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Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones

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Asymmetric Synthesis of Bioactive Lactones and the Development of a Catalytic Asymmetric Synthesis of α-Aryl Ketones

Doctoral Thesis accepted by
the University College Dublin, Ireland

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"Asymmetric Synthesis of Both Enantiomers of a δ-Lactone Analogue of Muricatacin" Doran, R.; Guiry, P. J., *Synthesis* **2014,** *46*, 761–770.

"Asymmetric Synthesis of (+)-Tanikolide and the β-Methyl-Substituted Analogues of (+)-Tanikolide and (–)-Malyngolide"
Doran, R.; Duggan, L.; Singh, S.; Duffy, C. D.; Guiry, P. J., *Eur. J. Org. Chem.* **2011**, 7097–7106.

To my parents and my sister
In memory of Tony

Supervisor's Foreword

Dr. Doran was awarded a prestigious Irish Research Council Embark Ph.D. Scholarship to work in my group on developing and applying synthetic methodology in total synthesis. He made substantial progress in his Ph.D. research and also contributed intellectually with suggestions for route improvement to analogues of the natural products, e.g. malyngolides and muricatacins. He was the first author on both papers from this section of his thesis [*Eur. J. Org. Chem.* **2011**, 7097–7106 and *Synthesis* **2014**, *46*, 761–770, respectively] and did an excellent job in applying zirconium tetrachloride as a novel catalyst for the preparation of δ-lactone marine natural products. As research can sometimes go against you, some of the initial ideas proved difficult practically and he showed real dedication to circumvent these problems and come out the other end with elegant solutions and good results.

He was keen to extend his Ph.D. research to include synthetic methodology development so he also joined our mini-group on the enantioselective preparation of α-aryl ketones using Pd-catalysed decarboxylative protonation. We had one paper in this area when Robert started and he extended the methodology to include the total synthesis of two naturally occurring isoflavanones. He showed real tenacity and demonstrated his excellent experimental technique to optimise this process up to 97 % ee and also discovered a stereodivergence in the protonation step depending on the proton source employed. This was a very important finding which has inspired us to look, with success, for this phenomenon with related substrates. He was the first author of a paper that reported this work in *Chem. Eur. J.* **2014**, *20*, 15354–15359. This paper, with its remarkable enantioselective switch depending on the acid source employed, has been highlighted as a Science Concentrate by Chemical & Engineering News (**2014**, October 20th, p. 30) and also as a Research Highlight by Chemistry World (**2014**, 11, issue 12, p. 31).

Robert also investigated the substrate scope of this protocol for the enantioselective preparation of α-aryl ketones by extending it to a series of 11 cyclopentanone and 10 cyclohexanone derivatives. This paper, with Robert as the only author responsible for the experimental work, was published in *J. Org. Chem.* **2014**, *79*, 9112–9124.

Robert's findings have inspired further work in the research group where we are currently investigating the enantioselective synthesis of a series of related α-aryl- and α-allyl-α-aryl ketones and lactones.

Robert wrote a superb Ph.D. thesis which is an excellent example of clarity of thought and presentation and is an exceptional piece of scholarly work. He was the deserved recipient of the Royal Irish Academy Ph.D. Prize for 2014 and now the Springer Thesis Award.

Dublin, Ireland
May 2015

Prof. Pat Guiry

Abstract

The total synthesis of natural products continues to be one of the most fascinating and well-studied areas of organic chemistry. The importance of natural products, their synthesis and the design of biologically relevant molecules continues to be the greatest source of potential new pharmaceuticals. The discovery and application of new and interesting methodologies of use in total synthesis is vital to the goals of designing shorter, more elegant and ultimately more reliable syntheses of natural products and analogues.

The asymmetric synthesis of all four diastereomers of β-methyl analogues of the marine natural products (+)-tanikolide, which displays antifungal activity, and (−)-malyngolide, which displays antimicrobial activity, has been successfully completed. The final two diastereomers were synthesised in this Ph.D. project in a 9-step synthesis in 24.9 % and 10.8 % overall yields, respectively. Key steps in the synthetic route included Sharpless asymmetric epoxidation and $ZrCl_4$-catalysed intramolecular acetalisation as the key steps. The β-methyl substituted analogues were designed to probe the effect the β-methyl group change would have on the bioactivity of these compounds. The biological testing of these compounds revealed that these analogues showed no antifungal activity, however, one of the analogues of malyngolide showed promising activity against MRSA with an MIC of 12.5 μg/mL.

