Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Total synthesis of cytotoxic pyranone B

Uma Maheshwar Gonela, Suresh Kanikarapu & Jhillu S. Yadav

To cite this article: Uma Maheshwar Gonela, Suresh Kanikarapu & Jhillu S. Yadav (2018): Total synthesis of cytotoxic pyranone B, Synthetic Communications

To link to this article: https://doi.org/10.1080/00397911.2018.1536787

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2018.1536787

Total synthesis of cytotoxic pyranone B

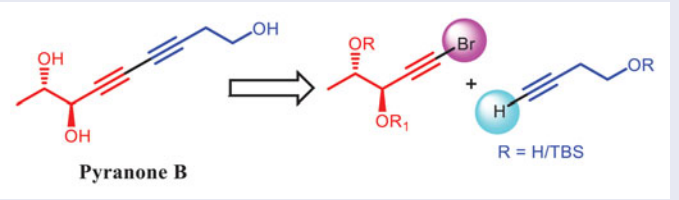
Uma Maheshwar Gonela[a], Suresh Kanikarapu[a], and Jhillu S. Yadav[a,b]

[a]Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, India; [b]School of Science, Indrashil University, Kadi, India

ABSTRACT

The first stereoselective total synthesis of cytotoxic diacetylene pyranone B is described. The key steps involved in the synthesis are base-induced elimination protocol to generate the chiral acetylenic alcohol and selective cross-coupling of unsymmetrical terminal acetylenes.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 2 July 2018

KEYWORDS
Diacetylene; cytotoxic; base-induced elimination; Cadiot–Chodkiewicz cross-coupling; Sonogashira cross-coupling

Introduction

Diacetylene containing molecules display a variety of biologically activities such as cytotoxic, antitumor, antiviral, antibiotic and antifungal activities.[1] For example, Iguchi and coworkers isolated Strongylodiols **1–6** from the Okinawan marine sponge of the genus *strongylohora*, which shows potent cytotoxic activity towards human T-lymphocyte leukaemia (MOLT-4) cells, IMR-90 and DLP-1 cell.[2] Panaxytriol **7** showed inhibitory activity against MK-1 cells with an IC_{50} of 8.5 ng/mL and suppressed the growth of B16 melanoma cells in mice.[3]

Very recently, unprecedented acetylenic natural products, pyranones **8–10** were isolated by Hu et al. from cultures of *junghuhnianitida.* All exhibit significant activity against five human cancer cell lines: breast cancer MCF-7, hepatocellular carcinoma SMMC-7721, human myeloid leukemia HL-60, colon cancer SW480, and lung cancer A-549 cells (Figure 1).[4]

In continuation of our program toward the development of new protocols and their applications in the total synthesis of biologically potent natural products,[5,6] we herein describe the first total synthesis of pyranone B (**8**).

CONTACT Jhillu S. Yadav yadavfna@gmail.com; jsyadav@indrashiluniversity.edu.in Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India; School of Science, Indrashil University, Kadi 382740, India.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

Supplemental data for this article can be accessed on the publisher's website.

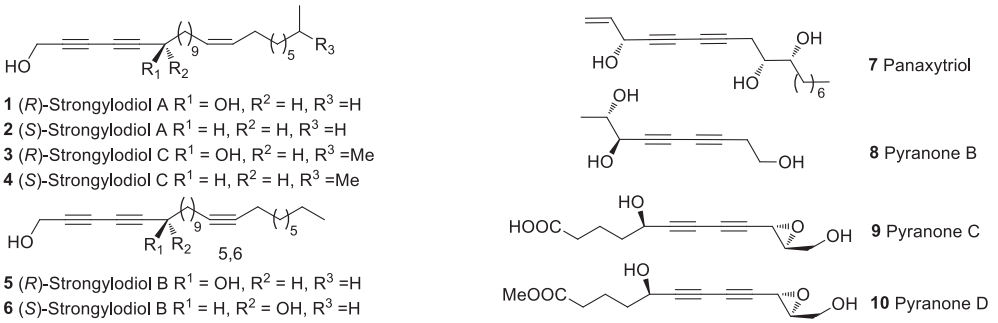
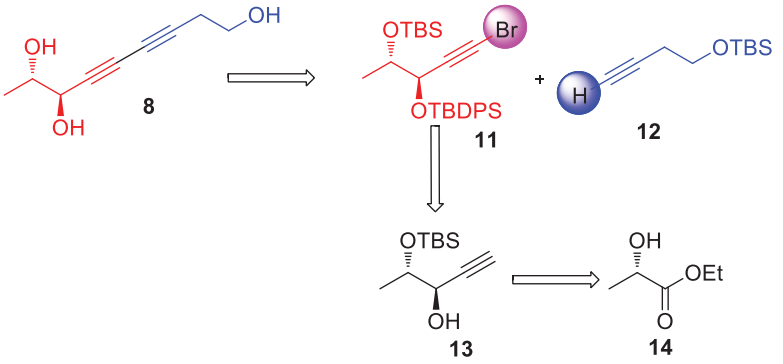


