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Total syntheses of bupleurynol and its analog

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ABSTRACT

An efficient route to the natural products bupleurynol and its analog (RB-2), isolated from *Bupleuri Radix*, was established based on versatile intermediate (**15**). In this synthetic route, Sonogashira and Cadiot–Chodkiewicz coupling as well as Julia–Kocienski olefination are utilized as key steps. The highly efficient synthetic route provides opportunities to explore the biological behavior of bupleurynol and RB-2.

1. Introduction

Polyacetylenes are a family of structurally diverse natural products [1], which show interesting biological activity, such as antitumor [2], antibacterial [3], anti-obesity [4], antidiabetic effect [5], cytoprotection [6], immunosuppressive activity [7,8] and anti-inflammatory effects [9]. Recently, 1,3-diyne-type polyacetylenes have attracted broad attention from both chemists and biologists [10,11]. Bupleurynol (**1**) and its analog (RB-2) (**2**) are natural products that were first isolated from the *Bupleurum longiradiatum* in 1987 [12] and 1999 [13], respectively (Fig. 1). We also isolated bupleurynol (**1**), RB-2 (**2**) and their isomers from *Bupleuri Radix* (Chaihu in Chinese) [14]. Our study further demonstrated that these natural products could increase the level of monoamines such as 5-hydroxytryptamine (5-HT) and norepinephrine (NE) in mice. Due to their low abundance in nature and exploring the relationship between the structural motifs and the interesting biological activities of bupleurynol (**1**) and RB-2 (**2**), a versatile and efficient route to synthesize them is required.

The first synthesis of bupleurynol was completed by the Organ and Antunes [15]. Ghasemi et al. further developed a single operation to synthesize bupleurynol using queued cross-coupling reactions [16]. However, these strategies suffered from low yields and lack of versatility for synthesizing other polyacetylene natural products. Hence, it remains as a challenge to develop a versatile and efficient strategy for the total syntheses of bupleurynol and its analogs. Herein, we reported a highly versatile route for the total syntheses of bupleurynol and RB-2 from a common intermediate.

2. Results and discussion

Our retrosynthetic analysis for RB-2 is depicted in Scheme 1. According to the previously reported method, RB-2 could be prepared from the terminal alkyne **3** and the enyne fragment **4** through the Cadiot–Chodkiewicz reaction [17]. The terminal alkyne **3** might be derived from the conjugated aldehyde **5** through a Corey–Fuchs reaction, while the enyne fragment **4** could be prepared from the methyl propionate **6** by a Sonogashira cross-coupling and bromination.

Our synthesis began with the preparation of the *cis* alkenyl iodide **7**, which was obtained in 89% yield by heating methyl propiolate **6** and lithium iodide in acetic acid [18] (Scheme 2). The alkenyl iodide **7** was treated with ethynyltrimethylsilane in a Sonogashira cross-coupling reaction to give the enyne product **8** in 96% yield without isomerization. Compound **8** was converted to allyl alcohol **9** using diisobutylaluminum hydride at −78 °C in 92% yield [19].

Initially, the trimethyl chlorosilane (TMS) protecting group was removed using potassium carbonate to make the terminal alkyne, which included the free alcohol group. However, the allyl alcohol is

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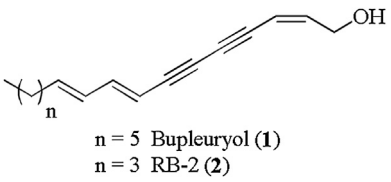
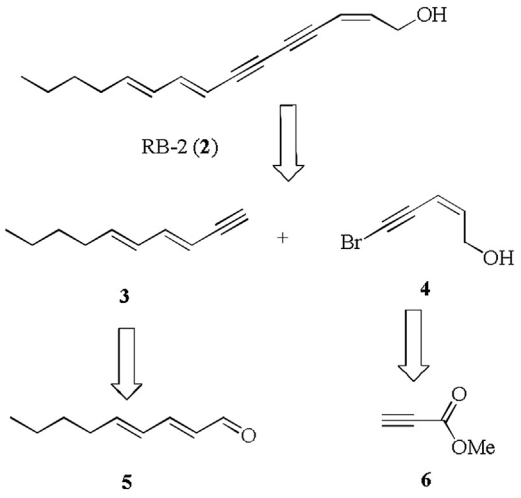


Fig. 1. The structures of bupleuryol and RB-2.



