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Synthesis of an Isochroman Analogue of the Michellamines

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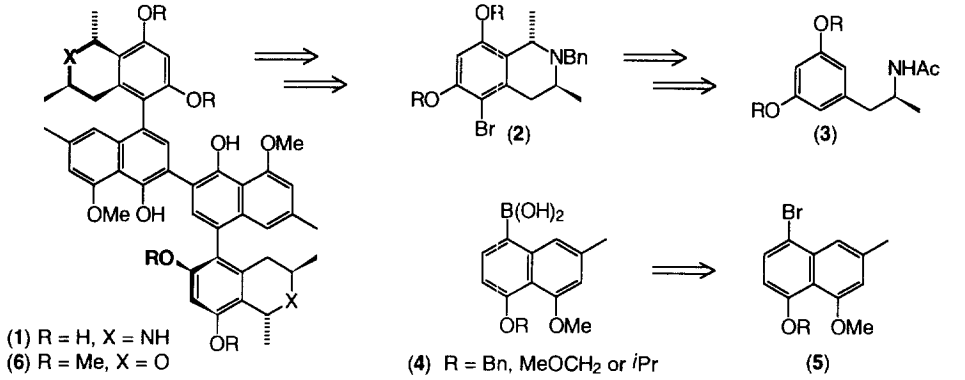
Abstract: The synthesis of racemic 5-iodo-6,8-dimethoxy-1,3-*trans*-dimethylisochroman (**16**) in eleven steps from 2,4-dimethoxybenzaldehyde is outlined. Compound (**16**) was coupled by means of Suzuki methodology with 4-isopropoxy-5-methoxy-7-methylnaphthaleneboronic acid (**19**) to yield (**20**). This was converted into (**6**), a racemic isochroman analogue of the michellamines.

Keywords: Biaryls; Naphthalenes; Isochromans; Suzuki Coupling

Michellamines[1] (e.g. michellamine B, **1**), novel naphthylisoquinolines isolated from *Ancistrocladus korupensis*, have stimulated interest in the scientific community mainly as a result of their anti-HIV activity.[2] These intriguing structures have thus become popular targets for synthesis.[3] Several of the published syntheses have relied on the construction of a suitably protected tetrahydroisoquinoline precursor, *e.g.* (**2**), by means of a Bischler-Napieralski cyclisation from substrates such as (**3**). Subsequently, the biaryl axes are formed between (**2**) and a naphthalene subunit (**4**), which is itself invariably prepared from a brominated precursor such as (**5**).



As a result of the biological activities associated with the michellamines, the USA's National Cancer Institute (NCI) has encouraged researchers to synthesise analogues of these naturally occurring products,[4a] and several have been prepared.[4b-e] In this paper we outline a novel method for the synthesis of (**6**), a racemic isochroman analogue of the michellamines.

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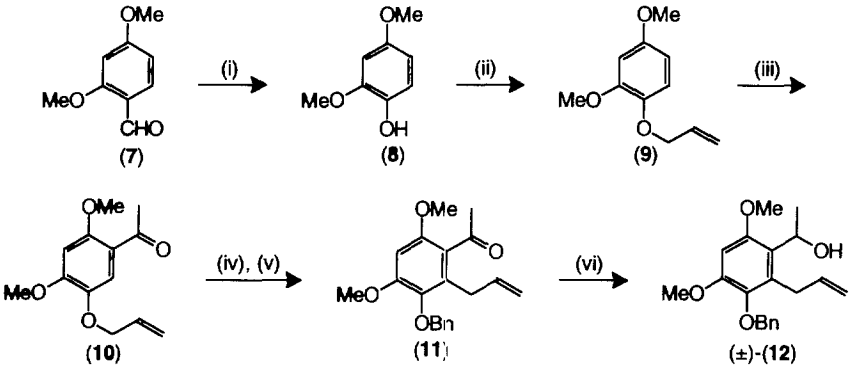
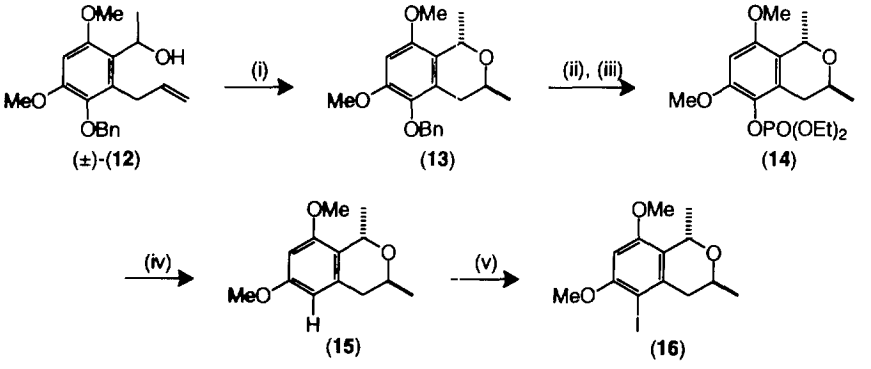
Baeyer-Villiger oxidation of commercially available 2,4-dimethoxybenzaldehyde (**7**) followed by hydrolysis and protection of the resulting phenol (**8**) as the allyl ether gave the 1,2,4-trisubstituted benzene (**9**) in 85% yield. Following protocol developed by Tedder and co-workers[5] and exploited extensively by Giles *et al.*,[6] we introduced an acetyl functionality at the C-5 position by stirring (**9**) with acetic acid and trifluoroacetic anhydride in dichloromethane to yield (**10**). Subsequent Claisen rearrangement of (**10**) and protection of the ensuing phenol as the benzyl ether afforded (**11**) in 94% yield. Finally, the ketone was reduced with lithium aluminium hydride to the alcohol (**12**) in excellent yield (93%). This compound put us in a position to make the isochroman ring system.



