TOTAL SYNTHESIS OF ANCISTROTANZANINE A

A Thesis

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By

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‘If it’s not red, it’s dead.’

Jason Brusnahan

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Chapter 5: Experimental

Abstract

This thesis describes the first total synthesis of ancistrotanzanine A, a member of the naphthylisoquinoline class of natural products. In Chapter 1 the synthetic challenges presented by the naphthylisoquinoline alkaloids are discussed and strategies that have been adopted in previous syntheses of naphthylisoquinoline alkaloids overviewed.

Chapter 2 describes the preparation of the key 5,3′-biaryl linkage via the Pinhey-Barton reaction. Studies into forming the linkage atropselectively were investigated using chiral hydrobenzoin acetal auxiliaries. This was found to have limited success with an atropisomeric ratio of 65:35 obtained. Changing the base from the achiral pyridine to the chiral brucine was also investigated and found to give no enhancement in the diastereoselectivity. From the results presented in Chapter 2, it was concluded that hydrobenzoin acetal auxiliaries were not appropriate for the diastereoselective synthesis of the key biaryl linkage of ancistrotanzanine A.

As the chiral acetal strategy outlined in Chapter 2 failed to yield an atropselective process, efforts were re-focused on a new approach to the naphthylisoquinolines. In Chapter 3, an overview of all the methods available for the synthesis of chiral 3,4-dihydroisoquinolines is provided. From this, it was decided to apply the alkylation of *o*-tolylnitriles with chiral sulfinimines, as originally developed by Davis, to the synthesis of naphthylisoquinolines. Synthesis of the *o*-tolylnitrile lead reagent was readily achieved, but it was found that the amount of lead tetraacetate had to be carefully controlled to avoid side-reactions in the Pinhey-Barton reaction. After careful optimisation, the key 5,3′-biaryl linkage was prepared in high yield. Application of the Davis methodology to the MOM protected biaryl failed, with no reaction resulting. After much experimentation, it was established that the reaction was very sensitive to steric hindrance. A successful reaction was finally achieved by changing the base to lithium diethylamide. However, it was found the diastereoselection of the alkylation was quite low when *p*-tolyl sulfinimine was used. The use of the *t*-butane sulfinimine meant that the diastereoselection was significantly improved, with a ratio of 85:15 being obtained. After 3 more steps, the total synthesis was completed and ancistrotanzanine A was obtained, as a

1:1 mixture of atropisomers. Efforts to separate the atropisomers formed failed and even the use of chiral HPLC failed to resolve the material. To complete the Chapter, two analogues of ancistrotanzanine A were prepared – the tetrahydroisoquinoline and the methoxy ether.

Chapter 4 summarises the above results and discusses the future potential of this research.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Jason Stewart Brusnahan and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Jason Stewart Brusnahan Date: 1st of October 2009

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
AIBN	2,2’-Azobisisobutyronitrile
aq	Aqueous
Ar	Aryl
BHA	2-*t*-Butyl-4-hydroxyanisole
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl amide
Bp	Boiling point
br	Broad
Bu	Butyl
BTMA	Benzyltrimethylammonium
cat	Catalytic
CD	Circular Dichroism
Conc	Concentrated
COSY	Correlation spectroscopy
δ	Chemical shift in parts per million downfield from tetramethylsilane
d	doublet (NMR)
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo[4.3.0]non-5-ene
DCC	Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIBAL	Diisobutylaluminium hydride

DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)pyridine
DME	Dimethyl ether
DMF	*N*, *N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppt	1,1’-Bis(diphenylphosphanyl)ferrocenyl
ee	Enantiomeric excess
eq	equivalents
Et	Ethyl
ESI-MS	Electrospray ionisation mass spectrometry
Fmoc	Fluorenyl methyloxycarbonyl
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoric triamide
HPLC	High-pressure liquid chromatography
HRMS	High-resolution mass spectrometry
INADEQUATE	Incredible natural abundance double quantum transfer experiment
J	Coupling constant (NMR)
IR	Infrared Radiation
LDA	Lithium diisopropylamide
m	Multiplet (NMR)
Me	Methyl
MHz	Megahertz
min	Minutes

MOM	Methoxymethyl
Mp	Melting point
Ms	Methanesulfonyl
MSD	Mass spectroscopy detection
NBS	*N*-Bromosuccinimide
NOE	Nuclear Overhauser Effect
NMR	Nuclear magnetic resonance
ppm	Parts per million
Pr	Propyl
q	Quartet (NMR)
Q	Quaternary carbon
ROESY	Rotating-frame overhauser effect spectroscopy
r.t.	Room temperature
s	Singlet (NMR)
t	Triplet (NMR)
sat	Saturated
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl

Ts	*p*-Toluenesulfonyl
WSC	Water soluble carbodiimide hydrochloride