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Efficient synthesis of bongkrekic acid. Three-component convergent strategy

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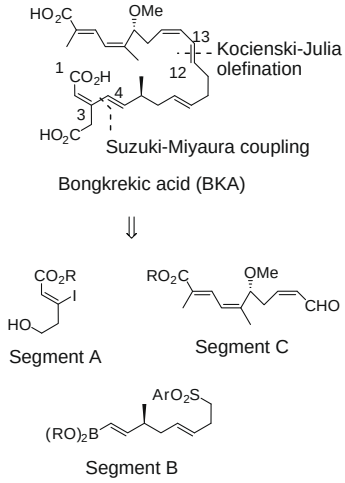
ABSTRACT

An efficient total synthesis of the apoptosis inhibitor bongkrekic acid was accomplished using a three-component convergent strategy involving a Kocienski-Julia olefination and a Suzuki–Miyaura coupling, in which the longest linear sequence was 18 steps and proceeded in 6.4% overall yield. The torquoselective olefination also contributed to the shortening of the synthesis.

Bongkrekic acid (BKA) is a natural toxic antibiotic produced by the bacterium Burkholderia *cocovenenans*.[1] By binding to the adenine nucleotide translocator (ANT)[2] from inside mitochondria and fixing its conformation in the m-state, BKA inhibits the mitochondrial permeability transition pore (MPT). It has therefore been used as a pharmacological and biological reagent to modulate the properties of the MPT or the ANT. Furthermore, BKA was also found to inhibit mitochondria-induced apoptosis by preventing the formation of MPT,[3] which is linked to numerous phenomena, such as inhibition of phosphatidylserine exposure,[4] inhibition of chloride channels,[5] and reduction of ischemic-induced neuronal death.[6] Although it is now an important tool as an apoptosis inhibitor, due to its limited availability from fermentation or chemical synthesis,[7] the bioactivity of BKA has not been extensively investigated, especially its in vivo activity. In order to assess its use in and potential contribution to apoptotic science, BKA and its analogues will have to be synthesized on a large scale in pure form. BKA is a heptaene-tricarboxylic fatty acid with two allylic chiral stereocenters. The total synthesis of BKA was reported by Corey[8] in 1984 and by our group in 2004.[9] Corey did not isolate BKA in pure form, owing to its instability; likewise our previous *semi*-convergent synthesis was quite long (32 steps in the longest linear sequence). In this Letter, we describe the second-generation synthesis of BKA, including a three-component convergent strategy using a doubly terminally functionalized middle segment.

In our previous synthesis, the final conversion, which required 16 steps after combining each segment, reduced the efficiency. The key point of this new synthesis would be a reduction in the number of steps after the three-component coupling. Our new synthetic strategy is shown in Scheme 1. BKA was separated at the C3–C4 and C12–C13 bonds into three segments, A, B, and C. Segments



Scheme 1. The second-generation BKA synthesis: a three-component convergent strategy.

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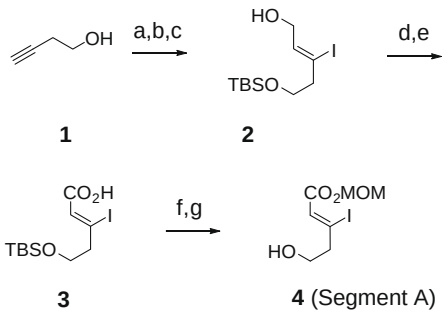


Scheme 2. Synthesis of Segment A. Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 0 °C then rt, 99%; (b) BuLi, −40 °C; $(HCHO)_n$, THF, rt, 94%; (c) Red-Al, ether, 0 °C; I_2, −50 °C then rt, 65%; (d) MnO_2, benzene/CH_2Cl_2, rt; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, THF, rt, 96% for two steps; (f) MOMCl, *i*-Pr_2NEt, rt, 99%; (g) 3 M HCl, THF, rt, 84%.

