Stereocontrol Of Intramolecular Diels-Alder Reactions

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

of

Doctor of Philosophy

in

Chemistry

at

Massey University

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July 1999

ABSTRACT

The use of the intramolecular Diels-Alder (IMDA) reaction in target synthesis has prompted investigation into methods of controlling the stereochemistry of this versatile cycloaddition. Linking the diene and dienophile *via* an ester-tether is a synthetically facile method of generating a range of precursors for the IMDA reaction and allows rapid access to the hydroisobenzofuranone skeleton. This bicyclic[4.3.0]nonane ring system is common to many natural products, including spongians and several novel steroids. Many of the previous examples of ester-tethered IMDA reactions exhibited a lack of stereoselectivity or were performed on racemic mixtures of starting materials. This thesis describes the synthesis of chiral dienols and tetraenols in enantiomerically pure form from monosaccharides. The esters derived from these alcohols possessed a sterically demanding substituent in the ester tether, and the influence of this bulky dioxolane substituent upon the stereochemical outcome of the IMDA reaction was the subject of this study. The purpose of these investigations was to gain information on stereocontrol in the ester-tethered IMDA reaction and, thus, provide a foundation for the tandem IMDA (TIMDA) reaction.

A chiral dienol was synthesised in an enantiomerically pure form from D-glucose and used to prepare *Z*-methyl, *E*-methyl and propynoate esters with a dioxolane substituent on the ester tether. The IMDA reactions of these substrates were studied and found to exhibit high levels of diastereoselectivity. In particular, the IMDA reaction of the *Z*-methyl ester had both extremely high *exo/endo* selectivity (86:14) and complete π-diastereofacial selectivity. The IMDA reaction of the *E*-methyl ester was less selective. The diastereoselectivities of the IMDA reactions were explained by the minimised $A^{1,3}$-strain in the favoured transition state.

It has been long contended in the literature that the IMDA reactions of maleate half-esters (carboxylic acids) produced *endo* adducts whereas the corresponding *Z*-methyl esters (of the maleate half-esters) produced *exo* adducts. Comparison of the IMDA reaction of the *Z*-methyl ester described above with that of its maleate half-ester, disputed this theory. The IMDA reactions of the acid and of the methyl ester exhibited the same diastereoselectivity, with the same ratio of *exo:endo* adduct in each case. This result prompted an investigation into previous research in this area. It was discovered that the previously made assumptions as to the mechanism of reaction between dienols and maleic anhydride (MA) were suspect.

With the purpose of studying the differences in diastereoselectivity and relative rate caused by altering one of two adjacent stereocentres, the results of the model study on the chiral dienol were extended to two diastereomeric tetraenol systems. Both diastereomeric tetraene substrates were synthesised from monosaccharide starting materials; D-glucose and D-galactose. The D-glucose-derived esters were found to undergo IMDA reactions with higher levels of diastereoselectivity than those of the D-galactose-derived esters. In the case of the IMDA reactions of the D-galactose-derived esters, all four of the possible diastereoisomers were produced. In addition to the decreased diastereoselectivity, an increase in the rate of IMDA reaction of the D-galactose-derived substrates was observed when compared to the D-glucose-derived esters. Notably, as with the dienol series, the D-glucose-derived *Z*-methyl ester exhibited extremely high levels of diastereoselectivity.

A disconnection analysis of the cyclopentano perhydroanthrene skeleton of the steroids reveals that a TIMDA reaction would be an elegant method of synthesis. Towards this end, and utilising the information garnered from the model studies on dienol and tetraenol-derived substrates, the ester-tethered TIMDA reaction was investigated. A range of TIMDA precursors, in which a *bis*-diene (tetraene moiety) and *bis*-dienophile were linked *via* an ester tether, were assembled and TIMDA reactions of these substrates were attempted. The most promising area of investigation proved to be a diketone intermediate and future work remains to be performed in this area.

ACKNOWLEDGEMENTS

I would like to thank my supervisors; Mick Sherburn, for providing me with a challenging area for research, and Dave Harding for his support and help during the latter stages of this thesis. I am grateful to everyone, staff and students, who made my time at Massey fun and interesting. In particular, I would like to thank David Officer and Tony Burrell for 'adopting' me into the porphyrin group. I would also like to thank all past and present members of the Massey 'Sherburnite' research group.

I am indebted to Pat Edwards and his NMR expertise, which was vital to the completion of this research. I would also like to acknowledge Craig Turner at Sydney University for his work in subjecting several recalcitrant samples to HPLC and high field NMR.

Lots and lots of thanks to Bob, Geedha and Sophie Reid, who have provided me with numerous cups of tea, biscuits, advice and morale-boosting when needed.

I would like to thank my Mum and Dad for their love, support and words of wisdom (here it is Dad, **D**!). My sister, Kiri, has been great - the packages of chocolate goodies were most appreciated! Special thanks to Gavin Collis for both his friendship and his help in realising what had to be done.

CONTENTS

ABBREVIATIONS

Δ	reflux
Ac	acetyl
AcOH	acetic acid
AIBN	2,2′-azo-*bis*-isobutyronitrile
aq.	aqueous
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Bz	benzoyl
CSA	camphorsulfonic acid
COSY	correlated specroscopy
CH_2Cl_2	dichloromethane
d	day(s) or doublet
DA	Diels-Alder
o-DCB	*ortho*-dichlorobenzene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	dimethoxypropane
DMSO	dimethylsulfoxide
dppb	1,4-*bis*(diphenylphosphino)butane
EDG	electron donating group
EI	electron impact
eq	molar equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
eV	electron Volts
EWG	electron withdrawing group
FMO	frontier molecular orbital
FT	Fourier transform

h	hour(s)
H_2O	water
HETCOR	heteronuclear COSY
Hex	hexane
HOMO	highest occupied molecular orbital
Hz	Hertz
Im	imidazole
IR	infra-red
IMDA	intramolecular Diels-Alder reaction
^{i}Pr	*iso*-propyl
LUMO	lowest unoccupied molecular orbital
M	mol L^{-1}
MA	maleic anhydride
Me	methyl
MeOH	methanol
min	minute
MOM	methoxymethyl
MP	melting point
n-BuLi	*n*-butyl lithium
NMM	*N*-methylmaleiimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
Ph	phenyl
PhMe	toluene
PhH	benzene
ppm	parts per million
py	pyridine
q	quartet
R_f	retention factor
RT	room temperature
s	singlet
S.M.	starting material
t	time or triplet
^{t}Bu	*tert*-butyl
T	temperature
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran

TIMDA	tandem intramolecular Diels-Alder
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet-visible