Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of the polyketide moiety of the jamaicamides

Ayano Tanaka-Yanuma, Satoshi Watanabe, Keita Ogawa, Sho Watanabe, Naoto Aoki, Tetsuhiro Ogura, Toyonobu Usuki *

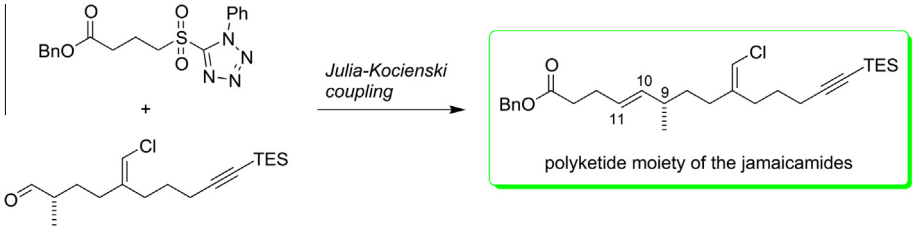
Department of Materials and Life Sciences, Faculty of Science and Technology, Sophia University, 7-1 Kioicho, Chiyoda-ku, Tokyo 102-8554, Japan

ARTICLE INFO

Article history:
Received 16 September 2015
Revised 15 October 2015
Accepted 20 October 2015
Available online xxxx

Keywords:
Marine natural products
Jamaicamides
Total synthesis
Polyketide
Julia–Kocienski coupling

ABSTRACT



Isolated from the Jamaican cyanobacterium *Lyngbya majuscula*, the jamaicamides are unique, mixed polyketide-peptides reported to be sodium channel blockers. The polyketide moiety contains an (*E*)-chloroolefin, an undetermined methyl stereocenter (C9), and an (*E*)-olefin (C10–C11). Herein we report the stereo- and regioselective synthesis of the polyketide moiety of the jamaicamides via a Julia–Kocienski coupling as the key step.

The jamaicamides A, B, and C (Fig. 1) were isolated by Gerwick and co-workers from a dark green strain of Lyngbya majuscula found in Hector's Bay, Jamaica.[1] These marine natural products have a rare and mixed polyketide-peptide structure that includes a trisubstituted (*E*)-chloroolefin, an unconfirmed methyl stereocenter (C9), an (*E*)-olefin (C10–C11), an unusual alkynyl bromide (only in jamaicamide A), a pyrrolinone ring, and a β-methoxy enone. The jamaicamide family exhibits sodium channel-blocking activity and displays cytotoxicity against both H-460 human lung and Neuro-2a mouse neuroblastoma cell lines. Intriguingly, jamaicamide B also shows anti-malarial activity and cytotoxicity to Vero cells.[2]

Synthesis of (*S*)-jamaicamide C carboxylic acid employing a Negishi cross-coupling and Johnson-Claisen rearrangement as the key steps was reported by Paige and co-workers.[3] Separately, the synthesis of the *N*-di-*t*-butoxycarbonyl [$(Boc)_2$]-protected peptide moiety of the jamaicamides starting from natural amino acids was accomplished in our laboratory.[4] We also reported the construction of the (*E*)-olefin moiety of the polyketide unit of the jamaicamides employing a Julia–Kocienski coupling.[5]

Despite their intriguing bioactivity and the unique biosynthesis of these secondary metabolites,[1,6] the total synthesis and structure–activity relationship (SAR) studies of the jamaicamides have not yet been accomplished. Herein we report the stereo- and regioselective synthesis of the polyketide moiety of the jamaicamides wherein the alkyne and carboxylic acid functionalities have respectively been protected with triethylsilyl (TES) and benzyl (Bn) groups.

As illustrated in Scheme 1, the polyketide moiety **1** of the jamaicamides was retrosynthetically divided into two parts. The (*E*)-

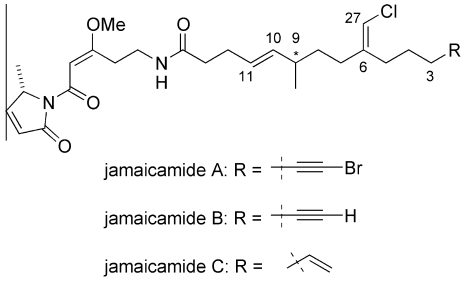


Figure 1. Structures of the jamaicamides.