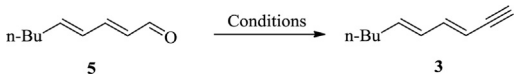
Scheme 1. Retrosynthetic analysis of RB-2 (**2**).

extremely volatile and unstable. Therefore, it was protected with *tert*-butyl(chloro)diphenylsilane (TBDPS) group, which was followed by the removal of TMS to give the compound **11** [20]. The bromoacetylene **12** was eventually obtained by the treatment of **11** with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of $AgNO_3$ [21] and the absence of light.

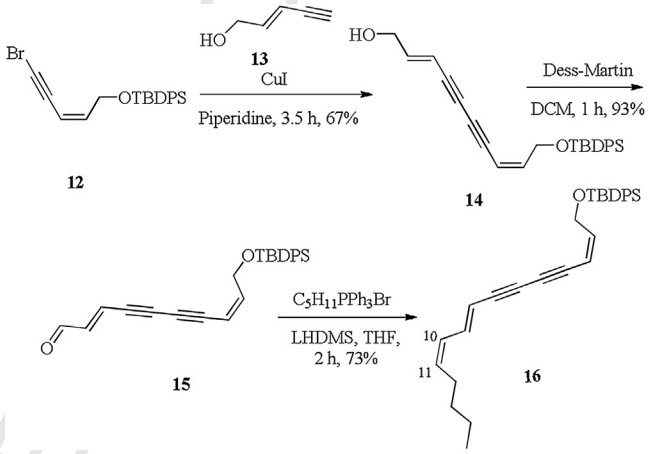
With the requisite protection version of right fragment in hand, we developed a concise route to synthesize the (3*E*, 5*E*)-deca-3,5-dien-1-yne **3** fragment from the commercially available aldehyde **5**. However, the expected homologation product turned out to be more difficult to prepare. As summarized in Table 1, treatment of compound **5** *via* the Corey–Fuchs reaction gave only a trace amount of desired product [22]. Treatment of the aldehyde **5** with (bromomethyl)triphenylphosphonium bromide in the presence of potassium *tert*-butoxide afforded the bromo alkene compound [23]. The alkyne **3** was also detected based on the NMR of the crude product using the dimethyl-(1-diazo-2-oxopropyl) phosphonate (the Bestmann–Ohira reagent) [24], but the further purification of the alkyne turned out to be impractical due to the instability of compound **3**.

In view of these results, a new approach was developed to synthesize the natural product, by coupling (*E*)-pent-2-en-4-yn-1-ol **13** and fragment **12** to form the C10–C11 double bond.

Table 1
Conversion of aldehyde **5** to the terminal alkyne **3**.



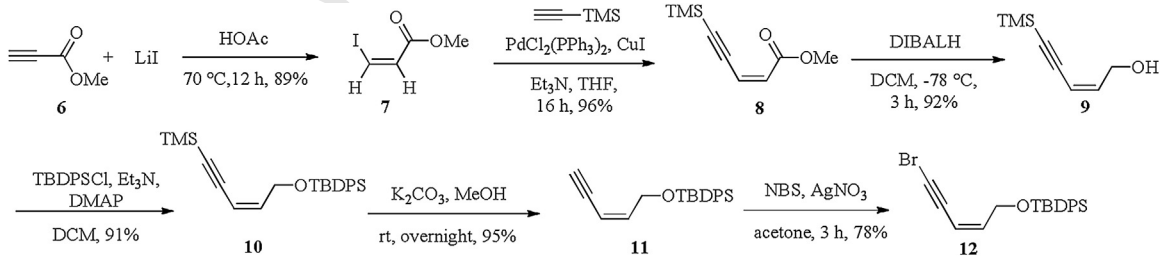
Entry	Conditions	Yield
1	CBr_4, PPh_3, DCM, then *n*-BuLi, THF, −78 °C	Decomposition
2	$BrCH_2PPh_3Br$, *t*-BuOK,	Bromoalkene formed
3	Ohira–Bestmann reagent, NaOMe, MeOH, 0 °C	Decomposition



