Methods for the Asymmetric Synthesis of α-Fluoro and α,α-Difluoro-β^3-Amino Acids

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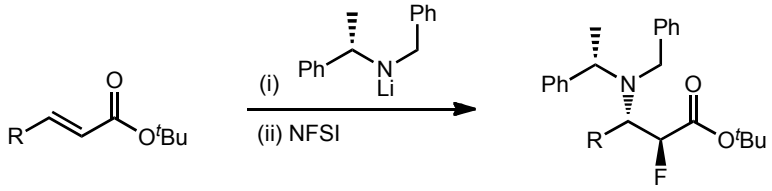
CONTENTS

SUMMARY

Fluorinated β^3-amino acids are becoming increasingly important due to their potential therapeutic applications, particularly with regard to enzyme inhibition, however research in this area is somewhat limited by a lack of adequate methods for their preparation. Strategies to prepare β-amino acids that feature complex side chains e.g., lysine and arginine, receive even less attention, and are thus the focus of this work, which details the development of two complementary methodologies for the asymmetric synthesis of α-fluoro- and α,α-difluoro-β^3-amino acids.

Chapter 1 discusses the tandem conjugate addition of a chiral lithium amide to an α,β-unsaturated ester, whereby the intermediate enolate is quenched with an electrophilic source of fluorine. A series of α-fluoro-β^3-amino esters were subsequently prepared using this method, with silyl-protected substrates proving the most suitable (*Figure 1*). A stepwise method involving separate deprotonation and fluorination reactions was also investigated, however this failed to match the diastereoselectivity of the tandem reaction.



R = Me, TBSO(CH$_2$)$_2$, TBSO(CH$_2$)$_3$, Boc$_2$N(CH$_2$)$_3$, 4-Si(Ph$_2$)-piperidine(CH$_2$)$_3$

Figure 1 Tandem conjugate addition-fluorination method for the preparation of α-fluoro-β^3-amino esters.

Demonstrating the applicability of this tandem conjugate addition-fluorination reaction to the preparation of α-fluoro-β^3-amino acids, two silyl-protected conjugate adducts were then transformed into orthogonally protected α-fluoro-β^3-lysine and α-fluoro-β^3-arginine derivatives (*Figure 2*), as described in Chapter 2.

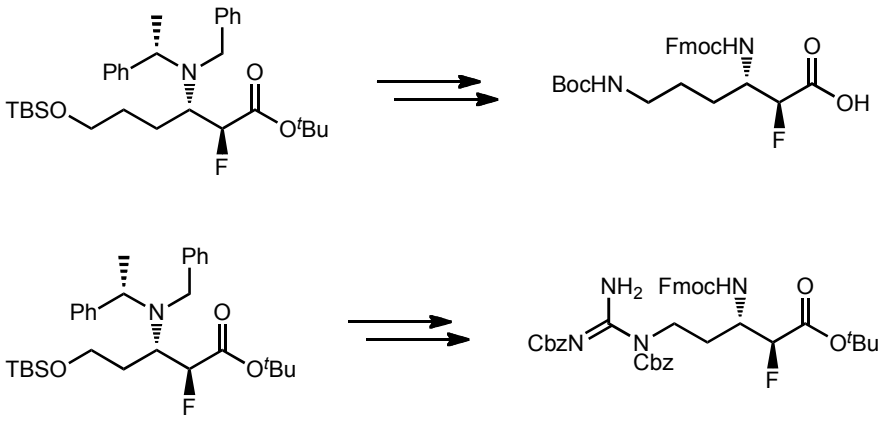
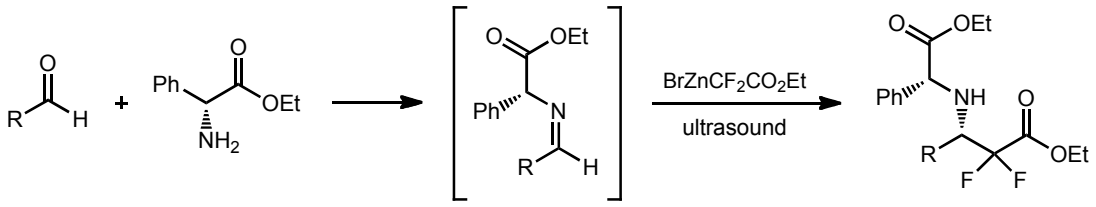


Figure 2 Fluorinated derivatives of β-lysine and β-arginine prepared from silyl-protected conjugate adducts

Access to the corresponding α,α-difluoro-β^3-amino esters was achieved via the development of a Reformatsky reaction employing chiral aliphatic imines derived from phenylglycine (*Figure 3*), which is discussed in Chapter 3. This method improves upon the Reformatsky methodologies currently available for the preparation of α,α-difluoro-β^3-amino esters bearing aliphatic β-substituents, which have historically given unsatisfactory yields and diastereoselectivities.



