Stereoselective synthesis of *O,O*-dimethylkorupensamine A *via* palladium(0)-mediated cross-coupling of a planar chiral (arene)$Cr(CO)_3$ complex with naphthylboronic acid

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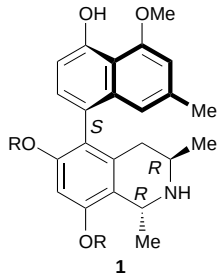
***O,O*-Dimethylkorupensamine A was stereoselectively synthesized by using the palladium(0)-mediated cross-coupling of the enantiomerically pure tricarbonylchromium complex of 3,5-dimethoxy-2-bromobenzene having a functional group at C-1 position with naphthylboronic acid as a key step.**

Korupensamines and michellamines have been isolated from the tropical liana *Ancistrocladus korupensis* in Cameroon and some of these alkaloids possess significant pharmacological activities such as antimalarial properties,[1] and remarkable antiviral activity against human immunodeficiency virus strains HIV-1 and HIV-2.[2] Structurally, the korupensamines have a naphthyltetrahydroisoquinoline skeleton with an axial chirality between the naphthalene and tetrahydroisoquinoline rings, and the michellamines are atropisomerically dimeric alkaloids of the korupensamines. These alkaloids have been previously synthesized *via* construction of the axial bond between the naphthalene and tetrahydroisoquinoline rings as a key step.[3,4] However, the palladium(0)-catalyzed cross-coupling[3] of two arene rings or nucleophilic addition[4] of aryl Grignards to the *o*-methoxyaryl oxazoline compounds for the central bond formation of the naphthalene and tetrahydroisoquinoline rings gave unfortunately various ratios of the atropisomeric mixture in the previous reports. In continuation of our studies on development of the planar chiral (arene)chromium complexes in the asymmetric reactions, we have recently reported[5,6] that both enantiomers of the axial biaryls could be stereoselectively prepared from a single planar chiral (arene) chromium complex by the palladium(0)-mediated cross-coupling of (2,6-disubstituted 1-bromobenzene)chromium complexes with arylboronic acids and following axial isomerization of the cross-coupling products under thermal conditions. This paper describes the asymmetric synthesis of (−)-*O,O*-dimethylkorupensamine A (**1**, R = Me) utilizing the stereoselective palladium(0)-catalyzed cross-coupling of the planar chiral (arylhalide)$Cr(CO)_3$ with napthylboronic acid as the key step.



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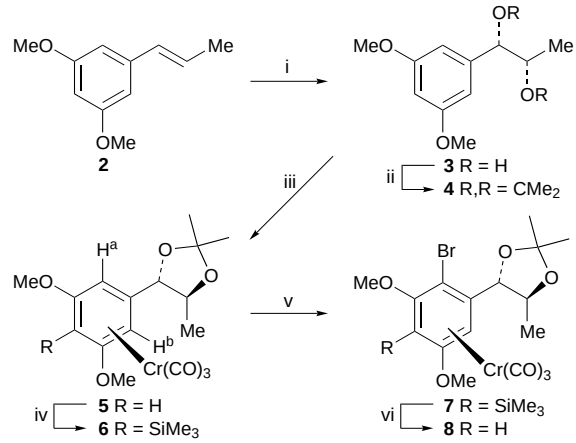
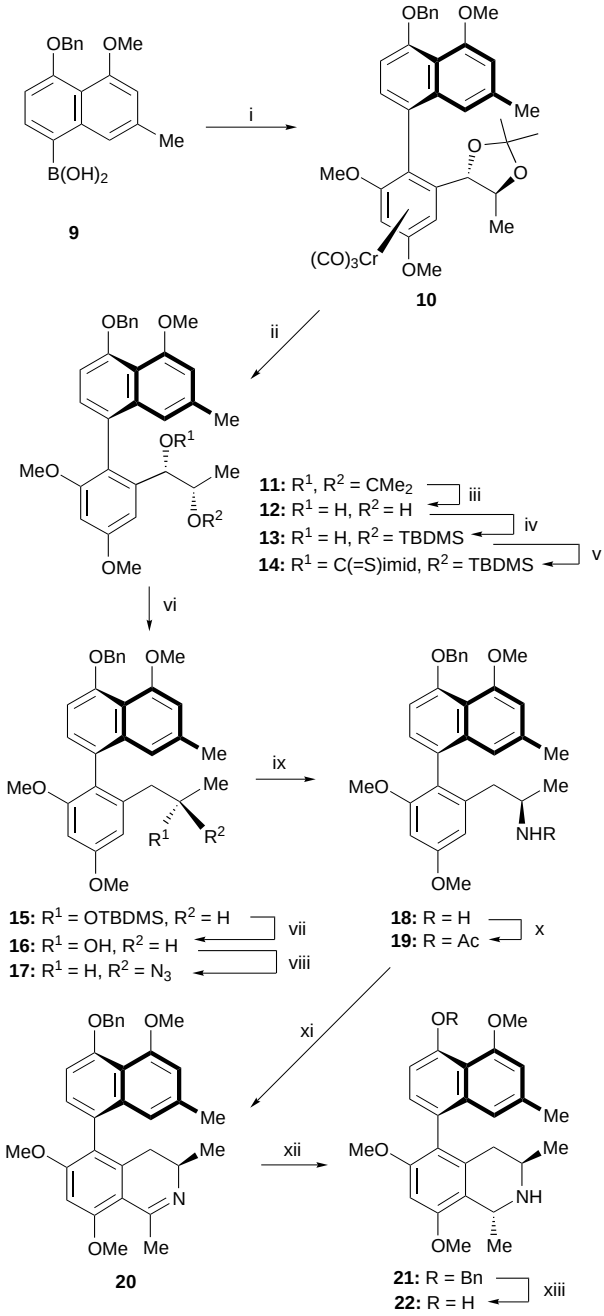
R = H; Korupensamine A
R = Me; *O,O*-Dimethylkorupensamine A

