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Perla Ramesh, Yarram Narasimha Reddy

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Graphical Abstract

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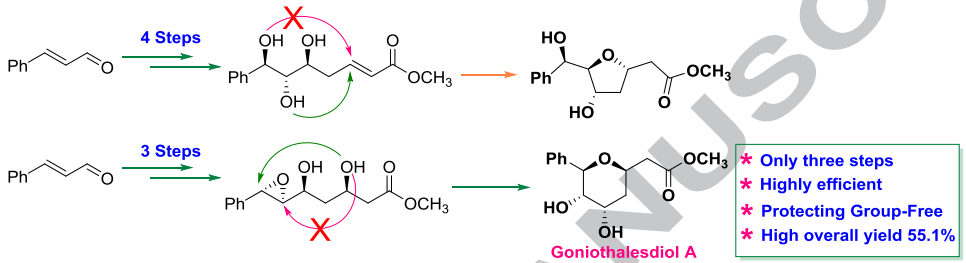

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A three-step total synthesis of goniothalesdiol A using a one-pot Sharpless epoxidation/regioselective epoxide ring-opening

Perla Ramesh* and Yarram Narasimha Reddy*

Natural Products Chemistry Division, Indian Institute of Chemical Technology, Uppal Road, Hyderabad-500007, India

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ABSTRACT

Using a one-pot Sharpless asymmetric epoxidation/regioselective epoxide ring-opening as a key step, the protecting-group-free total synthesis of goniothalesdiol A was accomplished in only three steps starting from commercially available *trans*-cinnamaldehyde in 55.1% overall yield. In 6 previously reported total syntheses, 6-11 steps were required.

1. Introduction

The tetrahydropyran backbone is a ubiquitous heterocyclic unit found in numerous bioactive natural products and pharmaceutically active compounds. Studies on natural products isolated from several species of the genus *Goniothalamus* have led to the discovery of various secondary metabolites including acetogenins, styryllactones, alkaloids, and flavonoids with interesting biological properties, such as pesticidal, teratogenic and cytotoxic.[1] Goniothalesdiol A (**1**) (Figure 1), a new natural 3,4-dihydroxy 2,6-disubstituted tetrahydropyran derivative, was isolated in 2006 from the stem of a southern Taiwan tree *Goniothalamus amuyon* by Wu and co-workers. The gross structure and relative stereochemistry of **1** were assigned on the basis of

^{1}H NMR, ^{13}C NMR and HRMS experiments, and the absolute configuration was confirmed by biosynthesis.[2]

To date, there have been six reports describing elegant synthetic efforts toward this natural product. In 2009, Yadav et al.[3] reported the first total synthesis of goniothalesdiol A (**1**) from homopropargyl alcohol in 11 steps with 35.1% overall yield by employing a Sharpless kinetic resolution and intramolecular oxa-Michael addition for the construction of the pyran ring. More recently, the same author has reported the synthesis of **1** that proceeded in nine steps using an intramolecular oxa-Michael reaction as a key step.[4] Fadnavis et al.[5] achieved the asymmetric synthesis of **1** from (*R*)-2,3-*O*-cyclohexylidine glyceraldehyde in 11 steps with an overall yield of 22%. Protecting-group-free total ~~synthesis~~ of **1** was accomplished by She et al. in six steps with 30% overall yield.[6] Recently, Sabitha and co-workers[7] reported the application of the Tandem α-aminoxylation–allylation reaction, resulting in the concise synthesis of **1**. Quite recently,[8] Rakeshwar has described the last synthesis of **1** in six steps with 31% overall yield, starting from the commercially available 2-deoxy-D-ribose. Most of these syntheses rely on the use of protecting groups and as a consequence are lengthy sequences. As part of our ongoing projects focused on improving the efficiency of natural products synthesis,[9] herein we describe the asymmetric total synthesis of goniothalesdiol A (**1**) by a unified strategy that requires no use of protecting groups.

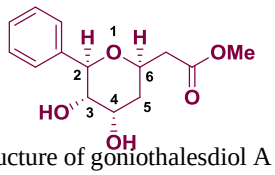


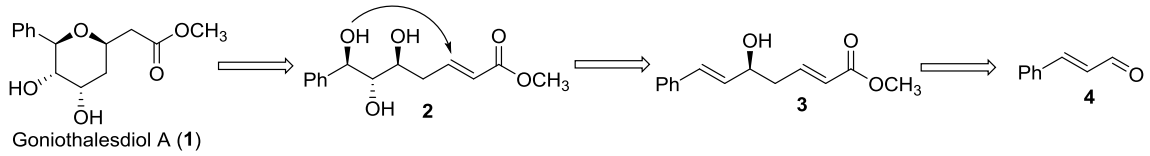
Figure 1. The structure of goniothalesdiol A (**1**).

