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Total Synthesis of the Anti-Apoptotic Agents Iso- and Bongkrekic Acids

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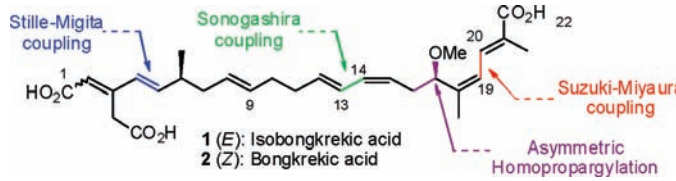
ABSTRACT



The first convergent total synthesis of isobongkrekic acid is reported involving three different stereospecific palladium cross-couplings for the formation of the diene units. Access to bongkrekic acid by this route is also demonstrated. These syntheses involve the formation of several potentially general building blocks.

Isobongkrekic acid (IBA, **1**) is a complex fatty triacid which was isolated from the fermentation of *Pseudomonas cocovenenants* in 1976.[1] Closely connected to its better known isomer bongkrekic acid (BA, **2**),[2] they form a small family of toxic antibiotics with potent antiapoptotic activity. These compounds act as inhibitors of adenine nucleotide translocase (ANT), which mediates the ADP/ATP exchange in mitochondria.[3] Mentioned in more than 700 publications, they are most commonly used to probe apoptosis mechanisms and to elucidate their link with mitochondrial function.[4] As a consequence, these substances attracted the interest of chemists. In particular, Corey and Tramontano devised a first very effective synthesis of BA in 1984,[5] while a second and longer total synthesis appeared some 20 years later.[6] Dissatisfied by this last approach, Shindo and Shishido continued to work in the area which culminated recently in two greatly improved second generation syntheses.[7] We too became interested in these molecules owing to the development of methods in our laboratory, which we deemed to be suitable to afford certain structural elements within these natural products.[8] In practice, however, while the methods proved to be unsatisfactory for either IBA and BA syntheses, a new highly efficient route has emerged leading to IBA (and BA), which we describe here. We have primarily targeted IBA as the center of our interest, since no synthesis has been reported, nor is any detailed biological evaluation currently available.

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(4) For example, see: (a) Zamzami, N.; Susin, S. A.; Marchetti, P.; Hirsch, T.; Gomez-Monterrey, I.; Castedo, M.; Kroemer, G. *J. Exp. Med.* **1996**, *183*, 1533–1544. (b) de Graaf, A. O.; Meijerink, J. P. P.; van den Heuvel, L. P.; DeAbreu, R. A.; de Witte, T.; Jansen, J. H.; Smeitink, J. A. M. *Biochim. Biophys. Acta* **2002**, *1554*, 57–65. (c) Schubert, A.; Grimm, S. *Cancer Res.* **2004**, *64*, 85–93. (d) Liu, J.; St. Clair, D. K.; Gu, X.; Zhao, Y. *FEBS Lett.* **2008**, *582*, 1319–1324.

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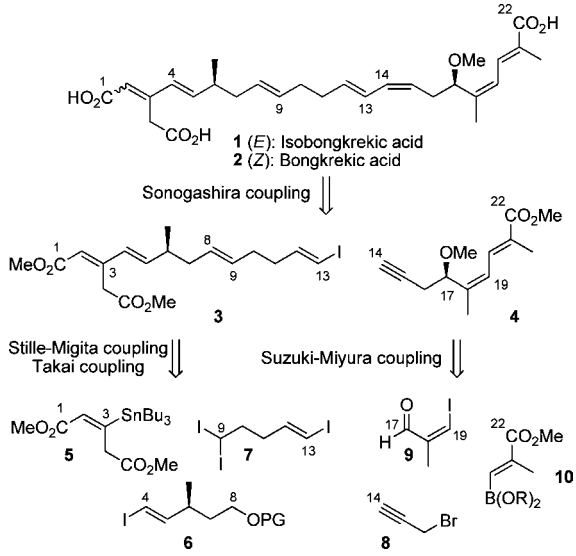
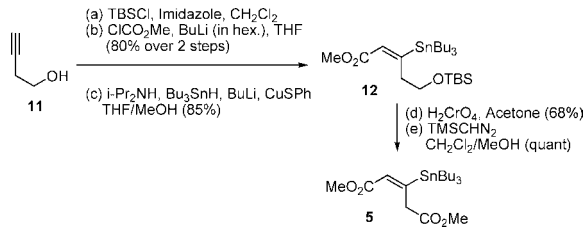
Retrosynthetically, we opted for the trimethylester of IBA ($IBAMe_3$) as our main target which could be constructed via a Sonogashira coupling between the vinyl iodide **3** and the alkyne **4**. In order to provide access to the vinyl iodide **3**, we envisioned the sequence of coupling reactions between stannane **5**, vinyl iodide **6**, and eventually novel triiodide **7**. Alkyne **4** was expected to arise via a Suzuki reaction and an asymmetric homopropargylation following anion generation from propargyl bromide **8** coupling with fragments **9** and **10** (Scheme 1).

