Lipid Synthesis and Manufacture

Lipid Synthesis and Manufacture

Edited by

FRANK D. GUNSTONE
Professor Emeritus
University of St Andrews
and
Honorary Research Professor
Scottish Crop Research Institute
Dundee





First published 1999 Copyright © 1999 Sheffield Academic Press

Published by Sheffield Academic Press Ltd Mansion House, 19 Kingfield Road Sheffield S11 9AS, England

ISBN 1-85075-931-6

Published in the U.S.A. and Canada (only) by CRC Press LLC 2000 Corporate Blvd., N.W. Boca Raton, FL 33431, U.S.A. Orders from the U.S.A. and Canada (only) to CRC Press LLC

U.S.A. and Canada only: ISBN 0-8493-9737-5

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying or otherwise, without the prior permission of the copyright owner.

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. Reasonable efforts have been made to publish reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequences of their use.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation, without intent to infringe.

Printed on acid-free paper in Great Britain by Bookcraft Ltd, Midsomer Norton, Bath

British Library Cataloguing-in-Publication Data:

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data:

Lipid synthesis and manufacture / edited by Frank D. Gunstone.

p. cm. -- (The chemistry and technology of oils and fats) Includes bibliographical references and index.

✓ ISBN 0-8493-9737-5 (alk. paper)

1. Lipids--Biotechnology. 2. Lipids--Synthesis. I. Gunstone, F.

D. II. Series. TP248.65.L57L56 1998 660.6'3--dc21

98-11206

Lipid Synthesis and Manufacture

vitter of series of comments and control of

Chemistry and Technology of Oils and Fats

Series Editor: R.J. Hamilton

A series which presents the current state of the art in chosen areas of oil and fat chemistry, including its relevance to food technology. Written at professional and reference level, it is directed at chemists and technologists working in oil and fat processing, the food industry, the oleochemicals industry and the pharmaceutical industry, at analytical chemists and quality assurance personnel, and at lipid chemists in academic research laboratories. Each volume in the series provides an accessible source of information on the science and technology of a particular area.

Titles in the Series:

Lipid Synthesis and Manufacture Edited by F.D. Gunstone

Spectral Properties of Lipids
Edited by R.J. Hamilton and J. Cast

Preface

This book has been planned and written to be useful to scientists working in industrial and academic research laboratories. Synthesis, whether on a laboratory scale or on the scale of an industrial plant, is an important chemical activity, with new and revised procedures being developed continually. This book has been planned to offer a balance of topics, drawing on the authors best equipped to write in particular areas. Chapters on lipid synthesis appear in many books devoted to individual types of lipid, but there are few books devoted to lipid synthesis *per se*.

Several chapters are devoted to the synthesis and production of fatty acids and closely related derivatives. These are compounds with a single acyl/alkyl chain and are basic requirements for the synthesis of lipids with two or more acyl/alkyl chains. The chapters cover polyene acids, isotopically labelled acids, acids with conjugated unsaturation (many of which are used as pheromones), eicosanoids, derivatives for analysis, and some new chemistry associated with Δ -5 acids.

The synthesis of lipids with two or more acyl/alkyl chains is covered in the chapters on triacylglycerols, phospholipids, and sphingolipids. Together, these provide an authoritative account of the latest synthetic methods in these areas of lipid synthesis. They describe important routes to molecules required to further our knowledge of the roles of these compounds in health and disease. On a large scale, triacylglycerols of specific composition are being made by exploiting the various specificities of lipases. This new and exciting area of lipid activity is fully described and will be of interest to both academic and industrial scientists.

Areas more immediately of interest to those working in the food and oleochemical industries are covered in the chapters devoted to vitamin E, other natural antioxidants, sugar esters and ethers, and food surfactants. These are significant contributions, based on growing concern about the nature of our food and the demand for what is perceived to be natural.

A final chapter is devoted to the biosynthesis of fatty acids and lipids. Underlying all modern synthetic work is the desire to develop ever simpler methods which do not damage the environment. This leads to a demand for improved catalysts with higher efficiency and greater selectivity. Nature has already designed such pathways and it is good for synthetic chemists to be reminded of these.

This book should have something for all lipid scientists and technologists, including those involved in academic research and those working in oil and fat processing, the food industry, the oleochemicals industry and the pharmaceutical industry. Analytical chemists and quality assurance personnel will find much of relevance.

I thank Dr Graeme MacKintosh of Sheffield Academic Press for offering me this challenge and for his invaluable help and encouragement in bringing this venture to a successful conclusion.

