Doctoral Thesis

Total synthesis of the epothilone natural products a nitrile oxide approach

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Part I: Total Synthesis of the Epothilone Natural Products: A Nitrile Oxide Approach

Part II: New Methodologies for the Nitrile Oxide Approach to Beta-Hydroxy Carbonyls

A dissertation submitted to the
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Presented by

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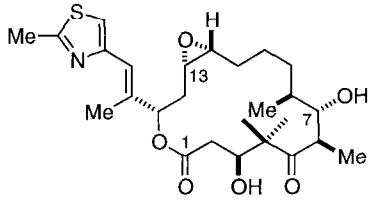
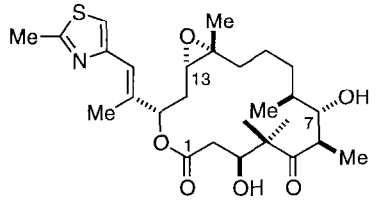
Zürich 2001

Abstract

Part I of this thesis describes the successful total synthesis of epothilones A and B.

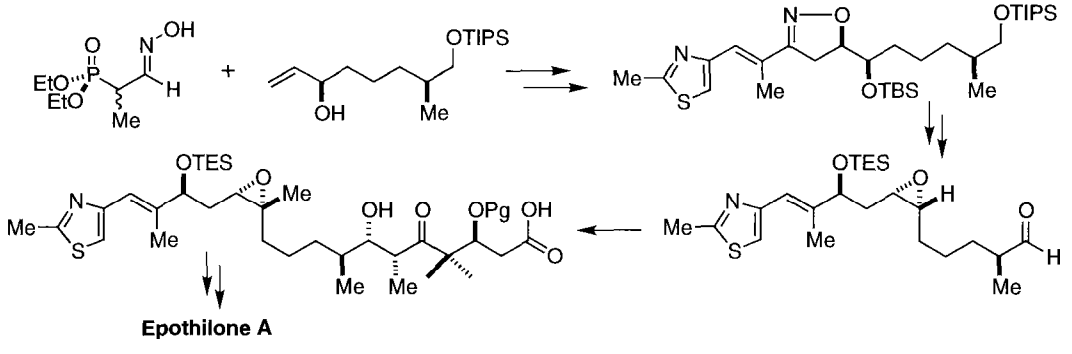


Epothilone A



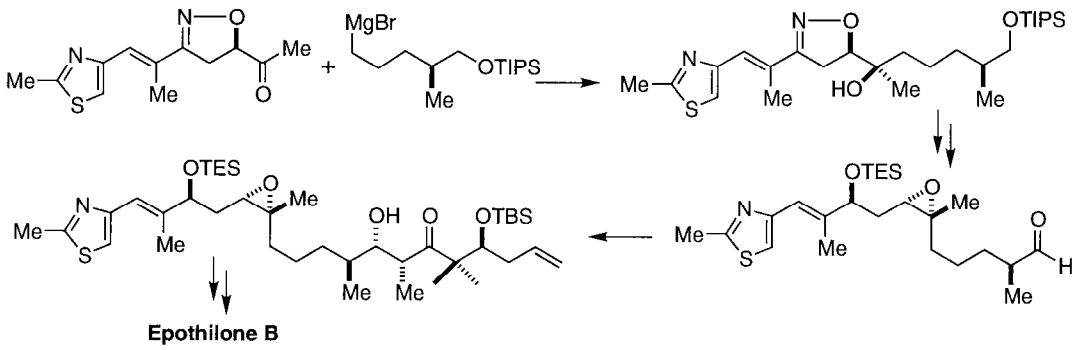
Epothilone B

Epothilone A was synthesized (21 linear steps) via a highly convergent nitrile oxide cycloaddition and a diastereoselective aldol coupling reaction.

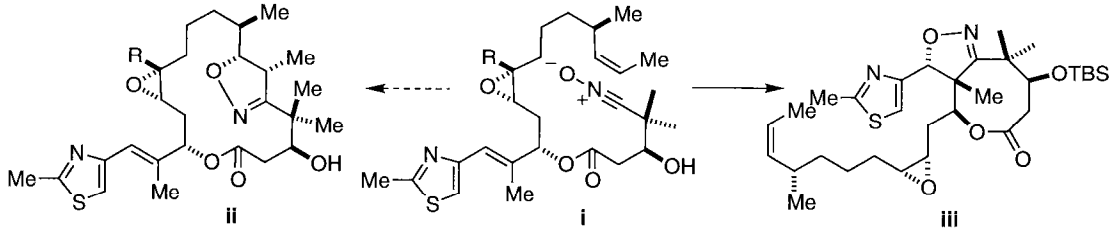


Epothilone A

The formal total synthesis of epothilone B (18 steps in total) features a concise preparation of the epothilone B carbon chain (11 steps) by stereoselective Grignard coupling and a diastereoselective aldol reaction.



