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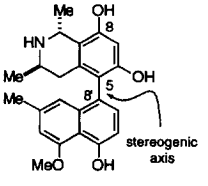
Total Syntheses of Korupensamine C and Ancistrobrevine B

Thomas R Hoye* and Liang Mi

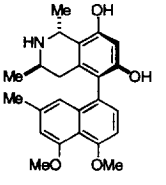
Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Abstract *The first total syntheses of korupensamine C (3) and ancistrobrevine B (4) have been achieved. Important benzyne chemistry related to the construction of the naphthalene moiety, manipulation of methoxy groups on the tetrahydroisoquinoline unit, and hindered biaryl formation are described.*

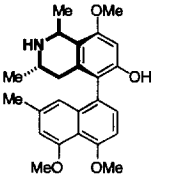
The isolation (from the liana *Ancistrocladus korupensis*), structures, and anti-HIV properties of the atropisomeric michellamines A-C were recently reported.[1] Along with the michellamines, some of their presumed biogenetic precursors, the korupensamines A-D, were later isolated from the same plant. These 'monomeric' tetrahydroisoquinoline naphthalenes do not possess anti-HIV activity; the A and B members (**1** and **2**) are antimalarial.[2] Total syntheses of michellamine B[3a-c] and of korupensamines A and B[3c,d] have been described recently. The michellamines and the related korupensamines are unusual among the naphthylisoquinoline family of alkaloids[4] in that the biaryl linkage occurs between C(5)/C(8'). Ancistrobrevine B (**4**), isolated from the related vine *A. abbreviatus*,[5] is one of only two other 5,8'-linked naphthylisoquinolines. We describe here the synthesis of korupensamine C (**3**) and ancistrobrevine B (**4**) and in the following *Letter* a synthesis of *ent*-korupensamine D (***ent*-5**).



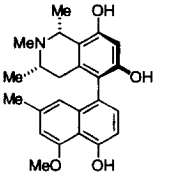
1 Korupensamine A (*aS*)
2 Korupensamine B (*aR*)