Figure 1. Structures of strongylodiols, panaxytriol, and pyranones.

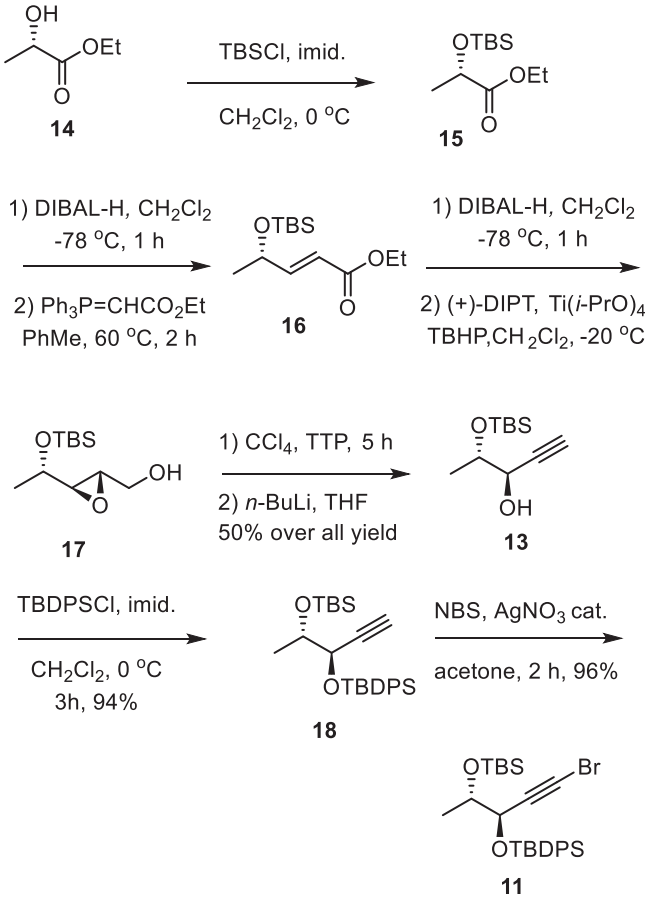


Scheme 1. Retrosynthesis of Pyranone B (**8**).

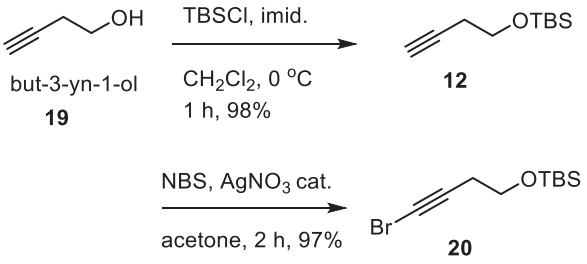
As per our retrosynthetic analysis outlined in Scheme 1, acetylenic bond disconnection furnishes the two terminal acetylenes. The key fragment could be stereoselectively synthesized using our base-induced elimination protocol for the construction of chiral propargylic alcohols. These fragments would be accessible from the commercially available (*L*)-ethyl lactate and the homopropargyl alcohol.