The asymmetric synthesis of both enantiomers of the δ-lactone analogue of the anti-tumoral natural product γ-lactone muricatacin has also been carried out in a 9-step sequence with overall yields of 17.8 % and 11.2 %, respectively. Initial attempts to also synthesise the natural product proved unsuccessful due to the poor reactivity of the Grignard reagent derived from 2-(bromomethyl)-1,3-dioxolane. The designed synthetic route enabled us to increase the ring size to generate the δ-lactone analogue employing Sharpless asymmetric epoxidation and $ZrCl_4$-catalysed intramolecular acetalisation as the key steps.

The development of new methods for the synthesis of enantioenriched molecules is a key area of modern organic chemistry. Catalytic asymmetric synthesis is one method by which enantioenriched compounds can be synthesised. A key class of

compounds which are challenging to prepare in an enantioselective manner are tertiary α-aryl ketones, present in isoflavanones and many other bioactive molecules.

A modular, 6-step asymmetric synthesis of 2 naturally occurring and 3 non-natural isoflavanones containing tertiary α-aryl carbonyls was developed. This synthetic route, utilising a Pd-catalysed decarboxylative asymmetric protonation, allows access to isoflavanones in excellent enantioselectivities from 76–97 % *ee*. A switch in the sense of stereoinduction was observed when different H^+ sources were employed showing the first example of dual stereocontrol in an asymmetric protonation reaction whereby the same chiral ligand is used with a different achiral proton donor. The first enantioselective synthesis of the naturally occurring isoflavanones sativanone and 3-*O*-methylviolanone also has been accomplished using this methodology.

To test the substrate scope, the catalytic asymmetric synthesis of a series of tertiary α-aryl cyclopentanones and cyclohexanones has also been achieved *via* a Pd-catalysed decarboxylative protonation of the corresponding α-aryl-β-keto allyl esters. Enantioselectivities of up to 92 % *ee* and 74 % *ee* were achieved for cyclopentanone and cyclohexanone substrates, respectively. The route described gives access to these important structural motifs in moderate to high levels of enantioselectivity. In particular, this is only the second direct approach for the preparation of tertiary α-aryl cyclopentanones. The synthetic approach allows for simple modification of the aryl group and, significantly, substrates containing sterically hindered aryl groups gave the highest levels of enantioselectivity and these aryl groups were readily installed by a Pb-mediated arylation of a β-keto allyl ester.

Acknowledgments

First, I would like to thank my supervisor Prof. Pat Guiry. From the moment I started as a fourth-year undergraduate project student I was treated as part of the research group. He has shown a huge amount of confidence and belief in my abilities, something for which I will always be grateful. He was a constant support throughout my Ph.D., providing me with the research projects and a brilliantly equipped lab in which to conduct research. He gave up huge amounts of his time to help get me to this point and was not only a great source of knowledge and encouragement but also helped put everything in perspective, particularly during difficult periods. Thank you.

I would like to acknowledge the facilities provided by University College Dublin, in particular, the Centre for Synthesis and Chemical Biology (CSCB) which is a world-class research facility where I feel privileged to have conducted research. A huge thank you must also go to the School of Chemistry and Chemical Biology. All of the academic staff were always approachable and happy to help and discuss any chemistry. Particular thanks to Dr. Mike Casey and Prof. Stefan Oscarson as members of my doctoral studies panel and to Dr. Paul Evans for acting as the internal examiner for my viva. Thanks to the technical staff of the school, in particular Dr. Jimmy Muldoon, Dr. Yanick Ortin and Ms. Geraldine Fitzpatrick for endless help with NMR analysis. Thanks also to Mr. Adam Coburn and Mr. Kevin Conboy for HRMS analysis. Thank you to the administrative staff of the school for all of their help throughout my time at UCD.

A massive thank you to all of the members of the Guiry group. There are so many to mention: Surrendra, Christina, Barry, Suribabu, Ramu, Andy, Ludovic, Caroline, Cathal, Xin, Gavin, Michael, Dennis, Caoimhe, Eibhlin, Steven, Claire, Mark, Kieran, Catherine, Chris, Joe, Denise, Cian, Brian, Kevin and Andrea. To start with, I would like to thank Gavin who supervised my fourth-year project and was a big help when I began my Ph.D. and a good friend. In my first year Christina was always there and could answer any question I asked. Thanks to Barry for giving me some extra work to do and for the verbal abuse. Thanks to Michael for his generous help when my Ph.D. branched into asymmetric catalysis. To Eibhlin and Claire for all the Heck chapter fun times and thanks to Claire for her support.

Mark and Kieran are friends for life and great craic. To Ramu for his expertise and support in my final year, a massive thank you. A special thanks to Caoimhe who was such a close friend through all of my Ph.D. and a constant source of entertainment. Finally, the last member of the group I wish to thank is one of my closest friends, Steven. I have been fortunate to know Steven since our first year as undergraduates and I can't thank him enough.

An important thank you must also go to Schering-Plough in Rathdrum and in particular, Dr. Ronan Lockhart, for giving me the opportunity to work there before I started my Ph.D. The guidance given to me by Dr. Robert Collins was invaluable and played a crucial role in my development as a chemist.

The most important thanks of all goes to my family, Mum, Dad and Laura. There are no words to describe how grateful I am to them all. Mum and Dad have supported me every step of the way, I would not have achieved this without them. To my best friend and sister, Laura, simply thanks for being so wonderful.

Collaborations

The biological testing carried out on the β-methyl analogues of tanikolide and malyngolide described in Chap. 2 was carried out by our collaborators in UCD. The antifungal testing was carried out by Dr. Linda Holland in the research group of Prof. Geraldine Butler at the UCD Conway Institute. The antimicrobial testing of the β-methyl tanikolide and malyngolide analogues as well as the isoflavanones prepared in Chap. 5 were conducted by Dr. Marta Martins in the group of Prof. Séamus Fanning at the UCD Centre for Food Science, UCD School of Public Health, Physiotherapy & Population Science. Testing of the δ-muricatacin analogues against a number of tumour cell lines was carried out by Joana Silva and Prof. Pedro V. Baptista, Departamento de Ciências da Vida, Faculdade de Ciências e Tecnologias, Universidade Nova de Lisboa, Caparica, Portugal.

In Chap. 5 the synthesis of the α-aryl-β-keto allyl ester was developed by a former Ph.D. student in our group, Dr. Michael Carroll and a final-year undergraduate student Bryan Hogan. They also carried out the initial catalysis on the three substrates shown in Scheme 5.3.

Contents

Symbols and Abbreviations

ν_{max}	Wavenumbers (IR)
δ	Chemical shift in degrees downfield from TMS
$[\alpha]_D^{20}$	Specific rotation
°	Degrees
°C	Degrees Celsius
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon nuclear magnetic resonance spectroscopy
Å	Ångström (10^{-10} m)
Ac	Acetyl
API	Active pharmaceutical ingredient
app. t	Apparent triplet (NMR)
app. d	Apparent doublet (NMR)
app. dd	Apparent doublet of doublets (NMR)
aq.	Aqueous
atm	Atmosphere
Ar	Aryl
Bn	Benzyl
BnBr	Benzyl bromide
br s	Broad singlet (NMR)
c	Concentration in g per 100 mL (optical rotation)
calcd.	Calculated
cm^{-1}	Reciprocal centimetres
conv.	Conversion
cod	Cyclooctadiene
d	Doublet (NMR)
dba	Dibenzylideneacetone
dd	Doublet of doublets (NMR)
ddd	Doublet of doublet of doublets (NMR)
de	Diastereomeric excess
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride

DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dt	Doublet of triplets (NMR)
ee	Enantiomeric excess
equiv.	Equivalent(s)
Et	Ethyl
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
ESI	Electrospray ionisation (mass spectrometry)
FDA	Food and Drug Administration
g	Gram(s)
h	Hour(s)
HMDS	Hexamethyldisilazane
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz, GHz, MHz	Hertz, gigahertz, megahertz
i-Pr	*iso*-propyl
IR	Infrared spectroscopy
J	Coupling constant
LiHMDS	Lithium hexamethydisilazide
lit.	Literature reference
m	Multiplet (NMR)
M	Molar
Me	Methyl
MeOH	Methanol
MP	Melting point
$[M]^+$	Molecular ion (mass spectrometry)
$[M + H]^+$	Protonated molecular ion (mass spectrometry)
$[M + Na]^+$	Molecular ion plus sodium
μm	Micrometres
mg	Milligram
min	Minute(s)
mL, μL	Millilitre, microlitre
mmol	Millimole
mol	Mole
MW	Microwave irradiation
n-BuLi	*n*-butyllithium
NAP	2-naphtylmethyl
NCE	New chemical entity
n.d.	Not determined
NOE	Nuclear overhauser effect
Nu	Nucleophile