Scheme 3. The synthesis of the olefination reaction precursor **15** and the Wittig reaction.

Compound **13** is commercial available. Using copper iodide as the catalyst [25], coupling compound **12** with **13** under Cadiot–Chodkiewicz conditions provided the diyne intermediate **14** with 67% yield (Scheme 3). The free alcohol **14** was easily transformed into the key intermediate **15** in the presence of the Dess–Martin reagent which paved the way for the chain elongation through olefination [26]. With the main intermediate **15** in hand, we next focused on the olefination reaction to assemble the *trans* double bond. We first examined the feasibility of constructing the *trans* double bond under Wittig reaction conditions using commercially available pentyltriphenylphosphonium bromide [27]. Unfortunately, we obtained only the *cis* double bond rather than the *trans* double bond.

In our previous study [28], the one-pot Julia–Kocienski (J–K) olefination with a proper substrate pair proved be a powerful tool to prepare the *trans* conjugated double bond. Thus, the sulfide **18** was obtained in good yield upon the treatment of the primary alcohol **17** through a Mitsunobu thioetherification. The sulfide **18** underwent a molybdenum-catalyzed oxidation and smoothly afforded the sulfone **19** that could be the substrate for the J–K



Scheme 2. The synthesis of intermediate **12**.

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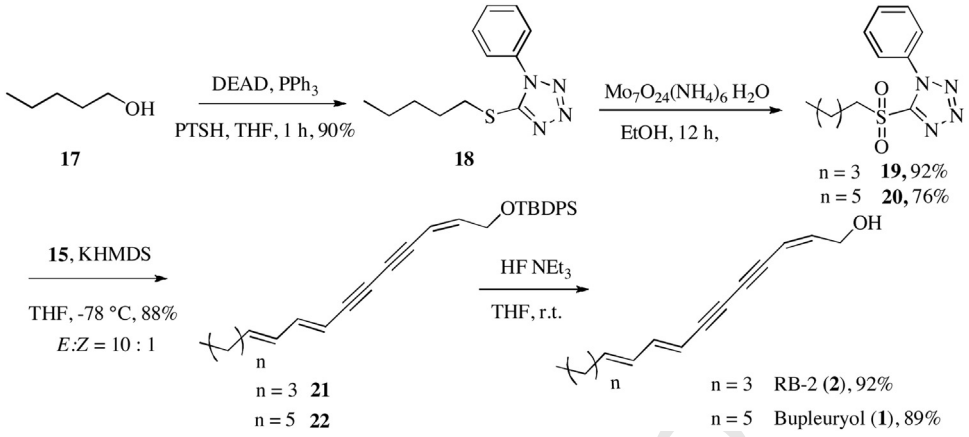

Scheme 4. Total synthesis of RB-2 (**2**) and bupleurynol (**1**).

olefination (Scheme 4). Delightfully, the coupling of **15** and **19** through one-pot J–K olefination furnished the desired (*E*/*E*/*Z*)-triene substrate **21** in a good yield with excellent *E*/*Z*-selectivity (10:1) using the Barbier-type J–K protocol. Remarkably, the diyne and the *cis* double bond were stable even under strongly basic conditions. Finally, the removal of the TBDPS group with triethylamine trihydrofluoride successfully yielded the natural product RB-2 (**2**) in 92% yield. The general applicability of this strategy was further demonstrated in the synthesis of bupleurynol **1**.