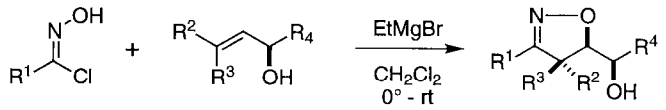
In addition, efforts towards a macrocyclic ring closing nitrile oxide cycloaddition approach are described. Although we observed clean formation of the requisite nitrile oxide **i** followed by diastereo- and regioselective cycloaddition, the reaction occurred at the more substituted double bond to provide eight-membered ring lactone **iii** and did not provide access to the epothilones.



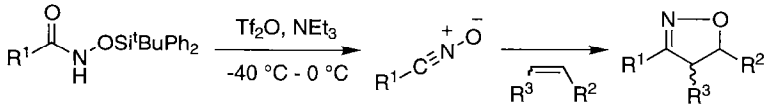
In the course of our studies on the epothilones, we have encountered several opportunities to develop and apply new reaction methodologies. In this regard, we have discovered a new procedure for the selective cleavage of conjugated isoxazolines (Part II, Chapter 4), a rearrangement of 1,3-cyclic sulfites to epoxides which provides several advantages over traditional methods, and a protocol for the synthesis of terminal allylic alcohols based on the addition of chiral zinc acetylides. Likewise, we have documented the first applications of the TiF_4-BINOL allylsilylation of aldehydes, the Kanemasa hydroxy-directed nitrile oxide cycloaddition, and the Falck-Misokowski epoxide opening to give chiral allylic alcohols.

Part II of this thesis outlines new methodologies complimenting the nitrile oxide approach to beta-hydroxy carbonyls. This alternative to traditional aldol reactions offers several attractive features, but has so far seen only limited use due to complications in the preparation and transformation of enantiomerically pure isoxazolines. Our new methodologies significantly extend the practicality and generality of this approach to beta-hydroxy carbonyls.

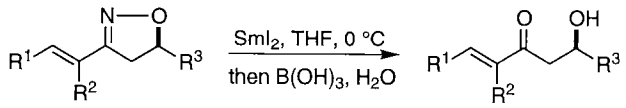
Chapter 2 describes our study and advancement of a magnesium (II) mediated, hydroxyl-directed nitrile oxide cycloaddition of chiral allylic alcohols. Our efforts have led to broadly applicable, operationally simple reaction conditions for a wide variety of nitrile oxide precursors and allylic alcohols, including substrates previously difficult to employ in nitrile oxide cycloadditions.



Chapter 3 details the development, in conjunction with D. Muri, of a novel, general method for the generation of nitrile oxides from O-silylhydroxamates.

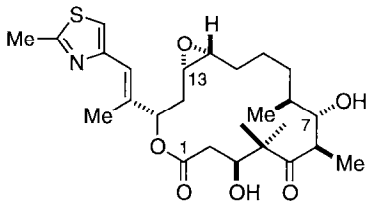


Chapter 4 describes our efforts to overcome difficulties in achieving the chemoselective reduction of conjugated isoxazolines to the corresponding alpha, beta-unsaturated hydroxy ketones. These studies have led to the identification and development of a new protocol for this reaction with SmI_2 and $B(OH)_3$.

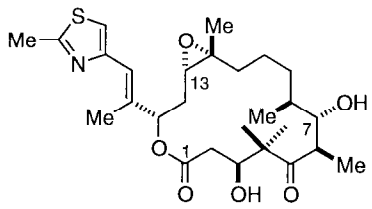


Zusammenfassung

Im **Part I** wird die erflogreiche Synthese von Epothilon A und B beschrieben.