OAc	Acetate
o, *m*, *p*	*Ortho*, *meta*, *para*
PHOX	Phosphinooxazoline
Ph	Phenyl
Ph.D.	*Philosophiae doctor*
PLP	Pyridoxal-phosphate
ppm	Parts per million
qC	Quaternary carbon (NMR)
q	Quartet (NMR)
rac	Racemic mixture
R_f	Retention factor
RBF	Round bottom flask
R_t	Retention time
rt	Room temperature
s	Singlet (NMR)
$scCO_2$	Supercritical CO_2
SFC	Supercritical fluid chromatography
t	Triplet (NMR)
t-Bu	*tert*-butyl
t-BuLi	*tert*-butyllithium
temp.	Temperature
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	*N,N*-tetramethylethylenediamine
TMS	Tetramethylsilane
TMSBr	Tetramethylsilyl bromide
TOF	Time-of-flight (mass spectrometry)
UV	Ultraviolet irradiation
W	Watts

Chapter 1
Introduction to the Total Synthesis of Lactone-Containing Natural Products Using $ZrCl_4$

1.1 Total Synthesis of Natural Products

> There is excitement, adventure, and challenge, and there can be great art in organic synthesis.
>
> R.B. Woodward

The construction of the molecules of nature in the laboratory from simple molecules or atoms is known as *total synthesis* [1]. The total synthesis of natural products continues to be one of the most fascinating and well-studied areas of organic chemistry. Natural products and designed analogues continues to be the greatest source of potential new pharmaceuticals. The discovery and application of new and interesting methodologies of use in total synthesis is vital to the goals of designing shorter, more elegant and ultimately more reliable syntheses of natural products and analogues.

The total synthesis of complex natural products and designed analogues is still a huge challenge in synthetic chemistry. The ease at which nature can use enzymes to control the orientation and reactivity of organic molecules is astounding and incredibly complex. The ultimate goal in organic synthesis is to someday possess a similar level of control in a synthetic laboratory as nature can already do now. Although this might seem like an unrealistic goal, huge strides have been made over the last century and will continue to be made over the coming ones. The discovery and development of new synthetic reactions, reagents and catalysts is known as *synthetic methodology* and this is fundamental to increasing the power and efficiency of organic synthesis.

The history of organic synthesis is a fascinating one. The first rational synthesis of an organic compound, urea, was carried out by Wöhler in 1828 (Fig. 1.1). This was followed by a number of other landmark syntheses: acetic acid (Kolbe 1845), glucose (Fischer 1890), α-terpinol (Perkin 1904), camphor (Komppa 1903; Perkin 1904), tropinone (Robinson 1917), haemin (Fischer 1929), equilenin (Bachmann

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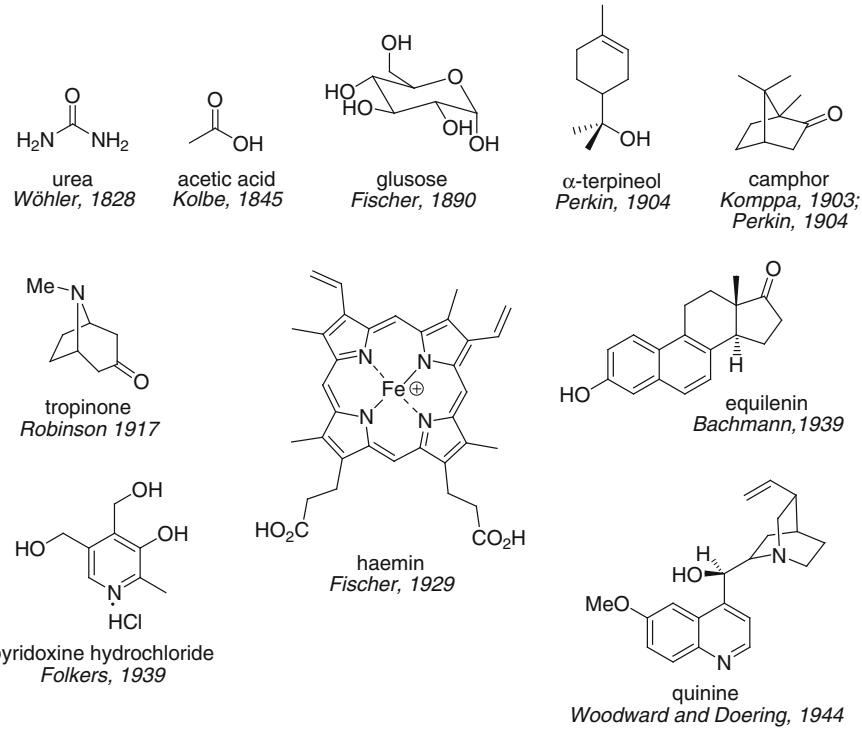

Fig. 1.1 Early achievements in organic synthesis

1939), pyridoxine hydrochloride (Folkers 1939) and quinine (Woodward and Doering 1944).[1]

