

Prof. A. Douglas Kinghorn, College of Pharmacy,
Ohio State University, Columbus, OH, USA

em. Univ.-Prof. Dr. H. Falk, Institut für Organische Chemie,
Johannes-Kepler-Universität, Linz, Austria

Prof. Dr. J. Kobayashi, Graduate School of Pharmaceutical Sciences,
Hokkaido University, Sapporo, Japan

This work is subject to copyright.

All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machines or similar means, and storage in data banks.

© 2009 Springer-Verlag/Wien
Printed in Germany

SpringerWienNewYork is part of
Springer Science + Business Media
springer.at

Product Liability: The publisher can give no guarantee for the information contained in this book. This also refers to that on drug dosage and application thereof. In each individual case the respective user must check the accuracy of the information given by consulting other pharmaceutical literature. The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Library of Congress Catalog Card Number AC 39-1015

Typesetting: Thomson Digital, Chennai
Printing and binding: Strauss GmbH, 69509 Mörlenbach, Germany

Printed on acid-free and chlorine-free bleached paper
SPIN: 12174249

With 52 partly coloured Figures

ISSN 0071-7886
ISBN 978-3-211-78206-4 SpringerWienNewYork

The Epothilones: An Outstanding Family of Anti-Tumor Agents From Soil to the Clinic

Contents

List of Contributors.	IX
1. Preface	
<i>J. Mulzer</i>	1
2. General Aspects	
<i>G. Höfle</i>	5
2.1. History of Epothilone Discovery and Development	5
2.1.1. The Early Days	5
2.1.2. Industry Becomes Interested in Epothilones – and Loses Interest Again	7
2.1.3. Re-Discovery of Epothilone in the Nineties	8
2.1.4. Development of Epothilones as Anticancer Drugs	10
2.1.5. Epilogue	13
Acknowledgements	13
References	14
2.2. Natural Epothilones	16
2.2.1. Isolation and Large Scale Production	16
2.2.2. Structure of Epothilones and Related Compounds.	20
2.2.3. Physical and Chemical Properties.	23
Acknowledgements	27
References	27
3. Biosynthesis and Heterologous Production of Epothilones	
<i>R. Müller</i>	29
3.1. Introduction.	29
3.2. Feeding Studies and the Discovery of Natural Epothilone Variants.	32

3.3. Identification of the Epothilone Biosynthesis Gene Cluster	36
3.4. Studies <i>in vitro</i> into the Biochemistry of Epothilone Assembly	39
3.5. Heterologous Expression and Genetic Engineering of the Epothilone Biosynthesis Gene Cluster	43
3.6. Nutrient Regulation in <i>S. cellulosum</i> and <i>M. xanthus</i>	47
3.7. Conclusions.	49
Acknowledgements	50
References	50
 4. Total Synthesis of Epothilones A–F	
<i>J. Mulzer, K. Prantz</i>	55
4.1. Introduction.	56
4.2. Synthesis Approaches to both the Epothilone A/C- and B/D-Series	58
4.2.1. <i>Danishefsky</i> Syntheses.	58
4.2.2. <i>Nicolaou</i> Syntheses.	67
4.2.3. <i>Schinz</i> Synthesis	73
4.2.4. <i>Sinha</i> Syntheses	77
4.2.5. <i>Carreira</i> 's Synthesis of 2a and 2b	81
4.2.6. <i>Shibasaki</i> Approach	84
4.3. Syntheses of Epothilone A/C (1a , 2a).	87
4.3.1. <i>Fürstner</i> 's Alkyne RCM	87
4.3.2. <i>Liu</i> Synthesis	87
4.3.3. <i>Panek</i> Approach	93
4.3.4. <i>Wong</i> 's DERA Approach	93
4.3.5. <i>Ley</i> 's Approach	96
4.4. Synthesis of Epothilones B/D (1b , 2b)	97
4.4.1. <i>Mulzer</i> Syntheses	97
4.4.2. <i>Grieco</i> 's Formal Synthesis of 2b	101
4.4.3. <i>White</i> 's Syntheses	101
4.4.4. <i>Ermolenko</i> Variation of the <i>White</i> Synthesis.	105
4.4.5. Synthesis by <i>E. J. Thomas</i>	107
4.4.6. <i>Avery</i> 's Synthesis	109
4.4.7. <i>R. E. Taylor</i> 's Synthesis.	111
4.5. Syntheses of Fragments	112
4.5.1. <i>Kalesse</i> 's Synthesis of <i>Nicolaou</i> 's Intermediates 60 and 82	112
4.5.2. <i>Chandrasekhar</i> 's Synthesis of Keto Acid 378 and C7–C16 Fragment 381	113
4.5.3. <i>Ramachandran</i> 's Synthesis of the MEM-protected <i>Nicolaou</i> -Aldehyde (390).	115
4.5.4. <i>De Brabander</i> 's Synthesis of Aldehyde 63 and Acid 59	115
4.5.5. <i>Wessjohann</i> 's Synthesis of Fragments 398 and 401	115
4.5.6. <i>Kulinkovich</i> 's Synthesis of Aldehyde 408	117
4.5.7. <i>Georg</i> 's Synthesis of Aldehyde 70	117
4.5.8. Lipase-Catalyzed Synthesis of the C1–C6 Fragment 414	118
4.6. Semisynthetic Degradation/Reconstruction of 2b	118