F. D. Gunstone

Contributors

Mr Richard O. Adlof

USDA, ARS, NEAUR, 1815 North University St. Peoria IL 61604. USA

Professor Robert Bittman

Department of Chemistry and Biochemistry, Queens College of the City University of New York, Flushing, New York 11367, USA

Professor Francisco Camps

Department of Biological Organic Chemistry, C.I.D. (CSIC), Jordi Girona, 18-26. 08034-Barcelona, Spain

Dr Angel Guerrero

Department of Biological Organic Chemistry, C.I.D. (CSIC), Jordi Girona, 18-26. 08034-Barcelona, Spain

Professor Frank D. Gunstone

Scottish Crop Research Institute, Invergowrie, Dundee, DD2 5DA, Scotland

Professor John L. Harwood

School of Biosciences, Cardiff University, Cardiff CF1 3US

Dr G. L. Hasenhuettl

Kraft Foods, Inc., 801 Waukegan Rd., Glenview, IL 60025, USA

Dr Karl-Heinz Jung

Fakultät Chemie, Universität Konstanz, Fach M 725, D-78457 Konstanz, Germany

Dr. Gerald P. McNeill

Unilever Research Colworth, Colworth House, Sharnbrook, Bedford MK44 1LQ, England

Dr Thomas Netscher

Vitamin Research and Technology Development, F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

Dr Sakidja

Center for Food and Nutrition Study. Institut Pertainian Bogor-Darmaga, Bogor, Indonesia Dr Philip E. Sonnet

Visiting Assistant Professor, Chemistry

Department, Temple University, Phila-

delphia, PA 19122, USA

Professor B.G. Swanson

Department of Food Science and Human Nutrition, Washington State University,

Pullman, WA 99164-6376, USA

Professor Dr Richard R. Schmidt Fakultät Chemie, Universität Konstanz,

Fach M 725, D-78457 Konstanz, Germany

Dr Fernand C. Thyrion

Chemical Engineering Institute, Université Catholique de Louvain, 1, Voie Minckelers,

B - 1348 Louvain-la-Neuve, Belgium

Dr Jean-Michel Vatèle

Laboratoire de Chimie Organique I, associé au CNRS, Université Claude Bernard, CPE-

Lyon, 43 Bd. du 11 Novembre 1918, 69622

Villeurbanne, France

Dr N.H. Wilson

Department of Pharmacology, University of

Edinburgh, 1-3, George Square, Edinburgh,

EH8 9JZ, Scotland

Contents

1	Polyene acids JM. VATÈLE	1
	1.1 Introduction	1
	1.2 Synthesis of methylene-interrupted polyenoic fatty acids	2
	1.2.1 Preparation of all-Z-skipped polyenoic acids1.2.2 Synthesis of polyunsaturated fatty acids containing one	2
	or two E double bonds	18
	1.3 Synthesis of fatty acids containing at least one double bond not in the	
	1,4-pattern of skipped unsaturation	27
	1.3.1 Polyenoic acids having one double bond not in the 1,4-pattern	
	of skipped unsaturation	27
	1.3.2 Synthesis of non-methylene-interrupted polyene fatty acids	28
	1.4 Conclusion	30
	References	31
	Appendix to Chapter 1: The availability of polyunsaturated	
	fatty acids	39
	F. D. GUNSTONE	
	A.1 Introduction	39
	A.2 Preparing concentrates of particular acids	39
	A.2.1 Molecular distillation	39
	A.2.2 Urea fractionation	40
	A.2.3 Enzymic enhancement	40
	A.3 Sources of n-3 and n-6 PUFA	41
	A.3.1 γ-Linolenic acid	41
	A.3.2 Arachidonic acid	42
	A.3.3 Stearidonic acid	42
	A.3.4 Eicosapentaenoic acid	43
	A.3.5 Docosahexaenoic acid	43
	References	44
2	Isotopically labelled fatty acids	46
	R. O. ADLOF	
	2.1 Introduction	46
	2.2 Stable-isotope-labelled fatty acids	47
	2.2.1 Deuterium-labelled fatty acids	47
	2.2.2 ¹³ C-labelled fatty acids	76
	2.3 Radioactive-isotope-labelled fatty acids	76
	2.3.1 ³ H-labelled fatty acids	77
	2.3.2 ¹¹ C-labelled fatty acids	78
	2.5.2 Cimotion latty words	, 0