Results and discussion

The chiral bromoalkyne fragment **11** was synthesized in a stereoselective manner starting from commercially available (*L*)-ethyl lactate. TBS protected (*L*)-ethyl lactate (**15**) was converted to the aldehyde with DIBAL-*H* at −78 °C.[6] It was treated with two carbon Wittig-ylide to furnish the *α,β*-unsaturated ester **16**. The ester was converted to corresponding allylic alcohol with DIBAL-*H*, which was subjected to the Sharpless asymmetric epoxidation. Furthermore, the epoxy alcohol **17** was converted to its epoxy chloride using CCl_4-Ph_3P at reflux conditions, which was then subjected to a base-induced elimination protocol in presence of *n*-BuLi to give the chiral acetylenic alcohol **13**.[6] Newly generated hydroxyl group was protected as its TBDPS ether with TBDPSCl and imidazole to obtain **18** in 94% yield. The free terminal acetylene **18** was brominated with NBS and catalytic $AgNO_3$ to give **11** in 96% yield (Scheme 2).[7]



Scheme 2. Synthesis of fragment **11**.



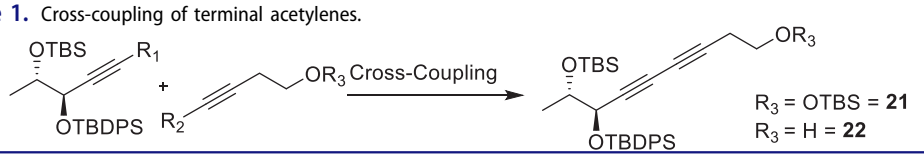
Scheme 3. Synthesis of fragment **20**.

Another coupling partner alkyne **12** was prepared from readily available homopropargyl alcohol **19** using TBSCl and imidazole, which was further brominated using NBS and catalytical $AgNO_3$ to afford **20** in 95% yield for two steps (Scheme 3).

In general, alkynyl electrophiles readily participated in Cu-catalyzed Cadiot–Chodkiewicz[8] and Pd-catalyzed alkyne-alkyne cross couplings,[9] where undesired homocoupling is the main problem in these cross-couplings.

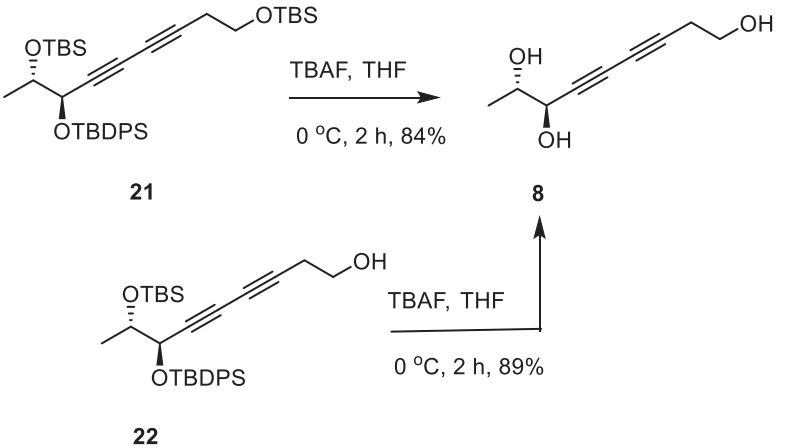
Our preliminary experiment using standard conditions of Cadiot–Chodkiewicz with the combination of **11** and **12** furnished the target compound in moderate yields along

Table 1. Cross-coupling of terminal acetylenes.



S. No.	R_1	R_2	R_3	Conditions[a]	Yield %[b]
1	Br	H	-TBS	CuCl, $NH_2OH.H_2O$, *n*-$BuNH_2.H_2O$	68
2	H	Br	-TBS	CuCl, $NH_2OH.H_2O$, *n*-$BuNH_2.H_2O$	72
3	Br	H	-TBS	$Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF	79
4	H	Br	-TBS	$Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF	91
5	Br	H	-H	$Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF	83

[a]Alkyne (1eq.), Bromo alkyne (1.2 eq.).
[b]Isolated yields.



