The efficient synthesis of d-xylulose and formal synthesis of Syringolide 1

Sudhakar Kalagara
Gabriel Orozco
Shizue Mito

The University of Texas Rio Grande Valley
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Sudhakar Kalagara a, Gabriel Orozco a, and Shizue Mito a,b

a Department of Chemistry, the University of Texas at El Paso, El Paso, TX 79968, USA
b Department of Chemistry, the University of Texas Rio Grande Valley, Edinburg, TX 78539, USA

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ABSTRACT

Wittig reaction and asymmetric dihydroxylation were used as the key steps in the synthesis of D-xylulose, a commercially available but costly carbohydrate. The effects of protecting groups and reactions conditions on asymmetric dihydroxylation are demonstrated. Optically pure D-xylulose was obtained after 4–6 steps from readily available hydroxyacetone and ethylene glycol. The method also involves some other valuable intermediates along the synthesis. Those intermediates were applied in the formal synthesis of Syringolides. A key precursor butenolide to Syringolide 1, the first non-proteinaceous specific elicitors of plant hypersensitive response, was obtained after 3 steps from the intermediate (8–10 steps from hydroxyacetone and ethylene glycol).

1. Introduction

Syringolides 1 and 2 (1a and 1b, Scheme 1) were isolated from P. syringae pv. tomato in 1993 by Sims et al. as the first non-proteinaceous specific elicitors of plant hypersensitive response (HR).1 They also proposed the biosynthetic pathway of Syringolides 1 from D-xylulose 2 and the corresponding β-ketoacids 3 (Scheme 1).2 Accordingly, the acylation of D-xylulose produces the ester 4 which, upon an intramolecular Knoevenagel condensation yields butenolide 5. Intramolecular Michael addition followed by hemiketalization then affords Syringolides 1. There have been several reports for the total synthesis of Syringolides.3,4 Most of them through the butenolide intermediate 5 using various alcohol protecting groups.4

Scheme 1. Proposed biosynthesis of Syringolides: (a) acylation, (b) Knoevenagel condensation, (c) Michael addition followed by hemiketalization

Rickards et al. synthesized Syringolides with the correct stereocenters using the biomimetic pathway, which starts with D-xylulose.5 Although D-xylulose is commercially available, its high cost is a drawback of this approach. To circumvent such disadvantage, several groups have employed other chiral starting materials, in lieu of D-xylulose, as the source of asymmetry. Some of the precursors are L-threonol,4a D-tartrate,4b,c D-xylotaranose,4f D-xylene,5j and D-arabinose.4h,4k Chemoenzymatic aldol reaction has also been reported.9 However, D-xylulose is one of the rare ketoses and plays an important role in several prokaryotic and eukaryotic metabolic pathways. Therefore, the generation of D-xylulose is still of interests to organic chemists. Isomerization of D-xylene to D-xylulose has been accomplished enzymatically with various carbohydrate isomerases during the past two decades.2 The enzymatic route is an efficient C–C bond construction in the synthesis of xylulose, however, the enzymatic approaches have certain limitations in terms of substrate specificity and reaction conditions. Recently, isomerization with inorganic catalysts has been reported using Lewis acid catalysts as Sn-beta,6 CrCl3,7 Sn-MoMoF8 MgF210 and Al2O310 but low conversions are the problem. Although chemical synthesis of D-xylulose (as well as other carbohydrates) appears to be more challenging due to multiple hydroxyl groups and stereocenters in the molecule,11 it is beneficial to develop a new synthetic methodology to prepare D-xylulose. Herein we report the synthesis of D-xylulose via Wittig reaction and asymmetric dihydroxylation from the readily available ethylene glycol (6) and hydroxyacetone (8) (Scheme 2). The proposed strategy is straightforward, and the choice of protecting

Scheme 2. Strategy of the synthesis of D-xylulose

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groups is key to the success of this method. In addition, protected D-xylulose was applied in the formal synthesis of Syringolide 1 (1a).

2. Results and Discussion

2.1 Synthesis of D-xylulose 2

Scheme 3 shows the synthesis of the aldehydes 7 in Scheme 2. The monoprotection of ethylene glycol 6 with various protecting groups gave 12a–c in good yields (74–84%). Swern oxidation of the protected alcohols 12a–c yielded 7a–c in 76–88%.

**Scheme 3.**

![Chemical structure](image)

The α-bromo ketone 9 shown in Scheme 2 was synthesized from hydroxyacetone 8 by protection followed by bromination (Scheme 4). Protection of 8 with TBS was carried out to produce 13a in 74% yield. However, α-bromination of 13a using different brominating agents, such as NBS, Br2, and HBr, proved unsuccessful, despite the various reaction conditions studied. Acetylation of 8 was then carried out instead and gave 1-acetoxy-2-propanone 13b in 92% yield. α-Bromination of 13b afforded α-bromoketone 9b, which was used without further purification in the next step and gave the phosphonium bromide 14b in quantitative yield (2 steps).

