Tetrahedron 72 (2016) 7135–7142

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chiral approach to total synthesis of phytotoxic and related nonenolides: (*Z*)-isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone, herbarumin-III and their C-9 epimers☆

Lingaiah Maram, Raghavendar Reddy Parigi, Biswanath Das *

Natural Products Chemistry Division, CSIR – Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 14 June 2016
Received in revised form 20 September 2016
Accepted 22 September 2016
Available online 22 September 2016

Keywords:
Nonenolides
Phytotoxic activity
Total synthesis
(*Z*)-Isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone
Herbarumin-III
C-9 epimers
Stereoselective synthesis
Mosher's method
Yamaguchi esterification
Ring closing metathesis

ABSTRACT

A new and efficient strategy has been developed for the stereoselective total synthesis of nonenolides: (*Z*)-isomer of (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone, herbarumin-III and their C-9 epimers starting from D (−) ribose. The synthesis includes the coupling of the alcohol and acid fragments of the molecules, employing Yamaguchi esterification protocol followed by intramolecular ring closure metathesis. The method has efficiently constructed the 10-membered lactone skeleton of the compounds with proper stereogenic centers containing appropriate functionalities.

1. Introduction

Natural nonenolides are 10-membered lactonic compounds with interesting structural features and important pharmacological activities. They have been discovered as the common chemical constituents of several fungi.[1] These compounds are found to contain various functionalities in different stereoconfigurations and to exhibit impressive biological properties such as anticancer, antifungal, antimalarial, antibacterial and phytotoxic activities.[2] The term phytotoxicity refers to the toxic effect of compounds on plant growth and the nonenolides with phytotoxic activity have been isolated from various sources.[3]

The novel phytotoxic nonenolide, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone (**1**) (Fig. 1) was obtained from solid cultures of the endophytic fungus *Phomopsis* sp. HCCB03520, together with three known compounds.[4] The compound **1** showed activity on germination and radicle growth of *Medicago sativa*, *Trifolium hybridum*, and *Buchloe dactyloides*. The IC_{50} values of **1** on germination of *M. sativa*, *T. hybridum*, and *B. dactyloides* were 15.8, 24.2, and 31.2 μg/ml, and for radicle growth of these plants were 31.9, 63.3, 130.9 μg/ml, respectively, and the compound is less active then positive control [2-(2, 4-dichlorophenoxy) acetic acid (IC_{50}: 1.5, 1.6, and 1.2 μg/ml for germination, and 3.7, 7.4, 1.5 μg/ml for radicle growth)]. Earlier the synthesis of the (*Z*)-isomer of (6*R*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone (**3**) was accomplished.[5] We have now planned for the synthesis of **1**, but we have achieved the synthesis of its *Z*-isomer **3** and also for the first time the synthesis of the C-9 epimer (**3a**) of **3** through a common route.

Another phytotoxic nonenolide, namely (7*R*,9*R*)-7-hydroxy-9-propyl-5-nonen-9-olide which was designated with the trivial name herbarumin-III (**2**) (Fig. 1) was isolated from reinvestigation of the fermentation broth and mycelium of the fungus *Phoma herbarum*.[6] The compound **2** interacted with bovine-brain calmodulin and inhibited the activation of the calmodulin dependent enzyme cAMP phosphodiesterase. It showed relevant phytotoxic effects (IC_{50}: 2×10^{-5} M) and inhibited radicle growth with higher potency than 2, 2-dichlorophenoxyacetic acid (IC_{50}: 2×10^{-4} M),

☆ Part 87 in the series, 'Synthetic studies on natural products'.

