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Synthesis and Analysis of Libraries of Potential Flavour Compounds

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Kyong-A (Karen) Bang

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Science is organised knowledge. Wisdom is organised life.

Immanuel Kant

(1724 - 1804)

Abstract

The goal of this project was to synthesise potential flavour compounds combinatorially and identify key components for further investigation as flavourants in dairy products. This thesis describes the design and synthesis of libraries of ketones and γ-lactones that will be evaluated for flavour potential. Gas chromatography-mass spectrometry (GC-MS), the Fox, and gas chromatography-olfactometry (GC-O) were used throughout this study.

Ketones were synthesised individually *via* a two-step sequence: a Grignard reaction followed by the oxidation of the resulting alcohol in Chapter 2. Some compounds selected from the Fox analysis were assessed by GC-O. The analysis gave promising results for aromatic and cyclopropyl ketones and a library of cyclopropyl ketones was prepared. Individual racemic lactones were synthesised *via* a two-step sequence: the Linstead modification of the Knoevenagel reaction and subsequent lactonisation in Chapter 3. Libraries of racemic γ-lactones (C_8-C_{12}), including α-substituted γ-lactones, were produced combinatorially. Further, synthesis of a library of γ-thionolactones was achieved by treatment of a library of γ-lactones with Lawesson's reagent. The libraries were analysed by GC-O. A (*R*)-dodecalactone was synthesised from *L*-glutamic acid and the (*S*)-enantiomer was synthesised by the same sequence from D-glutamic acid in Chapter 4. Asymmetric syntheses of both enantiomeric series of γ-lactones utilizing the Sharpless asymmetric dihydroxylation reaction was employed to give the libraries in Chapter 5. Libraries of α-substituted and β-substituted γ-lactones were synthesised combinatorially and analysed by GC-O.

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Abbreviations

AD	asymmetric dihydroxylation
AEDA	aroma extract dilution analysis
AIBN	Azo*bis*isobutyronitrile
aq.	aqueous
b.p.	boiling point
Boc	butyloxycarbonyl
CBS	Corey-Bakshi-Shibata
CoA	coenzyme A
DDC	*N,N*'-dicyclohexyldicarbodiimide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
$(DHQ)_2PHAL$	dihydroquinidine derivative of the phthalazine class of ligands
$(DHQD)_2PHAL$	dihydroquinine derivative of the phthalazine class of ligands
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
E1	elimination, first order
E2	elimination, second order
EN	electronic nose
EtOAc	ethyl acetate
FD	factor of dilution
FID	flame ionisation detector
FMDV	foot and mouth disease virus
g	gram
GC-MS	gas chromatography-mass spectrometry
GC-O	gas chromatography-olfactometry
h	hour
hex	hexane
HLE	horse liver esterase
HRMS	high resolution mass spectrometry
IR	infra-red
L	litre

LAB	lactic acid bacteria
M^+	molecular ion
m.p.	melting point
M.S.	molecular sieve
mg	milligram
min	minute
mL	milliliter
MsCl	methanesulfonyl chloride
μL	microlitre
N	normal
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PC	principal component
PCA	principal component analysis
PDC	pyridinium dichromate
pKa	acid dissociation constant
PLE	pig liver esterase
ppm	parts per million
R_f	retention factor
RT	room temperature
R_T	retention time
s	second
sat'd	saturated
TBDPS	*tert*-butyldiphenylsilyl
TFAA	trifluoroperacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane