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Progress toward the Total Synthesis of Bielschowskysin

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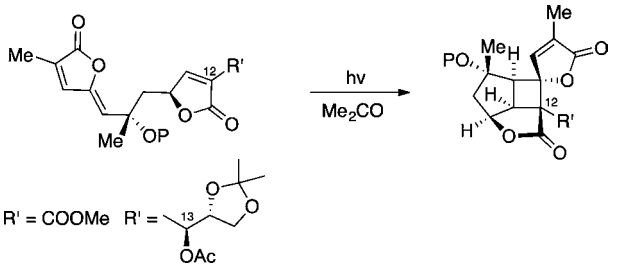
ABSTRACT



Progress toward the total synthesis of bielschowskysin is described including introduction of the quaternary C12 and neighboring C13 stereocenters.

In 2004 Rodriguez and co-workers reported the structure of bielschowskysin, a diterpene isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*.[1,2] In addition to possessing a compelling structure for total synthesis studies, bielschowskysin was reported to exhibit antiplasmodial activity and selective in vitro cytotoxicity against small-cell lung and renal cancer cell lines. This complex marine diterpene has proven to be a formidable target for total synthesis as its structural features include a highly oxygenated polycyclic ring system containing 11 stereocenters. Of particular interest is an almost fully substituted, central cyclobutane ring that incorporates a spirocyclic center. While a total synthesis of bielschowskysin has remained elusive, multiple groups have described various approaches toward its core ring system.[3]

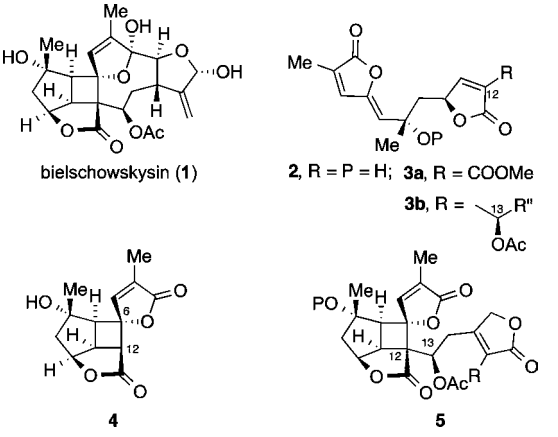


Figure 1. Structure of bielschowskysin, reported [2 + 2]-photocycloaddition,[3a] and current synthetic analysis.

In 2006 our lab reported an intramolecular [2 + 2]-photocycloaddition upon irradiation of an acetone solution of bis-butenolide **2** to produce the Western half of bielschowskysin (**4**) including 5 of the 13 stereocenters.[3a] Notably, this approach demonstrated stereocontrolled introduction of the tetrasubstituted C6 stereocenter of the desired configuration regardless of starting alkylidene

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(2) Reviews on furanocembrane diterpenes: (a) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298–317. (b) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.

(3) (a) Doroh, B.; Sulikowski, G. *Org. Lett.* **2006**, *8*, 903–906. (b) Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 1731–1733. (c) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5149–5152. (d) Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Org. Lett.* **2012**, *14*, 2195–2197. (e) Jana, A.; Mondal, S.; Hossain, M. F.; Ghosh, S. *Tetrahedron Lett.* **2012**, *53*, 6830–6833. (f) Himmelbauer, M.; Farcet, J.-B.; Gagnepain, J.; Mulzer, J. *Org. Lett.* **2013**, *15*, 3098–3101. (g) Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A. *Tetrahedron Lett.* **2013**, *54*, 1612–1615. (h) Meyer, M. E.; Phillips, J. H.; Ferreira, E. M.; Stoltz, B. M. *Tetrahedron* **2013**, *69*, 7627–7635.

