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

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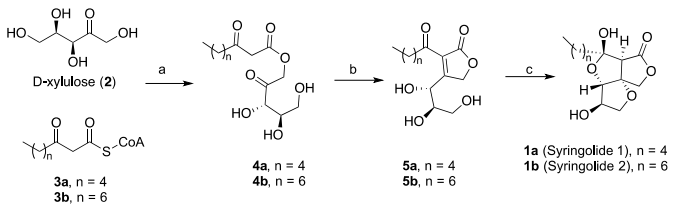
ABSTRACT

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).

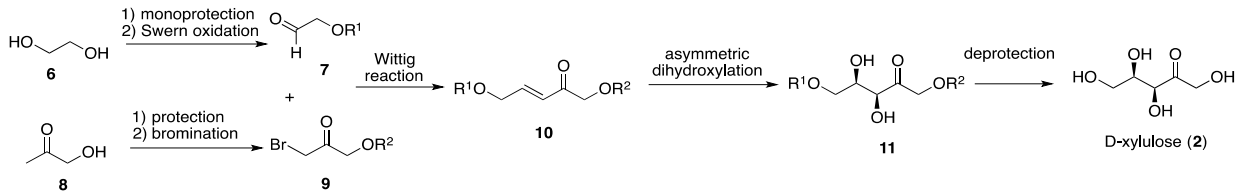
1. Introduction

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



Scheme 2. Strategy of the synthesis of D-xylulose



Rickards et al. synthesized Syringolides with the correct stereocenters using the biomimetic pathway, which starts with D-xylulose.[3] 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-threitol,[4a] D-tartrate,[4b,4c] D-xylofuranose,[4f] D-xylose,[4g] and D-arabinose.[4i, 4k] Chemoenzymatic aldol reaction has also been reported.[4j] 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-xylose to D-xylulose has been accomplished enzymatically with various carbohydrate isomerases during the past two decades.[5] 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] $CrCl_3$,[7] Sn-MFI,[8] MgF_2[9] and Al_2O_3,[10] 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

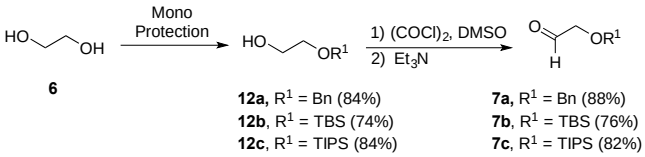
groups is key to the success of this method. In addition, protected D-xylulose was applied in the formal synthesis of Syringolide 1 (**1a**).

2. Results and Discussion

2.1 Synthesis of D-xylulose 2

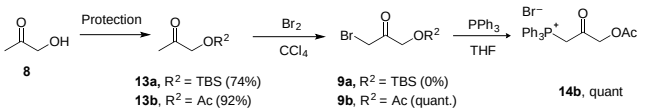
Scheme 3 shows the synthesis of the aldehydes **7** in Scheme 2. The monoprotection of ethylene glycol **6** with various protecting groups gave **12a–c** in good yields (74-84%). Swern oxidation of the protected alcohols **12a–c** yielded **7a–c** in 76-88 %.

Scheme 3.



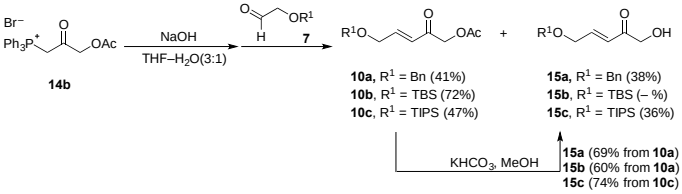
The α-bromo ketone **9** shown in Scheme 2 was synthesized from hydroxyacetone **8** by protection followed by bromination (Scheme 4). Protection of **8** with TBS was carried out to produce **13a** in 74% yield. However, α-bromination of **13a** using different brominating agents, such as NBS, Br_2, 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.



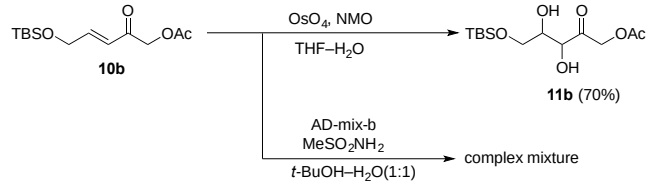
Wittig reaction[12] between phosphonium salt **14b** and several aldehydes (**7a–c**) yielded the enones (**10a–c**) in moderated to good yields (41-72 %) along with the deprotected enone **15** (Scheme 5). Conversion of **10** to **15** were also possible under mild basic conditions using $KHCO_3$.

