SYNTHESIS OF OPTICALLY ACTIVE O,O,O-TRIMETHYLKORUPENSAMINES A AND B

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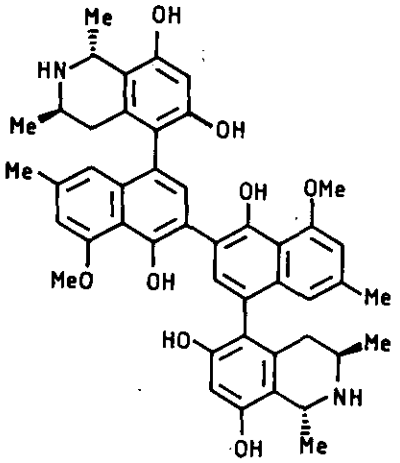
Abstract - Hydrolysis of benzofuran derivative (**10**) with concomitant aromatisation produced the biaryl system (**11**). Subsequent Sharpless asymmetric epoxidation of the cinnamyl alcohol (**13**) gave atropisomers (**14**) and (**15**) conveniently separated by chromatography. Independent derivatisation of naphthylisoquinoline ring with **14** and **15** furnished korupensamine analogues (**18**) and (**19**). Comparison of CD spectra with those of natural products assigned the stereostructures of **18** and **19**.

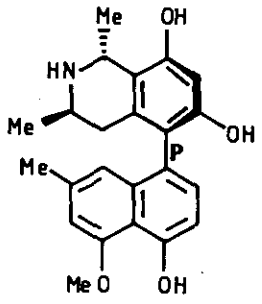
Naphthylisoquinoline alkaloids are associated with many biological activities, including the potent anti-HIV-I and anti-HIV-II activities shown by dimeric alkaloids, michellamines (**1**).[1] Recently the monomeric alkaloids korupensamine A-D, possessing anti-malarial activity, are isolated from Ancistrocladus korupensis.[2] Our interest in dimeric alkaloids emanated with a desire to identify a synthetic protocol that could lead to atropisomerically enriched alkaloids as convenient intermediates, for elaboration. We believe, that this strategy would lead to michellamine synthesis in a more stereocontrolled way, despite the fact that separation of michellamines A, B and C from the mixture of isomers, by hplc has been successfully employed in the total synthesis of these alkaloids.[3] In this communication we report a synthetic route to monomeric alkaloids korupensamines A and B (methyl ethers) involving the Sharpless asymmetric epoxidation[4] to complete the tetrahydroisoquinoline ring

system coupled with separation of atropisomers.



