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学位論文要旨

Abstract

Commercially available D-tartaric acid diisopropyl ester has two chiral centers which could be successfully incorporated in target molecules. In order to complete stereoselective synthesis of target molecules, we took advantage of inherent properties of alkyne-cobalt complex, namely (i) sterical bulkiness, (ii) stabilization of propargyl cation. Thus we have accomplished a highly stereoselective total synthesis of (+)-bengamide E, isolated from a Choristid sponge collected in the Fiji Islands, and the first total synthesis of (+)-secosyrins 1 and 2, thereby confirming their stereochemistry. In addition we could develop a new procedure for synthesis of (+)-syributins 1 and 2.

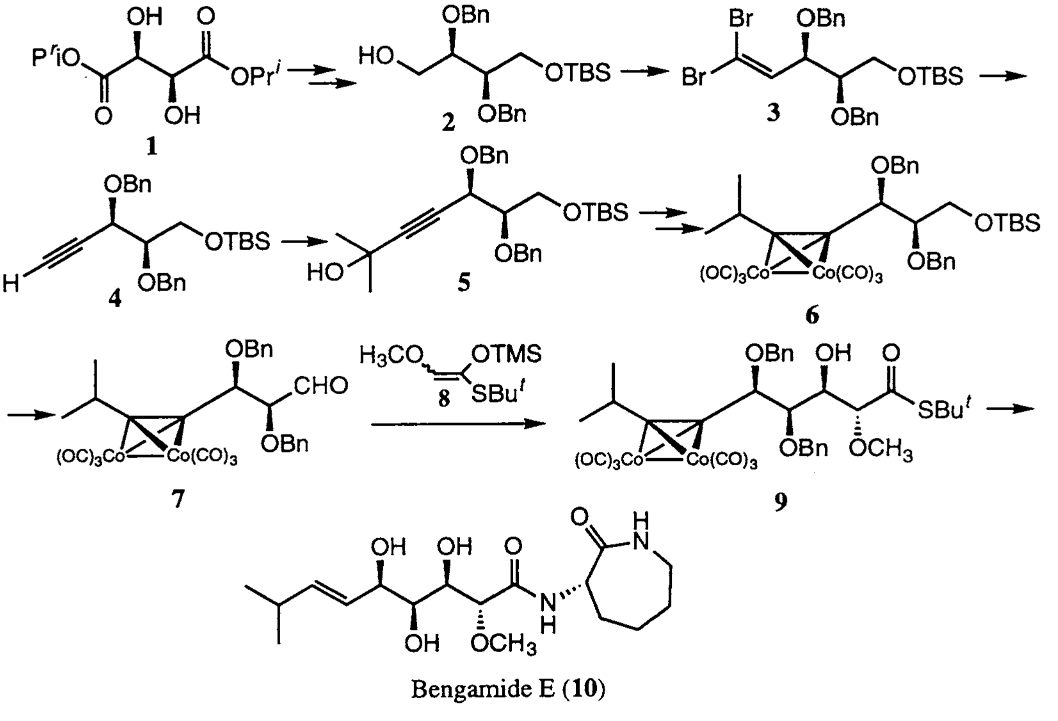
Introduction

There are several natural resources available which would be useful building blocks in organic synthesis. Among these natural resources tartaric acid is particularly intriguing one because tartaric acid has two carboxylic moieties and two hydroxy groups in a system of C_2-symmetry and actually has been extensively used in the total synthesis of natural products. The other benefit of tartaric acid is that it is commercially available at reasonable price. This valuable precursor is a simple natural product readily available in both enantiomeric forms. We have been able to incorporate this inexpensive starting material in our target molecules and completed a highly efficient total syntheses of natural products.

The stable alkyne-cobalt complexes can be prepared from the reaction of the corresponding alkyne and dicobaltoctacarbonyl at ambient temperature. In this thesis we used the major fabulous properties of the stable alkyne-cobalt complexes such as easy generation, stabilization of the propargyl cation, and its bulkiness.

Highly stereocontrolled total synthesis of (+)-bengamide E.

Bengamides have been isolated from a Choristid sponge collected in Fiji Islands. The biological screening showed that they possess significant anti-infectious, antiparasitic, and antimicrobial activity. At the outset, commercially available diisopropyl D-tartrate **1** was converted to the monosilyl-protected alcohol **2**. Swern oxidation of **2** followed by Corey and Fuchs' dibromoolefination produced the olefin **3**. Transformation of the dibromoolefin moiety into a triple bond was realized by treatment of **3** with *n*-BuLi to give the acetylene derivative **4** (Scheme 1). The next step required for our synthesis was the introduction of an isopropyl group at the triple bond terminus of **4**. The acetylide anion of **4** was generated with *n*-BuLi and subsequently trapped with acetone to furnish **5**. The hexacarbonyldicobalt complexation of the triple bond in **5** followed by reductive deoxygenation proceeded effectively to yield the deoxygenated product **6**



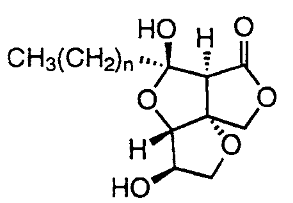
Bengamide E (**10**)

Scheme 1

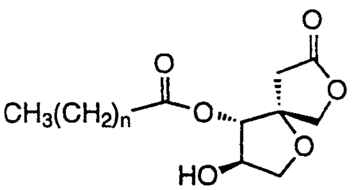
The presence of a bulky hexacarbonyldicobalt-complexed triple bond would differentiate between the two oxygen functionality at the C-2 and C-3 positions of **7** during the next aldol condensation. This differentiation would favor the five-membered ring transition state with the α-oxygen functionality over that of the six-membered ring transition state with the β-oxygen functionality. On the basis of these considerations, **6** was desilylated to afford the alcohol which was oxidized under Swern conditions to produce the corresponding aldehyde **7**. Aldehyde **7** was subsequently exposed to the aldol conditions using *O,S*-acetal **8** leading to the exclusive formation of the cobalt-complexed aldol product **9**. It should be mentioned that no diastereoisomers could be detected in the reaction mixture. Complete stereocontrol was realized by using the cobalt-complexed aldehyde. The intermediate **9** was then easily converted to bengamide E (**10**). The synthetic (+)-bengamide E was identified with an authentic specimen by comparison of the NMR and IR spectra.

First total synthesis of (+)-secosyrins 1 and 2 in a highly stereoselective manner and total synthesis of (+)-syributins 1 and 2.

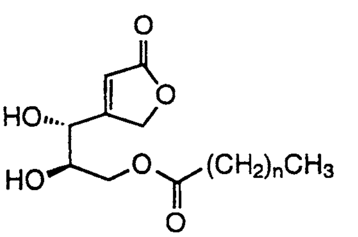
In 1993, syringolides 1 and 2 (**11** and **12**, respectively), novel nonproteinaceous low molecular weight metabolites, have been isolated from *Pseudomonas syringae* pv. *tomato*. Two years later since the first report on isolation of syringolides 1 and 2, Sims and co-workers isolated four structurally related compounds secosyrins 1 and 2 (**13** and **14**, respectively), and syributins 1 and 2 (**15** and **16**, respectively) from the same medium (Figure 1).



Syringolide 1 n = 4 (**11**)
Syringolide 2 n = 6 (**12**)



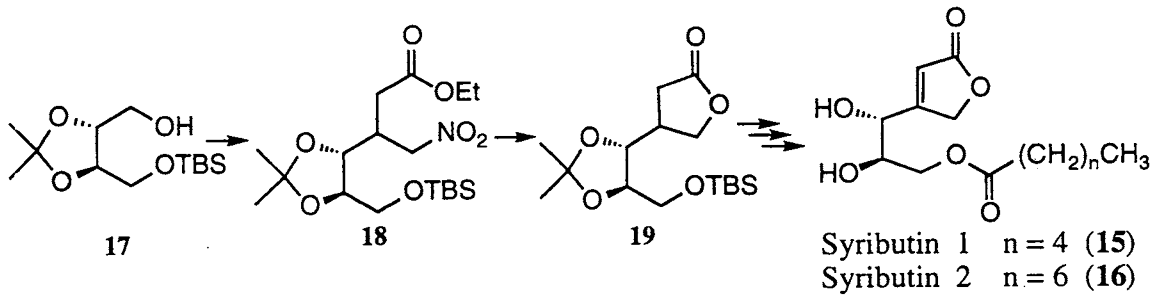
Secosyrin 1 n = 4 (**13**)
Secosyrin 2 n = 6 (**14**)