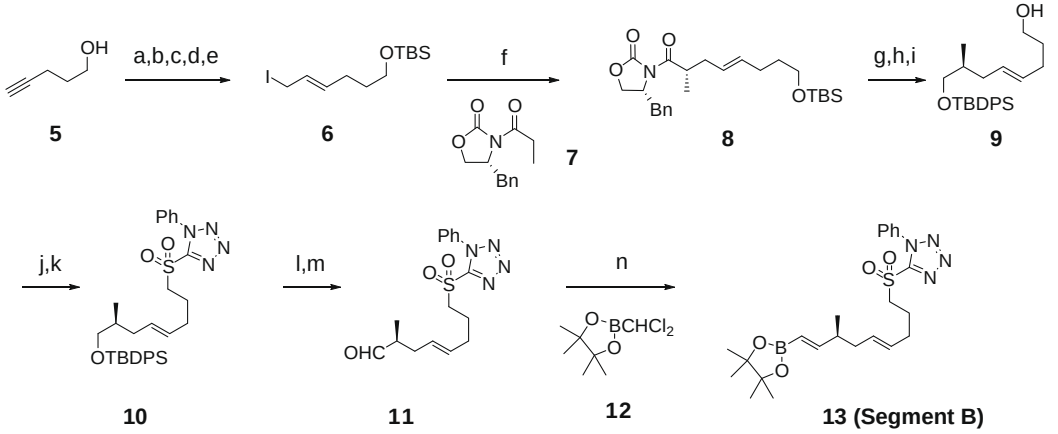
B and C would be connected by the modified Julia olefination,[10] and Segment A would be coupled with the resulting Segment B–C via the Suzuki–Miyaura coupling.[11] The oxidation state of Segment A should be high so as to decrease the number of final oxidation steps leading to the dicarboxylic acid. Segment B, which has the dual functions of alkenyl boronate for the Suzuki–Miyaura coupling and arylsulfone for the Julia olefination, would be prepared through asymmetric alkylation. The question was whether the alkenyl boronate would be compatible with the Julia olefination. Segment C would be prepared from the readily available enantiomerically pure glycidol.

Scheme 2 shows the preparation of Segment A starting from 3-butyn-1-ol (**1**), which was converted into (*Z*)-iodoalkene **2** by the successive TBS protection, homologation of the lithium acetylide with paraformaldehyde, and reductive alumination with Red-Al followed by iodination. The alcohol of **2** was subjected to a stepwise oxidation with MnO_2 followed by $NaClO_2$ to afford the carboxylic acid **3**. After several attempts to protect the carboxylic acid, the MOM ester was found to be suitable for acid-mediated deprotection at the final stage, since under basic conditions, the C2–C3 alkene conjugated to the C1-ester of BKA was readily isomerized to the *E*-isomer. The TBS group could be removed selectively by treatment with 3 M HCl to provide **4.**

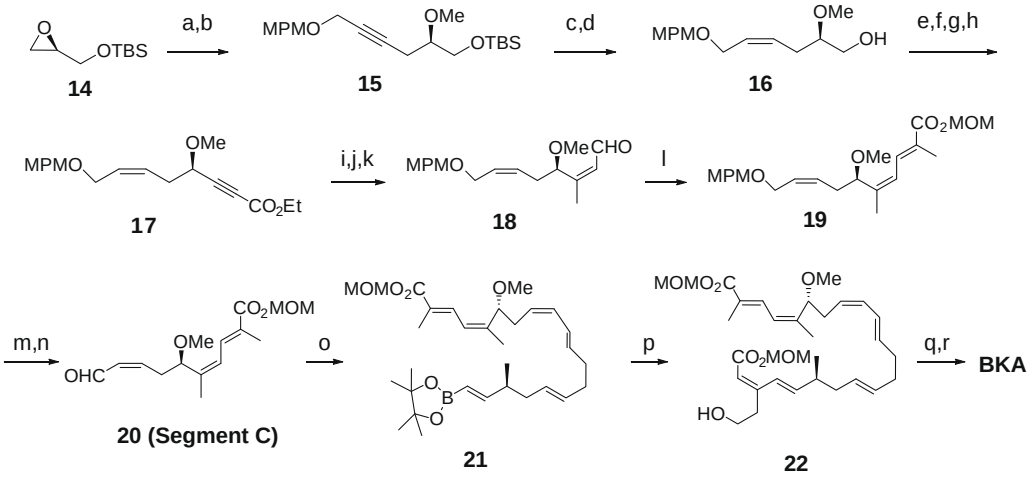
The synthesis of Segment B commenced with the asymmetric alkylation of the Evans oxazolidinone **7** with **6**, prepared from 4-pentyn-1-ol (**5**) in five steps, to afford **8** with excellent diastereoselectivity in good yield (Scheme 3). Reductive removal of the chiral auxiliary, followed by protection of the alcohol with a TBDPS group, gave **9**, which was subjected to the Mitsunobu reaction, followed by oxidation, to provide the tetrazolylsulfonyl compound **10**. After deprotection of the TBDPS group with TBAF/AcOH and then Swern oxidation, the aldehyde **11** was subjected to the $CrCl_2$-catalyzed borylalkenylation[12] to furnish the doubly terminally functionalized middle segment **13** (Segment B).

