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Tetrahedron Letters 45 (2004) 8863–8866
Tetrahedron Letters

Total synthesis of (+)-bongkrekic acid

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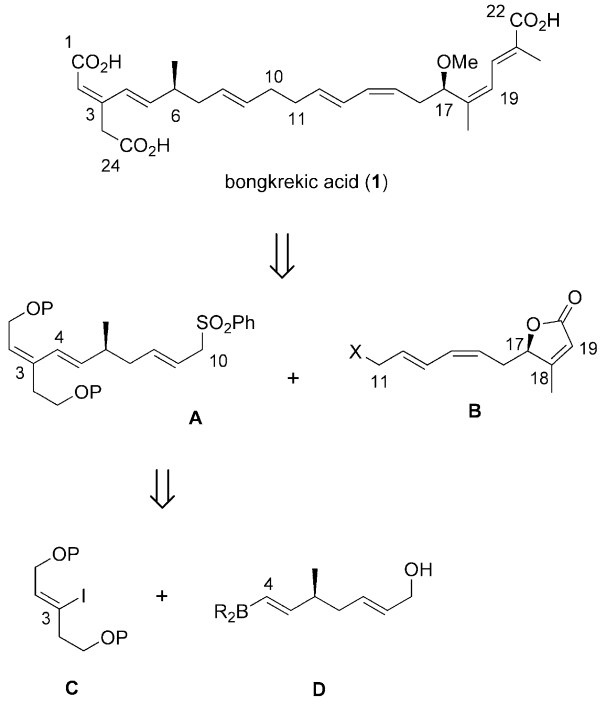
Received 31 August 2004; revised 22 September 2004; accepted 29 September 2004
Available online 14 October 2004

Abstract—Total synthesis of bongkrekic acid, an important apoptosis inhibitor, has been accomplished. The strategy includes inexpensive starting materials, asymmetric alkylation, anionic allyl coupling and oxidative manipulations. This process would provide a sufficient amount of bongkrekic acid and its analogues.

Bongkrekic acid (**1**)[1] is a natural toxic antibiotic produced by the microorganism *Pseudomonas cocovenenans*. The high toxicity of **1** has been attributed to its affinity for the ATP/ADP translocator protein residing in the mitochondrial inner membrane, which prevents oxidative phosphorylation ($IC_{50} = 2 \times 10^{-8}$ M).[2] Furthermore, by binding to the protein to prevent opening of mitochondrial permeability transition pores, bongkrekic acid **1** has been found to be an inhibitor of apoptosis,[3] making it a significant biochemical tool for investigation. However, due to the difficulty in obtaining **1** by fermentation, an efficient chemical synthesis of **1** is still required. Since Corey's first total synthesis in 1984,[4] including optical resolution steps, there have been no reports on the synthetic investigation of **1**.[5] We report herein the stereocontrolled, asymmetric synthesis of (+)-bongkrekic acid.

Bongkrekic acid (**1**), a polyene–tricarboxylic fatty acid, has three pairs of conjugated dienes and two allylic stereogenic centres. The efficiency of the synthesis depends upon the stereocontrolled construction of this characteristic polyene skeleton, especially the C2–C3 and C18–C19 trisubstituted *(Z)*-alkenes and oxidation to give the terminal carboxylic acids, since the polyene unit might be unstable under harsh conditions. Our synthetic strategy is outlined in Scheme 1. Since a convergent synthesis would be useful for the preparation of bongkrekic acid analogues for biochemical investigation, **1** was divided at the C10 and C11 bond into segments **A** (C1–C10) and **B** (C11–C22), which would be connected by allylic coupling. Segment **A** would be synthesized via the Suzuki coupling[6] of the (*E*)-vinyl borane **D** with the (*Z*)-iodoalkene **C**. For the preparation of segment **B**, the construction of the trisubstituted (*Z*)-alkene (C18–C19) next to the chiral carbon (C17) would constitute the key step, which would be accomplished using the chiral butenolide (Scheme 2).



Scheme 1. Retrosynthesis of bongkrekic acid **1**.

