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Synthetic studies of biologically active lignan and neolignan natural products

Claire Rye

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

The University of Auckland

2011
Abstract

Biologically active natural products have been of increasing interest to chemists due to the growing demand for new medicines. Lignans are a family of secondary plant metabolites known to exhibit both interesting biological activities and immense structural variety. This thesis describes the synthesis of a number of lignan and neolignan natural products and analogues thereof, with the overall aim of synthesising the complex dineolignan manassantin B 29. The interest in 29 originates from its potent inhibition of the transcription factor HIF-1, which is a potential target for a new class of selective anticancer drugs targeting the hypoxic region common in solid tumours.

Initially, a series of 2,5-diaryl-3,4-dimethyl tetrahydrofuran lignans were synthesised via the strategy proposed for the synthesis of the more complex 29. During the course of this work, it was found that varying the substrates in the final cyclisation step could significantly influence the products formed. This serendipitous discovery led to extensive investigation into the mechanisms controlling the reaction and the different compounds synthesised. With this knowledge three different subclasses of lignan were successfully synthesised, with the relative and absolute stereochemistry of a number of the natural compounds determined for the first time.

With the test synthesis proving successful the synthesis of 29 was undertaken via the envisaged convergent strategy, the three fragments syn-dimethyl compound 58 and two similar diaryl bromides 59 and 60 were synthesised enantioselectively and in pleasing yields. Unfortunately the fragments could not be joined using the established aryl lithium addition methodology which had proved very successful on the test substrates. Despite several modifications to the syn-dimethyl compound and adjusted strategies, the synthesis of manassantin B 29 remains elusive. The diaryl bromides 59 and 60 were however successfully employed in the synthesis of a series of 8,4'-oxyneolignans using a Suzuki-Miyaura strategy.

Selected synthetic natural products and analogues were sent to NCI for testing against a panel of the sixty common cancer cell lines. Whilst a further series of natural and analogous 8,4'-oxyneolignans were sent to the Swiss Tropical and Public Health Institute for evaluation against both leishmanias and malaria.
Declaration

This is to certify that:

1) This thesis comprises only the authors original work, except where indicated below;

2) Due acknowledgment to all other material used has been made in the main text of the thesis

My overall contribution to the work presented in this thesis is approximately 98%, based on the following:

Chapter 8
   Anticancer testing results shown were determined at the National Cancer Institute (NCI) USA.
Acknowledgements

Most importantly I would like to thank my supervisor David Barker. You have been a phenomenal mentor, a real inspiration and have had a pivotal role in my development as a chemist. I will be forever grateful for your guidance and support, your never ending list of ideas and positive attitude throughout. I am honoured to have been part of the Barker group for the last four years.

I am grateful to my co-supervisor Brent Copp, for your help deciphering the Crazies, as well as your guidance on a variety of subjects, with just a small amount of teasing.

I am also very obliged to my fume hood buddy Nora. You have been awesome to work alongside and I feel we make a great team in the lab, even if we don’t clean up our silica often enough. I am also very grateful for your friendship, not to mention all the assistance you have given me with proofing!

Also to Lisa, who has been equally industrious with regard to proof reading. I have enjoyed our missions for NaCl and AcOH and the friendship that ensued, long may they continue.

The Barker and Copp groups past and present, thank you for making the west wing such a great working environment. For sharing the highs and lows with a collective sense of humour and much teasing, I will definitely miss the lab.

And finally, I am greatly indebted to my husband James for your love and support throughout. You still mean the world to me babe!
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Abbreviations

1^H-NMR Proton nuclear magnetic resonance
2D Two dimensional
9BBN-H 9-Borabicyclo[3.3.1]nonane
15-cr-5 15-crown-5
18-cr-6 18-crown-6
Ac_2O Acetic anhydride
AcOH Acetic acid
ALL Acute lymphoblastic leukaemia
Ar Aromatic
BDNF Brain-derived nerve factor
BEMP 2-tert-Butylimino-2-dimethylamino-1,3-dimethyl-perhydro-1,3,2-diazophosphine
CAB Ceric ammonium nitrate
COSY Correlation spectroscopy
DCC N,N’-Dicyclohexylcarbodiimide
DCM Dichloromethane
2DQ Dichlorodicyanoquinone
d Diastereomeric excess
DIBAL Diisobutylaluminum hydride
DMAP N,N-Dimethyl-4-aminopyridine
DMF Dimethoxyethane
DMP Dess-Martin periodinane
DMF Dimethylformamide
DMSO Dimethylsulfoxide
DNA Deoxyribonucleic acid
EAT Ehrlich ascites tumour
ee Enantiomeric excess
Et_2O Diethyl ether
equiv. Equivalents
FDA Food and Drug Administration
HIF-1 Hypoxia inducible factor
HMDA Hexamethyldisilane
HPLC High pressure liquid chromatography
IBX 1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide
IC_50 Half maximal inhibitory concentration
i-PrOH iso-Propanol
iPr_2EtN Diisopropylethylamine
IR Infra-red
LDA Lithium diisopropylamine
LiHMDS Lithium hexamethyldisilazane
Li(acac) Lithium acetylacetone
m-CPBA meta-Chloroperoxybenzoic acid
MgBr_2OEt_2 Magnesium bromide diethyl etherate
mech. Mechanism
MeCN Acetonitrile
MeOH Methanol
NGF Nerve growth factor
mol Mole
MsCl Methanesulfonyl Chloride
MOM  Methoxymethyl
MOMCl Methoxymethyl chloride
MsCl Methanesulfonyl chloride
n-BuLi n-Butyllithium
NBS N-Bromosuccinimide
NCI National Cancer Institute
NEt₃ Triethylamine
NBS N-Methylmorpholine-N-oxide
NMP N-Methyl-2-pyrrolidinone
NMR Nuclear magnetic resonance
NOE Nuclear Overhauser effect
NSCLC Non-small cell lung cancer
PCC Pyridinium chlorochromate
Pd₂(dba) Palladium dibenzylideneacetone
Pd/C Palladium on carbon
PPh₃ Triphenylphosphine
PPTS Pyridinium para-toluenesulfonate
PS-BEMP 2-tert-butylimino-2-dimethylamino-1,3-dimethyl-perhydro-1,3,2-diazophosphine on polystyrene
PS-BH₄ Polymer supported- borohydride
quant. Quantitative
Red-Al Sodium bis(2-methoxyethoxy)aluminum hydride
Rf Retention factor
rt Room temperature
SM Starting Material
S₈ Nucleophilic substitution (unimolecular)
S₈₂ Nucleophilic substitution (bimolecular)
TBAF Tetrabutylammonium fluoride
TBAI Tetrabutylammonium iodide
tₚ Retention time
t-BuLi t-Butyllithium
t-BuOH t-Butanol
TBS tert-Butyl dimethylsilyl
TBSCl tert-Butyl dimethylsilyl chloride
TBS-triflate tert-Butyldimethylsilyl trifluoromethanesulfonate
tet Tetrahedral
TES Triethyl silyl
TESCl Triethyl silyl chloride
THF Tetrahydrofuran
TLC Thin layer chromatography
TMS Trimethylsilane
TMSOTf Trimethylsilyl triflate
Ts₂O Tosyl anhydride
TsCl Tosyl chloride
VEGF Vascular Epithelial Growth Factor