		2.3.3 ¹⁴ C-labelled fatty acids	79
	2.4	Biosynthesis/conversion of fatty acids labelled with stable and	
		radioactive isotopes	81
		2.4.1 ² H- and ³ H-labelled fatty acids	81
		2.4.2 ¹³ C- and ¹⁴ C-labelled fatty acids	81
		2.4.3 Enzymatic conversion of labelled fatty acids	82
	2.5	Analysis of isotopically labelled fatty acids	82
		2.5.1 Mass spectrometry	83
		2.5.2 Nuclear magnetic resonance	83
		2.5.3 Infrared spectrometry	83
		2.5.4 Positron emission tomography	83
	2.6	Storage of isotopically labelled fatty acids	84
		2.6.1 Storage of ² H- and ¹³ C-labelled fatty acids	84
		2.6.2 Storage ³ H- and ¹⁴ C-labelled fatty acids	84
	Ack	cnowledgements	84
		erences The results of the results o	84
	Ap	pendix A: Suppliers of isotopically-labelled fatty acids	93
3		nthesis of long-chain compounds with conjugated unsaturation CAMPS AND A. GUERRERO	94
	2.1	transfer and desire there is not a second and the second	0.4
	3.1		94
	3.2		94
		3.2.1 Direct formation of enyne systems	94
		3.2.2 Indirect formation of enyne systems	97
	3.3	Dienes	99
		3.3.1 Direct formation of conjugated diene systems	99
		3.3.2 Indirect formation of conjugated diene systems	103
	3.4	Trienes	111
		3.4.1 Direct formation of triene systems	112
		3.4.2 Indirect formation of triene systems	114
	3.5	Polyenes	117
		3.5.1 Direct formation of polyene systems	117
		3.5.2 Indirect formation of polyene systems	118
		Commercial manufacture of conjugated dienic fatty acids and related products	118
		knowledgements	121
	Rei	ferences	121
4	Ei	cosanoids: oxygenated derivatives of polyunsaturated fatty acids	
		ntaining twenty carbon atoms	127
			141
	IN.	H. WILSON	
	4.1	Eicosanoids	127
	4.2	Prostanoids	128
		Synthetic routes to prostaglandins	131
		4.3.1 The Corey synthesis	132
		4.3.2 The conjugate addition approach	135
		4.2.2 Three companies counting	127

GOV IMPOVIME	
CONTENTS	V1
COLLIE	V.

		4.3.4 The synthesis of the labile prostanoids PGH, PGG and TXA	138
		4.3.5 The synthesis of PGI ₂	142
	4.4	Problems in PG synthesis and biology	146
	4.5	Lipoxygenase pathway products: leucotrienes and lipoxins	147
		4.5.1 Chemical synthesis of lipoxygenase-derived eicosanoids	149
	4.6	The monooxygenase pathway (cytochrome P450)	153
	4.7	Problems in oxylipin synthesis and use	154
	4.8	Suppliers and manufacturers of eicosanoids	154
	4.9	Abbreviations	155
	Ref	erences	156
5		nthesis of triacylglycerols	162
	P.	E. SONNET	
	5.1	Introduction	162
	5.2	Review of triacylglycerol synthesis and configuration designation	162
	5.3	Ester synthesis	164
		5.3.1 Esterification	164
		5.3.2 Transesterification	166
		5.3.3 Structured triacylglycerols	166
	5.4	Acyl migration	167
		5.4.1 1,2-Acyl migration	167
		5.4.2 1,3-Acyl migration	168
	5.5	Protection/deprotection	169
	5.6	C ₁ synthons	170
		5.6.1 1,2-Glycerol acetonide (1,2-O-isopropylidene glycerol)	170
		5.6.2 Allyl alcohol and chiral monoethers	172
		5.6.3 Glycidol and epichlorohydrin	175
		5.6.4 Additional enzymatic transformations	179
	5.7	Conclusion	180
	Ref	erences	180
	~-		
6		emical synthesis of glycerophospholipids and their analogs	185
	K.	BITTMAN	
	6.1	Introduction	185
	6.2	Precursors of the glycerol backbone	186
	6.3	Addition of oxygen nucleophiles to glycidol (2,3-epoxy-1-propanol) at C-3	187
	6.4	O-Protected glycidyl derivatives: BF ₃ catalyzed epoxy ring opening	
		with a fatty alcohol	188
	6.5	Homo-chain and mixed-chain diacylphosphatidylcholines	189
	6.6	Transphosphatidylation	191
	6.7	Phosphorylation of glycerol derivatives	194
	6.8		198
		6.8.1 H-Phosphonates	200
	6.9	Phosphonates	202
		nowledgement	204
		erences	204