2. Results and discussion

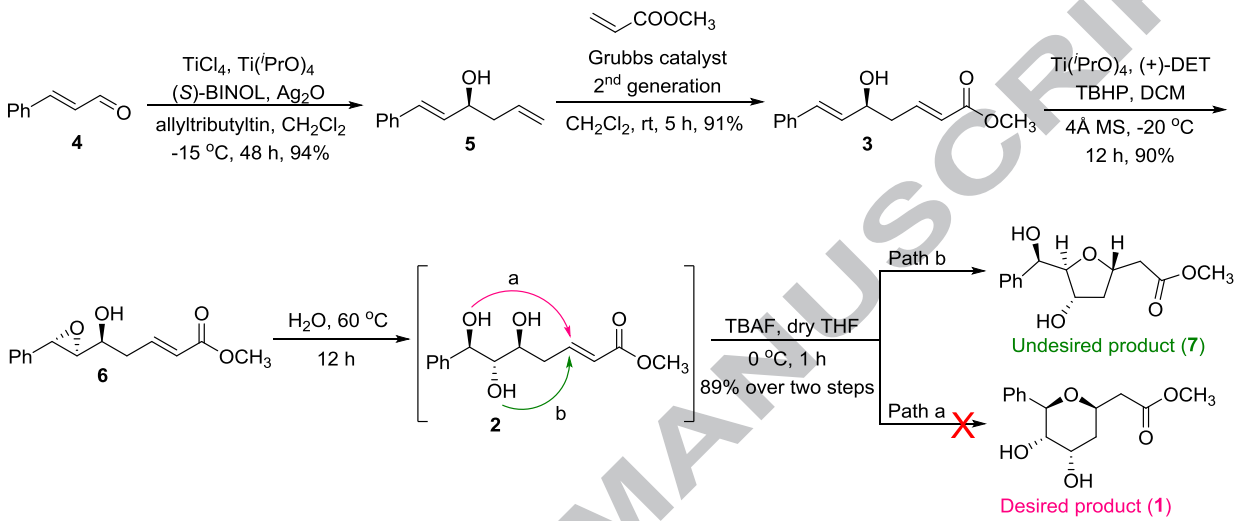
Our first retrosynthetic analysis for the synthesis of **1** is shown in Scheme 1. Goniothalesdiol A (**1**) would be obtained from triol **2** through an intramolecular oxa-Michael addition of the hydroxyl group present at the active benzylic position. Triol **2** would be built by using a Sharpless asymmetric epoxidation applied to compound **3**, followed by a regioselective epoxide ring opening with water to control the stereogenic centers at C2 and C3. Finally, the α,β-unsaturated ester **3** would be synthesized

* Corresponding authors. Tel.: +91-40-27191631; fax: +91-40-27160512; e-mails: perlaramesh@yahoo.co.in (P. Ramesh); nyarram20@gmail.com (Y. Narasimha Reddy)

from commercially available *trans*-cinnamaldehyde **4** using an asymmetric allylation followed by an olefin cross-metathesis.



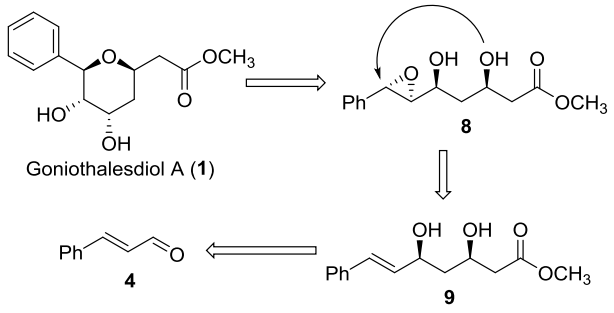
Scheme1. First retrosynthetic analysis to goniothalesdiol A (**1**).



Scheme 2. End-game: first attempt.