R = ^{i}Pr, ^{i}Bu, ^{n}C$_7$H$_{15}$, ^{c}C$_6$H$_{11}$, Ph(CH$_2$)$_2$, CH$_2$=CH(CH$_2$)$_2$,TBSO(CH$_2$)$_2$, TBSO(CH$_2$)$_3$, Phth(CH$_2$)$_3$

Figure 3 Preparation of α,α-difluoro-β^3-amino esters via the Reformatsky reaction.

The versatility of these conjugate addition and Reformatsky methodologies was further demonstrated in Chapter 4, in which the preparation of three β^3-arginine analogues is detailed. An unfluorinated and α-fluoro analogue were both prepared from substrates synthesised via the conjugate addition methodology, while the corresponding α,α-difluoro analogue was prepared using the Reformatsky reaction.

The complementarity of the two techniques is demonstrated by the fact that each of the analogues was derived from the same achiral aldehyde (*Figure 4*). Given the successful synthesis of these compounds, each of the two methodologies discussed in this thesis should find greater use amongst the synthetic community for the preparation of α-fluoro and α,α-difluoro-β^3-amino acids.

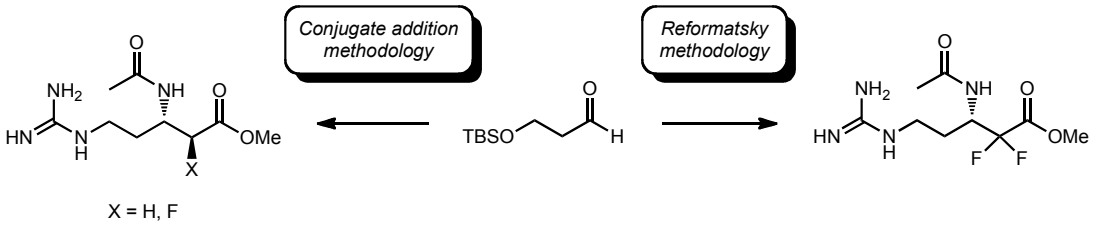


Figure 4 Preparation of unfluorinated, monofluoro and difluoro analogues of β^3-arginine.

DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in 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.

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Taryn March

Dated: .....

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Lastly, to Sean Graney, who I feel utterly privileged to be able to call a friend. You know how big a role you've played in my life, and I think you will agree it's been an interesting ride...

LIST OF ABBREVIATIONS

2,4-DNP	2,4-dinitrophenylhydrazine
9-BBN	9-borabicyclo[3.3.1]nonane
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
AIBN	2,2-azo-bis-isobutyronitrile
Alloc	allyloxycarbonyl
atm	atmospheres
Bn	benzyl
BnBr	benzyl bromide
Boc	*tert*-butyloxycarbonyl
Boc_2O	*tert*-butyl dicarbonate
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate
bs	broad singlet
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
Cl-Cbz	2-chlorobenzyloxycarbonyl
COSY	correlation spectroscopy
d	doublet
DAST	diethylaminosulfur trifluoride
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine

DME	dimethyl ether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPSide	diphenylsilyldiethylene
dq	doublet of quartets
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
ESI	electrospray ionisation
Et	ethyl
Et_2Zn	diethylzinc
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc	9-fluorenylmethoxycarbonyl
Fmoc-OSu	9-fluorenylmethoxycarbonyl succinimide
HIU	high intensity ultrasound
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
m	multiplet
Me	methyl
MeCN	acetonitrile
MeI	methyl iodide
$MeNH_2$	methylamine
MeO	methoxy
MeOH	methanol

MIS	1,2-dimethoxyindole-3-sulfonyl
^{n}BuLi	*n*-butyllithium
NFOBS	*N*-fluoro-*o*-benzenedisulfonimide
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Pbf	2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
R_f	retention factor
RT	room temperature
s	singlet
SAR	structure activity relationship
SPPS	solid phase peptide synthesis
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSO	*tert*-butyldimethylsilyloxy
^{t}BuOH	*tert*-butanol
TFA	trifluoroacetic acid
TFMK	trifluoromethyl ketone
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TolSH	thiotoluene
TsCl	*p*-toluenesulfonyl chloride