Tetrahedron 72 (2016) 6634–6639

Contents lists available at ScienceDirect

Tetrahedron

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

Enantioselective synthesis of the tricyclic core of (+)-strigol

Aiko Takahashi, Yusuke Ogura, Masaru Enomoto, Shigefumi Kuwahara *

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

ARTICLE INFO

Article history:
Received 30 July 2016
Received in revised form 25 August 2016
Accepted 29 August 2016
Available online 31 August 2016

Keywords:
Strigol
Strigolactone
Plant hormone
Epoxide
Total synthesis

ABSTRACT

An enantioselective synthesis of the tricyclic core structure of (+)-strigol, a potent seed germination stimulant for root parasitic weeds, has been achieved from 2-iodo-4,4-dimethyl-2-cyclohexen-1-one in 14 steps. The key steps include a CBS reduction of an iodo enone to obtain a cyclohexenol derivative of high enantiomeric excess, regioselective epoxide ring opening with a Grignard reagent in a low-polarity solvent, highly diastereoselective addition of vinyllithium to a ketone, and Lewis acid-promoted installation an acetate unit onto a bicyclic allylic acetate intermediate.

1. Introduction

(+)-Strigol (**1**) is the first member of the strigolactone family of natural products discovered in 1966 as a potent seed germination stimulant for the root parasitic weed *Striga lutea* (*syn. Striga asiatica*) which causes significant damage to crops of gramineous and leguminous plants mainly in the tropical and subtropical areas of Africa and Asia (Fig. 1).[1,2] It was originally isolated from the root exudates of cotton (a non-host plant for the weed),[1a] and later from those of its genuine hosts of economical importance (maize, proso millet, and sorghum).[3] Strigolactones are now known to be produced also by a wide range of plants other than host plants for parasitic weeds and consist of 15 members.[4] This family of natural products are structurally characterized by a fused tricyclic γ-lactone core (ABC scaffold) connected through an enol ether linkage to an α,β-unsaturated γ-lactone unit (D ring). They all have the same C/D ring structure as **1**, while their A/B ring portions show some structural diversity.[4] Besides the seed germination stimulatory activity toward parasitic weeds,[5] strigolactones have been elucidated to possess some additional functions of enormous biological importance, especially: (1) induction of hyphal branching in arbuscular mycorrhizal fungi that enables the fungi to establish their symbiosis with plants;[6] and (2) activity as a plant hormone to suppress the growth of preformed axillary shoot buds and thereby inhibit shoot branching.[7] These plant physiologically and agriculturally important functions of strigolactones prompted a great deal of studies from various aspects such as isolation of new members, mode of action, biosynthesis, and identification of receptor.[4,8]

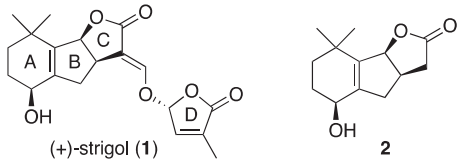


Fig. 1. Structures of (+)-strigol (**1**) and its tricyclic core (**2**).

Synthetic studies on strigolactones and their analogs for structure–activity relationship investigations have also been actively conducted by many research groups and numerous publications have appeared since the first total synthesis of (±)-strigol by Sih and co-workers in 1974[9–11] As for the synthesis of optically active forms of naturally occurring strigolactones, four types of synthetic strategies have been adopted with the exception of direct resolution of their synthetic racemates: (1) preparation of an optically active ABC scaffold via optical resolution (including enzymatic or chiral HPLC separation) and its non-diastereoselective connection to a racemic D ring unit followed by chromatographic separation of the resulting diastereomeric mixture;[12] (2) preparation of an optically active ABC scaffold from the chiral pool followed by the same

