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THE PREPARATION OF NOVEL DOPAMINE ANALOGUES *VIA* PALLADIUM CATALYSED CYCLISATION REACTIONS

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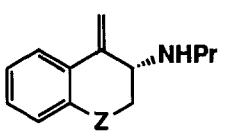
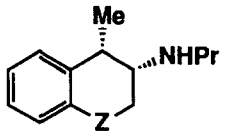
Abstract: The preparation of a range of tetrahydronaphthalene derivatives *via* palladium catalysed cyclisation reactions is described. The application of the cyclisation methodology to the synthesis of enantiomerically pure amino-chromans, as potential dopamine analogues, is also discussed.

The recent discovery of novel, pharmacologically distinct D_3 and D_4 dopamine receptors, using molecular biological techniques,[1] has given renewed impetus to the search for selective agonists and antagonists for dopamine receptor sub-types. Importantly, this exciting development has significant implications for the design of more discriminating and effective therapeutic agents for use in psychiatry and neurology.[2] As part of our continuing programme to design and synthesise novel dopamine analogues,[3] we required a versatile synthetic route to a range of aminotetralin analogues exemplified by structures (**1**) and (**2**). We decided to investigate the utility of the intramolecular Heck reaction and related palladium-catalysed cyclisation procedures[4,5] for this purpose. Scheme 1 illustrates investigations carried out to confirm the viability of this approach for the preparation of simple tetrahydronaphthalene derivatives and Scheme 2 shows studies which establish that the palladium methodology can be employed to prepare the desired structural types in enantiomerically pure form.[6]



(**1**) Z = CH_2, O



(**2**)

The preliminary investigations were carried out on adducts (**4**) - (**8**) derived from 3-(2-iodophenyl)propanal (**3**)[7] by the organometallic addition reactions shown in Scheme 1.[8] All yields in Scheme 1 are unoptimised. The straightforward intramolecular Heck reaction to give

alkene (**9**) was achieved efficiently by treatment of iodo-alkene (**4**) with $Pd(OAc)_2/AgNO_3/Et_4NCl/MeCN$, reflux.[9] The corresponding bromide did not react under these conditions. The 2-propenyl substrate (**5**) cannot undergo Heck cyclisation but palladium catalysed cyclisation-hydride anion capture[5] using piperidinium formate[10] gave the dimethyl tetralin (**10**) in good yield. We also established that alkynes could be employed in these palladium catalysed cyclisation-hydride anion capture processes although the yields were lower (Scheme 1). Thus, silyl alkyne (**6**) gave vinyl silane (**11**) in the presence of piperidinium formate and the phenyl substituted analogue (**12**) when $NaBPh_4$ was used as the anion capture reagent. In a similar manner alkyne (**7**) and phenylthioalkyne (**8**) gave alkene (**9**) and vinyl sulphide (**13**), respectively. Nuclear Overhauser experiments were carried out on compounds (**11**)-(**13**)[11] and confirmed that palladium cyclisation/anion capture occurred *via* cis addition.

With the basic methodology in place, we applied the procedure to the synthesis of the enantiomerically pure dopamine analogues (**19**) and (**20**) as shown in Scheme 2. Mitsunobu coupling of methionine-derived alcohol (**15**)[12] with 2-iodophenol (**14**) proceeded efficiently to give cyclisation precursor (**16**). Heck cyclisation was effected in an extremely high yielding and reproducible reaction giving styrene (**17**) (the vinylic protons appear as two singlets in the N.M.R. spectrum at δ5.23 and 5.62). Propylation of (**17**) to (**18**) went in quantitative yield and removal of the protecting group using aq. HCl-EtOAc gave the target compound (**19**); $[\alpha]_D$ -109.6° (c 0.94, MeOH), m.p. 172-175 °C (dec.). Interestingly, the use of anhydrous conditions for the deprotection reaction gave the tricyclic product (**21**) in 75% yield. Hydrogenation of alkene (**18**) using Pearlman's catalyst proceeded efficiently and stereoselectively[13] to give, after deprotection, the second target molecule (**20**); $[\alpha]_D$ -2.13° (c 0.4, MeOH), m.p. *ca.* 210 °C (sealed tube, sublimes 183-185 °C).

Chromans (**19**) and (**20**) were tested for binding affinity at the dopamine D_3 receptor. Neither compound showed significant affinity for this receptor (pKi < 6.5; rat D_3 receptor expressed in Chinese hamster ovary cells.[1]