Scheme 5.



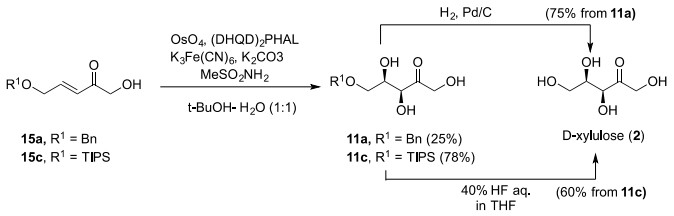
Dihydroxylation of enone **10b** using OsO_4 yielded 70% of **11b** as a racemic mixture (Scheme 6). Asymmetric dihydroxylation of **10b** using AD mix-beta was unsuccessful. A complex mixture of compounds was obtained with less than 50 % of the enone reacted, even after extended reaction time. We observed that both of the acetyl and TBS protecting groups in **10b** were not stable under the reaction conditions.

Scheme 6.



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.

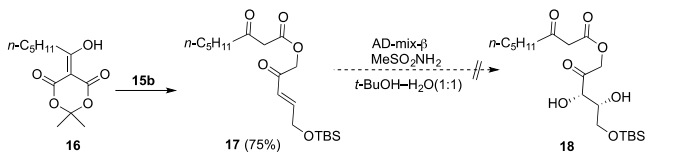


Debenzylation of **11a** by hydrogenation gave D-xylulose **2** in 75% yield (Scheme 7). Similarly, the TIPS protected D-xylulose **11c** was treated with aqueous HF in THF at room temperature, producing **2** in 60% yield. NMR data and optical rotation value of the product obtained from both pathways 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**[3] and/or **5**[4] (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.[3a] 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.[4e] Furthermore, the TBS group was removed under the basic reaction conditions.

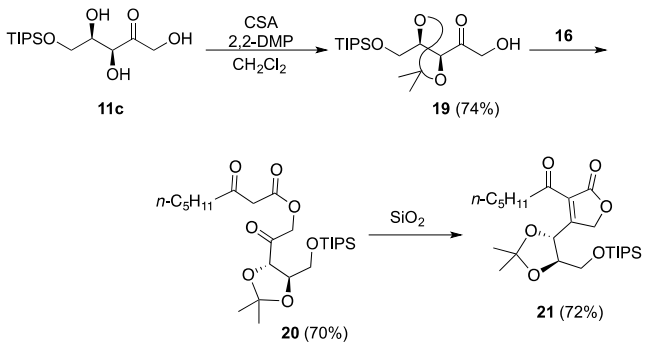
Scheme 8.



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-DMP[15] resulting in the acetonide **19** in 74% yield (Scheme 9). The acetonide **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 butenolide **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,[4] 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.