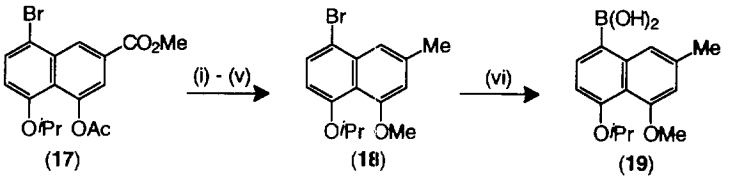
Reagents: (i) Magnesium monoperoxyphthalate hexahydrate (MMPP), silica gel, MeOH, 88%; (ii) $H_2C{=}CHCH_2Br$, K_2CO_3, Me_2CO, 96%; (iii) AcOH, TFAA, CH_2Cl_2, 81%; (iv) Heat (160°C); (v) $PhCH_2Br$, K_2CO_3, Me_2CO, 94% (2 steps); (vi) $LiAlH_4$, Et_2O, 93%.

Utilising methodology developed by Giles *et al.*,[7] we easily converted the alcohol (**12**) into the desired *trans*-1,3-disubstituted isochroman (**13**) by treatment with potassium *t*-butoxide. With (**13**) in hand, conversion into the iodide (**16**) was achieved as shown by deoxygenation of the benzyl ether *via* phosphate ester[8] (**14**), followed by a regioselective aromatic iodination[9] of the defunctionalised compound (**15**). We confirmed the position of the iodine atom by NOE spectroscopy.



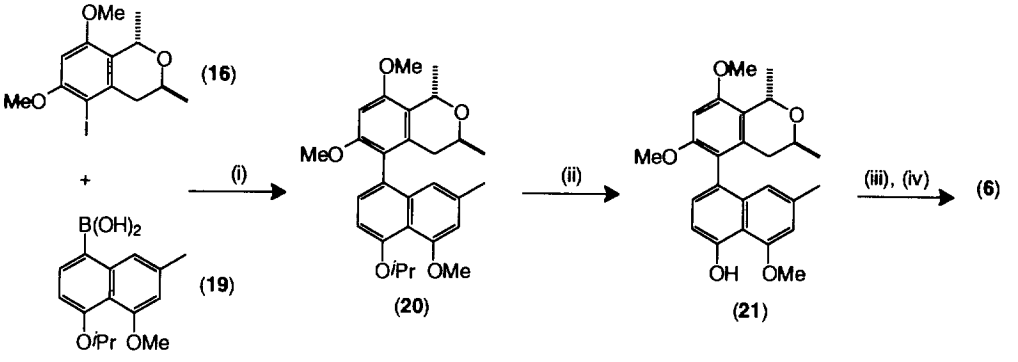
Reagents: (i) KOBu^t, DMF, 91%; (ii) H_2, Pd/C, MeOH, 100%; (iii) NaH, $(EtO)_2POCl$, THF, 100%; (iv) K, NH_3, -78°C, 100%; (v) Ag_2SO_4, I_2, EtOH, 94%.

The naphthalene (17) was synthesised from 2-bromo-5-isopropoxybenzaldehyde in two steps in 39% yield using Stobbe condensation methodology.[10] Compound (17) was converted through the intermediacy of (18)[3b] into the naphthaleneboronic acid (19) utilising standard conditions.[3d]



Reagents: (i) KOH/MeOH, 95%; (ii) $(MeO)_2SO_2$, K_2CO_3, Me_2CO, 99%; (iii) LAH, THF, 100%; (iv) $(CBrCl_2)_2$, PPh_3, CH_2Cl_2, 84%; (v) L-Selectride, CH_2Cl_2, 100%; (vi) (a) *n*-BuLi, THF, –78°C; (b) $B(O^iPr)_3$, NH_4Cl, H_2O, not purified.

A Suzuki coupling reaction[11] between isochroman (16) and the naphthalene moiety (19) under standard conditions afforded the biaryl compound (20) in an excellent yield of 85% as a mixture of two atropisomers in a ratio of 1:1.5. Removal of the isopropyl protecting group by treatment with boron trichloride yielded naphthol (21).[3b] This was treated with silver(I) oxide followed by hydrogenation on a palladium-charcoal catalyst[3g] to yield the desired product (6)[12] as a mixture of atropisomers. This reaction sequence completes the first synthesis of an isochroman analogue of the michellamines. We are currently investigating the technically demanding separation of the three atropisomers of (6), after which biological evaluation of these new michellamine analogues will be undertaken.



Reagents: (i) 20% $Pd(PPh_3)_4$, K_3PO_4, DMF, 95-100°C, 85%; (ii) BCl_3, CH_2Cl_2, –78°C, 58%; (iii) Ag_2O, 0.2% Et_3NH, $CHCl_3$, (iv) H_2 (1 atm), Pd/C, MeOH-CH_2Cl_2, 75% (two steps).

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