7	Sphingolipids KH. JUNG AND R. R. SCHMIDT	208
	7.1 Introduction	208
	7.2 Synthesis of sphingosines	209
	7.2.1 Racemic sphingosines	209
	7.2.2 Chiral pool syntheses	213
	7.2.3 Enantioselective syntheses	223
	7.3 Syntheses of phytosphingosines	232
	7.3.1 Racemic phytosphingosines	232
	7.3.2 Chiral pool syntheses	234
	7.3.3 Enantioselective syntheses	241
	7.4 Conclusion	243
	References	244
8	Synthesis and production of vitamin E T. NETSCHER	250
	8.1 Introduction	250
	8.2 Natural occurrence and biosynthesis	250
	8.3 Biological functions	252
	8.4 Global market	255
	8.5 Production of totally synthetic vitamin E	256
	8.6 Synthesis of stereoisomers	259
	8.7. Analytical methods	260
	8.8 Production from natural sources by isolation	262
	8.9 Chemical transformation to α-tocopherol	263
	References	265
9	The production of natural antioxidants (other than vitamin E) F. C. THYRION	268
	9.1 Introduction	268
	9.2 Autoxidation and antioxidants	268
	9.2.1 Radical chain-breaking mechanism antioxidants	269
	9.3 Antioxidant recovery from natural sources	271
	9.3.1 Production of natural antioxidants at the laboratory level	271
	9.3.2 Extraction of carotenoids from palm oil	272
	9.3.3 Extraction of carotenoids from other sources	282
	9.3.4 Extraction of spice antioxidants	282
	9.4. Conclusion References	283
		283
10	Enzymic processes	288
	G. P. McNEILL	
	10.1 Introduction	288
	10.2 Enzymes	289
	10.2.1 Lipases	289
	10.2.2 Phospholipases and glycosideses	202

CONTENTS	
----------	--

хiii

	10.2.3 Enzyme immobilisation	293
	10.3 Triacylglycerols	294
	10.3.1 Medium-chain structured triacylglycerols	294
	10.3.2 Triacylglycerols containing polyunsaturated fatty acids	292
	10.3.3 Cocoa butter substitutes	296
	10.3.4 Infant-formula fats	
	10.4 Diacylglycerols	296
	10.5 Monoacylglycerols	297
	10.5.1 Synthesis by glycerolysis of triacylglycerols	297
	10.5.2 Synthesis from glycerol and fatty acids/esters	299
	10.5.3 Selective hydrolysis (alcoholysis) of triacylglycerols	299
	10.6 Fatty acids	300
	10.6.1 Non-selective processes	301
		301
	10.6.2 Long-chain polyunsaturated fatty acids 10.6.3 Gamma-linclenic acid	301
	10.6.4 Erucic acid	303
	10.6.5 Others	304
		304
	10.7 Phospholipids	305
	10.7.1 Acyl modifications	306
	10.7.2 Modification of the polar head group	307
	10.8 Sugar esters and glycosides	308
	10.8.1 Lipase-catalysed acylations/deacylations	308
	10.8.2 Alkylation with glycosidases	310
	10.9 Wax esters	311
	10.10 Summary and outlook	312
	References	313
11	The preparation of derivatives for lipid analysis	321
	F. D. GUNSTONE	
	,	
	11.1 Introduction	221
	11.2 Free acids by hydrolysis	321
	11.3 General comments on ester preparation	322
	11.4 Base-catalysed transesterification	323
	11.5 Acid-catalysed esterification and transesterification	323
	11.6 Methylation using methanolic boron trifluoride	324
	11.7 Diazomethane	325
	11.8 Tetramethylguanidine	326
		327
	11.10 Phonocul extens	327
	11.10 Phenacyl esters	328
	11.11 Picolinyl esters	329
	11.12 Reaction of sodium salts with methyl iodide or other alkyl halides	330
	11.13 Special cases	330
	11.14 Pyrrolidides	332
	11.15 4,4-Dimethyloxazolines (DMOX)	333
	11.16 Reaction with Grignard reagent	334
	11.17 Hydroxyl groups	336
	11.18 Nicotinates	336
	11.19 Acetates	336
	11.20 Trifluoroacetates	337
	11.21 Silyl ethers	337

