Tetrahedron Letters 104 (2022) 154015

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Efficient total synthesis of three alpinoids via the Au(I)-catalyzed Meyer-Schuster rearrangement

Jasmine K. Keyes, Mauri B. Butzke, Kenneth A. Miller *

Department of Chemistry and Biochemistry, Fort Lewis College, 1000 Rim Drive, Durango, CO 81301, United States

ARTICLE INFO

Article history:
Received 18 June 2022
Revised 1 July 2022
Accepted 6 July 2022
Available online 14 July 2022

Keywords:
Alpinoids
Deoxyalpinoid B
Meyer-Schuster rearrangement

ABSTRACT

The total syntheses of three structurally related natural products, deoxyalpinoid B, deoxyalpinoid A, and alpinoid F, are reported, and each features a Au(I)-catalyzed Meyer-Schuster rearrangement as the key step. The synthesis of alpinoid F is reported for the first time. The syntheses of these natural products, all of which exhibit potent anticancer activity, are readily amenable to the preparation of structural analogs.

The alpinoids are a diverse and highly biologically active group of compounds isolated from *Alpinia officinarum* Hance, an herb found in Southeast Asia whose rhizomes have been used for centuries in Chinese traditional medicine [1]. Many alpinoids possess a diarylhepanoid structure and have been shown to exhibit cytotoxic [2], antiemetic [3], anti-inflammatory [4], antioxidant [5], and antiproliferative activities [6] among others. Recently, Goswami and coworkers reported that deoxyalpinoid B (**1**) (Fig. 1) is potently and selectively cytotoxic to human breast cancer (MCF-7) cells and human osteosarcoma (U2-OS) cells with IC_{50} values of 3.9 and 10.7 μM respectively [7]. Additionally, **1** was nontoxic to normal human intestinal cells (INT-407) at concentrations up to 50 μM. The authors showed that **1** acts against cancer cells by increasing reactive oxygen species and inducing lysosomal membrane permeabilization ultimately leading to apoptotic cell death. Deoxyalpinoid A (**2**) and alpinoid F (**3**) are structurally similar to **1** and have been shown to possess potent cytotoxic activity against IMR-32 human neuroblastoma cells with IC_{50} values of 5.28 and 1.19 μM respectively [8]. Given the anticancer activity of **1**–**3**, the development of a flexible and general route to the synthesis of these alpinoids is warranted.

The Meyer-Schuster rearrangement (MSR) is a redox neutral conversion of a propargylic alcohol to a α,β -unsaturated ketone [9]. This rearrangement has been known for over a century and originally was conducted with strong acid and high heat [10]. Modern catalytic variants are milder, and a wider scope of substrates are now tolerated. A large variety of Lewis acidic metal salts have been used to facilitate the catalytic Meyer-Schuster rearrangement including Sc [11], Hg [12], V [13], Re [14], Mo [15], Ru [16], Ag [17], and Au [18]. The use of the Meyer-Schuster rearrangement in total synthesis has greatly increased in the last decade, most prominently catalytic MSRs using Au(I) based catalysts. High yielding examples of the Au(I)-catalyzed MSR in the syntheses of prostaglandins [19], macrolides [20], and terpenoids [21] are particularly notable. Despite these advances, the Meyer-Schuster rearrangement continues to be underutilized in natural product synthesis. More frequently α,β -unsaturated ketones are prepared by olefination reactions such as the aldol reaction, the Horner-Wadworth-Emmons (HWE) reaction [22], and alkene metathesis [23]. These reactions all have well-known drawbacks. The aldol reaction can be limited in scope and generally requires harsh, strongly basic conditions that are incompatible with many complex molecules. While the HWE reaction is milder, these organophosphorous reagents often require multistep synthesis and generate phospine oxide side products. Ruthenium based alkene metathesis catalysts are expensive and cross metathesis often requires excess of one alkene reactant to obtain reasonable yields [7]. In contrast, the MSR proceeds with high atom economy and the synthesis of the propargylic alcohols typically involves straightforward addition of an acyetylide ion to the appropriate carbonyl moiety which is generally high yielding even with sterically demanding aldehydes and ketones.