Scheme 4. Accomplishment of **8**.

with the homocoupling products in 17% yields (Table 1, entry 1). Likewise combining **18** and **20** led to improved yields (entry 2). Interestingly, the coupling reaction with modified Sonogashira conditions (Table 1, entries 3–5)[9] gave the desired cross-coupling product in better yields, along with lowering the homocoupling of alkyne. Improved selectivity was observed with the less substituted bromoalkyne which was in an excess amount.

Lastly, the accomplishment of the total synthesis of pyranone B (**8**) was achieved by the treatment of TBAF on silyl protected compounds **21**/**22** in 84/89% yields respectively (Scheme 4). The ^1H and ^{13}C NMR spectra and the specific rotation ($[\alpha]_D^{27}$ −25.9 (*c* = 0.5, MeOH)), lit.[4] ($[\alpha]_D^{27}$ −27.5 (*c* = 0.22, MeOH)) were consistent with those of the natural product **8**.

Experimental section

General experimental details

Solvents were dried over standard drying agents and freshly distilled prior to use. All commercially available chemicals were used without further purification. All reactions were performed under Nitrogen. ^1H NMR and ^{13}C NMR spectra were measured with

Varian Gemini FT 200 MHz spectrometer, Bruker Avance 300 MHz, Unity 400 MHz and Inova 500 MHz with tetramethylsilane as an internal standard for solutions in $CDCl_3$, *J* values are given in Hz. Chemical shifts were reported in ppm relative to the solvent signal. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in *vacuo*. IR-spectra were recorded on FT IR (Perkin-Elmer IR-683) spectrophotometer with NaCl optics. JASCO DIP 300 digital polarimeter was used for measurement of optical rotations at 25 °C. Mass spectra were recorded on direct inlet system or LC by MSD trap SL (Agilent Technologies), the HRMS data were obtained using Q-TOF mass spectrometry.

(7R,8S)-nona-3,5-diyne-1,7,8-triol 8

To a solution of **21**(40 mg, 0.062 mmol) in THF (2 mL) at 0 °C, TBAF (0.28 mL, 0.28 mmol, 1 M in THF) was added and the reaction mixture was stirred for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with a saturated solution of NH_4Cl (5 mL) and diluted with ethyl acetate (5 mL). The layers were separated and the aqueous layer extracted twice with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the crude product was purified by silica gel chromatography (methanol/chloroform = 1:9) to afford **8** (8.8 mg, 84%) as a colorless liquid. $[\alpha]_D^{27}$ −25.9 (*c* = 0.5, MeOH); IR (neat): ν 2918, 2899, 1693, 1511, 1469, 1433, 1383, 1270, 962, 771 cm^{-1}; ^1H NMR (500 MHz, MeOD):δ 4.19 (d, *J* = 4.5 Hz, 1H), 3.74 (m, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.49 (t, *J* = 6.6 Hz, 2H), 1.20 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, MeOD):δ 78.8, 76.1, 71.3, 70.9, 68.1, 66.4, 61.1, 24.0, 18.4 ppm; HRMS (ESI): *m/z* calcd.for $C_9H_{13}O_3$ $[M + H]^+$ 169.0868; found: 169.0859.

Conclusion

In summary, the synthesis of pyranone B was accomplished with a longest linear sequence of nine steps in 33% overall yield, starting from commercially available (*L*)-ethyl lactate. It is anticipated that the synthesis in the strategy described herein will offer access to other pyranone analogs and also predicted that the synthetic methods developed may have value in our further ventures.

Funding

U.M.G., S.K. thanks UGC and CSIR, New Delhi, India for financial assistance in the form of fellowships.

References

[1] (a) Pellati, F.; Calo, S.; Benvenuti, S.; Adinolfi, B.; Nieri, P.; Melegari, M. *Phytochemistry* **2006**, *67*, 1359–1364. (b) Resch, M.; Heilman, J.; Steigel, A.; Bauer, R. *Planta Med.* **2001**, *67*, 437–442. (c) Choi, Y. E.; Ahn, H.; Ryu, J.-H. *Biol. Pharm. Bull.* **2000**, *23*, 884–886. (d) Zgoda, J. R.; Freyer, A. J.; Killmer, L. B.; Porter, J. R. *J. Nat. Prod.* **2001**, *64*, 1348–1349.

