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Synthesis of biaryl substituted isoquinolines based on the reticuline scaffold

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Synthesis of Biaryl Substituted
Isoquinolines Based on the
Reticuline Scaffold

A thesis submitted in fulfilment of the requirements
for the award of the degree of

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From
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Stephen Roy Taylor
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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>ABq</td>
<td>AB quartet</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic Acid</td>
</tr>
<tr>
<td>AgOTFA</td>
<td>Silver Trifluoroacetate</td>
</tr>
<tr>
<td>AlMe₃</td>
<td>Trimethylaluminium</td>
</tr>
<tr>
<td>amu</td>
<td>Atomic mass unit</td>
</tr>
<tr>
<td>Ar</td>
<td>Argon</td>
</tr>
<tr>
<td>BF₃,Et₂O</td>
<td>Borontrifluoride diethyletherate</td>
</tr>
<tr>
<td>Br₂</td>
<td>Bromine</td>
</tr>
<tr>
<td>BRSM</td>
<td>Based on Recovered Starting Material</td>
</tr>
<tr>
<td>bs</td>
<td>Broad singlet</td>
</tr>
<tr>
<td>CI⁺</td>
<td>Chemical Ionisation</td>
</tr>
<tr>
<td>Ce(OH)₄</td>
<td>Cerium(IV) Hydroxide</td>
</tr>
<tr>
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</tr>
<tr>
<td>CHCl₃</td>
<td>Chloroform</td>
</tr>
<tr>
<td>δ</td>
<td>Delta (Chemical Shift in Parts per million)</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>ddd</td>
<td>Double doublet of doublets</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarisation Transfer</td>
</tr>
<tr>
<td>DMA</td>
<td>Dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-N,N-Dimethylaminopyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>dt</td>
<td>Doublet of triplets</td>
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<tr>
<td>EDCI</td>
<td>1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
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<td>EDG</td>
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<tr>
<td>EI+</td>
<td>Electron Impact Ionisation</td>
</tr>
<tr>
<td>ES+</td>
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<tr>
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<td>Ethyl Acetate</td>
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<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
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<tr>
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<td>gradient Heteronuclear Single Quantum Correlation</td>
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</tr>
<tr>
<td>HOBT</td>
<td>1-Hydroxybenzotriazole</td>
</tr>
<tr>
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<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>I₂</td>
<td>Iodine</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>Potassium Carbonate</td>
</tr>
<tr>
<td>KOAc</td>
<td>Potassium Acetate</td>
</tr>
<tr>
<td>LRMS</td>
<td>Low Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>M</td>
<td>Molar (moles / litre)</td>
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<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
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<td>MeI</td>
<td>Methyl Iodide</td>
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<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>Magnesium Sulfate</td>
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<tr>
<td>Symbol</td>
<td>Definition</td>
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<td>--------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>mL</td>
<td>millilitre</td>
</tr>
<tr>
<td>mmol</td>
<td>milli mol</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting Point</td>
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<tr>
<td>MoCl₅</td>
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<tr>
<td>MS</td>
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</tr>
<tr>
<td>[M⁺]</td>
<td>Molecular ion</td>
</tr>
<tr>
<td>[M+H⁺]</td>
<td>Protonated Molecular ion</td>
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<td>Hertz</td>
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<td>micro</td>
</tr>
<tr>
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<td>NaCNBH₃</td>
<td>Sodium Cyanoborohydride</td>
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<tr>
<td>NEt₃</td>
<td>Triethylamine</td>
</tr>
<tr>
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</tr>
<tr>
<td>¹³C NMR</td>
<td>Carbon Nuclear Magnetic Resonance</td>
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<tr>
<td>PCl₅</td>
<td>Phosphorus Pentachloride</td>
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<tr>
<td>(Ph₃P)₂PdCl₂</td>
<td>Dichlorobis(triphenylphosphine)palladium(II)</td>
</tr>
<tr>
<td>PIFA</td>
<td>Phenyliodine(III) bis(trifluoroacetate)</td>
</tr>
<tr>
<td>PS</td>
<td>Petroleum Spirit (b.p. 40-60 °C)</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>Abbreviation</td>
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<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
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<td>Triplet</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<tr>
<td>TTFA</td>
<td>Thallium(III) trifluoroacetae</td>
</tr>
<tr>
<td>VOF$_3$</td>
<td>Vanadium Oxyfluoride</td>
</tr>
</tbody>
</table>
Declaration

I, Stephen Roy Taylor, declare that this thesis, submitted in fulfillment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless due reference is provided. This document has not been submitted for qualifications at any other academic institution.

Stephen Roy Taylor

January, 2006
ABSTRACT

This thesis examines the preparation of phenyl-, benzyl-, bisbenzyl- and phenylethylisoquinolines possessing a biaryl moiety, based on the structures of reticuline and laudanosine. The synthetic strategy involves the formation of an appropriately protected biphenyl unit followed by construction of the isoquinoline unit by converting the biphenyl into a 2-[3,4-dimethoxyphenyl]ethylamide, cyclising the amide under Bischler-Napieralski cyclisation conditions and reducing the resulting imine under conditions that will also reductively methylate the isoquinoline nitrogen.