Syributin 1 n = 4 (**15**)
Syributin 2 n = 6 (**16**)

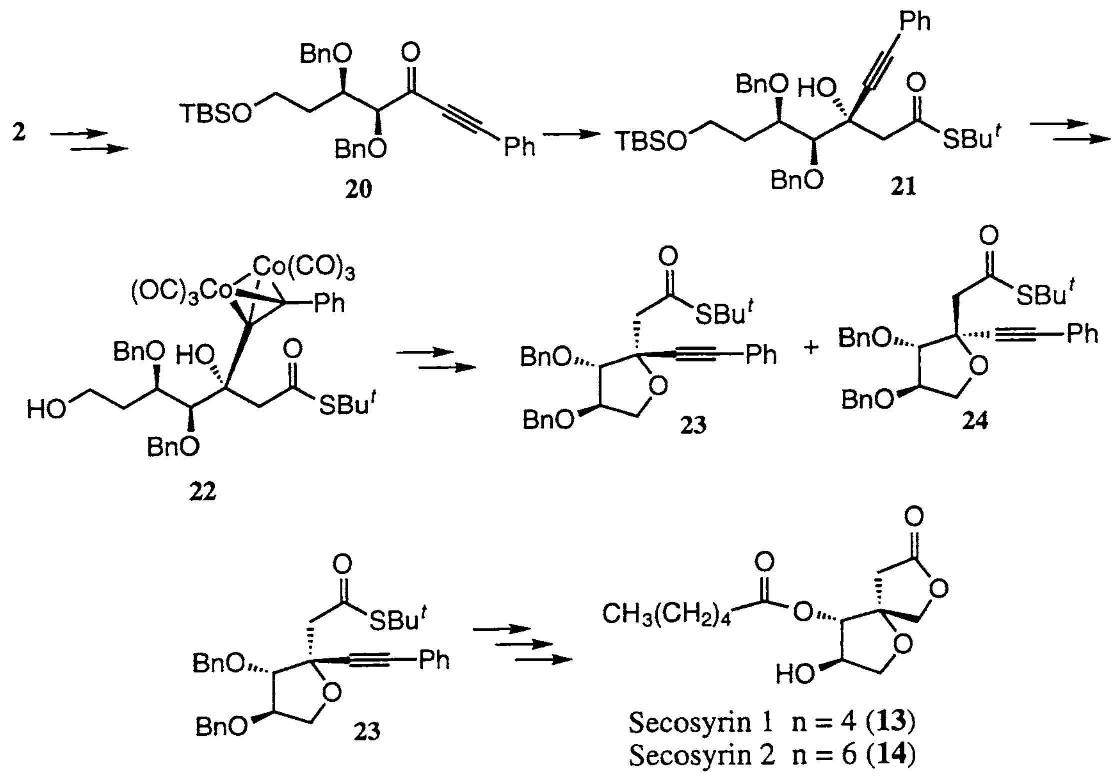
Figure 1

As our point of departure, the known acetonide **17** derived from D-tartaric acid was converted to the nitro compound **18** in a highly efficient manner. Treatment of **18** with $KOH/KMnO_4$ and $NaBH_4$ effected conversion of nitromethyl group into aldehyde functionality, reduction, and spontaneous lactone formation to provide the γ-lactone derivative (+)-**19** in 72% yield. Compound **19** was then transformed to **15** and **16** efficiently. Synthetic syributins 1 and 2 were identified with corresponding natural ones by comparison of ^{1}H NMR spectra.



Scheme 2

Several efforts to convert the simplest monocyclic butenolide derivatives into the corresponding more complex bicyclic spiro derivatives according to the retrobiosynthetic pathway were attempted, but no spiro derivative could be detected. Therefore, we devised an alternative synthetic pathway for spiro derivatives, secosyrins 1 (**13**) and 2 (**14**).



