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 leishmania 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!

Table of Contents

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
CAN	Ceric ammonium nitrate
COSY	Correlation spectroscopy
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	Dichlorodicyanoquinone
de	Diastereomeric excess
DIBAL	Diisobutylaluminum hydride
DMAP	*N*, *N*-Dimethyl-4-aminopyridine
DME	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
HMDS	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
LHMDS	Lithium hexamethyldisilazane
Li(acac)	Lithium acetylacetone
m-CPBA	*meta*-Chloroperoxybenzoic acid
$MgBr_2{\cdot}OEt_2$	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
NEt_3	Triethylamine
NMO	*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
Pd_2(dba)	Palladium dibenzylideneacetone
Pd/C	Palladium on carbon
PPh_3	Triphenylphosphine
PPTS	Pyridinium *para*-toluenesulfonate
PS-BEMP	2-*tert*-butylimino-2-dimethylamino-1,3-dimethyl-perhydro-1,3,2-diazophosphine on polystyrene
PS-BH_4	Polymer supported- borohydride
quant.	Quantitative
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
Rf	Retention factor
rt	Room temperature
SM	Starting Material
S_N1	Nucleophilic substitution (unimolecular)
S_N2	Nucleophilic substitution (bimolecular)
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
t_R	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
Ts_2O	Tosyl anhydride
TsCl	Tosyl chloride
VEGF	Vascular Epithelial Growth Factor