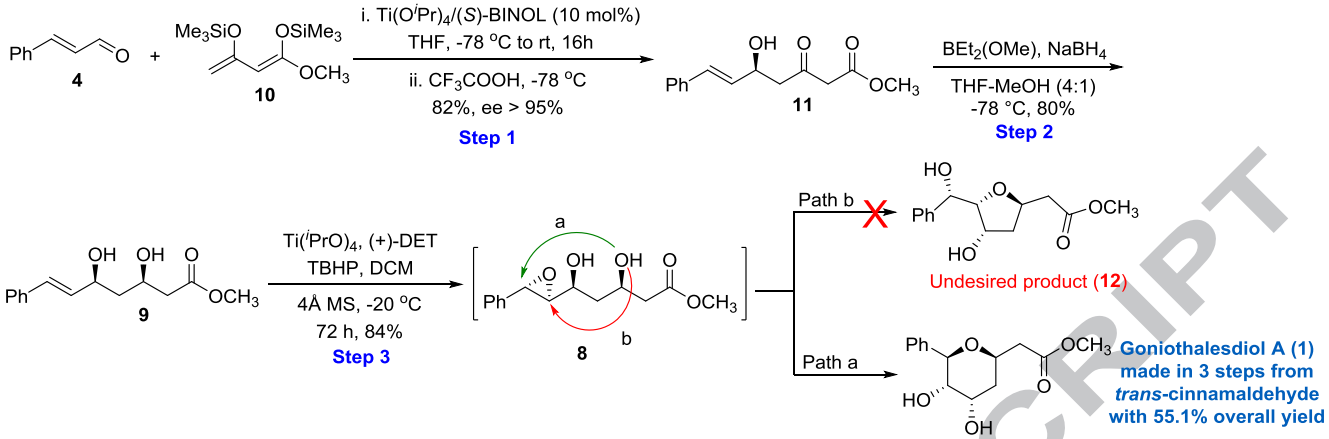
The synthesis of goniothalesdiol A (**1**) started with the known homoallylic alcohol **5**,[9d,e] which is readily available in high enantiomeric excess from (*E*)-cinnamaldehyde by an asymmetric allylation. Chemoselective olefin cross-metathesis (OCM)[10] of compound **5** with methyl acrylate in the presence of second-generation Grubbs catalyst provided the desired (*E*)-α,β-unsaturated ester **3** in 91% yield as a single stereoisomer (judged by ^{1}H NMR analysis). Sharpless asymmetric epoxidation[11] of allylic alcohol **3** using (+)-diethyl tartrate as a chiral ligand proceeded efficiently to produce epoxy alcohol **6** in 90% yield. Regioselective epoxide ring opening of epoxy alcohol **6** using hot water under the catalyst-free condition at 60 °C provided triol **2**,[12,9e] which was then subjected to intramolecular oxa-Michael addition using the acid catalyst. At this stage, we anticipated that a desired THP product **1** would be obtained from triol **2** through an intramolecular 1,4-addition of the hydroxyl group present at the active benzylic position on the unsaturated ester. Unfortunately, when compound **2** was treated with TBAF in dry THF at 0 °C, an excellent yield in the unexpected intramolecular 1,4-addition product *trans*-THF **7** was obtained with 97:3 diastereomeric ratio.[13] The 2,5-*trans* configuration of the tetrahydrofuran ring in undesired product **2** was confirmed by NOE data (Scheme 2).

Due to the first strategy failure, a second strategy was then envisaged, utilizing asymmetric reactions in order to reduce the number of steps. In this strategy (Scheme 3), the required *cis*-THP **1** would be achieved from **8** by using an intramolecular regioselective epoxide ring opening at the active benzylic position. Compound **8** would be emerged from **9** by a Sharpless asymmetric epoxidation, while **9** would be derived from commercially available *trans*-cinnamaldehyde by the successful implementation of asymmetric aldol addition followed by 1,3-*syn* reduction.



Scheme 3. Second retrosynthetic analysis for **1**.

As delineated in scheme 4, the synthesis of **1** commenced with methyl(*S*,*E*)-5-hydroxy-3-oxo-7-phenylhept-6-enoate (**11**), which is a known intermediate easily available from *trans*-cinnamaldehyde by an asymmetric Mukaiyama aldol reaction.[14] As we reported previously,[14a] the stereoselective *syn* reduction of **11** under Narasaka's conditions[15] using $Et_2BOMe/NaBH_4$ in THF-MeOH (4:1) at −78 °C gave *syn*-diol **9**, which was then subjected to Sharpless asymmetric epoxidation using (+)-diethyl tartrate as a chiral ligand. Surprisingly, under Sharpless conditions, asymmetric epoxidation (formation of **8**) and concomitant cyclization *via* intramolecular regioselective epoxide ring opening proceeded smoothly to form a tetrahydropyran ring, and the desired *cis*-THP product (**1**) was obtained in 84% yield for a single step. Goniothalesdiol A (**1**) was identical in all respect with the spectral data (^{1}H NMR, ^{13}C NMR and HRMS) and the specific rotation reported previously.[2-8] It is noteworthy that this three-step synthesis of **1** compares well with those reported in the literature that ranges in length from 6 to 11 steps.



Scheme 4. Synthesis of goniothalesdiol A (**1**).

3. Conclusions

In summary, two approaches of the goniothalesdiol A (**1**) were examined. One of them failed in the formation of the *cis*-THP ring, utilizing an intramolecular oxa-Michael addition of active benzylic hydroxyl group on an unsaturated ester. On the contrary, the second approach allowed us to minimize the number of steps by using a one-pot Sharpless epoxidation/regioselective epoxide ring-opening strategy. This highly concise synthesis relied on the use of a key one-pot Sharpless epoxidation/regioselective epoxide ring-opening reaction to rapidly construct the unique six-membered *cis*-tetrahydropyran ring and two continuous stereocenters in a single step. In contrast to previous approaches,[2-8] this protocol is atom economical, step-economical and devoid of any protecting group manipulations. Our route to goniothalesdiol A (**1**) is significantly shorter than the previous approaches, requiring only three steps instead of 6-11 steps.

Acknowledgments

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Supplementary Material

^{1}H and ^{13}C spectra of all compounds have been provided in a separate electronic file as a supplementary data.

Highlights:

- The protecting-group-free total synthesis of goniothalesdiol A is described.
- Only three steps starting from *trans*-cinnamaldehyde in 55.1% overall yield.
- A one-pot Sharpless epoxidation/regioselective epoxide opening is a key step.
- Atom economical, step-economical and devoid of protecting group manipulations.