* Corresponding author. Tel.: +81 3 3238 3446; fax: +81 3 3238 3361.
E-mail address: t-usuki@sophia.ac.jp (T. Usuki).

http://dx.doi.org/10.1016/j.tetlet.2015.10.069
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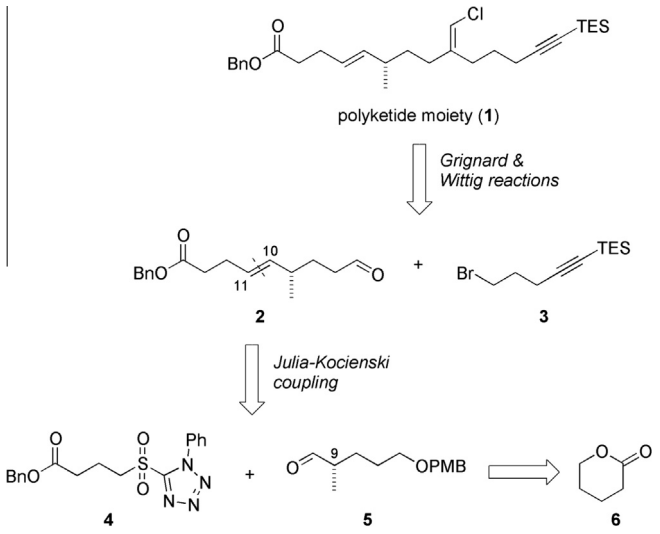


Scheme 1. Retrosynthesis of **1**.

chloroolefin would be formed at the last stage via Grignard and Wittig reactions of aldehyde **2** and bromoalkyne **3**. The (*E*)-olefin (C10–C11) of **2** would be established stereoselectively via a Julia–Kocienski coupling reaction of phenyl tetrazol sulfone **4**, which was prepared previously,[5] and aldehyde **5**. In the previous study, **5** was protected using a Bn group.[5] However, in the present investigation, a *p*-methoxybenzyl (PMB) group, which can be easily removed under milder conditions, was employed. The fragment **5** would be obtained from commercially available δ-valerolactone **6**.[7]

The synthesis commenced with the preparation of aldehyde **5** from lactone **6** (Scheme 2). Treatment of **6** with potassium hydroxide (KOH) and *p*-methoxybenzyl chloride (PMBCl) in toluene gave carboxylic acid **7** in 58% yield.[7] After acylation of **7** with pivaloyl chloride (PivCl), the resultant ester was converted to imide **8** in 92% yield using (*S*)-4-benzyl-2-oxazolidinone and *n*-butyllithium (*n*-BuLi).[8] Utilizing the Evans reaction, stereoselective methylation with sodium hexamethyldisilazide (NaHMDS) and iodomethane (MeI) from −78 to −40 °C in tetrahydrofuran (THF) gave **9** in 63% yield.[9,10] Removal of the chiral auxiliary via treatment with lithium borohydride ($LiBH_4$) in diethyl ether (Et_2O) led to alcohol **10**.[11] Finally, **10** was oxidized using the Dess–Martin periodinane (DMP) reagent to afford aldehyde **5** in 86% yield.