Close analysis of several structurally related alpinoids reveals that an identical sequence of reactions with structurally varied starting materials could lead to a large number these targets (Scheme 1). Compounds **1**–**3** are identical except for the substitution pattern on the aromatic ring closest of the alkene moiety. All

---

* Corresponding author.
E-mail address: miller_k@fortlewis.edu (K.A. Miller).

https://doi.org/10.1016/j.tetlet.2022.154015
0040-4039/

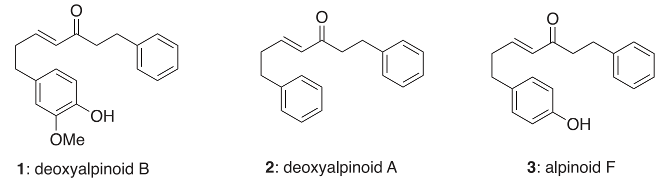
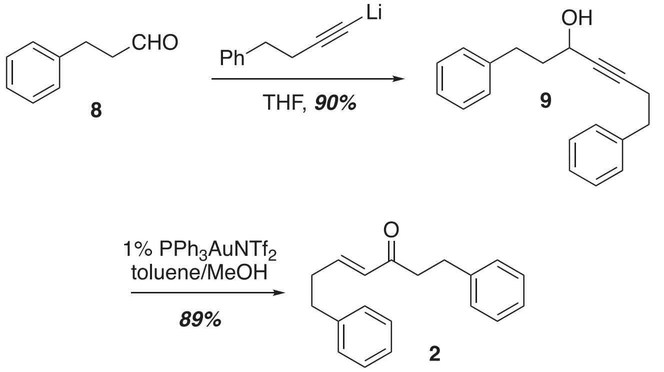


Fig. 1. Deoxyalpinoid B, deoxyalpinoid A, and alpinoid F share a diarylheptanoid structure containing an α,β -unsaturated ketone in the linker. Each of these compounds are cytotoxic to cancer cell lines in the low micromolar range.

compounds share a diarylheptenone structure with a α,β -unsaturated ketone. Given this structural similarity and given the ease with which α,β -unsaturated ketones can be installed by a Meyer-Schuster rearrangement, we envisioned that each of these targets would arise from the aforementioned Au(I)-catalyzed rearrangement of an appropriately substituted propargyl alcohol **5**. These propargyl alcohols could readily be accessed from treatment of aldehydes **6** varying in aromatic substitution with the acetylide ion **7**. An advantage of this approach is that the acetylide **7** is derived from the commercially available alkyne 4-phenyl-1-butyne. A similar sequence of reactions, addition of an acetylide ion to an aldehyde followed by Au(I)-cataluzed MSR, was employed in the syntheses of *E*-isoegomaketone and a cytotoxic daphenone lending support to this synthetic approach [24].

In order to determine whether this approach was viable, the synthesis of deoxyalpinoid A (**2**) was undertaken as a model (Scheme 2). Beginning with the commercially available hydrocinnamaldehyde **8**, addition of the lithium acetylide of 4-phenyl-1 butyne led to propargylic alcohol **9** in exellenent yield. Following the procedure of Sheppard and coworkers, alcohol **9** was treated with 1% PPh_3AuNTf_2 in toluene/MeOH to give the corresponding α,β -unsaturated ketone **2** (E:Z ratio = >19:1), deoxyalpinoid A, in excellent yield by MSR. All spectral data matched previous reports [25]. Given the ease with which these MSR substrates could be prepared as well as the high yield of the rearrangement, subsequent experiments were undertaken toward the syntheses of related alpinoids.