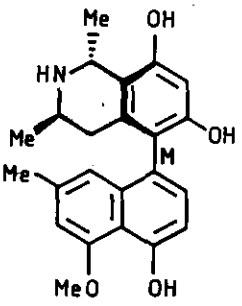
Michellamine A-C

1



Korupensamine-A

2

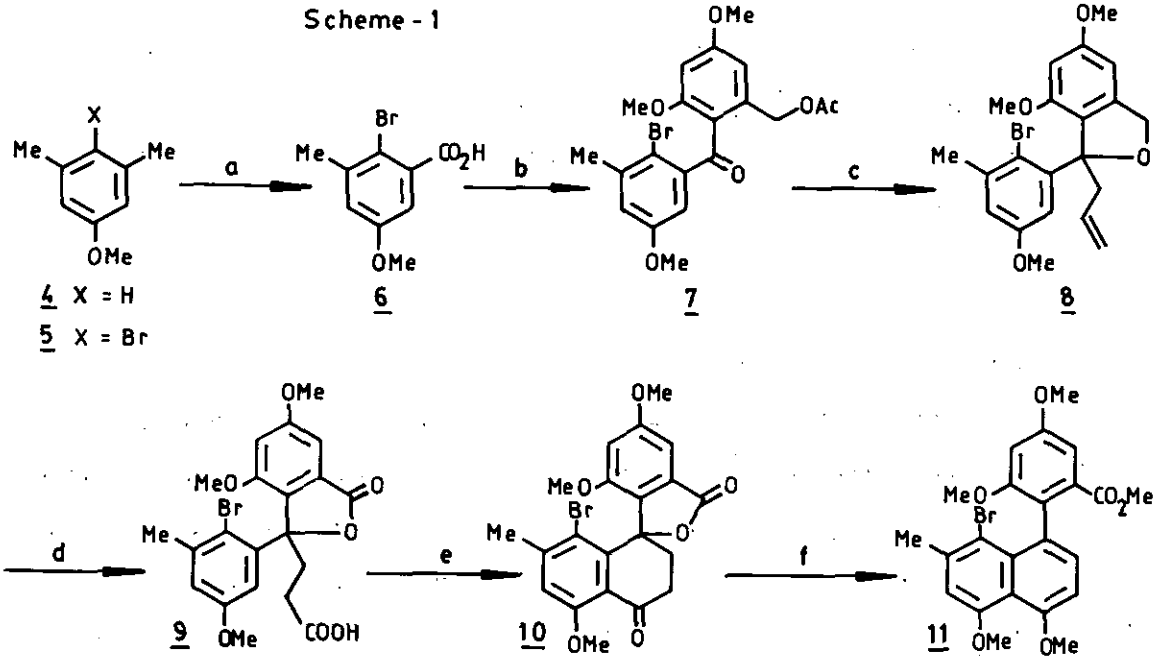


Korupensamine-B

3

The synthesis was initiated by first carrying out the nuclear bromination of **4** followed by conversion of **5** into **6** in a straightforward synthetic sequence (Scheme 1) (over all

Scheme-1



Reagents and conditions : a) i) NBS, $CHCl_3$, Δ, 10 h; ii) NBS, AIBN, CCl_4, Δ, 4 h; iii) $CaCO_3$, H_2O, Dioxane, Δ, 5 h; iv) Jones reagent, MeCOMe, 0°C, 1 h; b) i) $SOCl_2$, C_6H_6, Δ, 1 h; ii) 3,5-Dimethoxybenzyl acetate, $AlCl_3$, $ClCH_2CH_2Cl$, 0°C, 1 h; c) i) Allyl-MgBr, THF-Ether, 0°C, 1 h; ii) PTSA, CH_2Cl_2, 0°, 36 h; d) i) $BH_3.SMe_2$, THF, NaOH, H_2O_2, 0°C-room temperature, 2 h; ii) Jones reagent, MeCOMe, 0°C, 10 h; e) PPE, $CHCl_3$, 12 h; f) MeOH, HCl, Δ, 5 h.

yield 72%). The derived acid chloride of **6** and 3,5-dimethoxybenzyl acetate[5] were coupled in presence of $AlCl_3$-$ClCH_2CH_2Cl$ to afford the benzophenone (**7**) (yield 72%).

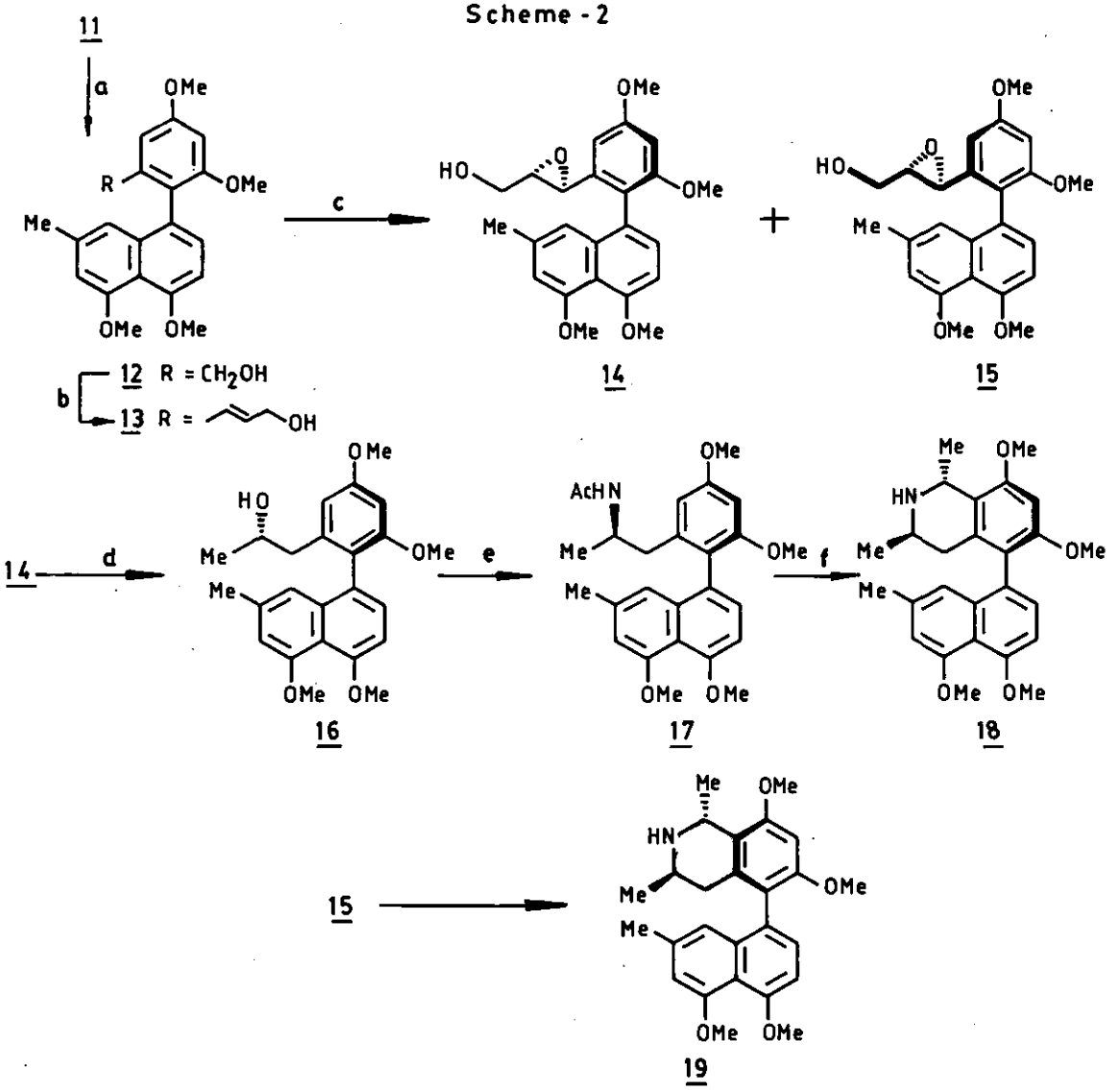
The intermediate diol, obtained after the Grignard reaction of **7** with allylmagnesium bromide, was judiciously locked intramolecularly in the form of benzofuran (**8**) with PTSA-CH_2Cl_2 (72% overall yield). With OH groups now protected, the hydroboration-oxidation of **8** occurred smoothly (yield 78%), subsequent Jones oxidation then provided the acid lactone (**9**) (yield 74%). Oxidation of benzylic carbon turned out to be convenient event for the subsequent aromatisation. The PPE-$CHCl_3$ promoted cyclisation of **9** afforded the tetralone (**10**) (yield 84%) which when exposed to methanolic HCl underwent aromatisation leading to the formation of the methyl ester (**11**) (Yield 80%).

At this point we elaborate the ester group of **11** into the isoquinoline ring system based on Sharpless asymmetric epoxidation as the key step. Treatment of **11** with LAH in refluxing THF not only produced the benzyl alcohol (**12**) but simultaneously removed the bromo group (yield 90%). Transformation of **12** into the cinnamyl alcohol (**13**) was a straightforward proposition (70% overall yield). Sharpless asymmetric epoxidation of **13** with (+)-DIPT (diisopropyl tartrate), as a chiral auxiliary, gave two atropisomeric epoxides (**14**) (42% yield) (ee, > 95%) and (**15**) (43% yield) (ee, > 95%) (hplc on Chiralcel OD, n-hexane-isopropanol, 225 *nm*) conveniently separated by chromatography on silica gel. Although the structures of **14** and **15** were substantiated by the ^1H nmr spectra, the absolute configuration at the biaryl axis was assigned by CD spectral analysis at a later stage.

