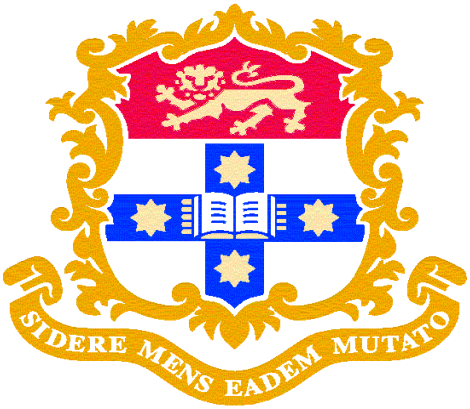
STUDIES TOWARD THE SYNTHESIS OF THE MICROSCLERODERMIN NATURAL PRODUCTS

A thesis submitted in partial fulfilment
of the requirements for the degree of

Doctor of Philosophy (Science)

by

Emily Clare Shuter



School of Chemistry
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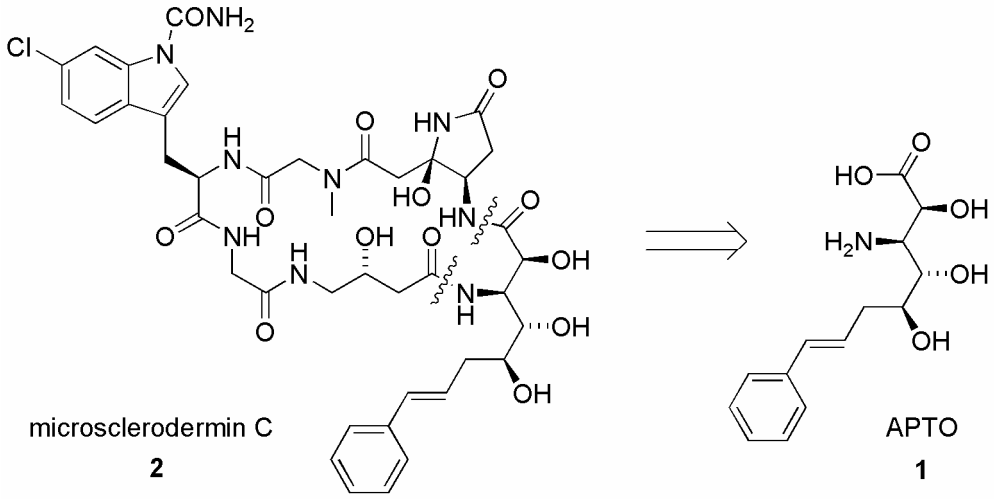
Declaration

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at the University of Sydney or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at the University of Sydney, is explicitly acknowledged in the thesis.

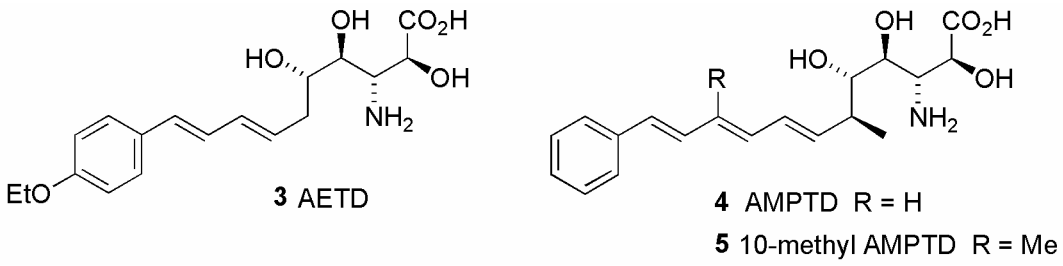
Emily Clare Shuter

Summary

A concise stereo-selective synthesis of a protected form of APTO **1**, an unusual amino acid component of microsclerodermin C **2**, was undertaken. Sequential Sharpless Asymmetric Aminohydroxylation (AA) and Asymmetric Dihydroxylation (AD) reactions were used to introduce the chiral amino and hydroxyl groups. Specific directing groups were chosen to ensure high regio- and enantio-selectivity in these reactions. The target compound was reached in a linear reaction sequence of fourteen steps.



The strategy was designed to generate common intermediates which could be used to access analogous amino acid fragments in other microsclerodermins. A protected form of AETD **3**, from microsclerodermin E, was synthesised *via* a late-stage common intermediate. Initial studies into the modification of the sequence to allow access to AMPTD **4** and 10-methyl AMPTD **5** were made.