After this time, rapid advancements were made in the total synthesis of complex natural products. In particular the work of Woodward deserves special mention, his vision and foresight and ability to understand the subtle reactivity of complex systems and ultimately to design and carry out synthetic routes was inspirational. His report on the synthesis of strychnine in 1954 was a remarkable achievement given the beautiful simplicity of the transformations carried out and the difficulties of the characterisation of complex intermediates at that time (Fig. 1.2). Woodward followed this up with the similarly remarkable syntheses of reserpine in 1958 and vitamin B12 with Eschenmoser in 1973.[1]

The contribution to the field by Corey also deserves special mention as someone who systematically developed the idea of retrosynthetic analysis as a tool to design organic synthesis, not to mention a raft of new synthetic methodologies and extraordinary total synthesis including ginkgolide B (Fig. 1.2). One of Corey's former students, Nicolaou also deserves huge recognition for the sheer number of incredibly complex natural products which have been synthesised by his research group, most notably brevetoxin B, containing 11 trans-fused rings and 23 stereocentres, and the key antibiotic vancomycin (Fig. 1.2).

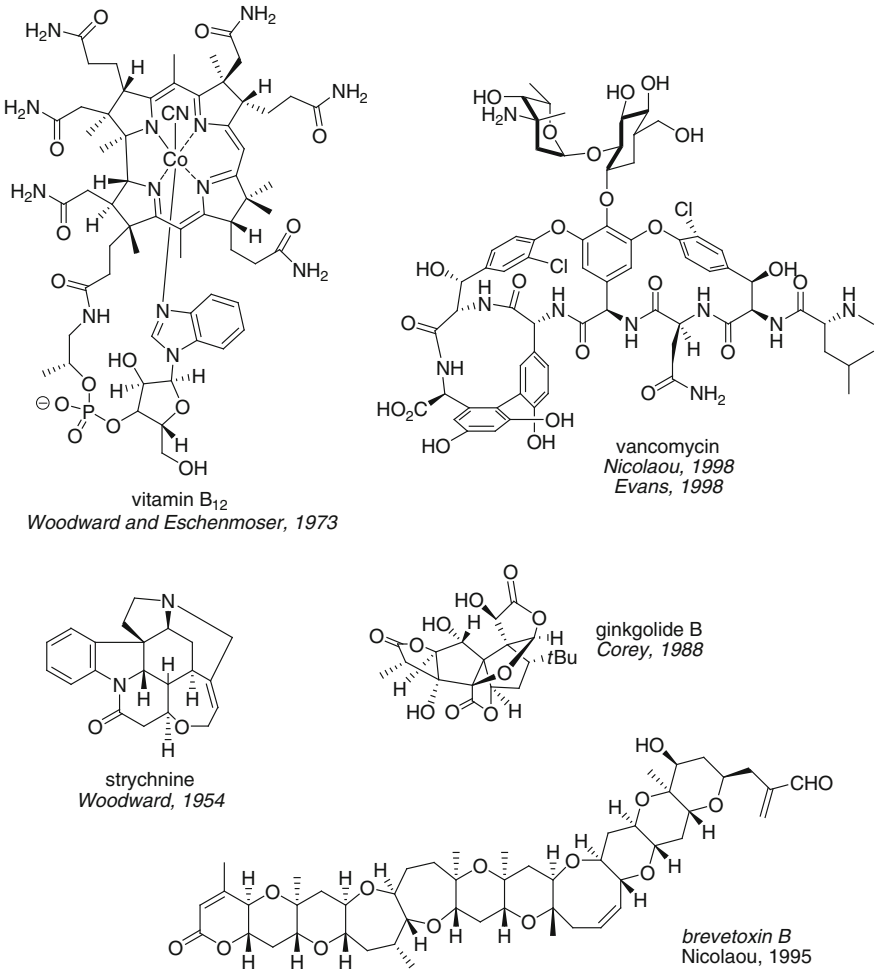

Fig. 1.2 Synthesis of highly complex natural products

1.2 Natural Products as Pharmaceuticals

Natural products have been used as therapeutic agents or medicinal products for millennia in one form or another and a huge number of these, especially prior to the last 50 years, are derived from plants [2]. Today, natural products derived from plant sources continue to play a vital role in the treatment of diseases. There are many examples where the active compound in plant-derived traditional medicines has been used as a pharmaceutical agent. A particularly important example is the discovery and development of anti-malarial drugs such as quinine and artemisinin (Fig. 1.3). Quinine was isolated as early as 1820 and was used extensively until the