Spectroscopic characterization (^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry) confirmed that our synthetic bupleurynol and RB-2 and bupleurynol **1** were identical to the natural products [12,13]. The spectral data of RB-2 and bupleurynol **1** are presented in the Supporting information. Consistent with the report for the natural isolate, a slow isomerization to the (*Z*/*E*/*Z*) isomer in neat form was observed in bupleurynol.

3. Conclusion

In summary, the concise total syntheses of RB-2 and bupleurynol have been achieved in 10 linear steps with 26% and 22% yield, respectively. The synthesis relies on a Sonogashira cross-coupling, a Cadiot–Chodkiewicz coupling and a one-pot J–K olefination. Moreover, the access to the versatile intermediate **15**, which is a common structural motif in the related polyacetylenes [29,30], would facilitate synthetic endeavors toward other natural products. Further studies focusing on the biological evaluation of RB-2 and its derivatives are in progress and will be reported in due course.

4. Experimental

All reactions were carried out under an argon atmosphere with dry solvents. All reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded on Bruker AV-600 spectrometers at ambient temperature, using TMS as an internal standard. High resolution mass spectra (HRMS) were recorded at a Mass Spectrometry Laboratory using a Thermo Scientific Q Exactive. Spectra of all the compounds are presented in the Supporting information.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.11.032.

References

[1] R. Negri, Polyacetylenes from terrestrial plants and fungi: recent phytochemical and biological advances, Fitoterapia 106 (2015) 92–109.
[2] W. Heydenreuter, E. Kunold, S.A. Sieber, Alkynol natural products target ALDH2 in cancer cells by irreversible binding to the active site, Chem. Commun. 51 (2015) 15784–15787.
[3] H. Matsuura, G. Saxena, S. Farmer, et al., Antibacterial and antifungal polyine compounds from *Glehnia littoralis ssp. leiocarpa*, Planta Med. 62 (1996) 256–259.
[4] L.F. Liang, T. Wang, Y.S. Cai, et al., Brominated polyunsaturated lipids from the Chinese sponge *Xestospongia testudinaria* as a new class of pancreatic lipase inhibitors, Eur. J. Med. Chem. 79 (2014) 290–297.
[5] H. Kim, J. Chin, H. Choi, et al., Phosphoiodyns A and B, unique phosphorus-containing iodinated polyacetylenes from a Korean sponge *Placospongia sp*, Org. Lett. 15 (2012) 100–103.
[6] T.C. Chou, H. Dong, X. Zhang, et al., Multifaceted cytoprotection by synthetic polyacetylenes inspired by the ginseng-derived natural product panaxytriol, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 14336–14341.
[7] B. Zhang, Y. Wang, S.P. Yang, et al., Ivorenolide A, an unprecedented immunosuppressive macrolide from *Khaya ivorensis*: structural elucidation and bioinspired total synthesis, J. Am. Chem. Soc. 134 (2012) 20605–20608.
[8] Y. Wang, Q.F. Liu, J.J. Xue, et al., Ivorenolide B, an immunosuppressive 17-membered macrolide from *Khaya ivorensis*: structural determination and total synthesis, Org. Lett. 16 (2014) 2062–2065.
[9] H. Dong, L. He, M. Huang, et al., Anti-inflammatory components isolated from *Atractylodes macrocephala Koidz*, Nat. Prod. Res. 22 (2008) 1418–1427.
[10] Z.F. Zhou, M. Menna, Y.S. Cai, et al., Polyacetylenes of marine origin: chemistry and bioactivity, Chem. Rev. 115 (2015) 1543–1596.
[11] A.L. Shi Shun, R.R. Tykwinski, Synthesis of naturally occurring polyynes, Angew. Chem. Int. Ed. 45 (2006) 1034–1057.
[12] J. Zhao, Y.Z. Guo, X.S. Meng, The toxic principles of *Bupleurum longiradiatum*, Acta Pharm. Sin. 22 (1987) 507–511.
[13] H.Q. Huang, X. Zhang, Y.H. Shen, et al., Polyacetylenes from *Bupleurum longiradiatum*, J. Nat. Prod. 72 (2009) 2153–2157.
[14] J. Liu, Y. Fang, L. Yang, et al., A qualitative and quantitative determination and pharmacokinetic study of four polyacetylenes from *Radix Bupleuri* by UPLC-PDA-MS, J. Pharm. Biomed. Anal. 111 (2015) 257–265.
[15] L.M. Antunes, M.G. Organ, Metal-catalyzed coupling reactions on an olefin template: the total synthesis of bupleurynol, Tetrahedron Lett. 44 (2003) 6805–6808.
[16] H. Ghasemi, L.M. Antunes, M.G. Organ, Use of olefin templates in queued chemical transformations using late transition metal catalysis. Total synthesis of *cis* and *trans* bupleurynol *via* a single multireaction sequence, Org. Lett. 6 (2004) 2913–2916.
[17] K.S. Sindhu, A.P. Thankachan, P.S. Sajitha, et al., Recent developments and applications of the Cadiot–Chodkiewicz reaction, Org. Biomol. Chem. 13 (2015) 6891–6905.
[18] S. Ma, X. Lu, Z. Li, A novel regio-and stereospecific hydrohalogenation reaction of 2-propynoic acid and its derivatives, J. Org. Chem. 57 (1992) 709–713.