Acknowledgements

I would like to thank Dr Malcolm McLeod for his invaluable guidance on everything organic chemistry over the last three and a half years and for his efforts in editing this manuscript.

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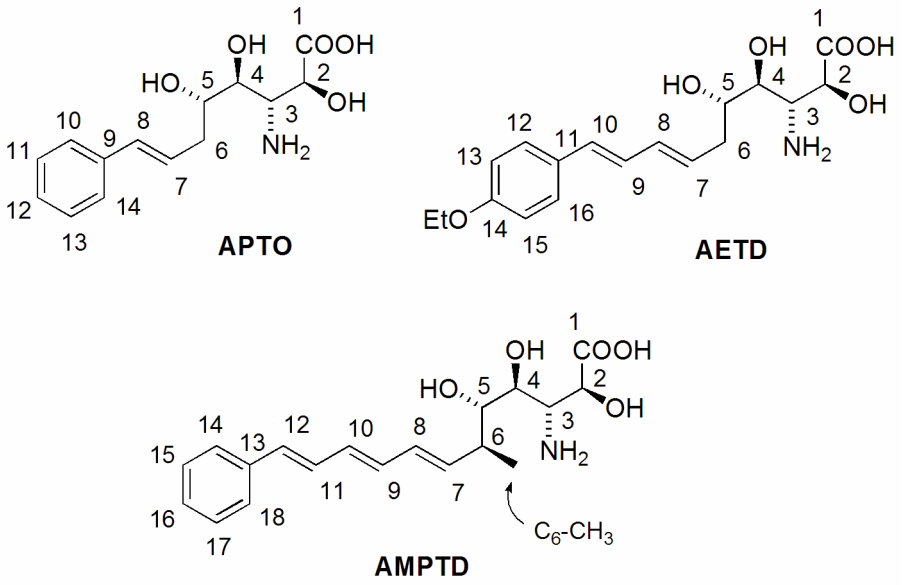
Thanks Mum and Borrr for your ongoing support and pressure from such a distance – your understanding is much appreciated. Mike, I've heard that slow and steady wins the race…thanks for providing a sympathetic ear during the whole PhD process. Andrew, your words of wisdom, encouragement and unfathomable ability to keep things in perspective has kept me sane – I really appreciate it. Ta!

Nomenclature

A. Compound Numbering and Naming

The numbering system for intermediates is based on the numbering within the amino acid backbone as shown below unless specifically stated otherwise.



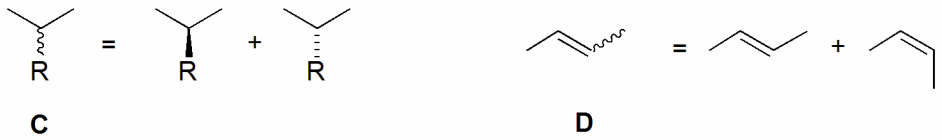
The naming of intermediates follows the naming system provided by Name=Struct within the ChemDraw 9.0 Ultra software.

B. *Syn* and *Anti* Isomers

The *syn* and *anti* descriptors are used to describe the relative configuration of non-hydrogen substituents in stereoisomers. When the carbon chain of the molecule is drawn in a zigzag manner in the plane of the page if the non-hydrogen substituents (R^1, R^2) are on the same side of the plane, as in **A** below, they are described as *syn*, and if they are on opposite sides of the plane, as in **B** below, they are designated as *anti*.

C. Other Stereochemical Nomenclature

A wavy line in a structure indicates that the sample contains a mixture of stereoisomers as shown below for **C** (sp^3 hybridised) and **D** (sp^2 hybridised).



C **D**

(*R*)- and (*S*)- are used to describe the absolute stereochemistry at a carbon centre as defined by IUPAC recommendations.

Abbreviations

AA	asymmetric aminohydroxylation
Ac	acetyl
AD	asymmetric dihydroxylation
AETD	(2*S*,3*R*,4*S*,5*S*,7*E*,9*E*)-3-amino-10-(4-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid
AIBN	azobisisobutyronitrile
AIDS	acquired immunodeficiency syndrome
AMMTD	(2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-12-(4-methoxyphenyl)-6-methyl-2,4,5-trihydroxydodec-11-enoic acid
AMPTD	(2*S*,3*R*,4*S*,5*S*,6*S*,7*E*,9*E*,11*E*)-3-amino-6-methyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid
APTO	(2*S*,3*R*,4*S*,5*S*,7*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid
aq.	aqueous
AQN	anthraquinone derived part of ligand
Ar	aryl
o-Ar	position on a mono-substituted aromatic ring that is ortho to the substituent
m-Ar	position on a mono-substituted aromatic ring that is meta to the substituent
p-Ar	position on a mono-substituted aromatic ring that is para to the substituent
q-Ar	position on a mono-substituted aromatic ring where the substituent is attached
b.p.	boiling point
$BF_3.Et_2O$	boron trifluoride diethyl etherate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad

brine	saturated aqueous sodium chloride solution
BT	benzothiazol-2-yl
BTSH	2-mercaptobenzothiazole
t-Bu	*tert*-butyl
Bz	benzoyl
°C	degree Celsius
c	concentration
calc.	calculated
cat.	catalytic
CLB	chlorobenzoyl derived part of ligand
cm	centimetre
COSY	^{1}H-^{1}H correlation spectroscopy
10-CSA	(1*S*)-(+)-10-camphorsulfonic acid
d	doublet
DCC	1,3-dicyclohexylcarbodiimide
DCDM-hydantoin	1,3-dichloro-5,5-dimethylhydantoin
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DHQ	dihydroquinine
$(DHQ)_2AQN$	1,4-bis(9-*O*-dihydroquininyl)-anthraquinone
$(DHQ)_2PHAL$	1,4-bis(9-*O*-dihydroquininyl)-phthalazine
DHQD	dihydroquinidine
$(DHQD)_2AQN$	1,4-bis(9-*O*-dihydroquinidinyl)-anthraquinone
$(DHQD)_2PHAL$	1,4-bis(9-*O*-dihydroquinidinyl)-phthalazine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
dm	decimetre
DMAP	4-*N*,*N*-dimethylaminopyridine
1,2-DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
2,2-DMP	2,2-dimethoxypropane

DMP	Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one
DMSO	dimethyl sulfoxide
E : *Z*	ratio of *E* to *Z* isomers
% ee	enantiomeric excess
EI	electron impact
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
eV	electronvolt
FT-ICR	Fourier transform ion cyclotron resonance
FTIR	Fourier transform infrared
g	gram
GABOB	(3*R*)-4-amino-3-hydroxybutyric acid
Grubbs cat.	Grubbs second generation catalyst: (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro (phenylmethylene)(tricyclohexylphosphine)ruthenium
h	hours
hexanes	hexanes with b.p. 65 - 69 °C
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IBX	1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide
IC_{50}	inhibition concentration 50% (conc. at which 50% survive)
IND	indoline derived part of ligand
IR	infra-red spectroscopy
J	^{1}H-^{1}H coupling constant (in Hz)
$^{x}J_{PC}$	^{13}C-^{31}P coupling constant between atoms x bonds apart
JO	Julia olefination

K	Kelvin
L	unspecified ligand, litre
LDA	lithium diisopropylamide
lit.	literature value
LRMS	low resolution mass spectroscopy
M	molar
m	multiplet, medium
m.p.	melting point
m/z	mass to charge ratio
mCPBA	3-chloroperoxybenzoic acid
Me	methyl
10-methyl AMPTD	(2*S*,3*R*,4*S*,5*S*,6*S*,7*E*,9*E*,11*E*)-3-amino-6,10-dimethyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid
MHz	megahertz
min	minute(s)
ml	millilitre
mm	millimetre
mm Hg	millimetre of mercury
mmol	millimole
mol	mole
MOM	methoxymethyl
2-MP	2-methoxypropene
MPM	*p*-methoxybenzyl
(*R*)-MTPA	(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid
(*S*)-MTPA	(*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid
nm	nanometre
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
PFK	perfluorokerosene
PG	generic protecting group

Ph	phenyl
PHAL	phthalazine derived part of ligand
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium p-toluenesulfonate
i-Pr	isopropyl
n-PrOH	propanol
PT	1-phenyl-1*H*-tetrazol-5-yl
PTSH	1-phenyl-1*H*-tetrazole-5-thiol
q	quartet
quant.	quantitative
quin	quintet
R	unspecified alkyl group
R_f	thin layer chromatography retention factor
RT	room temperature
s	singlet, strong
sat.	saturated
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
t_R	HPLC retention time
Ts	*p*-toluenesulfonyl (tosyl)
TsOH	*p*-toluenesulfonic acid (tosic acid)
v/v	volume to volume ratio
w	weak
w/v	weight to volume ratio
WHO	World Health Organisation
wt.	weight