University of Texas Rio Grande Valley

ScholarWorks @ UTRGV

Chemistry Faculty Publications and
Presentations

College of Sciences

10-8-2020

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

Follow this and additional works at: https://scholarworks.utrgv.edu/chem_fac

Part of the [Chemistry Commons](#)

Recommended Citation

Kalagara, Sudhakar, Gabriel Orozco, and Shizue Mito. 2020. "The Efficient Synthesis of D-Xylulose and Formal Synthesis of Syringolide 1." *Tetrahedron Letters* 61 (41): 152321. <https://doi.org/10.1016/j.tetlet.2020.152321>.

This Article is brought to you for free and open access by the College of Sciences at ScholarWorks @ UTRGV. It has been accepted for inclusion in Chemistry Faculty Publications and Presentations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact justin.white@utrgv.edu, william.flores01@utrgv.edu.

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

Sudhakar Kalagara ^a, Gabriel Orozco ^a, and Shizue Mito*^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

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

D-xylulose

Syringolides

Protecting groups

Formal synthesis

Asymmetric dihydroxylation

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 CrCl₃,⁷ Sn-MFI,⁸ MgF₂⁹ and Al₂O₃,¹⁰ 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

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

This work was supported by the College of Science Dean's Research Enhancement Fund at the University of Texas at El Paso (UTEP), and the Department of Chemistry at the University of Texas Rio Grande Valley is grateful for the generous support provided by a Departmental Grant from the Robert A. Welch Foundation (Grant No. BX-0048-20151106). S. K. was supported by the Department of Chemistry at UTEP and the portions of this work has appeared as his thesis dissertation (2015).¹⁶ The authors thank Salvando Rivera for synthesis of starting materials. Dr. Junha Jeon (University of Texas at Arlington) is greatly acknowledged for helpful discussions.

References and notes

- 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.
- 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.
- (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.
- (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.
- (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.
- (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.
- Choudhary, V.; Sandler, S. I.; Vlachos, D. G. *ACS Catalysis* **2012**, 2, 2022.
- (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.
- (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.
- Ekeberg, D.; Morgenlie, S.; Stenstrøm, Y. *Carbohydrate Research* **2005**, 340, 373.
- (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.
- Seo, J.; Fain, H.; Blanc, J.-B.; Montgomery, J. *The Journal of Organic Chemistry* **1999**, 64, 6060.
- 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.
- Wu, Q.; Pan, Q.; Zhao, S.; Imker, H.; Serianni, A. S. *The Journal of Organic Chemistry* **2007**, 72, 3081.
- 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.
- 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.

* 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