Keywords: Apoptosis; Carboxylic acid; Oxidation; Natural product; Total synthesis.
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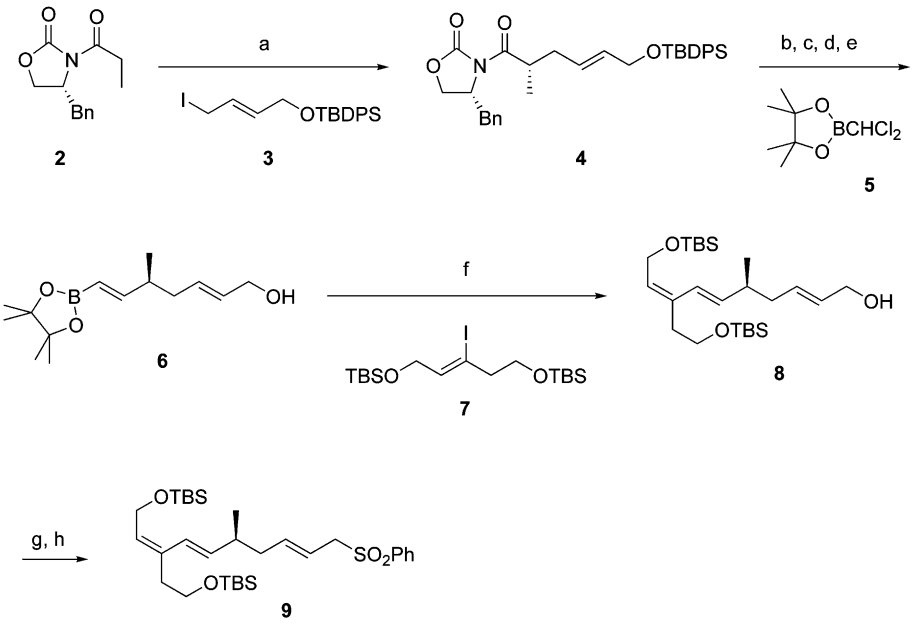
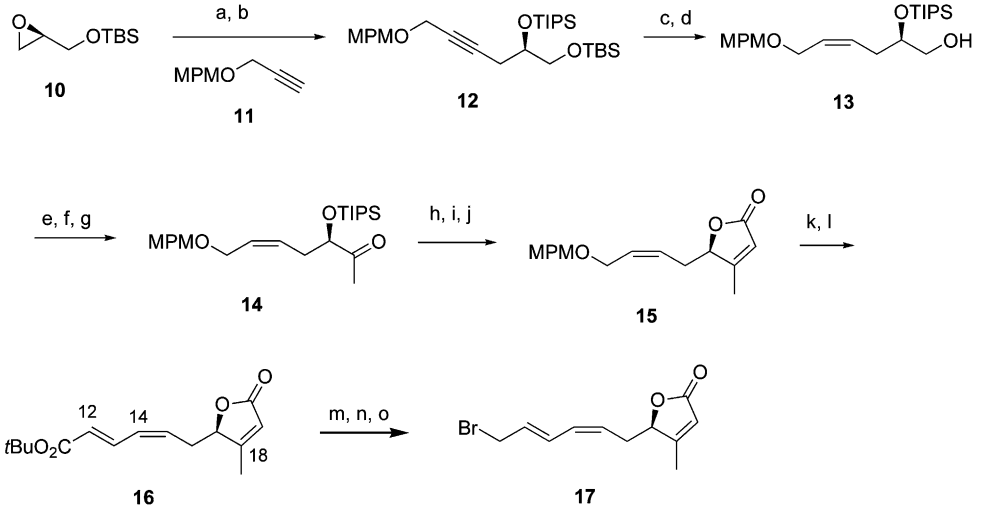
doi:10.1016/j.tetlet.2004.09.162



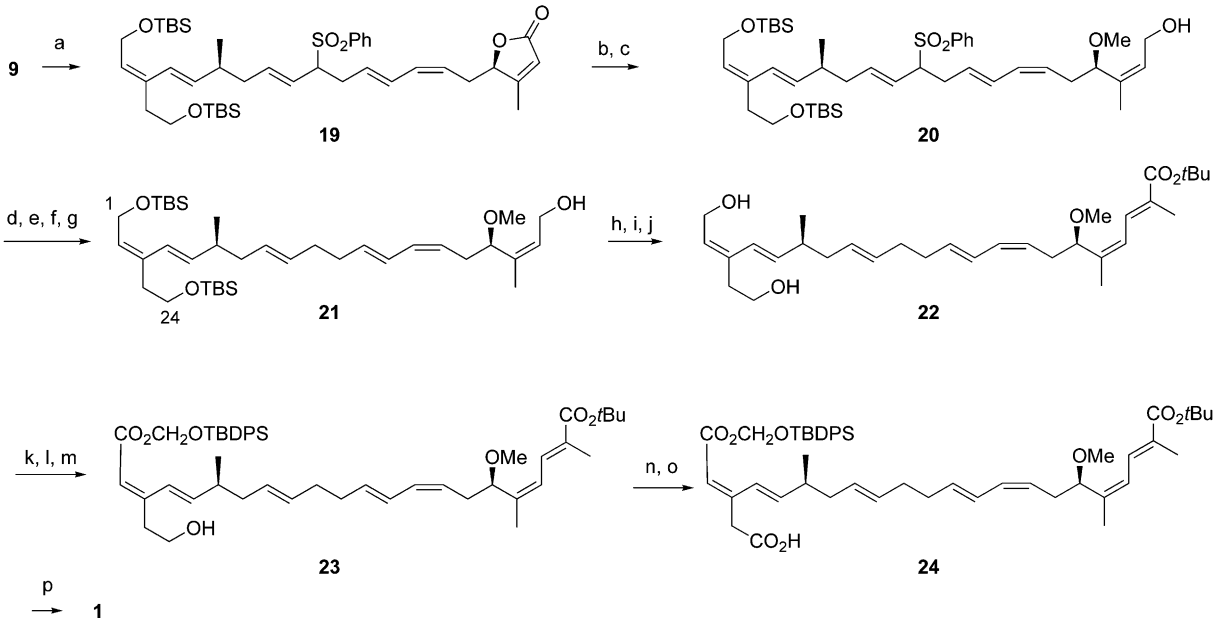
Scheme 2. Reagents and conditions. (a) LDA, THF, **3**, 85%, >95% de; (b) $LiAlH_4$, THF, 88%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) **5**, $CrCl_2$ (0.35 equiv), LiI, Mn, TMSCl, THF; 74% for two steps; (e) TBAF, THF, 92%; (f) **7**, $PdCl_2(PPh_3)_2$, Et_3N, MeOH, 92%; (g) MsCl, $^iPr_2EtN$, 4-DMAP, CH_2Cl_2; (h) $PhSO_2Na$, DMF, 81% for two steps.