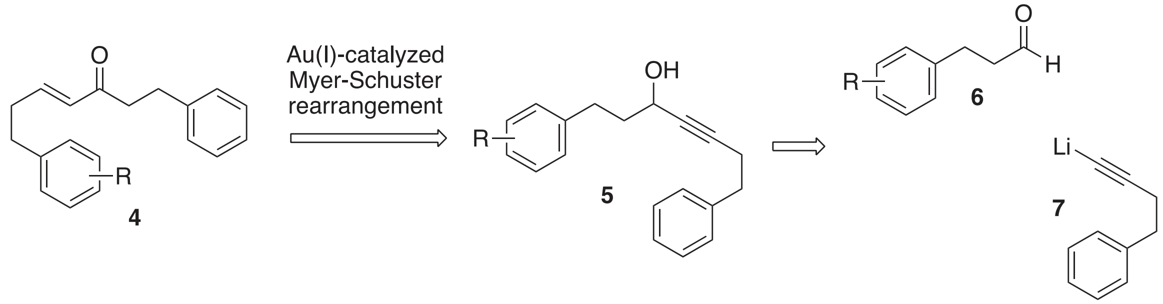
The next goal was to prepare alpinoid F (**3**), which had not been prepared previously. Access to the known aldehyde **12** was possible beginning with 4-hydroxyphenylpropionic acid (**10**) (Scheme 3). Quantitative conversion to the Weinreb amide and protection of the phenol as the corresponding silyl ether delivered **11**, which underwent reduction to the corresponding aldehyde **12**. Interception of the aldehyde with the same acetylide of 4-phenyl-1 butyne furnished the propargyl alcohol **13**. MSR with 1% catalyst loading led once again to a good yield of the α,β -unsaturated ketone **14** without any of the *Z*-alkene present based on analysis of the NMR spectrum. Standard deprotection with fluoride gave synthetic alpinoid F (**3**), and spectral data from **3** matched those previously reported [26].



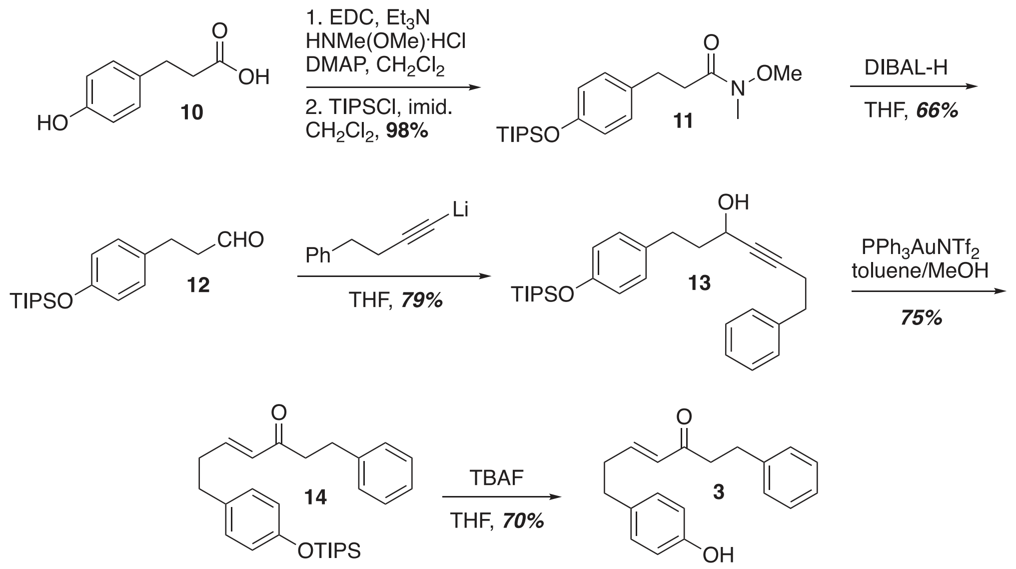
Scheme 2. The total synthesis of deoxyalpinoid A was completed in two steps, acetylide ion addition and Au(I)-catalyzed Meyer-Schuster rearrangement.

With the potent anticancer of **1** in mind, application of the MSR to this natural product was undertaken. While **1** has been synthesized in the past [7], this synthesis featured a cross metathesis of two alkene partners which each required four steps to synthesize. Given the expense of the Hoveyda – Grubbs II catalyst used previously and given that a twofold excess of one alkene was required previously, we envisioned that the MSR might offer an optimal alterative. Starting with eugenol (**15**) TIPS protection and hydroboration/oxidation could be used to produce the alcohol **17** followed by PCC oxidation to the aldehyde (Scheme 4). Reaction with the acetylide from 4-phenyl-1 butyne gave propargyl alcohol **19**, which underwent MSR in excellent yield. Deprotection with fluoride yielded deoxyalpinoid B whose data were in agreement with those previously reported [7,25]. The synthesis of **1** was accomplished in a 44% overall yield and six steps, an improvement over prior reported syntheses [7].