	11.22 Isopropylidene derivatives 11.23 Butylboronates 11.24 Methyl ethers 11.25 Double bond derivatives 11.26 Deuteration	338 338 339 339 340 340
	11.27 Epoxidation 11.28 Mercuration	341
	11.29 Dimethyl disulphide adducts	341
	11.30 MTAD adducts	342
	11.31 Ozonolysis	343
	References	344
12	Alkyl and acyl sugars	347
14	SAKIDJA AND B. G. SWANSON	547
	- AAA	
	12.1 Introduction	347
	12.2 Alkyl and acyl sugar syntheses	349
	12.2.1 Preparation of fatty acid methyl esters	349
	12.2.2 Sucrose fatty acid polyesters	350 352
	12.2.3 Carbohydrate fatty acid polyesters	357
	12.3 Isolation and purification of alkyl and acyl sugars 12.4 Analysis and structural elucidation	359
	12.5 Physical properties	361
	12.6 Ether and alkoxy derivatives	364
	12.7 Future syntheses of fat substitutes	365
	References	366
13	Synthesis and commercial preparation of surfactants	
	for the food industry	371
	G. L. HASENHUETTL	
	12.1 Disciples of find out for your design	271
	13.1 Principles of food surfactant design 13.2 The synthesis of food surfactants	371 372
	13.2.1 Polyol esters of fatty acids	372
	13.2.2 Elaboration of polyol head groups	381
	13.2.3 Ethoxylation of polyol lesters	384
	13.2.4 Modification of naturally occurring compounds	385
	13.2.5 Enzymatic techniques for surfactant synthesis	387
	13.3 Commercial manufacturing equipment	389
	13.3.1 Batch and continuous esterification reactors	389
	13.3.2 Ethoxylation/propoxylation reactors	395
	13.3.3 Bioreactors	395
	Acknowledgements	396
	References	396
14		401
	T. A. ISBELL	
	14.1 Introduction	401
	14.2 Sources of A.5 fetty soids	401

CO	ATT	ושו	TI	2
	ILA.		ΑI	0

	 14.3 Halolactonization 14.4 Regioselective formation of δ-lactones 	402
	14.5 Reactivity of δ - and γ -lactones	407
	14.5 Reactivity of δ- and γ-factones 14.6 Synthesis of 5,6-epoxy fatty acids and their cyclization to hydroxy δ-lactones	411
	14.7 Secondary ethers	412
	14.8 Oxidative stability of 5-alkenoic acids	413
	References	417
	References	419
15	Lipid biosynthesis	422
	J. L. HARWOOD	
	15.1 Introduction	422
	15.2 Fatty acid formation	422
	15.2.1 De novo synthesis	422
	15.2.2 Desaturation	431
	15.2.3 Elongation	435
	15.2.4 Principal differences between microbes, plants and animals	436
	15.3 Complex lipid assembly	441
	15.3.1 Phosphoglycerides	441
	15.3.2 Sphingolipids	443
	15.3.3 Glycosylglycerides	445
	15.3.4 Neutral glycerides (especially triacylglycerols)	445
	15.3.5 Other lipids	449
	15.4 Diseases of lipid metabolism	451
	15.4.1 Skin disease	451
	15.4.2 Respiratory distress	451
	15.4.3 Endotoxic shock and sepsis	452
	15.4.4 Inflammation	452
	15.4.5 Arteriovascular disease	452
	15.4.6 Cancer	453
	15.4.7 Inherited diseases	453
	15.5 Transgenic crops	456
	15.6. Concluding remarks	458
	References	459

Index

1 Polyene acids

Jean-Michel Vatèle

1.1 Introduction

Polyenoic fatty acids are widely distributed in the plant and animal kingdoms. Most of these acids have double bonds in the Z configuration arranged in a 1,4-skipped pattern of unsaturation. Also found in nature, but in much lower abundance, are fatty acids that have all or part of their unsaturation in a conjugated system with Z and/or E double bonds or in which double bonds are not entirely in a methylene-interrupted arrangement. Skipped polyunsaturated fatty acids possessing one or two E double bonds are formed during the heat treatment or hydrogenation of edible oils and represent a significant part of total dietary fatty acid intake. These compounds have emerged as an important group of fatty acids because of their possible physiological impact and their metabolites. As illustrated in Figure 1.1, polyunsaturated fatty acids possess a large variety of structural features and biological activities (Gunstone, 1994).

Figure 1.1 Examples of polyunsaturated fatty acids.

The first syntheses of oleic and linoleic acids, containing one and two double bonds appeared in the literature in 1934 (Noller and Bannerot) and 1950 (Raphael and Sondheimer), respectively. Methods for the synthesis of fatty acids