Synthesis of the (*E*)-vinyl borane **D** commenced with asymmetric alkylation of Evans' oxazolidinone **2**[7] with (*E*)-1-*tert*-butyldiphenylsiloxy-4-iodo-2-butene (**3**)[8] to provide **4** with excellent diastereoselectivity in good yield. After reductive removal of the chiral auxiliary, the resulting alcohol was oxidized to furnish the aldehyde, which was subjected to $CrCl_2$ catalyzed borylalkenylation[9] with dichloromethylboronic ester **5**[10] to produce the (*E*)-alkenylboronic ester **6** after deprotection. Suzuki coupling of the boronic ester **6** with the (*Z*)-iodoalkene **7**, prepared from 3-butyn-1-ol,[11] provided the desired (2*Z*,4*E*,8*E*)-triene alcohol **8** in 92% yield without any detected stereoisomers. The alcohol **8** was converted to the unstable **9** as segment **A**, which was immediately subjected to the next coupling reaction.

The synthesis of segment **B** was completed as shown in Scheme 3. The (*S*)-glycidyl ether **10**, prepared by silylation of the readily available (*S*)-glycidol,[12] was reacted with the lithium acetylide of 3-(*p*-methoxyphenylmethoxy)propyne in the presence of $BF_3{\cdot}OEt_2$,[13] followed by protection of the resulting hydroxyl group, to afford **12**. The alkyne was hydrogenated using the Lindlar catalyst to give the *cis*-alkenyl alcohol **13** after selective deprotection of TBS ether. Swern oxidation, followed by methylation of the resulting aldehyde, furnished the



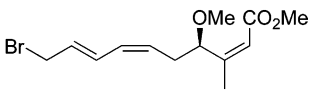
Scheme 3. Reagents and conditions. (a) **11**, BuLi, $BF_3{\cdot}OEt_2$, THF, 75%; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 88%; (c) Pd–$CaCO_3$–$Pb(OAc)_2$, H_2, quinoline, hexane, 93%; (d) 3 M HCl aq, THF, 91%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (f) MeMgBr, THF, 87% for two steps; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%; (h) AcOEt, LDA, THF; (i) TBAF, THF, 80% for two steps; (j) MsCl, Et_3N, CH_2Cl_2, 99%; (k) DDQ, CH_2Cl_2, H_2O, 92%; (l) MnO_2, CH_2Cl_2; $Ph_3P{=}CHCO_2{}^tBu$, 87%; (m) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (n) $ClCO_2Et$, Et_3N, THF; $NaBH_4$, 97% for two steps; (o) CBr_4, PPh_3, CH_2Cl_2, 99%.



Scheme 4. Reagents and conditions. (a) BuLi, HMPA, THF; **17**, 86%; (b) DIBAH, THF; (c) $NaBH_4$, THF, H_2O, 70% for two steps; (d) 5% Na–Hg, Na_2HPO_4, MeOH, 93%; (e) ^tBuCOCl, Et_3N, CH_2Cl_2, 96%; (f) MeOTf, 2,6-di-*tert*-butylpyridine, benzene, 83%; (g) DIBAH, THF, 81%; (h) Dess–Martin reagent, benzene–CH_2Cl_2 (2:1); (i) $Ph_3P{=}C(CH_3)CO_2{}^tBu$, benzene, 80% for two steps; (j) 3 M HCl aq, THF, 82%; (k) MnO_2, benzene–CH_2Cl_2 (2:1); (l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, ^tBuOH, H_2O; (m) $ClCH_2OTBDPS$, Et_3N, THF, 40% for three steps; (n) Dess–Martin reagent, benzene–CH_2Cl_2 (2:1); (o) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, ^tBuOH, H_2O; (p) 3 M HCl, MeOH, 50% for three steps.