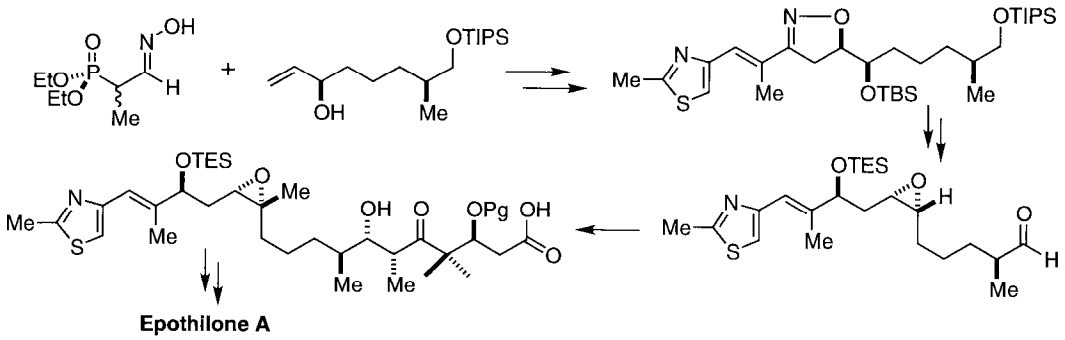


Epothilone A



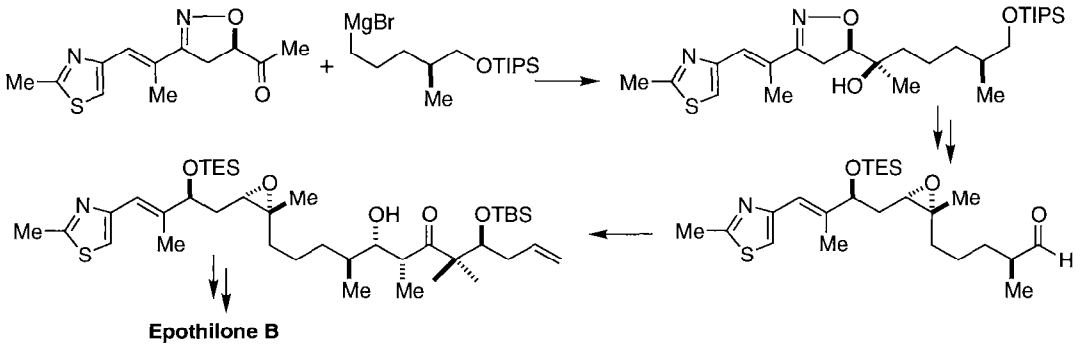
Epothilone B

Epothilon A konnte über eine hochkonvergente Nitriloxid Cycloaddition und eine diastereoselektive Aldolkopplung synthesiert werden.

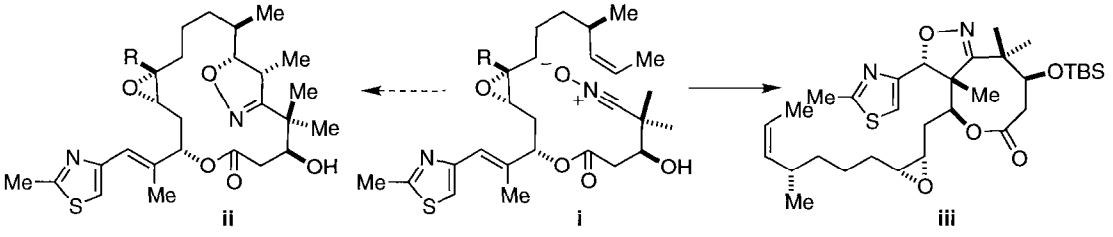


Epothilone A

Das Hauptaugenmerk in der formalen Synthese von Epothilon B ist auf die effiziente Darstellung der Epothilon B Kohlenstoffkette zu richten, welche mit Hilfe einer stereoselektiven Grignard Kopplung erreicht wurde.



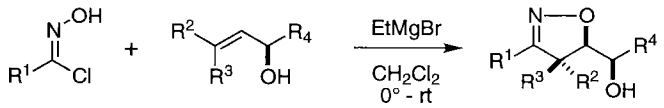
Ferner wurden Syntheseversuche für den makrocyclischen Ringschluss mittels Nitriloxide Cycloaddition unternommen. Obwohl eine diastereo- und regioselktive Cycloaddition nach erflogreicher Herstellung des Nitriloxids beobachtet wurde, reagierte dieses selektiv mit der Thiazol-Doppelebindung um das 8-Ring Lacton **iii** zu bilden. Dies verwährte den möglichen Zugang zu den Epothilonen.



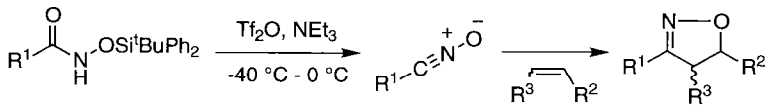
Während der Synthesestudien des Epothilonprojektes, wurden mehrere neue Reaktionsmethoden entwickelt und angewand. So wurde eine Methode für die selektive Spaltung von konjugierten Isoxazolinen, eine Umlagerung von 1,3-Sulfiten zu Epoxiden und die Synthese von terminalen, allylischen Alkoholen studiert. Desweiteren wurden die erste Anwendung der TiF_4-BINOL Allylsilylierung von Aldehyden, die Kanemasa hydroxyl-dirigierte Nitriloxid Cycloaddition und die Falck-Misokowski Epoxidöffnung untersucht.

In **Part II** werden neue Methoden für den "Nitrile Oxide Approach" zu Beta-hydroxycarbonylen beschrieben.

Kapitel 2 beschreibt Studien und Fortschritte der Magensium (II) unterstüzten hydroxyl-dirigierten Nitriloxid Cycloaddition chiraler, allylische Alkohole.



In **Kaptiel 3** wird näher auf die Entwicklung einer generellen Methode für die Darstellung von Nitriloxiden aus *O*-Silylhydroxamaten eingeganen (in Zusammenarbeit mit D. Muri).



Kapitel 4 geht auf die chemoselektive Reduktion konjugierer Isoxazoline zu den entsprechenden alpha, beta-ungesättigten Hydroxyketonen ein.