

**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

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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 except where due reference is made in the text.

A handwritten signature in black ink that reads "E. Dennis". The letter "E" is blocky, followed by a period, and "Dennis" is written in a cursive style.

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-electrophilic 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-trimethoxyphenylzinc 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)Cl₂ 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 ₂ O | 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 ₃ CN | 1,1,1,-trideuteroacetonitrile |
| CD ₃ OD | <i>O</i> -deutero, 1,1,1-trideuteromethane |
| CDCl ₃ | 1-deutero-chloroform |
| CH ₂ Cl ₂ | Dichloromethane |
| CHCl ₃ | Chloroform, 1,1,1-trichloromethane |
| CsF | Caesium Fluoride |
| CuCN | Copper-(I)-Cyanide |
| CuI | Copper-(I)-Iodide |
| Dbp | dibenzylideneacetone |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-quinone |
| DMA | <i>N,N</i> -dimethylacetamide |
| DMF | <i>N,N</i> -dimethylformamide |
| DPEPhos | bis(<i>o</i> -diphenylphosphinophenyl)ether |
| Dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| Et ₃ N | Triethylamine |
| EtMgBr | Ethylmagnesium Bromide |
| EtOAc | Ethyl Acetate |

| | |
|-------------------------------------|---|
| <i>i</i> -PrMgCl | <i>iso</i> -propylmagnesium Chloride |
| K ₂ CO ₃ | Potassium Carbonate |
| K ₃ PO 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 | <i>N</i> -methylimidodiacetic acid |
| Na ₂ CO ₃ | Sodium Carbonate |
| Na ₂ SO ₄ | Sodium Sulphate |
| NaH | Sodium Hydride |
| NBS | <i>N</i> -bromouccinimide |
| <i>n</i> -BuLi | <i>n</i> -Butyllithium |
| NIS | <i>N</i> -iodosuccinimide |
| PhB(OH) ₂ | Phenylboronic acid |
| PhBr | Bromobenzene |
| PhCl | Chlorobenzene |
| PhI | Iodobenzene |
| PhMgBr | Phenylmagnesium Bromide |
| PPh ₃ | Triphenylphosphine |
| R _f | Retention factor |
| rt | Room temperature |
| Sat. aq. NaHCO ₃ | Saturated aqueous sodium bicarbonate solution |
| Sat. aq. NH ₄ Cl | Saturated aqueous Ammonium Chloride solution |
| <i>t</i> -BuLi | <i>tert</i> -Butyllithium |
| THF | Tetrahydrofuran |
| TiCl ₄ | Titanium-(IV)-tetrachloride |
| TMSOTf | Trimethylsilyl-triflate |
| ZnCl ₂ | Zinc Chloride |