(*R*)-α-siloxy methyl ketone **14**. The lithium enolate of ethyl acetate efficiently added to the ketone **14** to give an adduct, which was treated with TBAF followed by dehydration, to provide the butenolide **15** in excellent yield. After deprotection of the MPM group, the resulting allylic alcohol was oxidized to the aldehyde, which was subjected to the Wittig reaction to give the unsaturated *t*-butyl ester **16** bearing the (12*E*,14*Z*,18*Z*)-triene unit of segment **B** with no detectable stereoisomers. The *tert*-butyl ester was converted to **17** as segment **B**.

With both segments **A** and **B** in hand, the task of coupling them was addressed. Attempted coupling of the lithiated **9** with **18** as segment **B** led to the desired product in only 42% yield. After attempts to improve the efficiency of the coupling, compound **17** bearing the butenolide function was found to be a much better coupling partner and **19** was isolated in 86% yield. The lactone **19** was reduced to afford the diol **20**. Desulfonylation was carried out with Na–Hg, then protection of the primary alcohol, methylation of the secondary alcohol and deprotection were successively employed to afford **21** in good overall yield. Oxidation of **21**, followed by Wittig olefination, afforded **22** with excellent *E*-selectivity, after removal of the TBS groups.



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Our final concern in the synthesis was oxidation of the terminal hydroxyl groups to the tricarboxylic acid in the presence of the conjugated dienes. In the presence of C-1 carboxylic acid, the oxidation of C-24 was found to be extremely poor. To improve the yields in the final sequence, we set the triester of **1** as the initial target. Although the yield of oxidative functionalization was improved, the hydrolysis at C-1 and C-24 methyl esters was poor. After investigation on suitable esters of **1**, we found that the 2-*tert*-butyldiphenylsiloxymethyl ester[14] was easily removed under mild conditions without isomerization and survived oxidative conditions. The diol **22** was oxidized by MnO_2, followed by $NaClO_2$, to give the C-1 carboxylic acid, which was esterified by 2-*tert*-butyldiphenylsiloxymethyl chloride with triethylamine to give **23**. The C-24 oxidation was performed using the Dess–Martin reagent, followed by $NaClO_2$, to afford **24**. Final hydrolysis of **24** was accomplished by HCl in methanol at room temperature to furnish **1** in 50% yield for three steps from **23**. Synthetic bongkrekic acid was identical with an authentic sample by HPLC. The corresponding trimethyl ester of **1**,[15] prepared by esterification using diazomethane, was spectroscopically indistinguishable from the trimethyl ester derived from natural sample (Scheme 4).

In conclusion, a convergent asymmetric synthesis of bongkrekic acid has been achieved. This process provides a sufficient amount of bongkrekic acid and also constitutes a route to a wide variety of analogues for apoptosis research.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan and

Suntory Institute of Bioorganic Research. We thank Professor Y. Shinohara and Professor H. Terada for providing natural bongkrekic acid and Daiso Co. Ltd for supplying (*S*)-3-chloro-1,2-propandiol.

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15. Trimethyl ester of **1**: $[\alpha]_D^{26}$ +80 (*c* 0.15, $CHCl_3$) (the naturally derived sample: $[\alpha]_D^{26}$ +84 (*c* 0.24, $CHCl_3$); IR($CDCl_3$): 1740, 1714, 1635, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.02 (3H, d, J = 7.2 Hz), 1.83 (3H, s), 1.94 (3H, s), 1.95–2.16 (5H, m), 2.33–2.39 (3H, m), 2.56 (1H, ddd, J = 7.2, 7.2, 14.0 Hz), 3.21 (3H, s), 3.32 (2H, s), 3.67 (3H, s), 3.71 (3H, s), 3.75 (3H, s), 4.34 (1H, t, J = 7.2 Hz), 5.22 (1H, m), 5.31–5.44 (2H, m), 5.67 (1H, dt, J = 6.0, 15.0 Hz), 5.69 (1H, s), 5.99 (1H, m), 6.04 (1H, m), 6.26 (1H, dd, J = 11.2, 15.6 Hz), 6.36 (1H, d, J = 11.2 Hz), 7.49–7.53 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 170.5, 168.9, 166.1, 147.0, 145.3, 144.7, 134.8, 132.0, 131.3, 130.4, 128.0, 126.2, 125.4, 124.8, 124.5, 124.1, 118.1, 78.2, 56.3, 52.1, 51.7, 51.1, 40.3, 39.6, 37.5, 32.8, 32.3, 32.0, 19.2, 18.6, 12.3. MS (EI) m/z 528 (M^+).