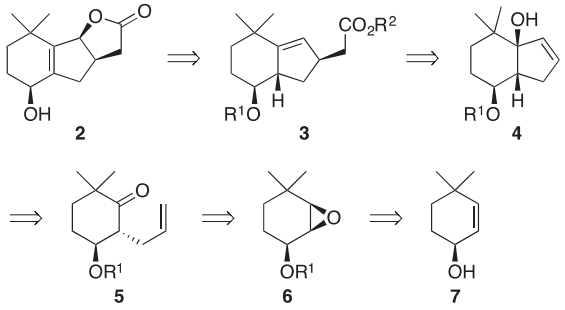
* Corresponding author. Fax: +81 22 717 8783; e-mail address: skuwahar@biochem.tohoku.ac.jp (S. Kuwahara).

http://dx.doi.org/10.1016/j.tet.2016.08.078
0040-4020/

sequence as described in (1);[13] (3) preparation of a racemic ABC scaffold and its connection to an optically active D ring unit followed by chromatographic separation of the resulting diastereomeric mixture;[14] and (4) asymmetric synthesis of an ABC scaffold and its connection to a racemic D ring unit followed by diastereomeric separation.[15] However, the strategy composed of asymmetric synthesis of an ABC scaffold and its diastereoselective unification with a D ring moiety has never been reported so far. As part of our efforts toward such a totally stereoselective synthesis of strigolactones, we describe herein a synthetic approach to the tricyclic ABC core (**2**) of (+)-strigol. To the best of our knowledge, this is the first example of the synthesis of **2** that uses neither optical resolution nor naturally occurring chiral starting materials.[12a–c,13a]

2. Results and discussion

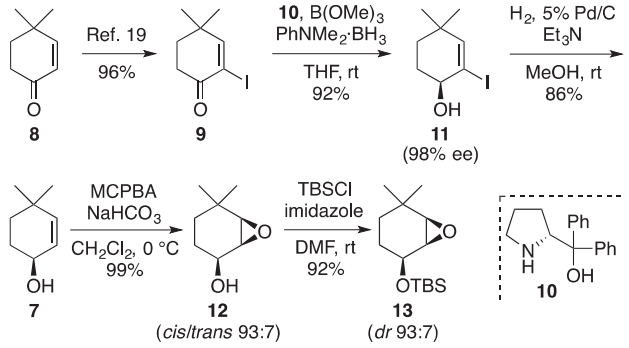
Scheme 1 outlines our retrosynthetic analysis of **2**. Compound **2** was traced back to olefinic carboxylate **3** with the intention of installing the γ-lactone and the double bond in **2** by halolactonization of **3** and subsequent dehydrohalogenation. The γ,δ-unsaturated carboxylate **3** would be obtainable by S_N2'-type introduction of an acetate unit into **4**. For the construction of the bicyclic allylic alcohol **4**, we envisaged a two-step sequence comprising the addition of a vinyl group to ketone **5** from its bottom face and ring-closing metathesis (RCM) of the resulting diene product. The ketone **5** would be prepared by regioselective ring opening of epoxide **6**, which in turn should be derived from optically active cyclohexenol derivative **7** by hydroxyl-directed epoxidation.



Scheme 1. Retrosynthetic analysis of **2**.