The planar chiral tricarbonylchromium complex of 3,5-dimethoxyphenylbromide having a functional group at C-1 position as a coupling partner was initially prepared as follows (Scheme 1). An asymmetric catalytic dihydroxylation of (*E*)-(3,5-dimethoxyphenyl)propene **2** was treated with AD-mix-α,[7] and the resulting diol was subsequently protected with acetone dimethylacetal to give the acetonide **4** ($[\alpha]_D^{27}$ +23.8)‡ in 96% yield with > 98% ee. Tricarbonylchromium complexation of **4** with $Cr(CO)_6$ in dibutyl ether and THF (10 : 1) at reflux gave the corresponding (arene)chromium complex **5** ($[\alpha]_D^{26}$ −4.0) in 89% yield. In order to introduce the bromine atom at either *ortho*-position of the C-1 side-chain group regioselectively, the C-4 position was initially protected by the introduction of the easily removable Me_3Si group. Thus, the lithiation of **5** with Bu^nLi followed by treatment with trimethylsilylchloride afforded the trimethylsilylated complex **6** ($[\alpha]_D^{27}$ −36.0) in 97% yield. Subsequent lithiation§ of **6** followed by quenching with 1,2-dibromo-1,1,2,2-tetrafluoroethane gave the bromination complex **8** ($[\alpha]_D^{26}$ −93.0) at the H^a-position without the regioisomeric complex after detrimethylsilylation in 95% overall yield. The planar chirality of **8** was determined by X-ray crystallography.¶



Scheme 1 *Reagents and conditions*: i, AD-mix-α, $CH_3SO_2NH_2$, Bu^tOH, H_2O, 99%, > 98% ee; ii, $Me_2C(OMe)_2$, TsOH, 97%; iii, $Cr(CO)_6$, dibutyl ether, THF, reflux, 20 h, 89%, > 99% ee; iv, Bu^nLi, THF, TMEDA, −78 °C, then Me_3SiCl, THF, −78 °C, 97%; v, Bu^nLi, THF, TMEDA, −78 °C, then $BrCF_2CF_2Br$, THF, −78 °C, 98%; vi, $Bu^n{}_4NF$, THF, AcOH, 97%