Segment C has a multi-substituted conjugated diene coupled with the MOM ester, a *cis*-alkene, and an asymmetric center. Alkynylation of the readily available (*S*)-glycidyl ether **14** with the lithium acetylide of the MPM-protected propargyl alcohol, followed by methylation, afforded **15**, which was subjected to the Lindlar partial reduction to give, after deprotection of the TBS group, the *cis*-alkene **16** (Scheme 4). The alcohol was oxidized via the Swern protocol, followed by the Corey–Fuchs alkynylation[13] to give the alkyne **17**, after carboxylation of the terminal alkyne. The cis-selective conjugate addition[14] with a cuprate, and then successive treatment with DIBAL and MnO_2, afforded the requisite trisubstituted alkene **18**. The next crucial step was the construction of the unsaturated MOM ester **19**. Attempts at the preparation of the Wittig reagent **23** bearing a MOM ester were unsuccessful, presumably due to its instability. Since the direct formation of the MOM ester would be favorable, we decided to use the torquoselective olefination via ynolates.[15] The aldehyde was reacted with the lithium ynolate **24**, prepared from the treatment of ethyl 2,2-dibromopropanoate with *t*-BuLi,[16] to give the unsaturated carboxylate, which was treated in situ with MOMCl to provide the desired conjugated MOM ester in 75% yield as a single isomer. After removal of the MPM group with DDQ, the resulting alcohol was oxidized to **20** (Segment C).

With the three segments in hand, we addressed the final challenge of the three-component coupling. The Kocienski-Julia olefination of Segment C (**20**) with Segment B (**13**) in the presence of KHMDS successfully furnished the coupled Segment B–C (**21**) with excellent *E*-selectivity in high yield. Next, **21** was coupled with Segment A (**4**) by the Suzuki–Miyaura coupling and provided **22** having the entire BKA skeleton in excellent yield. Finally, straightforward oxidation of the primary alcohol by the Jones reagent, followed by deprotection with 6 M HCl afforded BKA.



Scheme 3. Synthesis of Segment B. Reagents and conditions: (a) TBSCl, imidazole, 4-DMAP, CH_2Cl_2, rt, 91%; (b) BuLi, THF, −78 °C; $(HCHO)_n$, rt, 95%; (c) Red-Al, ether, 0 °C then rt, 94%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C then rt; (e) NaI, acetone, rt, 93% for two steps; (f) LDA, THF, **7**, −78 °C then **6**, −78 °C, allowed to −20 °C, 83%, >99% de; (g) $LiAlH_4$, THF, 0 °C, quant.; (h) TBDPSCl, imidazole, 4-DMAP, CH_2Cl_2, quant.; (i) 3 M HCl, THF, rt, 99%; (j) 1-phenyl-5-mercaptotetrazole, DEAD, Ph_3P, THF, 0 °C, 97%; (k) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30% H_2O_2, ethanol, 0 °C then rt, 90%; (l) TBAF, AcOH, THF, 96%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (n) $CrCl_2$, LiI, Mn, TMSCl, **12**, THF, 0 °C then rt, 66% for two steps.



Scheme 4. Synthesis of Segment C and completion of the total synthesis of BKA. Reagents and conditions: (a) 3-(4-methoxyphenylmethoxy)-1-propyne, BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 64%; (b) NaH, MeI, THF, 0 °C then rt, quant.; (c) Lindlar catalyst, quinoline, hexane, H_2, rt; (d) 3 M HCl, THF, rt, 93% for two steps; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (f) CBr_4, Ph_3P, CH_2Cl_2, 0 °C then rt, 77% for two steps; (g) BuLi, THF, −78 °C, 93%; (h) BuLi, $ClCO_2Et$, THF, −78 °C then −45 °C, 89%; (i) MeLi, CuI, THF, −78 °C, 94%; (j) DIBAL, THF, −78 °C, 96%; (k) MnO_2, benzene, 50 °C; (l) $CH_3CBr_2CO_2Et$, *t*-BuLi, THF, −78 °C then 0 °C; **18**, rt; MOMCl, 0 °C then rt, 75% for two steps; (m) DDQ, CH_2Cl_2, H_2O, rt, 93%; (n) MnO_2, benzene, rt; (o) **13**, KHMDS, THF, −78 °C; **20**, −78 °C, 92% for two steps; (p) **4**, $(Ph_3P)_2PdCl_2$, Et_3N, I_2, MeOH, rt, 86%; (q) Jones reagent, acetone, 0 °C; (r) 6 M HCl, THF, MeOH, rt, 34% for two steps.