The epoxide (**14**), after mesylation, was treated with LAH at 0°C to give the alcohol (**16**) in one step[6] (yield 91%) which was followed by nucleophilic displacement reaction with azide under Mitsunobu conditions[7] (yield 83%). The resulting azide was reduced and acetylated to form **17** (yield 89%). The conventional cyclisation of **17** with $POCl_3$-MeCN and stereocontrolled reduction by using Me_3Al-LAH produced the required compound (**18**) (70% yield).[8] Similarly compound (**15**) was converted into **19**.

In order to assign absolute stereochemistry at the biaryl axis of **18** and **19**, circular dichroism study was found to be most useful. The CD spectra of compounds (**18**) and (**19**) (Figure) showed opposite pattern and practically correlated with the spectra reported[2] for korupensamines **A** and **B**, respectively. This attributed to the stereochemical assign-

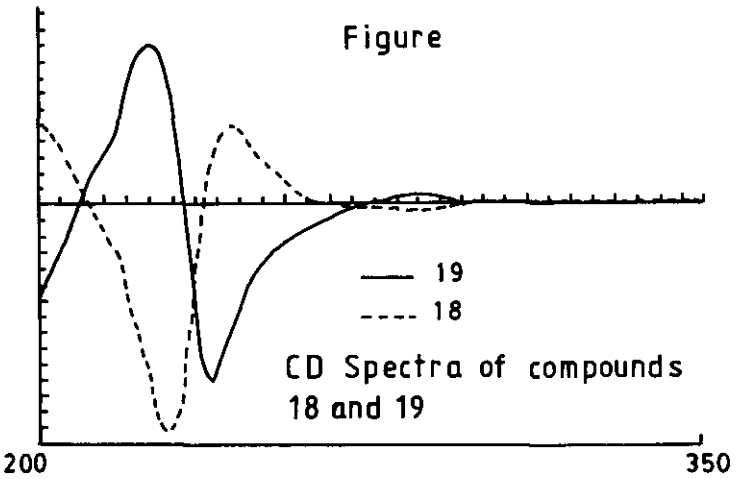
Scheme - 2



Reagents and Conditions : a) LAH, THF, Δ, 10 h; b) i) PCC, CH_2Cl_2, 0°C, 1 h; ii) $(EtO)_2PO$-CH_2CO_2Et, NaH, C_6H_6, 0°C, 1 h; iii) DIBAL-H, CH_2Cl_2, 0°C, 0.5 h; c) (+)DIPT, $Ti(OiPr)_4$, tBuOOH, CH_2Cl_2, Molecular sieves 4 A, -20°C, 4 h; d) MsCl, TEA, DCM, 0°C, 0.5 h; ii) LAH, THF, 0°C, 4 h; e) i) $(PhO)_2PON_3$, PPh_3, DEAD, C_6H_6, 0°C, 4 h; ii) Pd-C, H_2, Ac_2O, EtOAc, 2 h; f) i) $POCl_3$, MeCN, Δ, 0.5 h; ii) Me_3Al, LAH, -78°C-room temperature, 4 h.

ment of **18** and **19** at the biaryl axis, as indicated.[9]

In conclusion it is pertinent to mention that a number of naphthylisoquinoline alkaloids that are being isolated, can be synthesised by virtue of the synthetic protocol above. The Sharpless asymmetric epoxidation has been judiciously explored for the first time, to con-



struct the isoquinoline segment and to separate the two atropidiastereomers. The total synthesis of michellamines is forthcoming.

