding *Letter*) by virtue of the cis (rather than trans) arrangement of the methyl substituents on the tetrahydroisoquinoline (THIQ) substructure. Korupensamine D also possesses an N-methyl substituent rather than the free NH present in congeners A-C. We describe here the synthesis of **16*R***, the enantiomer of the natural antipode of korupensamine D, by a route that is also directly applicable to the natural antipode.

The synthesis starts with a new sequence for the preparation of the enantiomerically pure primary amine **4**, a valuable intermediate first used by Bringmann for the construction of non-racemic THIQs.[2] The ring opening of *R*-N-tosylaziridine **2** with the Grignard reagent derived from **1** in the presence of $CuBr{\bullet}SMe_2$[3] resulted in the formation of **3** in 100% yield. Either enantiomer of aziridine **2** is readily available from D- or L-alanine in three steps.[4] Cleavage of the toluenesulfonamide group in **3** delivered primary amine **4** (79%) as a single enantiomer (Mosher amide analysis).

The known acetamide **5** (99%) underwent Bischler-Napieralski cyclization to afford the cyclic imine **6** (82%).[2] The cis-configured THIQ **7** has previously been prepared by reduction of cyclic imine **6** with sodium borohydride in high diastereoselectivity (ds>95%).[2b] We reduced **6** with H_2 and 10% Pd/C, which also gave the cis-configured compound **7** (93%) as the only observable (^1H NMR) diastereomer. Demethylation of **7** with excess boron tribromide gave the resorcinol amine HBr salt **8** (~99 %).

The next key intermediate we envisioned was an N-methylated, doubly OH-protected THIQ derivative. A one-pot procedure was developed to selectively generate the hindered carbamate in **9**, leaving the phenolic hydroxyl groups intact. Sequential silylation of compound **8** (2.1 equivalents of triethylsilyl chloride and Et_3N in CH_2Cl_2), carbamate formation (2 equivalents of ethyl chloroformate and Et_3N), and removal of the silyl groups [~5 equiv of TBAF (1.0M in THF)] gave compound **9** (87% for the three steps). Benzylation with benzyl bromide and potassium carbonate smoothly afforded compound **10** (72%), which was reduced with $LiAlH_4$ to give the N-methylated compound **11** in 94% yield.



a) Mg°, 5 mol% $BrCH_2CH_2Br$, THF; 10 mol% CuBr•SMe_2, 0 °C; **2** (100%); b) Na/NH_3, -78 °C (79%); c) Ac_2O, Et_3N (99%); d) $POCl_3$, MeC≡N, reflux (82%); e) H_2, Pd/C (93%); f) xs BBr_3, CH_2Cl_2, -78 °C to RT (~99%); g) 2.1 equiv TESCl, Et_3N, CH_2Cl_2; $ClCO_2Et$, Et_3N; TBAF/THF (87%); h) BnBr, K_2CO_3 (72%); i) $LiAlH_4$ (94%); j) I_2, Ag_2SO_4, EtOH (80%); k) **13**, $Pd(PPh_3)_4$, sat'd $NaHCO_3$, $PhCH_3$, reflux (73%); l) HCl, MeOH/CH_2Cl_2 (92%); m) H_2, Pd/C, MeOH/CH_2Cl_2 (100%).

Regiospecific iodination of **11** with iodine and silver sulfate gave the cis-configured, N-methylated, C(5)-activated iodide **12** in 80% yield. Palladium(0) catalyzed coupling of **12** with the naphthalene boronic acid (**13**[5] or its boronic anhydride) gave an ~4:5 ratio of atropisomers ***14R*** and ***14S*** in 73% yield. Hydrolysis of the MOM ethers in the mixture of **14** gave the naphthols ***15R*** and ***15S*** (92%). These naphthols were partially separable by MPLC (hexanes:EtOAc-2:1, with 3% Et_3N). Hydrogenolysis of the benzyl groups in the single atropisomer ***15R*** quantitatively provided the enantiomer of korupensamine D (***16R***), which had identical ^{1}HNMR spectral data to those reported for korupensamine D.[1] Hydrogenolysis of a mixture of ***15R*** and ***15S*** similarly provided a mixture of the enantiomer of korupensamine D (***16R***) and its diastereomer ***16S***. The specific rotation of the synthetic ***16R*** is opposite in sign to that of natural korupensamine D, thus confirming the assigned absolute configuration.[1] Preparation of structural analogs of the korupensamines and michellamines from precursors like **16** continues.[6]

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6. All new compounds described here and in the preceding *Letter* have been characterized by ^{1}HNMR spectroscopy and combustion and/or high resolution mass spectrometric analysis. ^{13}CNMR data are available for most.

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