Scheme 3

After transforming the alcohol **2** to the ketone **20**, stereoselective introduction of C_2-unit was realized by treatment of **20** with lithium enolate, derived from *tert*-butyl thioacetate, to provide **21** as a sole product. Configuration of the newly generated quaternary carbon center of **21** was established as depicted in Scheme 3, thereby **21** was shown to have undesired stereochemistry at the quaternary carbon center. To invert this stereocenter, **21** was subjected to desilylation followed by dicobalthexacarbonyl complexation to provide **22**. Exposure of **22** to $BF_3 \cdot Et_2O$ in CH_2Cl_2 at room temperature effected ring closure with inversion of configuration at the quaternary center to provide tetrahydrofuran derivatives with cobalt complex, which were demetallated by treatment with CAN to afford the desired **23** in 74% yield together with the undesired **24** in 15% yield. The compound **23** was efficiently converted to secosyrins 1 and 2. Synthetic secosyrins 1 and 2 were identified with the corresponding natural ones by comparison of their spectral data.

Conclusion

In this thesis we accomplished a highly stereocontrolled total synthesis of (+)-bengamide E starting from diisopropyl D-tartrate. We have also succeeded in not only first total synthesis of (+)-secosyrins 1 and 2, but also total synthesis of (+)-syributins 1 and 2. Our first stereoselective total synthesis established unambiguously the stereochemistry of secosyrins 1 and 2 to be (+)-(3*R*,4*S*,5*R*)-4-hexanoyloxy-3-hydroxy-1,7-dioxaspiro[4.4]nonan-8-one and (+)-(3*R*,4*S*,5*R*)-4-octanoyloxy-3-hydroxy-1,7-dioxaspiro[4.4]nonan-8-one, respectively.

The procedure developed for the total synthesis of secosyrins and syributins will provide a good chance to screen their accurate biological activity as well as examining their structure activity relationship.

学位論文審査結果の要旨

安価な天然資源を活用し，より複雑な生理活性物質への効率のよい変換法を開拓することは有機合成化学における重要な課題の1つである。申請者は市販品として両鏡像体共安価に入手可能な酒石酸に着目し，特にD-酒石酸の2つの不斉炭素を利用した天然物の合成研究を行い，以下の成果を得た。

1）D-酒石酸ジイソプロピル(**1**)を出発原料とし，数工程を経てアルキン末端にヒドロキシイソプロピルを有する化合物(**2**)とした。**2**を対応するアルキン－コバルト錯体とし，錯体の特性を活用して目的の脱ヒドロキシル体(**3**)へ導いた。

2）上記で合成した**3**の化学修飾により誘導したアルキン－アルデヒド体を一旦，アルキン－コバルト錯体として嵩高くし，α位の酸素官能基を活用したキレーションコントロール条件下，*O,S*-acetal(**4**)とのアルドール反応を行い，bengamide類に共通する炭素10個からなる側鎖を高立体選択的に合成した。

3）高立体選択的アルドール反応により得られた側鎖とα-アミノカプロラクタムとの縮合反応を行い，(+)-bengamideEの高立体選択的全合成を完成させた。

4）D-酒石酸ジイソプロピル(**1**)からα，β-不飽和エステル体を合成後，ニトロメタンとのMichael型付加反応，引き続くNef型反応，環化反応によりγ－ラクトン体(**5**)に誘導した。**5**の官能基変換により，(+)-syributin 1と（+)-syributin 2の全合成を完成させた。

5）D-酒石酸ジイソプロピル(**1**)から数工程でケトーアルキン誘導体とした後，チオ酢酸エステルとのアルドール反応を行い，目的と反対の立体配置を有する付加体(**6**)を一方的に得た。**6**の3級水酸基を利用して環化反応を行い，(+)-5-epi-secosyrin 1の高立体選択的合成を行った。

6）**6**を対応するコバルト錯体とした後，ルイス酸の存在下環化反応を行い，立体の反転を伴ったテトラヒドロフラン構築を進行させることに成功した。この化合物から5)の手法に従って，(+)-secosyrin 1及び（+)-secosyrin 2の最初の全合成を達成した。

以上の成果は，D-酒石酸ジイソプロピル(**1**)を出発原料とし，アルキン－コバルト錯体の特性並びにアルキン類が他の官能基の前駆体と成り得る事実を巧みに活用して，光学活性天然物を高立体選択的に合成したもので，安価な光学活性天然資源を利用し，より複雑な生理活性物質へ効率よく変換する手法を例示したものである。申請者が開発した上記の手法は，更に多くの生理活性化合物合成への応用が可能と考えられることから，有機合成化学におけるその有用性は高い。よって，本論文は博士（薬学）論文に値するものと判定した。