* Corresponding author. Fax: +91 40 27193198; e-mail address: biswanathdas@yahoo.com (B. Das).

http://dx.doi.org/10.1016/j.tet.2016.09.052
0040-4020/

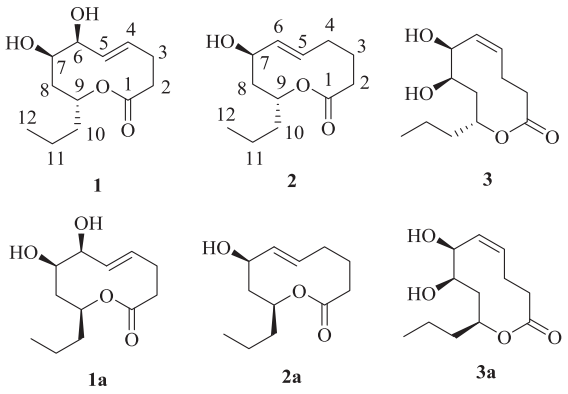
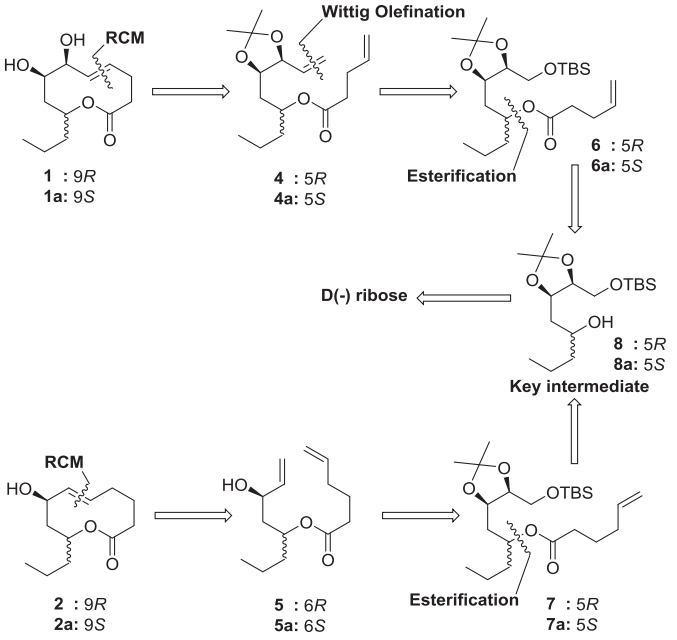


Fig. 1. Structures of phytotoxic nonenolides and their C-9 epimers.

used as positive control. Some syntheses of the herbarumin-III have been achieved but our approach is effective and different from earlier reports.[7] However, for the first time we have accomplished the synthesis of C-9 epimer (**2a**) of herbarumin-III (**2**).

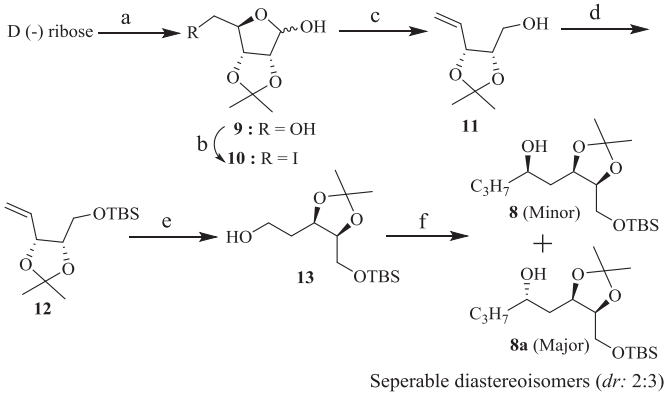
2. Results and discussions

In continuation of our work[8] on the stereoselective construction of bioactive natural products we have realized that **1**, **2** and their C-9 epimers **1a**, **2a** can be synthesized from the dienes **4**, **5** and **4a**, **5a**, respectively (Scheme 1). The dienes **4**, **4a** and **5**, **5a** in turn, can be prepared from the esters **6**, **6a** and **7**, **7a** while the esters **6**, **6a** and **7**, **7a** from the diastereoisomeric alcohols **8** and **8a**. Both the alcohols **8**, **8a** can be generated from the D (−) ribose which is commercially available.



Scheme 1. Retrosynthesis of **1**, **2** and their C-9 epimers **1a** and **2a**.