In Chapter 2, the bisbenzylisoquinoline 49 was the primary synthetic target. Formation of the biphenyl moiety was investigated using the Ullmann coupling reaction of halides 89 or the oxidative coupling of ester 97 to form the symmetrical biphenyl 94. The Ullmann reaction proved to be the best method for preparing dimer 94, isolated in 69 % yield. Oxidative formation of 94 was achieved with a best yield of 55 % with MoCl₅ as the oxidant, however a chlorinated side product was also observed. Following formation of 94, the isoquinoline rings of 49 were built up by formation of the bisamide 100, which cyclised under Bischler-Napieralski to an unstable bisimine. Reduction afforded diastereomeric amines 102, separable by silica gel column chromatography, and reductive methylation of the major diastereomer afforded the bisbenzylisoquinoline 49. Compounds 102 and 49 were subjected to biological assay and found to be poorly biologically active. Our synthetic effort then turned to the preparation of phenyl-, benzyl, and phenylethylisoquinolines each possessing a biaryl moiety. Oxidative coupling, Pd-mediated arylation and the Suzuki cross-coupling reaction were selected as methods for biaryl bond formation, after which we could elaborate the isoquinoline skeleton.
The focus of Chapter 3 was the formation of the biaryl bond by oxidative coupling. Ester 145 was selected as the substrate to optimise the oxidation conditions. The hypervalent iodine reagent PIFA proved the most efficient oxidant, yielding the desired biaryl product 146 in 85% under mild reaction conditions. Nucleophilic ring opening of biaryl lactone 146, hydroxyl protection, Bischler-Napieralski cyclisation and reductive amination afforded benzylisoquinolines 149 and 152. A series of aromatics, linked by an ester tether were prepared, and subjected to oxidation with PIFA. In most cases intramolecular biaryl bond formation failed to occur, largely due to the difference in electron density of the tethered aromatics. Rather, intermolecular dimerisation occurred. Dimers possessing hydroquinone character subsequently oxidised to quinones, while esters possessing a \( p \)-methoxy substitution pattern were uniformly cleaved in a DDQ type fashion.

In Chapter 4 our attention turned to the preparation of biaryl lactones using the Pd-mediated arylation of mono-iodinated aromatics, tethered to an electron rich aromatic by an ester tether. The tether was constructed at specific lengths, such that the biaryl lactone formed would be either a 6-, 7-, or 8-membered fused ring system following biaryl bond formation. Heating of our monoiodinated esters with Pd(II) and a base in DMA in a sealed tube revealed formation of 6-membered rings to be the favoured outcome, particularly when the halogenated ring also possessed an electron withdrawing substituent, thereby increasing the electrophilic nature of the palladium species following oxidative insertion into the aryl halide bond. Biaryl lactones 242, 243 and 245 were prepared under these conditions, however the lactone stability to aminolysis has prevented their conversion into phenylisoquinolines. Increasing the tether length by one methylene carbon revealed the fragility of phenol derived esters as compounds 258, 260, 262 and 263 all decomposed under the reaction conditions, preventing the
formation of 7-membered lactones by this methodology. Increasing the tether length by a second methylene carbon revealed a propensity to form a Pd-enolate, resulting in the formation of cinnamate 265 and isochromans 268 and 275. The chemistry presented in Chapters 3 and 4 revealed some interesting results, however the oxidative coupling and Pd-mediated arylation reactions described did not offer a systematic methodology for the preparation of various isoquinolines possessing a biaryl moiety.

In Chapter 5 the Suzuki cross coupling reaction was selected as the method of biaryl bond construction. Electron rich aryl halides 314, 325, and 340 were converted to aryl boronates with bis(pinacolato)diboron in the presence of a Pd catalyst. Boronates 315, 326 and 337 were cross-coupled with the electron deficient iodide 230 in uniformly good yields to furnish biaryls 316, 327 and 338, respectively. Deprotection of biaryl 316 afforded lactone the 317, a compound requiring AlMe₃ assisted (Weinreb technology) aminolysis with amine 90. Alcohol protection, Bischler-Napieralski cyclisation and reductive amination afforded phenylisoquinoline 323. Amide boronate 326 cross-coupled exceptionally well with 230 after which Bischler-Napieralski cyclisation and reductive amination afforded the phenylethylisoquinoline 309. Deprotection of biaryl 338 revealed a primary alcohol that required a 2-step oxidation, Dess-Martin periodinane and then NaClO₂, to generate the carboxylic acid precursor of the benzylisoquinoline 308. Amide formation, cyclisation and reductive amination converted acid 339 into the benzylisoquinoline 308 in respectable yield.

Final compounds and strategic intermediates prepared in Chapters 2-4 were subjected to biological assay. These compounds were tested against 3-cancer cell lines for cytotoxicity in addition to assessment for anti-HIV activity, anti-microbial activity and CNS receptor binding potency. Chapter 6 presents the results of the biological data collected. Unfortunately, each of the compounds assessed were not active enough to
warrant further investigation as therapeutic agents, or were totally inactive. We are yet to submit isoquinolines 308, 309 and 323, prepared in Chapter 5, for biological assay.