Synthesis of Procyanidin Oligomers. Development and Application of Cross-Coupling Reactions using Novel C8-organometallic Derivatives.

A thesis presented for the degree of doctor of philosophy

By

Eric Grant Dennis

At

Flinders University, South Australia

School of Chemical and Physical Sciences

January 2010

Contents

Acknowledgements

As with any scientific research endeavour, one cannot do it alone. Accordingly, there are a great number of people that require due acknowledgement for their efforts. First and foremost, I thank my principal supervisor Dr. Paul Smith of AWRI. You're a top notch supervisor no doubt about it and I hope you will resume supervising research students in the future. You got what it takes. Thanks for giving me the licence and support to plan and perform the project on my own terms and allowing me the freedom to pursue my own ideas, however daft at times. You have been as much a psychologist and guidance counsellor as compared to a supervisor throughout the years. I'm particularly grateful for your help in these areas, especially in the tough times. Basically, I can't thank you enough for all your efforts.

Many thanks also to my co-supervisor Assoc. Prof. Mike Perkins. You were always more than happy to help whenever I came knocking on your door in a tough spot. Your contributions to the project have been greatly appreciated. In particular, your discussions and assistance in NMR assignments were highly valuable.

It would be greatly remiss of me to not send a huge thanks to Dr. Dave Jeffery and Dr. Troy Lister, both as teachers and as friends. I couldn't think of two finer chemists to learn the tricks of the trade from. As well as being fine teachers of all things synthetic chemistry, I also thank you for your academic contributions to the project. In particular, a big cheers to Dave who stepped up as a pseudo-supervisor after moving to AWRI. Your knowledge of organometallic chemistry has been invaluable in the project.

To Assoc. Prof. Martin Johnston, thanks for being the resident NMR guru. The running and interpretation of NMR, particularly the 2D experiments, would have been much more difficult without your expert help. In fact, the ^{11}B NMR work would have been impossible if not for you. Keep up the good work with your babies.

To all my fellow colleagues from lab 341, the organic corridor and indeed the entire School of Chemistry, Physics and Earth Sciences at Flinders that I have shared useful scientific conversation, friendship or simply mutual laughs, thank you all. There are far too many of you to name individuals. This also applies to my colleagues at AWRI. I must give personal thanks to my colleague and great friend Claire Gregg. It's been overall a wonderful experience working with such a close, caring friend as you are. Your support has made a huge difference in getting me to the end of this project and I can't thank you enough.

The whole PhD process has been a long haul. A huge, huge thank to my parents, Alf and Helen, for their patience and support. I've been more than a little difficult to deal with at times and you've always been there for me no matter what. I'm lucky to have such great parents. Same goes for my brothers, Adam and Nigel. For the most of it you guys have been awesome.

Big thanks to the rest of my family and friends that I've failed to acknowledge till now. Cheers to all you for your well wishes along the way and your interest in my research, or at least thanks for pretending to take an interest and understanding. Now that this "monster" is all finished perhaps I'll get a chance to spend some more time with you all.

I must also thank the sources of funding for this project. Firstly, a personal thanks to Flinders University and the Ferry Scholarship trust for my stipend and to AWRI for their generous stipend top up. Secondly, I must acknowledge that this work has financially supported by Australia's grapegrowers and winemakers through their investment body the Grape and Wine Research and Development Cooperation, with matching funds from the Australian Government.

Last but not least, there are numerous members of the scientific communities of Australia and worldwide that I have engaged in useful academic discussions in regards to my project. Your input has been greatly appreciated.

Declaration

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma at any university, and that to the best of my knowledge and belief it does not contain any material previously published or written by another person expect where due reference is made in the text.

E. Dennis

Eric G. Dennis

Abstract

This thesis details the evolution of the iterative synthesis of 4→8 linked procyanidin (catechin) oligomers. This was achieved through the novel cross-coupling of a C4-electrophilc catechin species with a C8-organometallic catechin derivative.

Chapter 1 details a short discussion of relevant aspects of flavan-3-ols (catechins) such as nomenclature, reactivity, importance to red wine sensory perception and biological properties. Included is a short review of recent methods in biomimetic-type syntheses of procyanidin oligomers, with particular focus on dimeric and trimeric species.

A model cross-coupling system was developed and discussed in Chapter 2. In this chapter, a metallated 1,3,5-trimethoxybenzene derivative was employed as a C8-organometallic model. Coupling of a variety of metallated 1,3,5-trimethoxybenzenes to benzyl bromide revealed that 2,4,6-trimoxyphenylzinc chloride was readily coupled to this electrophile in moderate to good yields in the presence of numerous palladium catalysts. Following optimisation, the coupling product was obtained in very high yields using Pd(DPEPhos)Cl_2 as a catalyst. This procedure was then extended to the coupling of the organozinc with a variety of substituted benzylic and aryl halides in good to high yields.