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9. The ^{1}H nmr spectra (200 MHz, $CDCl_3$) and $[\alpha]_D$ of some selected compounds: **14:** δ 2.32 (s, 3H), 2.85 (m, 1H), 2.95 (m, 1H), 3.15 (m, 1H), 3.21 (d, 1H, J=2.5 Hz), 3.66, 3.87, 3.96, 3.99 (4s, 12H), 6.51 (d, 1H, J=2.1 Hz), 6.55 (d, 1H, J=2.1 Hz), 7.65 (s, 2H), 6.85 (d, 1H, J=8.5 Hz), 7.25 (d, 1H, J=8.5 Hz), $[\alpha]_D$ -42.5° (c 0.40, $CHCl_3$); **15:** δ 2.30 (s, 3H), 2.95 (m, 1H), 3.17 (d, 1H, J=2.5 Hz), 3.29 (dd, J=4.2, 12.7 Hz), 3.55 (dd, 1H, J=3.1, 12.7 Hz), 3.61, 3.85, 3.93, 3.95 (4s, 12H), 6.55 (s, 2H), 6.70 (s, 1H), 6.80 (s, 1H), 6.82 (d, 1H, J=8.0 Hz), 7.10 (d, 1H, J=8.0 Hz), $[\alpha]_D$ +27.7° [c 0.50, $CHCl_3$); **11:** δ 2.32 (s, 3H), 3.30, 3.62, 3.90, 3.92, 3.93 (5s, 15H), 6.60 (br, 1H), 6.66 (br, 2H), 6.76 (d, 1H, J=8.0 Hz), 6.98 (d, 1H, J=2.0 Hz), 7.02 (d, 1H, J=8.0 Hz); **16:** δ 0.91 (d, 3H, J=6.4 Hz), 2.25 (dd, 1H, J=8.5, 12.7 Hz), 2.29 (s, 3H), 2.36 (dd, 1H, J=2.1 Hz), 6.66 (s, 2H), 6.83 (d, 1H, J=8.5 Hz), 7.11 (d, 1H, J=8.5 Hz), $[\alpha]_D$ +20.28° (c 0.71, $CHCl_3$; **17:** δ 0.89 (d, 3H, J=6.4 Hz), 1.68 (s, 3H), 2.2 (m, 1H), 2.3 (s, 3H), 2.4 (m, 1H), 3.60, 3.85, 3.93, 4.00 (4s, 12H), 4.1 (m, 1H), 4.9 (d, 1H, J=8.5 Hz), 6.40 (d, 1H, J=2.1 Hz), 6.50 (d, 1H, J=2.1 Hz), 6.60 (s, 2H), 6.75 (d, 1H, J=8.5 Hz), 7.04 (d, 1H, J=8.5 Hz); **18:** δ 1.28 (d, 3H, J=6.6 Hz), 1.77 (d, 3H, J=6.5 Hz), 2.20 (dd, 1H, J=4.5, 16.6 Hz), 2.35 (s, 3H), 2.56 (dd, 1H, J=11.2, 16.6 Hz), 3.16 (m, 1H), 3.61, 3.86, 3.88, 3.93 (4s, 12H), 4.76 (m, 1H), 6.42 (br, 1H), 6.57 (br, 1H), 6.67 (b, 1H), 6.74 (d, 1H, J=8.4 Hz), 6.93 (d, 1H, J=8.4 Hz), $[\alpha]_D$ -34.33° (c 0.61, $CHCl_3$); **19:** δ 1.27 (d, 3H, J=6.8 Hz), 1.65 (d, 3H, J=6.7 Hz), 2.11 (dd, 1H, J=4.5, 17.0 Hz), 2.30 (s, 3H), 2.56 (dd, 1H, J=11.3, 17.0 Hz), 3.4 (m, 1H), 3.60, 3.88, 3.94, 3.95 (4s, 12H), 4.84 (q, 1H, J=6.7 Hz), 6.44 (s, 1H), 6.61 (br, 2H), 6.79 (d, 1H, J=8.2 Hz), 7.04 (d, 1H, J=8.2 Hz), $[\alpha]_D$ +30.00° (c 0.5, $CHCl_3$).

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