The palladium(0)-catalyzed cross-coupling of the planar chiral (arene)$Cr(CO)_3$ complex **8** with 4-benzyloxy-5-methoxy-6-methylnaphthylboronic acid **9**[8] in the presence of sodium carbonate in aqueous MeOH at reflux for 30 min produced a single atropisomeric coupling product **10** ($[\alpha]_D^{28}$ −142.9) in 90% yield without any formation of the atropisomers (Scheme 2). The axial stereochemistry of the coupling product **10** was assigned to be the (*S*)-configuration by ^1H NMR spectra, in which the *peri*-proton of the naphthalene ring appeared at lower field (δ 8.62) due to the anisotropic effect of the *syn*-$Cr(CO)_3$ fragment.[5] An oxidative demetallation of **10** and subsequent treatment with dilute HCl afforded the dihydroxyl compound **12** ($[\alpha]_D^{27}$ +3.5). Selective protection of the hydroxyl at the homobenzylic position of **12** with *tert*-butyltrimethylsilyl chloride gave the monosilylated compound **13** ($[\alpha]_D^{25}$ +35.8) in



Scheme 2 *Reagents and conditions*: i, **8**, $Pd(PPh_3)_4$ (0.05 mol equiv.), aq. Na_2CO_3, MeOH, 75 °C, 30 min, 90%; ii, *hv*, O_2, diethyl ether, 92%; iii, 1 M aq. HCl, THF, 50 °C, 96%; iv, Bu^tMe_2SiCl, imidazole, DMF, 84%; v, $(imid)_2C{=}S$, THF; vi, Bu^n_3SnH, AIBN, toluene, 62% from **13**; vii, Bu^n_4NF, THF, 96%; viii, $(PhO)_2PON_3$, DEAD, PPh_3, THF; ix, $SnCl_2$, MeOH; x, Ac_2O, py, 66%, from **16**; xi, $POCl_3$, MeCN; xii, $LiAlH_4$, Me_3Al, THF, −78 to 0 °C, 70% from **19**; xiii, Pd-black, HCO_2H, MeOH, 45 °C, 91%

84% yield. The benzylic hydroxyl of **13** was removed by the Barton method[9] to give the deoxygenation compound **15** ($[\alpha]_D^{26}$ +11.9) in 62% yield. The substitution of the hydroxyl to nitrogen atom with stereochemical inversion was achieved under Mitsunobu conditions.[10] Thus, deprotection of the silyl ether **15** and subsequent treatment with $(PhO)_2PON_3$ in the presence of DEAD and PPh_3 produced the azide compound **17** which was reduced with $SnCl_2$ followed by acetylation to give the amide compound **19** ($[\alpha]_D^{26}$ +8.1) in 66% overall yield. Bischler–Napieralski cyclization of **19** with $POCl_3$ in acetonitrile gave the naphthyldihydroisoquinoline compound **20**. Reduction[11] of the imine double bond of **20** with $LiAlH_4$ in the presence of Me_3Al afforded *trans*-dimethyl compound **21** ($[\alpha]_D^{23}$ −20.6) along with a small amount of the corresponding *cis*-isomer (ratio, 93 : 7) in 70% overall yield. Finally, debenzylation with Pd-black in a solution of 8.8% formic acid in MeOH gave *O*,*O*-dimethylkorupensamine A **22** (R = H) ($[\alpha]_D^{22}$ −29.1) in 91% yield.

In conclusion, we have demonstrated the asymmetric synthesis of *O*,*O*-dimethylkorupensamine A *via* a stereoselective Pd^0-mediated cross-coupling method for the construction of the highly hindered biaryl bond as the key bond forming reaction. This procedure should have broad utility for the stereoselective synthesis of structural analogs of the atropisomeric naphthyltetrahydroisoquinoline alkaloids.

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Notes and References

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‡ All optical rotation values were measured in $CHCl_3$ solution.

§ The corresponding di-MOM ether chromium complex analog instead of the dimethoxy ether complex **6** resulted in a regioisomeric mixture of the bromination compounds in a 85 : 15 ratio by the *ortho*-lithiation with Bu^nLi followed by bromination.

¶ *Crystal data* for **10**: $C_{17}H_{19}BrCrO_7$, M = 467.23, yellow prismatic, triclinic, space group $P\bar{1}$, a = 9.829(2), b = 13.393(3), c = 7.996(2) Å, α = 98.27(2), β = 110.31(2), γ = 94.38(2)°, U = 967.7(4) Å^3, Z = 2, D_c = 1.603 g cm^{-3}, $F(000)$ = 472.00, μ = 26.96 cm^{-1}, $R(R_w)$ = 0.039 (0.053). A total of 4729 data were collected using ω scans with 22.35 < 2θ < 24.98°. Of these 4467 were unique (R_{int} = 0.085). CCDC 182/795.

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