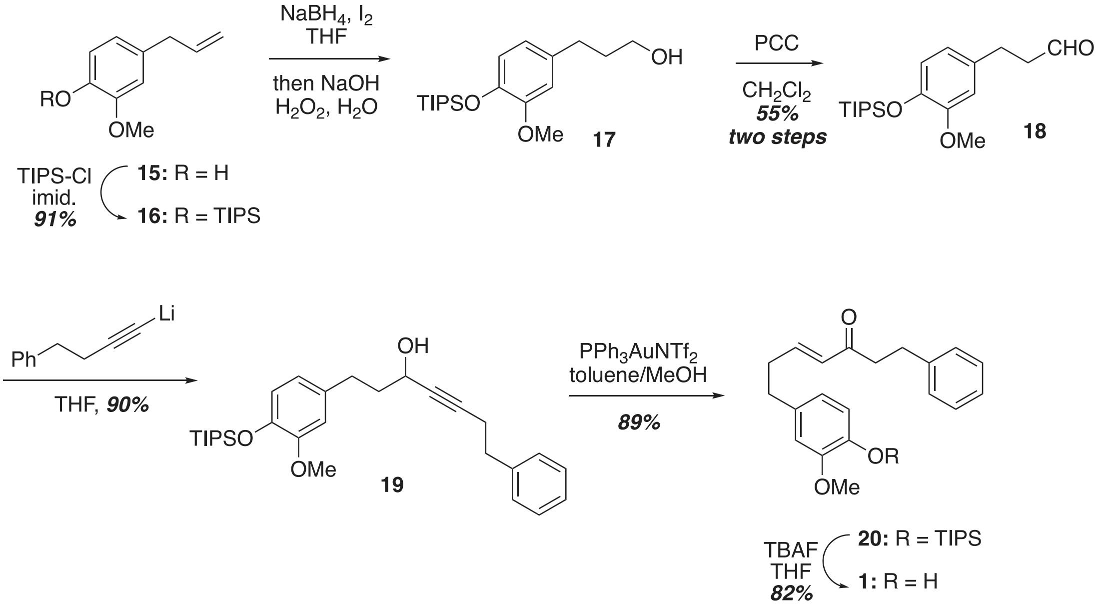
This work illustrates the utility of the Meyer-Schuster rearrangement as a key step in the syntheses of bioactive alpinoids. The synthesis of three alpinoids, deoxyalpinoid B, deoxyalpinoid A, and alpinoid F, were completed using a Au (I) catalyzed Meyer-Schuster rearrangement, and this work represents the first synthesis of alpinoid F reported to date. All syntheses were high yielding, amenable to scale-up, and delivered adequate access to quantities necessary for biological assays. We are confident that this work could be generalized to the synthesis of other bioactive α,β -unsaturated ketone containing natural products and to the synthesis of alpinoid analogs. These experiments are underway and will be reported in due course.



Scheme 1. Three biologically active natural products could be synthesized using the same retrosynthetic approach. The α,β -unsaturated ketone moiety common to these compounds could be installed by a Au(I)-catalyzed Meyer-Schuster rearrangement. The propargylic alcohol is readily synthsized by addition of an acetylide ion to the appropriate aldehyde.



Scheme 3. Alpinoid F was synthsized by first constructing a silyl ether protected aldehyde followed by acetylide ion addition, Meyer-Schuster rearrangement, and deprotection.



Scheme 4. Starting with eugenol, the cytotoxic natural product deoxyalpinoid B was synthesized in six steps and 44% overall yield.

Data availability

All relevant data is shared in the attached supplemental material.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the NIH-BLaST program at the University of Alaska-Fairbanks, the NIH-URISE program, and Fort Lewis College for financial support. BLaST is supported by the NIH Common Fund, through the Office of Strategic Coordination, Office of the NIH Director with the linked awards TL4GM118992, RL5GM118990, and UL1GM118991. Jasmine Keyes was funded by the NIH Undergraduate Research Training Initiative for Student Enhancement (U-RISE) award at Fort Lewis College (T34GM140909). This research was supported by a National Science Foundation – Major Research Instrumentation award (2017945). The authors wish to thank the Analytical Resources Core (RRID: SCR_021758) at Colorado State University for instrument access, training, and assistance with sample analysis.

Appendix A. Supplementary data

Copies of ^{1}H- and ^{13}C-NMR spectra for all new compounds (**9, 12-14, 16-20, 1-3**). Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2022.154015.