(e) Hudson, J. G.; Graham, E. A.; Chan, G.; Finlayson, A. J.; Towers, G. H. N. *Planta Med*. **1986**, 453–457. (f) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed*. **2006**, *45*, 1034–1057. doi:10.1016/j.phytochem.2006.05.006

[2] Watanabe, K.; Tsuda, Y.; Yamane, Y.; Takahashi, H.; Iguchi, K.; Naoki, H.; Fujita, T.; Van Soest, R. W. M. *Tetrahedron Lett*. **2000**, *41*, 9271–9276. doi:10.1016/S0040-4039(00)01692-0

[3] (a) Katano, M.; Yamamoto, H.; Matsunaga, H.; Mori, M.; Takata, K.; Nakamura, M. *Gan to Kagakuyoho* **1990**, 17, 1045–1049. (b) Matsunaga, H.; Saita, T.; Naguo, F.; Mori, M.; Katano, M. *Cancer Chemother. Pharmacol*. **1995**, *35*, 291–296.

[4] Hu, D.-B.; Li, W.-X.; Zhao, Z.-Z.; Feng, T.; Yin, R.-H.; Li, Z.-H.; Liu, J.-K.; Zhu, H.-J. *Tetrahedron Lett*. **2014**, *55*, 6530–6533. doi:10.1016/j.tetlet.2014.09.132

[5] (a) Yadav, J. S.; Chander, M. C.; Joshi, B. V. *Tetrahedron Lett*. **1988**, *29*, 2737–2740. (b) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett*. **1989**, *30*, 5455–5458. (c) Yadav, J. S.; Rajagopal, D. *Tetrahedron Lett*. **1990**, *31*, 5077–5080. (d) Yadav, J. S.; Chander, M. C.; Reddy, K. K. *Tetrahedron Lett*. **1992**, *33*, 135–138. (e) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033–7046. (f) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron Lett*. **1990**, *31*, 4495–4496. (g) Yadav, J. S.; Chander, M. C. *Tetrahedron Lett*. **1990**, *31*, 4349–4350. (h) Yadav, J. S.; Mishra, R. K. *Tetrahedron Lett*. **2002**, *43*, 1739–1741. (i) Yadav, J. S.; Maiti. A. *Tetrahedron* **2002**, *58*, 4955–4961. (j) Yadav, J. S.; Kumaraswamy, B.; Sathish, R. A.; Srihari, P.; Janakiram, R. V.; Shasi, V. K. *J. Org. Chem*. **2011**, *76*, 2568–2576. (k) Kanikarapu, S.Marumudi, K.; Kunwar, A. C.; Yadav, J. S.; Mohapatra, D. K. *Org. Lett*. **2017**, *19*, 4167–4170. (l) Rangaraju, S. K.; Gonela, U. M.; Kavita, A.; Yadav, J. S.; Mohapatra, D. K. *Eur. J. Org. Chem*. **2018**, *32*, 4376–4380. doi:10.1016/0040-4039(88)85274-2

[6] Mohapatra, D. K.; Umamaheshwar, G.; Rao, R. N.; Rao, T. S.; Kumar, S. R.; Yadav, J. S. *Org. Lett*. **2015**, *17*, 979–981. doi:10.1021/acs.orglett.5b00138

[7] Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 1994, 485–486. doi: 10.1055/s-1994-22897

[8] Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**, pp 597–647.

[9] Sonogashira, K. In *Handbook of Organopalladium Chemistryfor Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, **2002**; *Vol. 1*, pp 493–529. The formation of homo-coupling products during the cross-coupling reaction has been observed earlier. For reviews, see (b) Negishi, E.; Anastasia, L. *Chem. Rev*. **2003**, 103, 1979–2017. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed*. **2000**, *39*, 2632–2657.