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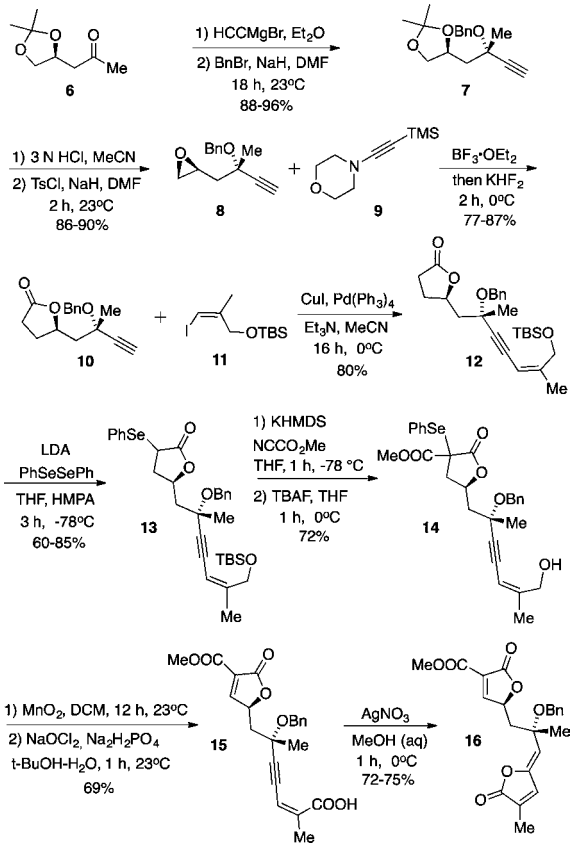
butenolide geometry. Since this communication, much of our effort has been directed toward introduction of the remaining elements of the bielschowskysin core structure in the form of butenolide **2**. Initial attempts to directly deprotonate C12 of photoadduct **4**, to react the resulting anion with an aldehyde, were unsuccessful. This is not surprising as the lactone is resistant to enolate formation, since deprotonation would result in the formation of a highly strained bridgehead olefin.[4] To circumvent this problem, we turned our attention toward preparation and examination of the C12 substituted photochemical substrates **3a**–**b**. This strategy would involve formation of the C12–C13 bond *before* the photocycloaddition, avoiding the unmanageable task of C12 alkylation. Substrate **3b** would have the added advantage and challenge of incorporating the C13 stereocenter.

Scheme 1. Synthesis of Methyl Ester **16**



We first examined the preparation of ester **3a** starting from methyl ketone **6**, available in four steps from (−)-malic acid.[3a] As demonstrated earlier,[3a] chelation-controlled addition of ethynylmagnesium bromide to ketone **6** proceeded with good stereoselectivity (ca. 5:1). Benzylation of the resulting tertiary alcohol afforded ether **7** in 88–96% yield over two steps (Scheme 1). Acetonide removal released an intermediate diol that underwent a one-pot sequence of

(4) Hayes, C. J.; Simpkins, N. S.; Kirk, D. T.; Mitchell, L.; Baudous, J.; Blake, A. J.; Wilson, C. *J. Am. Chem. Soc.* **2009**, *131*, 8196–8210.

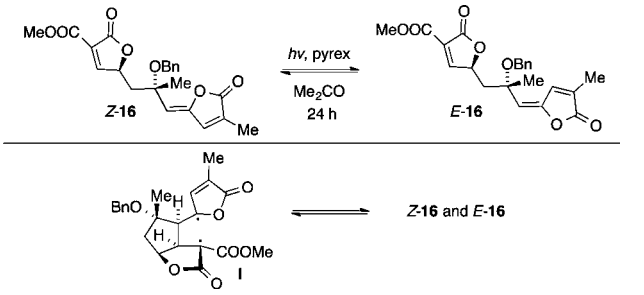
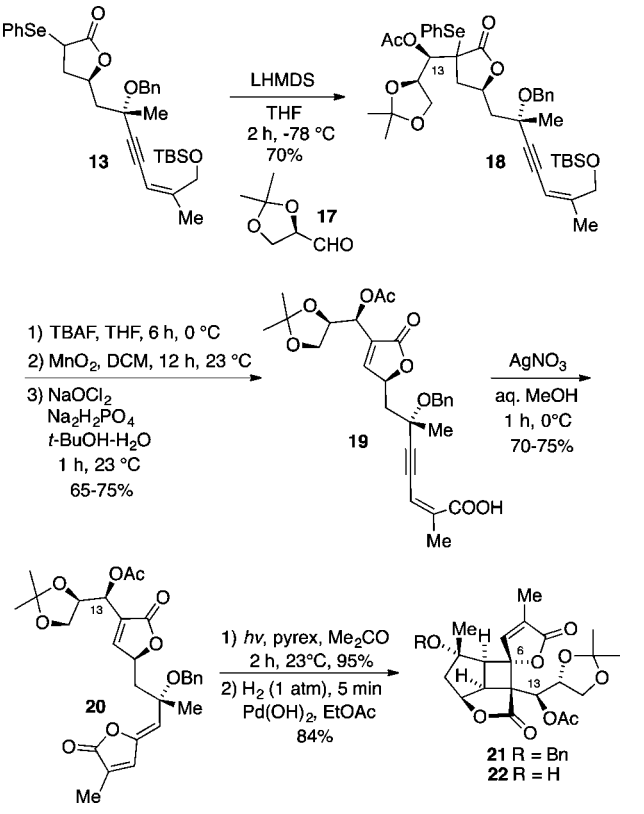


