様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

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研究課題名（和文）Synthetic Strategies for the Total Synthesis of Pyranonaphthoquinone Type Natural Products

研究課題名（英文）Synthetic Strategies for the Total Synthesis of Pyranonaphthoquinone Type Natural Products

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研究成果の概要（和文）：ruthmzcinにおける2つのビルディングブロックの効率的な合成を達成しました。本処方は、高度に位置選択的なベンゾシクロブテノールの形成、続くシクロブテンの開環を含みます。これにより、クライゼン前駆体の合成が最適化され、わずか12ステップでの合成を可能にしました。 脱芳香族クライゼン転位は、重水素標識モデル化合物の使用によりメカニズムを決定しました。すなわち、3,3-シグマトロピックシフトを介した古典的なクライゼン転位を経由する反応経路を強く示唆しました。また、本基質にてクライゼン転位の反応条件を最適化し、完全な位置選択制を備えたruthmycinの中間体の構築を可能にしました。

研究成果の学術的意義や社会的意義
The study of interest to the synthetic community investigation natural product synthesis of complex molecules.
The discovery of the new Claisen Rearrangement and its investigation will stimulate further research.

研究成果の概要（英文）：The efficient synthesis of two building blocks has been achieved. For the Synthesis of the aromatic building block, a three-step protocoll has been developed and partly published. This includes a highly regioselective benzocyclobutenol formation followed by bond-selective cyclobuten ring opening to access o-methylbenzaldehydes. The synthesis of a Claisen-precursor was optimized and allowed synthesis of the latter in 12 steps. The dearomative Claisen rearrangement (CR) was first investigated with a deuterium-labelled model compound. The results strongly suggest a reaction pathway following the classical CR via a 3,3-sigmatropic shift. Optimization of the reaction conditions for the CR on the real system was developed and comprises a two-step protocol. The developed synthesis allows for the construction of a synthetic intermediate for ruthmycin bearing the full carbon skeleton with an angular stereogenic center with perfect stereocontrol.

研究分野：organic chemistry

キーワード：naphthocyclinones　natural products　Claisen rearrangement

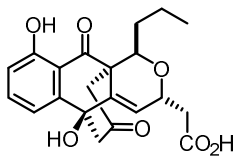
様　式　C－１９、F－１９－１、Z－１９（共通）

１．研究開始当初の背景

Ruthmycin, a polyketide natural product from the pyranonaphthoquinone family comprising an unusual tetracyclic skeleton. Its unique structure stems from an unprecedented signature three-carbon bridge, which forms the corresponding six membered ring onto the widely spread and well known pyranonaphthoquinone core scaffold. Within this research project the pyranonaphthoquinone core of ruthmycin will be rapidly assembled and the complete carbon skeleton will be constructed by an unprecedented mild dearomative *Claisen* rearrangement delivering the necessary all carbon quaternary stereocenter in a diastereoselective fashion. Further key synthetic transformations will include a deoxygenation of a phenol, a Wacker oxidation and a cyclization by means of an intramolecular aldol reaction.

２．研究の目的

The purpose of this research project was development of a synthetic rout and possible first total total synthesis of ruthmycin. In course of an ongoing project, an unprecedented mild dearomative *Claisen* rearrangement (CR) has been discovered. Mechanistic investigation of this unique CR, the development of a viable synthetic procedure and its implementation as the key step in a total synthesis of ruthmycin were main goals.



ruthmycin

３．研究の方法

a) Efficient preparation of suitable building blocks and upscaling

The efficient and large scale synthesis of building blocks is the base for an efficient synthesis. Therefore, we envisioned to develop and scale up a two step protocol for the synthesis of ortho-methyl benzaldehydes via aryne chemistry followed by a one-pot procedure for selective ring opening and oxidative esterification.

b) Construction of precursor for Claisen Rearrangement

The large scale synthesis of an advanced synthetic intermediate was envision to be another cornerstone in the synthesis. The goal was to develop the synthetic rout and to prepare large quantities of material for the investigation of the Claisen rearrangement and scale-up.

c) Mechanistic Investigations

In order to understand and to proof that the discovered Claisen Rearrangement is indeed a 3,3-sigmatropic rearrangement, mechanistic investigations were of fundamental interest. Deuterium labelled model compounds were to be designed for mechanistic investigations by NMR and structure determination.

d) Scale up of Claisen Rearrangement on real System

With the knowledge gained from the mechanistic investigations (temperature, reaction time, solvent) the development of a suitable procedure for large scale reaction was mandatory. Furthermore, the CR leads to the formation of an angular stereogenic center. Perfect stereocontrol of the newly formed asymmetric carbon was crucial.

４．研究成果

a) The efficient and large-scale synthesis of two building blocks has been achieved. For the Synthesis of the aromatic building block, a three-step protocoll has been developed. and partly published. The methodology developed includes highly regioselective benzocyclobutenol formation followed by bond-selective ring cleavage and cyclobuten ring opening to access o-methylbenzaldehydes. In due course, the envisioned two-step protocol was developed as well.

b) An efficient annulation protocol allowed assembly of a naphthalene precursor. The synthesis of a Claisen-precursor was optimized and allowed synthesis of the latter in 12 steps. This granted access to large quantities of material (>5 g) for intensive investigations.

c) The dearomative Claisen rearrangement (CR) was first investigated with a deuterium-labelled model compound. Therefore, mono-deuterated allyl alcohol was prepared from acrolein and NaBD4. After ether formation and Claisen rearrangement, the deuterium label was found at the terminal carbon of the olefin thus proofing the hypothesis of a 3,3-sigmatropic shift.

d) Optimization of the reaction conditions for the CR on the real system was developed and comprises a two-step protocol. Oxidation of a mask naphthohydroquinone to the naphthoquinone, followed by one-pot reduction and Claisen-rearrangement. The developed synthesis allows for the construction of a synthetic intermediate for ruthmycin bearing the full carbon skeleton with an angular stereogenic center with perfect stereocontrol.

５．主な発表論文等

〔雑誌論文〕　計0件

〔学会発表〕　計2件（うち招待講演　0件／うち国際学会　0件）

１．発表者名 ○Mark Marcello Maturi, Nozomi Tanaka, Yoshio Ando, Ken Ohmori, Keisuke Suzuki
２．発表標題 Synthetic Studies on beta-Naphthocyclinone (2): Design, Preparation and Reactivity of a Donor Unit
３．学会等名 CSJ 99th Annual Meeting
４．発表年 2019年

１．発表者名 ○Nozomi Tanaka, Mark Marcello Maturi, Yoshio Ando, Ken Ohmori, Keisuke Suzuki
２．発表標題 Synthetic Studies on beta-Naphthocyclinone (1): Preparation of an Acceptor Unit
３．学会等名 CSJ 99th Annual Meeting
４．発表年 2019年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

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