Acknowledgements

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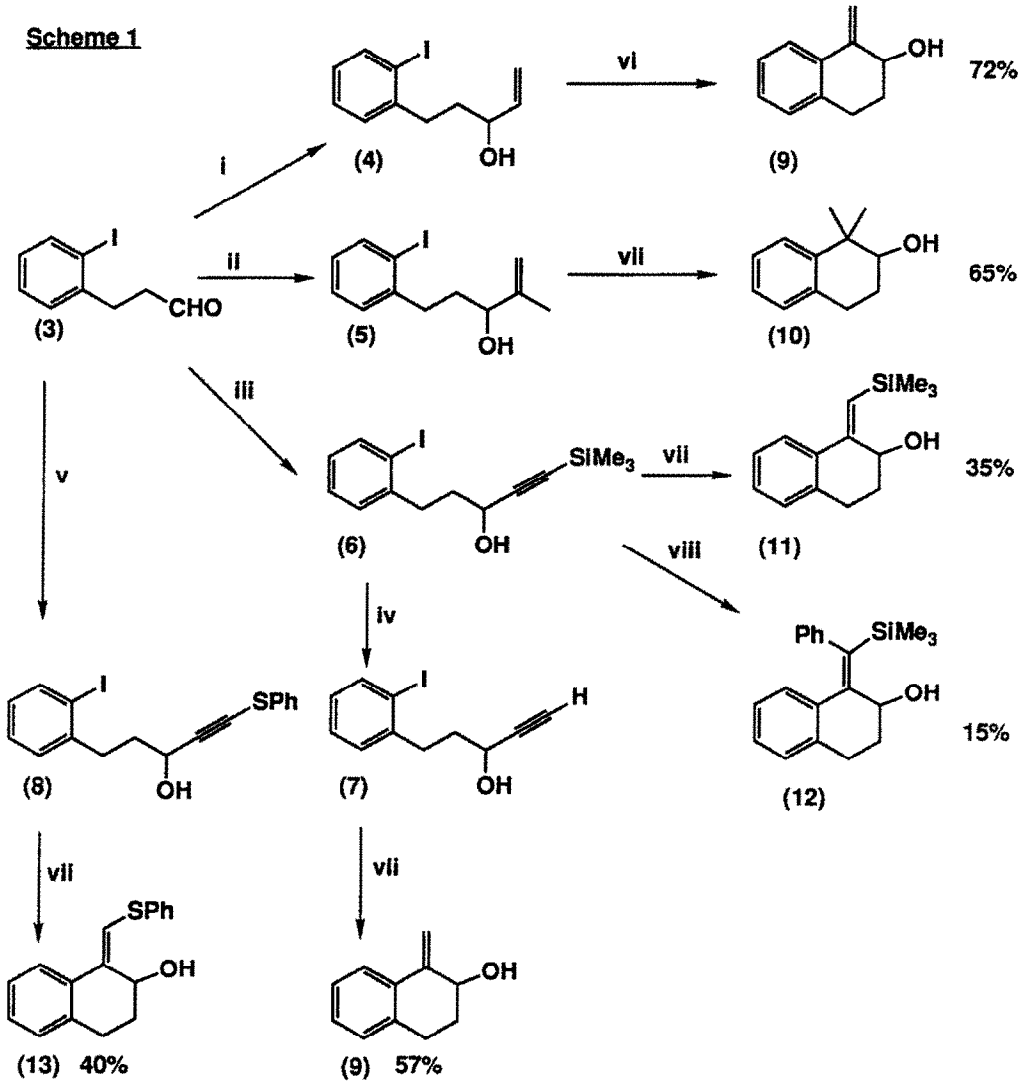
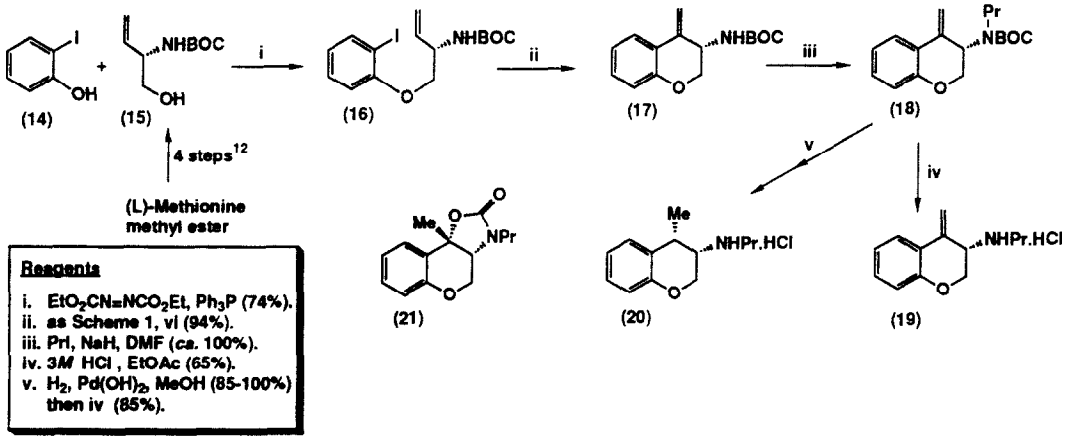
Scheme 1



Reagents

i. CH_2=CHMgBr, THF, -78°C (55%).
ii. CH_2=C(Me)MgBr, THF, -78°C (55%).
iii. Me_3SiC≡CH, BuLi, THF, -78°C (85%).
iv. K_2CO_3, MeOH (*ca.* 100%).
v. PhSC≡CH, BuLi, THF, -78°C (80%).
vi. $Pd(OAc)_2$ (0.1 eq), Ph_3P (0.2 eq), $AgNO_3$ (1.0 eq), Et_4NCl (1.0 eq), Et_3N (1.0 eq), MeCN, reflux.
vii. As vi but with $AgNO_3$/Et_3N replaced by piperidine (4.0 eq), HCO_2H (3.0 eq).
viii. $Pd(OAc)_2$ (0.1 eq), Ph_3P (0.2 eq), $AgNO_3$ (1.0 eq), Et_4NCl (1.0 eq), Ph_4BNa (1.0 eq), anisole, 120°C.

Scheme 2



Reagents

i. $EtO_2CN{=}NCO_2Et$, Ph_3P (74%).
ii. as Scheme 1, vi (94%).
iii. PrI, NaH, DMF (*ca.* 100%).
iv. 3*M* HCl, EtOAc (65%).
v. H_2, $Pd(OH)_2$, MeOH (85-100%) then iv (85%).

References and notes

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11. For example, for (**11**) NOE's of *ca.* 40% were observed between the vinyl hydrogen and the ortho aromatic proton, and in the reverse direction.
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13. Other hydrogenation catalysts (e.g. 5 and 10 % Pd/C and PtO_2) were ineffective for this conversion. Hydrogenation of compound (**17**) proceeded with low stereoselectivity (α:β *ca.* 3:1).