4.7. Syntheses of Epothilones E and F (1c , 1d) and Their 12,13-Deoxy Derivatives (2c , 2d)	119
4.7.1. <i>Nicolaou's</i> Synthesis of 1d	119
4.7.2. <i>Sinha's</i> Synthesis of 1c , 1d and 2c , 2d	119
4.8. <i>Nicolaou's</i> Synthesis of Epothilone Analogues	119
4.9. Conclusion and Industrial Application (ZK-Epo (Sagopilone)).	123
Abbreviations	125
References	126
5. Semisynthetic Derivatives of Epothilones	
<i>K.-H. Altmann</i>	135
5.1. Introduction.	135
5.2. The O16–C8 Sector (“Polyketide Sector”)	137
5.2.1. Modification of the Ester Moiety	137
5.2.2. Modification in the C2–C8 Region	139
5.3. Modification of the Epoxide Moiety	141
5.4. Side Chain Modifications	146
5.4.1. Modifications of the C16/C17 Bond and the Thiazole Moiety	146
5.4.2. Cleavage/Restitution of the C16/C17 Bond.	148
5.5. Removal/Incorporation of the C13–O16 Segment.	150
5.6. Conclusions.	153
References	154
6. Preclinical Pharmacology and Structure-Activity Studies of Epothilones	
<i>K.-H. Altmann</i>	157
6.1. Introduction.	157
6.2. <i>In vitro</i> Pharmacology of Epo B	161
6.3. <i>In vivo</i> Pharmacology of Epo B.	170
6.4. Epothilone Analogs and SAR Studies.	171
6.4.1. The O16–C8 Sector (“Polyketide Sector”)	171
6.4.1.1. Lactam-based Analogs	171
6.4.1.2. Modifications in the C2–C8 Region	174
6.4.2. The C9–C13 Sector (“Epoxide Sector”)	178
6.4.2.1. Modifications of the C9–C12 Segment	178
6.4.2.2. Modifications in the Epoxide Region (C12/C13).	182
6.4.3. The C14–C21 Sector.	191
6.4.3.1. Side Chain Modifications.	191
6.4.3.2. C14 Modifications	205
6.4.4. Miscellaneous Modifications	206
6.5. Structural Studies and Pharmacophore Modeling	206
6.6. Conclusions.	209
References	210

7. Clinical Studies with Epthilones	
<i>K.-H. Altmann</i>	221
7.1. Introduction.	221
7.2. Patupilone (EPO906, Epo B).	223
7.3. Ixabepilone	224
7.4. KOS-862.	228
7.5. BMS-310705.	229
7.6. KOS-1584.	230
7.7. Sagopilone (ZK-Epo)	232
7.8. ABJ879	232
7.9. Conclusions.	233
References	234
Author Index	239
Subject Index	251

List of Contributors

Altmann, Prof. Dr. K.-H., ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETH Hönggerberg. HCI H 405, Wolfgang-Pauli-Str. 10, 8093 Zürich, Switzerland
e-mail: karl-heinz.altmann@pharma.ethz.ch

Höfle, Prof. Dr. G., Helmholtz-Zentrum für Infektionsforschung, (formerly: *GBF*, Gesellschaft für Biotechnologische Forschung), Inhoffenstr. 7, 38124 Braunschweig, Germany
e-mail: G.Hofle@helmholtz-hzi.de

Müller, Prof. Dr. R., Institut für Pharmazeutische Biotechnologie, Universität des Saarlandes, Postfach 15 11 50, 66041 Saarbrücken, Germany
e-mail: rom@mx.uni-saarland.de

Mulzer, Prof. Dr. J., Institut für Organische Chemie, Fakultät für Chemie der Universität Wien, Währingerstr. 38, 1090 Wien, Austria
e-mail: johann.mulzer@univie.ac.at

Prantz, Mag. K., Institut für Organische Chemie, Fakultät für Chemie der Universität Wien, Währingerstr. 38, 1090 Wien, Austria
e-mail: kathrin.prantz@univie.ac.at

The Epothilones: An Outstanding Family of Anti-Tumor
Agents

From Soil to the Clinic

Mulzer, J.H. (Ed.)

2009, IX, 260 p., Hardcover

ISBN: 978-3-211-78206-4