References

[1] P.P.H. But, T. Kimura, J.X. Guo, C.K. Sung, B.H. Han, in: International Collation of Traditional and Folk Medicine, Vol 2: Northeast Asia Part 2, World Scientific Publishing Company, Singapore, 1997, pp. 201–202.

[2] A. Yokosuka, Y. Mimaki, H. Sakagami, Y. Sashida, J. Nat. Prod. 65 (2002) 283–289.

[3] Y. Yang, K. Kinoshita, K. Koyama, T. Takahashi, S. Kondo, K. Watanabe, Phytomed. 9 (2002) 146–152.

[4] P. Claeson, U. Pongprayoon, T. Sematong, P. Tuchinda, V. Reutrakul, P. Soontornsaratune, W.C. Taylor, Planta Med. 62 (1996) 236–240.

[5] T.N. Ly, M. Shimoyamada, K. Kato, R. Yamauchi, J. Agric. Food Chem. 51 (2003) 4924–4929.

[6] M.S. Ali, A.H. Banskota, Y. Tezuka, I. Saiki, S. Kadota, Biol. Pharm. Bull. 24 (2001) 525–528.

[7] S. Gamre, M. Tyagi, S. Chatterjee, B.S. Patro, S. Chattopadhyay, D. Goswami, J. Nat. Prod. 84 (2021) 352–363.

[8] Y. Sun, K. Tabata, H. Matsubara, S. Kitanaka, T. Suzuki, K. Yasukawa, Planta Med. 74 (2008) 427–431.

[9] a) D.A. Engel, G.B. Dudley, Org. Biomol. Chem. 7 (2009) 4149–4158;
b) F. Justaud, A. Hachem, R. Grée, Eur. J. Org. Chem. 4 (2021) 514–542.

[10] K.H. Meyer, K. Schuster, Ber. 55 (1922) 819.

[11] D.A. Engel, S.S. Lopez, G.B. Dudley, Tetrahedron 64 (2008) 6988–6996.

[12] M. Nishizawa, H. Hirakawa, Y. Nakagawa, H. Yamamoto, K. Namba, H. Imagawa, Org. Lett. 9 (2007) 5577–5580.

[13] C.J. Rieder, K.J. Winberg, F.G. West, J. Am. Chem. Soc. 131 (2009) 7504–7505.

[14] C. Sun, X. Lin, S.M. Weinreb, J. Org. Chem. 71 (2006) 3159–3166.

[15] M. Egi, Y. Yamaguchi, N. Fujiwara, S. Akai, Org. Lett. 10 (2008) 1867–1870.

[16] J. Borge, V. Cadierno, J. Diez, S.E. Garcia-Garrido, J. Gimeno, Dyes Pigm. 87 (2010) 209–217.

[17] N. Marion, P. Carlqvist, R. Gealageas, P. de Frémont, F. Maseras, S.P. Nolan, Chem. Eur. J. 13 (2007) 6437–6451.

[18] M.N. Pennel, M.G. Unthank, P. Turner, T.D. Sheppard, J. Org. Chem. 76 (2011) 1479–1482.

[19] R.S. Ramon, S. Gaillard, A.M.Z. Slawin, A. Porta, A. D'Alfonso, G. Zanoni, S.P. Nolan, Organometallics 29 (2010) 3665–3668.

[20] A. Riefert, M.E. Maier, Synthesis 50 (2018) 3131–3145.

[21] S. Bugoni, D. Boccato, A. Porta, G. Zanoni, G. Vidari, Chem. Eur. J. 21 (2015) 791–799.

[22] M.Q. Salih, C.M. Beaudry, Org. Lett. 14 (2012) 4026–4029.

[23] A.K. Chatterjee, T.L. Choi, D.P. Sanders, G.H. Grubbs, J. Am. Chem. Soc. 125 (2003) 11360–11370.

[24] M.N. Pennell, P.G. Turner, T.D. Sheppard, Chem. Eur. J. 18 (2012) 4748–4758.

[25] H. Itokawa, H. Morita, S. Mihashi, Chem. Pharm. Bull. 29 (1981) 2383–2385.

[26] H. Itokawa, H. Morita, I. Midorikawa, R. Aiyama, M. Morita, Chem. Pharm. Bull. 33 (1985) 4889–4893.