[19] X.Y. Jiang, X.H. Xu, F.L. Qing, Design and concise synthesis of gem-difluoromethylenated analogue of 7-*epi*-castanospermine, Chin. Chem. Lett. 25 (2014) 1115–1120.
[20] M. Wan, M. Yao, J.Y. Gong, et al., Synthesis of the tetracyclic core of chlorospermines, Chin. Chem. Lett. 26 (2015) 272–276.
[21] F. Bellina, A. Carpita, L. Mannocci, et al., First total synthesis of naturally occurring (−)-nitidon and its enantiomer, Eur. J. Org. Chem. 12 (2004) 2610–2619.
[22] E.J. Corey, P.L. Fuchs, A synthetic method for formyl → ethynyl conversion (RCHO → RCCH or RC=CR′), Tetrahedron Lett. 13 (1972) 3769–3772.
[23] P. Kiliçkiran, H. Hopf, I. Dix, et al., Preparation of highly hindered polyenynes, Eur. J. Org. Chem. 21 (2010) 4035–4045.
[24] J. Carreras, G. Gopakumar, L. Gu, et al., Polycationic ligands in gold catalysis: synthesis and applications of extremely π-acidic catalysts, J. Am. Chem. Soc. 135 (2013) 18815–18823.
[25] D.J. Galler, K.A. Parker, Five easy pieces. The total synthesis of phosphoiodyn A (and placotylene A), Org. Lett. 17 (2015) 5544–5546.
[26] D. Dess, J. Martin, Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, J. Org. Chem. 48 (1983) 4155–4156.
[27] D.L. Chen, F.P. Wang, X.Y. Liu, A convergent approach to the tetracyclic core of atisane diterpenes, Chin. Chem. Lett. 27 (2016) 59–62.
[28] K. Ma, D. Liao, S. Yang, et al., Studies towards the synthesis of the functionalized C3–C14 decalin framework of alchivemycin A, Org. Chem. Front. 3 (2016) 251–258.
[29] Z. Zhang, C. Lu, X. Liu, et al., Global and targeted metabolomics reveal that bupleurotoxin, a toxic type of polyacetylene, induces cerebral lesion by inhibiting GABA receptor in mice, J. Proteome Res. 13 (2013) 925–933.
[30] B. Schmidt, S. Audorsch, Stereoselective total synthesis of atractylodemayne A, a conjugated 2(*E*), 8(*Z*), 10(*E*)-triene-4, 6-diyne, Org. Lett. 18 (2016) 1162–1165.

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