The present synthesis was initiated by converting D (−) ribose (Scheme 2) into the iodo compound **10** via the formation of the primary alcohol **9** following reported methods.[9] The iodo compound **10** was reacted with Zn and AcOH (cat.) in MeOH under reflux to generate the olefinic aldehyde, which was not isolated but simultaneously reacted with $NaBH_4$ in MeOH to afford the alcohol **11**.[10] The hydroxyl group in **11** was protected as TBS to afford the **12**. The TBS ether **12** on treatment with $(c\text{-Hex})_2BH$[11] in THF followed by oxidation with H_2O_2/NaOH afforded the alcohol **13**. The alcohol **13** was oxidized with $SO_3\cdot Py$[12] to generate the corresponding aldehyde and the crude aldehyde was immediately treated with the Grignard reagent, C_3H_7MgBr to produce the diastereoisomeric alcohols **8** and **8a** (*dr*: *2*:*3*). Both the alcohols were separated by column chromatography and utilized for subsequent steps.



Scheme 2. Synthesis of alcohol **8** and its diastereomer **8a**.
Reagents and conditions: (a) acetone, Cat. H_2SO_4, rt, 4 h, 96%; (b) Ph_3P, Iodine, Imidazole, toluene, reflux, 2 h, 94%; (c) Zn, MeOH, AcOH (cat.), reflux, 2 h then $NaBH_4$, MeOH, 0 °C-rt, 4 h, 86% (for two steps); (d) TBS-Cl, imidazole, CH_2Cl_2, 0 °C-rt, 2 h, 96%; (e) $(c\text{-Hex})_2BH$, THF, 0 °C-rt, 2 h, then 30% aq H_2O_2, 20% aq NaOH, 0 °C-rt, 8 h, 84%; (f) SO_3.Py, CH_2Cl_2, DMSO (3:1), Et_3N, 0 °C, 1 h then C_3H_7MgBr in THF, THF, 0 °C-rt, 4 h, 96% (for two steps).

The absolute stereochemistry of the newly generated stereogenic center in compound **8a** bearing the hydroxyl group was determined by preparing the *S* and *R*-MTPA (α-Methoxy-α-trifluoromethylphenyl acetic acid) esters by a modified Mosher's method[13] and found to have (*S*)-configuration at C-5 (Fig. 2). The negative chemical shift difference to the left side of the MTPA plane and the positive chemical shift differences to the right side of the MTPA plane indicated that the hydroxyl stereochemistry has (*S*)-configuration (Fig. 2). Consequently, the stereochemistry of the same group in **8** is of *R*-configuration. These configurations of both **8** and **8a** were further confirmed by their subsequent transformations by coupling with the acid fragments into the target molecules.

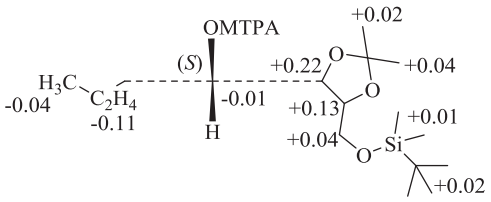


Fig. 2. Determination of absolute configuration and $\Delta\delta$ values for the (*S*) and (*R*)-MTPA ester derivatives of **8a** ($\Delta\delta=\delta_S-\delta_R$).

After successful achievement of the diastereomeric alcohols **8** and **8a**, they were individually esterified with 4-pentenoic acid under Yamaguchi esterification protocol[14] to afford the esters **6** and **6a** (Scheme 3). The TBS ether group of esters **6** and **6a** was separately cleaved with TBAF to form the alcohols **14** and **14a**, respectively. The alcohols **14** and **14a** were oxidized with $SO_3\cdot Py$[12] and the generated corresponding aldehydes were subjected to C-1 Wittig olefination with Ph_3PCH_3Br in the presence of NaHMDS to yield the dienes **4** and **4a** required for the synthesis of the nonenolide **1**. The dienes **4** and **4a** were individually, subjected to intramolecular ring closing metathesis using Grubbs' II-generation