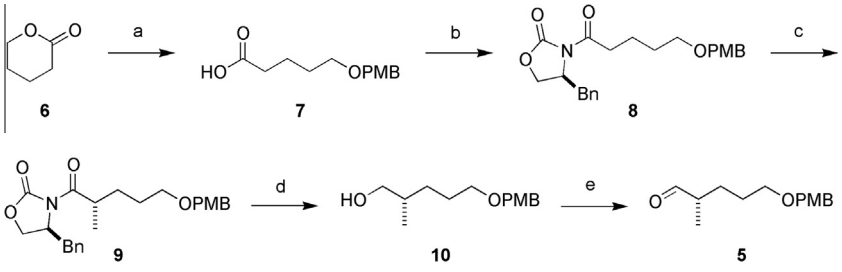
With the two segments **4** and **5** in hand, attention was focused on the construction of the (*E*)-olefin via a Julia–Kocienski coupling reaction (Scheme 3).[12,13] Sulfone **4** in THF was treated with NaHMDS at −78 °C for 30 min to produce the corresponding anion, which was then reacted with aldehyde **5** at −78 °C for 3 h to give the desired olefin **11** in 80% yield. The *E*/*Z* selectivity of **11** was determined to be 16:1 by ^{1}H NMR analysis.[14] Next, the *p*-methoxybenzyl (PMB) protecting group was removed using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to give alcohol **12**.[15] Finally, **12** was oxidized using DMP to afford aldehyde **2** in 88% yield.

To obtain compound **15**, a Grignard reaction between aldehyde **2** and (5-bromo-pent-1-ynyl)-triethylsilane **3** was attempted (Scheme 4).[16,17] Formation of the dianion of pent-4-yn-1-ol **13** with *n*-BuLi followed by successive treatment with triethylsilyl chloride (TESCl) and 2 M HCl produced **14** in 95% yield.[18,19] The Appel reaction was then performed to afford **3** in 97% yield. After insertion of magnesium into **3**, the reaction was then conducted from −78 °C to room temperature in THF. However, because the reaction did not proceed even after 18 h, likely due to the structurally complexity of **2**, this synthetic route was abandoned.

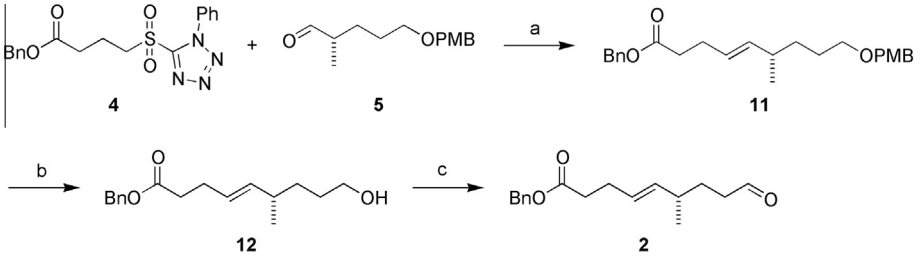
As an alternative strategy, the use of simplified aldehyde **17** was considered for the Grignard reaction with alkyl bromide **3**, as shown in Scheme 5. The (*E*)-olefin (C10–C11) of **1** would be constructed via a Julia–Kocienski coupling reaction between phenyl tetrazol sulfone **4**[5] and the corresponding aldehyde **16**.

Treatment of pentane-1,5-diol **18** with PMBCl and sodium hydride (NaH) in the presence of tetra-*n*-butyl ammonium iodide (TBAI) gave the monoprotected alcohol **19** in 64% yield (Scheme 6).[20] Swern oxidation of **19** furnished aldehyde **17** in 78% yield.[21] Next, the reaction of **17** with the Grignard reagent derived from **3** was performed to afford the desired product **20** in 53% yield.[16,17]

Formation of the (*E*)-chloroolefin was then attempted via a Wittig reaction (Scheme 7). First, Swern oxidation of **20** led to



Scheme 2. Synthesis of aldehyde **5**. Reagents and conditions: (a) KOH, PMBCl, toluene, reflux, 16 h, 58%; (b) PivCl, Et_3N, −78 to 0 °C, 2 h, then *n*-BuLi, (*S*)-oxazolidinone, THF, −78 to 0 °C, 3 h, 92%; (c) NaHMDS, MeI, THF, −78 to −40 °C, 3.5 h, 63%; (d) $LiBH_4$, MeOH, Et_2O, 0 °C to rt, 3 h, 87%; (e) DMP, CH_2Cl_2, rt, 3 h, 86%.



Scheme 3. Synthesis of aldehyde **2**. Reagents and conditions: (a) NaHMDS, THF, −78 °C, 3 h, 80%; (b) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C to rt, 4 h, 94%; (c) DMP, CH_2Cl_2, rt, 4 h, 88%.