The development of a Lewis acid-promoted coupling of a C4-ether with a C8-organometallic towards the synthesis of a 4→8 catechin-catechin dimer is outlined in Chapter 3. Once again, the metallated 1,3,5-trimethoxybenzene derivatives used in Chapter 2 were employed as a C8-organometallic model. The Lewis acid-promoted cross-coupling of a C4-ether with 2,4,6-trimethoxyphenylboronic acid afforded a model pseudo-4→8-dimer in excellent yield with the desired 3,4-*trans* stereochemistry obtained in excellent selectivity. Application of the model cross-coupling conditions using a C8-boronic acid-substituted catechin derivative provided a benzyl-protected catechin-4→8-dimer in consistent 90-95% yields. Debenzylation of the synthesised dimer provided catechin-4*α*→8-catechin dimer, or natural procyanidin B3. This natural procyanidin dimer was produced in 6 linear steps from (+)-catechin in 54% overall yield.

The synthesis of a boron-protected procyanidin dimer and trimer is presented in Chapter 4. The synthesis of these oligomers was achieved using a C8-boron-protected-C4-ether catechin derivative as a chain extension species. This species could be added to the C8-terminus of a growing oligomer chain in an iterative fashion using a coupling, boron-deprotection strategy. The C4-ether portion of this species selectively reacted with a free C8-boronic *n*-oligomer using the Lewis acid-promoted coupling method developed in Chapter 3 to provide an (*n*+1)-oligomer. Removal of the C8-boron protecting group furnished a free C8-boronic acid oligomer that could undergo further coupling to the chain extension species.

The synthesis of C8-substituted catechin derivatives is discussed in Chapter 5. C8-phenyl substituted catechins were produced in good to excellent yields using Suzuki and Kumada cross-couplings of both C8-boronic acid and C8-iodide-substituted catechins using a variety of palladium catalysts. The synthesis of an 8-8 linked catechin-catechin dimer and C8-alkyl substituted catechin derivatives was attempted using both Suzuki and Kumada methods, but were not successful.

Abbreviations

A number of non-standard abbreviations have been used throughout this thesis. Given here are the abbreviations followed by the systematic or trivial name.

Abbreviation	**Standard name**
Ac_2O	Acetic Anhydride
Allyl-MgBr	Allylmagnesium Bromide
$B(OMe)_3$	Trimethyl borate, boric acid-trimethyl ester
$BF_3.OEt_2$	Boron Trifluoride diethyl etherate
BnBr	Benzyl Bromide
BnCl	Benzyl Chloride
CaH_2	Calcium Hydride
CD_3CN	1,1,1,-trideuteroacetonitrile
CD_3OD	*O*-deutero, 1,1,1-trideuteromethane
$CDCl_3$	1-deutero-chloroform
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform, 1,1,1-trichloromethane
CsF	Caesium Fluoride
CuCN	Copper-(I)-Cyanide
CuI	Copper-(I)-Iodide
Dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-quinone
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DPEPhos	bis(*o*-diphenylphosphinophenyl)ether
Dppf	1,1′-bis(diphenylphosphino)ferrocene
Et_3N	Triethylamine
EtMgBr	Ethylmagnesium Bromide
EtOAc	Ethyl Acetate

i-PrMgCl	*iso*-propylmagnesium Chloride
K_2CO_3	Potassium Carbonate
K_3PO_4	Potassium Phosphate tribasic
MeI	Iodomethane, methyl iodide
$MgBr_2$	Magnesium Bromide
$MgBr_2.OEt_2$	Magnesium Bromide-diethyl etherate
$MgCl_2$	Magnesium Chloride
MIDA	*N*-methylimidodiacetic acid
Na_2CO_3	Sodium Carbonate
Na_2SO_4	Sodium Sulphate
NaH	Sodium Hydride
NBS	*N*-bromouccinimide
n-BuLi	*n*-Butyllithium
NIS	*N*-iodosuccinimide
$PhB(OH)_2$	Phenylboronic acid
PhBr	Bromobenzene
PhCl	Chlorobenzene
PhI	Iodobenzene
PhMgBr	Phenlymagnesium Bromide
PPh_3	Triphenylphosphine
R_f	Retention factor
rt	Room temperature
Sat. aq. $NaHCO_3$	Saturated aqueous sodium bicarbonate solution
Sat. aq. NH_4Cl	Saturated aqueous Ammonium Chloride solution
t-BuLi	*tert*-Butyllithium
THF	Tetrahydrofuran
$TiCl_4$	Titanium-(IV)-tetrachloride
TMSOTf	Trimethylsilyl-triflate
$ZnCl_2$	Zinc Chloride