The BKA produced herein was stable enough to be purified with normal phase HPLC and the ^1H and ^{13}C NMR spectral data of the synthetic BKA were identical to those of the natural BKA.[17] The optical rotation of the synthetic BKA, $[\alpha]_D^{23}$ −51.3 (*c* 1.5, $CHCl_3$), was quite different from that of the natural product ($[\alpha]_{589}^{25}$ +162.5 (the conditions were not described),[1b] in which even the sign is opposite. To verify the specific rotation, the synthetic BKA was esterified with diazomethane to convert it into the corresponding trimethyl ester, which showed $[\alpha]_D^{24}$ +81.5 (*c* 0.27, $CHCl_3$), which was identical with Corey's[8] ($[\alpha]_D^{23}$ +80) and our previous reports[9] ($[\alpha]_D^{26}$ +80.0 ($CHCl_3$)). From these results, we concluded that the optical rotation described herein is correct, since our synthetic BKA is chemically pure.

In conclusion, we have achieved an efficient convergent total synthesis of (+)-BKA, using a torquoselective olefination and the Kocienski-Julia olefination and the Suzuki–Miyaura coupling as the segment-binding steps. It is noteworthy that after combining the three segments, it took only two steps to complete the synthesis, indicating the high efficiency of this synthesis to provide BKA and its analogues. Furthermore, the torquoselective olefination also contributes to the shortening of the synthesis. The longest linear sequence is only 18 steps and proceeds in 6.4% overall yield, which is an improvement over our previous process (32 steps and 0.6% overall yield). Actually, we have prepared enough BKA to test for bioactivity. The biological evaluation of BKA and its analogues, including the apoptotic inhibitory activity in vitro and re-examination of the cytotoxicity in vivo, is now in progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.129.

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17. Analytical data of synthetic BKA: ^1H NMR (600 MHz, $CDCl_3$) δ: 1.07 (3H, d, J = 7.2 Hz), 1.88 (3H, s), 1.92 (1H, m), 1.94 (3H, s), 2.04 (2H, m), 2.13 (2H, m), 2.17 (1H, m), 2.27 (1H, ddd, J = 6.0, 8.4, 13.8 Hz), 2.36 (1H, m), 2.46 (1H, ddd, J = 7.8, 8.4, 13.8 Hz), 3.21 (3H, s), 3.33 (1H, d, J = 16.2 Hz), 3.47 (1H, d, J = 16.2 Hz), 4.33 (1H, dd, J = 4.8, 9.0 Hz), 5.33–5.43 (2H, m), 5.72 (1H, s), 5.74 (1H, dt, J = 6.6, 15.0 Hz), 6.01 (1H, dd, J = 8.4, 15.6 Hz), 6.05 (1H, dd, J = 10.2, 11.4 Hz), 6.30 (1H, dd, J = 10.8, 15.0 Hz), 6.34 (1H, d, J = 12.6 Hz), 7.44 (1H, d, J = 15.6 Hz), 7.64 (1H, d, J = 12.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 11.8, 18.6, 20.5, 32.2, 32.6, 33.2, 38.8, 40.0, 40.7, 56.8, 80.0, 118.2, 124.1, 124.3, 124.7, 125.2, 125.3, 128.1, 131.4, 131.5, 134.6, 135.9, 145.5, 148.5, 148.9, 170.4, 174.7, 176.8; IR (Neat): 2930, 1697, 1684 cm^{-1}; MS (FAB) m/z 509 (M+Na); HRMS (FAB) calcd for $C_{28}H_{28}NaO_7$: 509.2515 found 509.2509; $[\alpha]_D^{23}$ −51.3 (*c* 1.5, $CHCl_3$).