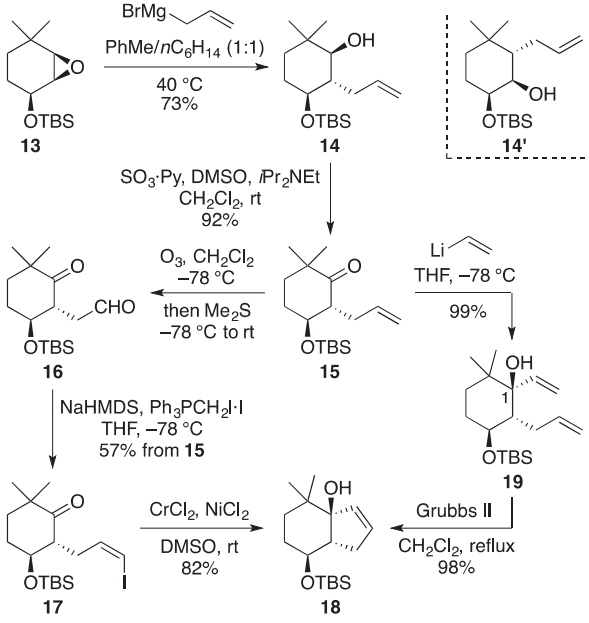
Our first task for the synthesis of **2** was the preparation of **7** in high enantiomeric purity (Scheme 2). Although compound **7** was known to be preparable by a Noyori asymmetric reduction of the corresponding enone, the enantiomeric excess (ee) of the alcoholic product **7** was reported to be only 47%.[16,17] We, therefore, adopted an alternative route via iodine-substituted cyclohexenol derivative **11**, the (*R*)-enantiomer of which had previously been synthesized in 98% ee by a modified Corey–Bakshi–Shibata (CBS) reduction using diethylaniline·BH_3 and a catalytic amount of (*S*)-2-methoxy-CBS-oxazaborolidine.[18] The reduction of **9** using (*R*)-2-methoxy-CBS oxazaborolidine as catalyst proceeded smoothly, providing **11** in 92% yield;[18c,19] the iodo enone **9** in turn was readily prepared from enone **8** almost quantitatively according to the literature (I_2, DMAP, K_2CO_3, THF–H_2O).[20] Hydrogenolytic removal of the iodine atom in **11** was best performed with 5% Pd/C in MeOH in the presence of Et_3N as catalyst poison,[21] furnishing **7** in a satisfactory overall yield of 76% from **8**. Diastereoselective epoxidation of **12** with MCPBA in the presence of solid $NaHCO_3$ afforded **12** as an inseparable 93:7 *cis*/*trans* mixture. Finally, protection of the alcohol as its TBS ether provided **13**.

With the protected *cis*-epoxy alcohol **13** in hand, we next proceeded to its epoxide ring opening with allylmagnesium bromide (Scheme 3). Although the epoxide **13**, upon exposure to



Scheme 2. Enantioselective preparation of **7** and its conversion into siloxy epoxide **13**.

allylmagnesium bromide in refluxing ether,[22] gave a 1.1:1 mixture of **14** and its regioisomer **14′**,[23] changing the solvent from ether to toluene/hexane (1:1) significantly increased the ratio to 3.2:1, providing the desired isomer **14** in 73% isolated yield.[24,25] To obtain bicyclic intermediate **18**, the alcohol **14** was first oxidized to olefinic ketone **15**, the ozonolysis of which afforded **16**. *Z*-Selective iodomethylenation of the aldehyde **16** followed by intramolecular Nozaki–Hiyama–Kishi coupling of the resulting iodo ketone **17** furnished **18**.[26,27] Compound **18** was also prepared much more efficiently in two steps from **15** by its exposure to vinyllithium in THF at −78 °C to form allylic alcohol **19** as the exclusive diastereomer and subsequent ring-closing metathesis of the diene product **19**.[28] It is worth mentioning that the reaction of **15** with vinylmagnesium chloride (instead of vinyllithium) in THF was very sluggish at low temperatures (−78 to −50 °C) presumably due to steric congestion around the ketone functionality, and a substantial amount of the corresponding epimeric alcohol (1-*epi*-**19**) was also produced when the reaction temperature was raised to room temperature.



Scheme 3. Preparation of bicyclic allylic alcohol **18**.

The installation of an acetate unit at the C2 position of **18** was first attempted by applying the Johnson–Claisen rearrangement to the cyclic allylic alcohol (Scheme 5, *a*). Treatment of **18** with triethyl or trimethyl orthoacetate in the presence of an acid catalyst (propionic acid, *p*-anisic acid, or *o*-nitrophenol) at high temperatures ranging from 135 to 180 °C, however, gave no desired product **20**,