Annulations of Diterpenoids
via Organomanganese and
Organoiron Complexes

A Thesis
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Doctor of Philosophy

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ABSTRACT

Chapter One of this Thesis reports an investigation of the synthesis of diterpenoids (as potential ligands for cyclomanganation reactions) from podocarpic acid, and one from dehydroabietic acid. A number of monocyclic aromatic and chalcone derivatives were synthesised to act as model compounds in the subsequent complexation reactions.

The second chapter describes successful complexations of the above ligands containing aldehyde, ketone, ester, or oxime groups as directing functionalities to form the resulting tetracarbonylmanganese sigma adducts in moderate to excellent yield. Attempted complexation of amide-containing ligands proved generally to be unsuccessful. Complexation of ligands containing either two potential sites for manganation or two potential ligating groups were investigated and the structures of the isolated complexes established unequivocally by N.M.R. spectroscopy or by X-ray crystallography.

Chapter Three describes the successful coupling reactions of the tetracarbonylmanganese complexes with ethene and with substituted electron-poor olefins to give pentaannulated derivatives of podocarpic acid in very good yields. The stereochemistry of two cyclised alcohols was assigned unambiguously by single-crystal X-ray diffraction experiments. Various methods of activating the tetracarbonyl complexes were investigated, including chemical oxidation, and palladium(II)-mediated or thermally-promoted reactions. Two of the pentaannulated adducts were converted successfully into benzannulated analogues in good yield.

Analogous coupling reactions of the activated complexes with ethyne and substituted alkynes are discussed in Chapter Four.

Chapter Five reports an investigation of the reactions of the tetracarbonylmanganese complexes with halogen electrophiles such as Br₂, ICl, or ICl₃. When these reactions were performed in non-protic solvents the corresponding aryl halides were isolated in moderate to excellent yield. However, in protic solvents carbonyl insertion occurred to afford γ-lactones in very good yield. The stereochemistry of one of these lactones was assigned unambiguously by a single-crystal X-ray diffraction experiment. Oxidative cleavage of the C-Mn bond with a number of reagents proved
generally to be unsuccessful, the isolation of oxygenated diterpenoids being observed only from reaction with Pb(OAc)$_4$.

Chapter Six describes various attempts at functionalising ring C of podocarpic acid derivatives via alternative methods to cyclomanganation. These include an investigation into the formation of $\eta^4$-dien ether and $\eta^4$-diene tricarbonyliron complexes derived from the Birch reduction products of podocarpic acid derivatives; attempted regioselective chlorination and mercuration studies of ring C arenes; functionalisation of chlorinated podocarpic acid derivatives via their tricarbonylchromium complexes; and attempted oxidation of ring C arenes with meta-chloroperbenzoic acid.
INTRODUCTION

The diterpenoid resin acid podocarpic acid (1), readily available in New Zealand from the heartwoods of various members of the Podocarpaceae, has been used as a starting point in the syntheses of naturally occurring compounds as well as for the elaboration of steroidal analogues containing an aromatic ring C. These conversions are desirable since naturally occurring compounds possessing a steroidal skeleton with an aromatic ring C are well known; for example, viridin (2) a mould metabolite with remarkably high fungistatic activity has been shown to be a C-benzenoid steroid. Although there are few reported syntheses of these compounds, one sequence involves the conversion of ergosterol into related derivatives.

![Chemical structures](image)

(1)  
(2)

Of relevance to the investigations undertaken in this Thesis, Davis and Watkins have converted podocarpic acid (1) into 4β-methoxycarbonyl-4α-methyl-12-methoxy-18-norandrostra-8,11,13-trien-17-one (3) in low overall yield (3%) via a three step sequence. Similarly, the 15-one (4) and its D-homo analogue (5) were synthesised by these workers in moderate yield (Scheme 1).

Recently, Cambie and his co-workers have utilized a route for removing the carboxyl group from podocarpic acid (1) to produce a Δ4-3-one system in ring A, their final product being 12-methoxy-18,19-bisnorpodocarpa-4,8,11,13-tetraen-3-one (6). This work has been extended to form the chiral intermediate (7) containing a diosphenol moiety in ring A en route to the synthesis of bruceantin (8), which is a typical quassinoid and a potent antileukaemia drug (Scheme 2).
Scheme 1

1) NaOH/EtOH/H₂O
2) Me₂SO₄

OMe

\[
\text{MeO}_2\text{C}
\]

acrylyl chloride
AlCl₃/Δ

OMe

\[
\text{MeO}_2\text{C}
\]

3% (3)

1) propionyl chloride/AlCl₃
2) sulfur/morpholine
3) 50% H₂SO₄/HOAc

OMe

\[
\text{CH}_2\text{CH}_2\text{CO}_2\text{H}
\]

OMe

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}
\]

1) PCl₅/80°C/1 h
2) AlCl₃/50°C/3 days

OMe

\[
\text{MeO}_2\text{C}
\]

1) succinic anhydride/AlCl₃/HCl₂CHCl₂
2) Zn(Hg)/HCl/toluene

OMe

\[
\text{MeO}_2\text{C}
\]

31% overall (5)
Wheeler and Witt\textsuperscript{14} have synthesised 4β-methoxycarbonyl-4α-methyl-18-norandrostane-12,16,17-trione (10) from methyl podocarp-13-en-12-on-19-oate (9) in low yield via the sequence shown in Scheme 3. The enone (9) has been synthesised by a number of groups,\textsuperscript{15-17} the highest yielding sequence being that due to Spencer \textit{et al.}\textsuperscript{17} (Scheme 4).

A number of other resin acids, such as abietic\textsuperscript{18,19} and dehydroabietic acids (pine tree extract), have also been used as starting material for the synthesis of steroidal analogues. For example, Tahara \textit{et al.}\textsuperscript{20,21} have reported the formation of (13) and (14) from dehydroabietic acid (11) via the sequence shown in Scheme 5. Settine and Gawish have obtained the 17-keto-C-aryl-18-norsteroid (16) in 12\% overall yield from dehydroabietonitrile (15), which was prepared from resin acids present in pine oleoresin\textsuperscript{22} (Scheme 6). More recently, Abad \textit{et al.}\textsuperscript{23} have successfully converted sandaracopimmaric acid (17) isolated from gum sandarac resin\textsuperscript{24} of the North African sandarac tree (\textit{Callitris quadrivalis})\textsuperscript{25,26} into the androstane analogue (18) (Scheme 7) in moderate overall yield.
Scheme 3

Scheme 4
\[
\text{Scheme 5}
\]
Woodgate et al. have attempted to use organometallic (chromium²⁷-³⁰ and iron³¹) complexes of podocarpic acid derivatives as a means of functionalising ring C of the diterpenoid with a view to effecting cyclopentaannulation across C(13) and C(14). A number of (n⁶-arene)tricarbonylchromium complexes of podocarpic acid derivatives have been synthesised in high yield and have been successfully functionalised, at C(13) of (19)²⁸ and at C(14) of (20)³⁰, via nucleophilic attack of a variety of carbanions. Subsequent attempted acid-catalysed cyclisation of a pendant acetal did not yield any cyclopentaannulated products.³⁰ However, reaction of the diterpenoid pentacarbonylchromium carbene complex (21) with diphenylacetylene in refluxing heptane afforded the steroidal analogues (22) and (23) in moderate yield (Scheme 8).²⁷
Scheme 7
Scheme 8

R₁   R₂  
H     Ph   (22) 11% 
Ph     H   (23) 21%
REFERENCES

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