Acknowledgments

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References and notes

1. Smith, M. J.; Mazzola, E. P.; Sims, J. J.; Midland, S. L.; Keen, N. T.; Burton, V.; Stayton, M. M. *Tetrahedron Letters* **1993**, *34*, 223.
2. Midland, S. L.; Keen, N. T.; Sims, J. J.; Midland, M. M.; Stayton, M. M.; Burton, V.; Smith, M. J.; Mazzola, E. P.; Graham, K. J.; Clardy, J. *The Journal of Organic Chemistry* **1993**, *58*, 2940.
3. (a) Henschke, J. P.; Rickards, R. W. *Tetrahedron Letters* **1996**, *37*, 3557; (b) Henschke, J. P.; Rickards, R. W. *Journal of Labelled Compounds and Radiopharmaceuticals* **1998**, *41*, 211; (c)Bennett, S. A.; Rickards, R. W. *Tetrahedron Letters* **2003**, *44*, 6927.
4. (a) Wood, J. L.; Jeong, S.; Salcedo, A.; Jenkins, J. *The Journal of Organic Chemistry* **1995**, *60*, 286; (b) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron* **1995**, *51*, 8809; (c) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron Letters* **1995**, *36*, 3201; (d) Honda, T.; Mizutani, H.; Kanai, K. *The Journal of Organic Chemistry* **1996**, *61*, 9374; (e) Ishihara, J.; Sugimoto, T.; Murai, A. *Tetrahedron* **1997**, *53*, 16029; (f) Yoda, H.; Kawauchi, M.; Takabe, K.; Hosoya, K. *Heterocycles* **1997**, *45*; (g) Zeng, C.-m.; Midland, S. L.; Keen, N. T.; Sims, J. J. *The Journal of Organic Chemistry* **1997**, *62*, 4780; (h) Yu, P.; Wang, Q.-G.; Mak, T. C. W.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1783; (i) Chênevert, R.; Dasser, M. *Canadian Journal of Chemistry* **2000**, *78*, 275; (j) Chênevert, R.; Dasser, M. *The Journal of Organic Chemistry* **2000**, *65*, 4529; (k) Varvogli, A.-A. C.; Karagiannis, I. N.; Koumbis, A. E. *Tetrahedron* **2009,** *65*, 1048; (l) Navarro Villalobos, M.; Wood, J. L.; Jeong, S.; Benson, C. L.; Zeman, S. M.; McCarty, C.; Weiss, M. M.; Salcedo, A.; Jenkins, J. *Tetrahedron* **2009**, *65*, 8091.
5. (a) Concia, A. L.; Lozano, C.; Castillo, J. A.; Parella, T.; Joglar, J.; Clapés, P. *Chemistry – A European Journal* **2009**, *15*, 3808; (b) Hochster, R. M.; Watson, R. W. *Journal of the American Chemical Society* **1953**, *75*, 3284; (c) Pronk, J. T.; Bakker, A. W.; van Dam, H. E.; Straathof, A. J. J.; Scheffers, W. A.; van Dijken, J. P. *Enzyme and Microbial Technology* **1988**, *10*, 537; (d) Roman, G. N.; Jansen, N. B.; Hsiao, H.-Y.; Tsao, G. T. *Enzyme and Microbial Technology* **1985**, *7*, 129; (e) Ståhlberg, T.; Woodley, J. M.; Riisager, A. *Catalysis Science & Technology* **2012**, *2*, 291; (f) Wang, P. Y.; Johnson, B. F.; Schneider, H. *Biotechnology Letters* **1980**, *2*, 273.
6. (a) Chang, C.-C.; Wang, Z.; Dornath, P.; Je Cho, H.; Fan, W. *RSC Advances* **2012**, *2*, 10475; (b) Choudhary, V.; Pinar, A. B.; Sandler, S. I.; Vlachos, D. G.; Lobo, R. F. *ACS Catalysis* **2011**, *1*, 1724; (c) Holm, M. S.; Pagán-Torres, Y. J.; Saravanamurugan, S.; Riisager, A.; Dumesic, J. A.; Taarning, E. *Green Chemistry* **2012**, *14*, 702.
7. Choudhary, V.; Sandler, S. I.; Vlachos, D. G. *ACS Catalysis* **2012**, *2*, 2022.
8. (a) Cho, H. J.; Dornath, P.; Fan, W. *ACS Catalysis* **2014**, *4*, 2029; (b) Dapsens, P. Y.; Mondelli, C.; Jagielski, J.; Hauert, R.; Pérez-Ramírez, J. *Catalysis Science & Technology* **2014**, *4*, 2302.
9. (a) Agirrezabal-Telleria, I.; Guo, Y.; Hemmann, F.; Arias, P. L.; Kemnitz, E. *Catalysis Science & Technology* **2014**, *4*, 1357; (b) Agirrezabal-Telleria, I.; Hemmann, F.; Jäger, C.; Arias, P. L.; Kemnitz, E. *Journal of Catalysis* **2013**, *305*, 81.
10. Ekeberg, D.; Morgenlie, S.; Stenstrøm, Y. *Carbohydrate Research* **2005**, *340*, 373.
11. (a) Glatthaar, C.; Reichstein, T. *Helvetica Chimica Acta* **1935**, *18*, 80; (b) Rabinsohn, Y.; Fletcher, H. G. *The Journal of Organic Chemistry* **1967**, *32*, 3452.
12. Seo, J.; Fain, H.; Blanc, J.-B.; Montgomery, J. *The Journal of Organic Chemistry* **1999**, *64*, 6060.
13. Bednarski, M. D.; Simon, E. S.; Bischofberger, N.; Fessner, W. D.; Kim, M. J.; Lees, W.; Saito, T.; Waldmann, H.; Whitesides, G. M. *Journal of the American Chemical Society* **1989**, *111*, 627.
14. Wu, Q.; Pan, Q.; Zhao, S.; Imker, H.; Serianni, A. S. *The Journal of Organic Chemistry* **2007**, *72*, 3081.
15. Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; Del Valle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angewandte Chemie International Edition* **2011**, *50*, 3497.
16. Sudhakar Kalagara, Ph.D dissertation, The University of Texas at El Paso (2015).

Supplementary Material

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

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