3 Korupensamine C

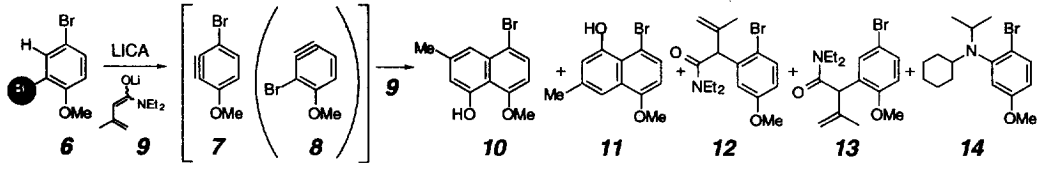


4 Ancistrobrevine B

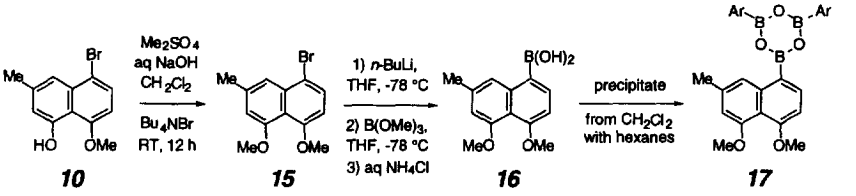


5 Korupensamine D

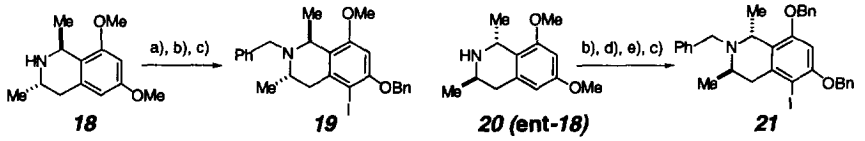
We have studied in some detail the benzyne cycloaddition reaction used to efficiently construct the naphthalene unit in our michellamine B synthesis.[3c] Thus, the dienolate **9** (*N,N*-diethyl-3,3-dimethylacrylamide and *n*-BuLi) reacted with the benzyne **7** formed *in situ* from one equivalent of 2,4-dibromoanisole (**6**) and one equivalent of lithium isopropylcyclohexylamide (LICA) in THF (-20 °C to RT) and gave the desired, highly functionalized, bromonaphthalenol **10** reproducibly in 21-26% yield. This is a remarkable event because among the several reaction products we have identified (**10**-**14**), *all* are derived from 3-bromo-6-methoxybenzyne (**7**) and *none* from the regioisomeric 3-bromo-4-methoxybenzyne (**8**). Perhaps the methoxy group delivers a Lewis acidic lithium ion to the ortho-bromine to promote heterolytic cleavage of that bond. A minor amount (~5%) of the regioisomeric naphthalenol **11** was typically seen. It arises from attack ortho rather than meta to the methoxy group in **7**. Monocyclic adducts **12** and **13** arise from α-attack of the benzyne onto the dienolate **9**. Finally, the amine-trapped product **14** was typically observed in 6-7% yield.



Phase-transfer methylation of **10** gave **15** in 92% yield. Metallation of this bromonaphthlene and subsequent reaction with trimethyl borate gave the naphthalene boronic acid **16** as a viscous oil in 84% yield. The ^{1}H NMR spectrum of this material was typically quite complex. The acid could be readily dehydrated by precipitation with hexanes from a dry methylene chloride solution to give the boronic anhydride **17**. Samples of **16** or **17** functioned equally well in subsequent, palladium-catalyzed biaryl cross-coupling reactions.

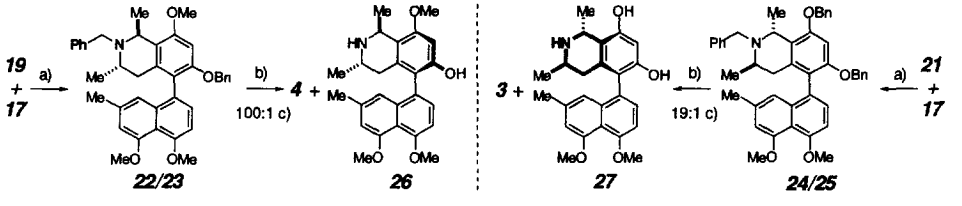


For the synthesis of ancistrobrevine B (**4**), mono-demethylation of **18** (43%),[6] *N*-benzylation (82%), and iodination (76%) gave the aryl iodide **19**. For korupensamine C, *N*-benzylation of **20** (the enantiomer of **18**, 94%), bis-demethylation using NaI/HBr (94%), bis-*O*-benzylation, and iodination gave **21** (62%).



a) HBr (49%), AcOH, 70 °C. b) BnBr, K_2CO_3, MEK, RT. c) I_2, Ag_2SO_4, EtOH, RT. d) HBr (49%), NaI, 100 °C. e) BnBr, Cs_2CO_3, DMF, RT

The independent Pd°-catalyzed biaryl coupling of iodide **19** or **21** with boronic anhydride **17** gave the inseparable pairs of atropisomers **22/23** or **24/25** in 71% and 76% yields, respectively. Hydrogenolysis of each mixture and HPLC separation gave (~2 mg samples of) ancistrobrevine B (**4**) and its atropisomer **26** or korupensamine C (**3**) and its atropisomer **27**, respectively.[7]



a) $Pd(PPh_3)_4$, sat'd $NaHCO_3$, $PhCH_3$, reflux, 71%-76%. b) Pd/C, H_2, MeOH/CH_2Cl_2, 4 h, 100%. c) HPLC, Microsorb Amino, CH_2Cl_2:3% methanolic $(NH_4)_2CO_3$.

References and Notes

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7. The synthetic sample of **4** or **3** gave appropriate HRMS data and a ^{1}HNMR spectrum identical to that reported.[5,2]

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