**Scheme 4.**

![Chemical structure](image)

Wittig reaction12 between phosphonium salt 14b and several aldehydes (7a–c) yielded the enones (10a–c) in moderate to good yields (41–72%) along with the deprotected enone 15 (Scheme 5). Conversion of 10 to 15 were also possible under mild basic conditions using KHCO3.

**Scheme 5.**

![Chemical structure](image)

Dihydroxylation of enone 10b using OsO4 yielded 70% of 11b as a racemic mixture (Scheme 6). Asymmetric dihydroxylation of 10b using AD mix-beta was unsuccessful. A complex mixture of compounds was obtained with less than 50% of the enone reacted, even after extended protection time. We observed that both of the acetyl and TBS protecting groups in 10b were not stable under the reaction conditions.

**Scheme 6.**

![Chemical structure](image)

The α,β-unsaturated compound 15a and 15c, both without acetyl and TBS protecting groups, was thus chosen for an alternative synthesis (Scheme 7). Asymmetric dihydroxylation of 15a through the Sharpless reaction gave the desired protected D-xylulose 11a in 25% yield. The optical rotation of 11a matched with the previously reported value.13 Part of the starting material 15a (18%) could be recovered. In addition, aldehyde 7a was also isolated in 27% yield, possibly due to the retro-aldol reaction of 11a. When the α,β-unsaturated compound 15c (TIPS protected) was employed, the asymmetric dihydroxylation yielded 78% of 11c (Scheme 7).

**Scheme 7.**

![Chemical structure](image)

Debenzylation of 11a by hydrogenation gave D-xylulose 2 in 75% yield (Scheme 7). Similarly, the TIPS protected D-xylulose 11c was treated with aqueous HF in THF at room temperature, producing 2 in 60% yield. NMR data and optical rotation value of the product obtained from both pathways are in good agreement with those previously reported for D-xylulose.14

2.2. Toward the formal synthesis of Syringolide 1 (1a)

As mentioned above, there are several reports for the total synthesis of Syringolides 1,3,4 In many of these routes, the common intermediates are protected 4’ and/or 5’ (Scheme 1). We hypothesize that derivatives of 4 or 5 could be obtained from intermediate 15 in the newly developed synthesis of D-xylulose (Scheme 8). Accordingly, Meldrum’s adduct 16 was prepared from hexanoyl chloride and Meldrum’s acid.14 The tricarbonyl compound 17 was obtained in 75% yield when treating 15b with 16. Attempts in dihydroxylation of 17 using AD-mix-β reagent resulted in a complex mixture, possibly due to the lability of 17 under the reaction conditions. The enol of 17 is likely oxidized faster than the target C=C double, as reported previously.4c Furthermore, the TBS group was removed under the basic reaction conditions.

**Scheme 8.**

![Chemical structure](image)

When the TIPS protected alcohol 15c was used, selective esterification of 15c with Meldrum’s adduct 16 was not successful at high temperature, resulting in the formation of primary and secondary esters and a diester. The starting material 15c was fully recovered when the reaction was carried out at room temperature. To circumvent the complications described above, we turned to compound 11c. Selective vicinal diol protection was successfully carried out with 2,2-DMP15 resulting in the acetoned 19 in 74% yield (Scheme 9). The acetone 19 was then treated with Meldrum’s adduct 16 under reflux to yield the tricarbonyl compound 20 in 70%. Knoevenagel condensation was performed by simply mixing 20 with silica gel in ethyl acetate:hexanes (1:9 mixture), affording butenolid 21, which is a protected 5 in Scheme 1, in 72% yield. 21 is protected 5 in Scheme 1. Since it has been reported syntheses of Syringolide 1 from 5 with various protecting groups,5,6 we envision that deprotection of 21 followed by cyclization should yield Syringolide 1 (1a).
Scheme 9.

3. Conclusions

A novel, inexpensive synthetic strategy for the preparation of D-xylulose was developed using readily available starting materials such as hydroxyacetone and ethylene glycol. The choice of protecting groups is crucial in the success of this synthesis. A key intermediate in the synthesis of Syringolide 1 was successfully synthesized using the protected D-xylulose obtained through the newly developed methodology.

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References and notes


Supplementary Material

Electronic Supplementary Information (ESI) available: Experimental procedures and NMR spectra.

* Corresponding author.

Shizue Mito

Department of Chemistry

University of Texas Rio Grande Valley

1201 W University Dr. Edinburg, TX 78539

Tel.: +1-956-665-8740; e-mail: shizue.mito@utrgv.edu