Figure 2. 1,4-Biradical intermediate **I** preferably reverts to ground state alkenes.

Scheme 2. Synthesis of of Acetate **21**



monotosylation and epoxide formation to give **8**.[5] Next, the terminal epoxide was reacted with ynamine **9** leading to **10** following the Movassaghi and Jacobsen protocol.[6] The lactone was extended though Sonagashira cross-coupling of its alkyne with vinyl iodide **11**, providing enyne **12** in 91% yield. Lactone **12** was further advanced to selenide **14** by a standard series of deprotonations, electrophilic quenches, and TBS removal. Sequential manganese dioxide and sodium hypochlorite oxidations served to convert the allylic alcohol to a carboxylic acid. Conveniently, the second

(5) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 5746–5747.
(6) Movassaghi, M.; Jacobsen, E. *J. Am. Chem. Soc.* **2002**, *124*, 2456–2457.

oxidation was accompanied by selenoxide formation and elimination affording butenolide **15** in 69% yield. Finally, silver(I)-promoted cycloisomerization gave alkylidene butenolide **16**, completing the desired photochemical substrate.

Unlike our earlier photocycloaddition (**2** to **4**, Figure 1) irradiation of *Z*-**16** was unproductive, resulting only in double bond isomerization, producing a 1:1 mixture of *Z*-**16** and *E*-**16** (Figure 2). We hypothesized the carbomethoxy group stabilizes the intermediate 1,4-diradical **I** (Figure 2), rendering the intermediate diradical recalcitrant to formation of the strained cyclobutane, instead favoring reversion to alkylidene butenolides *Z*-**16** and *E*-**16**.[7] To circumvent this effect, we reasoned it would be necessary to install the C13 oxygenation at a lower oxidation state. Our attention therefore turned to the assembly of the 13-acetoxy butenolide **20**, incorporating a key stereochemical element (C13) of bielschowskysin. To this end, substrate controlled addition of the enolate derived from lactone **13** to D-glyceraldehyde acetonide **17** resulted in adduct **18** following acetylation of the C13 hydroxyl group (Scheme 2).[8] A series of reactions identical to those described in Scheme 1 afforded alkylidenebutenolide **20**. To our delight, irradiation of **20** provided photoadduct **21** in 95% isolated yield as a single isomer. In accord with the previously published photocylization of **2** to **4** (Figure 1) the C6 stereochemistry emerged with the oxygen positioned with the desired exo orientation to provide adduct **21**, establishing 7 of 11 stereocenters common to bielschowskysin. Finally, brief hydrogenation of **21** under 1 atm of hydrogen over Pearlman's catalyst resulted in removal of the benzyl protecting group to give alcohol **22**.

In closing, we have demonstrated stereocontrolled introduction of the C6 and C12 vicinal quartenary centers of bielschowskysin (**1**) via photocycloaddition of an appropriate C12-substituted bis-butenolide. While a carbonyl substituent prevents formation of the desired cyclobutane, adjustment of the C13 oxidation level to an alcohol allows for smooth conversion to the photoadduct. Utilizing its stereochemical preference, D-glyceraldehdye acetonide was used to set the stereochemistry at C13. Future efforts are directed toward advancing to butenolide **5** and ultimately bielschowskysin.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.