Scheme 1. Retrosynthetic Analysis



The preparation of stannane **5** commenced from 3-butyn-1-ol (**11**) by a known sequence of silylation, homologation with methyl chloroformate, and a stereoselective Piers hydrostannylation reaction[9] to initially provide the stannane **12** with yields similar to the literature process (Scheme 2).[10]

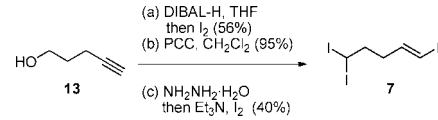
Scheme 2. Synthesis of Stannane **5**



Silyl ether **12** was then treated with the Jones reagent to simultaneously deprotect and oxidize in situ the intermediate alcohol to the carboxylic acid. Stannane **5** was finally obtained after a quantitative esterification using trimethylsilyldiazomethane. This approach proved to be reproducible and gave access to multigram quantities of the stannane **5** ready for the Stille coupling (Scheme 2).

The next crucial component of our synthesis plan involved the preparation of the triiodide **7**. This was designed as a new bidirectional coupling partner that effectively installs the unsymmetrical hexa-1,5-diene fragment (a common unit in a number of natural products)[11] by exploiting its orthogonal reactivity. Accordingly, pentynol (**13**) was transformed in its corresponding *E*-vinyl iodide, following a literature procedure (Scheme 3).[12] Subsequently, oxidation of the

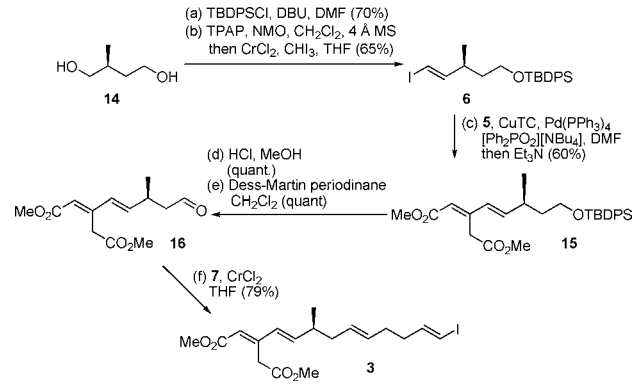
Scheme 3. Synthesis of *gem*-Diiodide **7**



intermediate alcohol with pyridinium chlorochromate gave optimal results. Formation of the *gem*-diiodide function was then achieved by employing a protocol developed by Sternhell et al.[13] While this method is often low yielding, in this case we were pleased to obtain this new building block **7** in an efficient and highly reproducible fashion.

In order to synthesize the homologated vinyl iodide **3**, the commercially available, chiral diol **14** was monoprotected at the less hindered hydroxyl group at low temperature (Scheme 4). However, the oxidation of this product to the

Scheme 4. Synthesis of Vinyl Iodide **3**



intermediate aldehyde was problematic owing to its instability. Nevertheless, inspired by our previous observations describing a sequential tetra-*n*-propylammonium perruthenate

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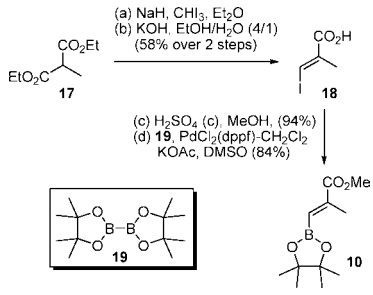
(TPAP) oxidation/Wittig reaction,[14] we investigated use the TPAP oxidation immediately followed by a Takai reaction, in one-pot, to give vinyl iodide **6**. This proceeded in a moderate 65% yield but was reproducible on multigram scale.

Next, the crucial elaboration of the left-hand diene geometry to distinguish IBA from BA was studied. The Stille−Migita coupling[15] was used for this process and involved modified conditions[16] using a phosphonate salt as a tin scavenger as this proved to be the most efficient procedure (60% yield). The deprotection of diene **15** with HCl in methanol followed by a Dess−Martin oxidation led to aldehyde **16**. Noteworthy in this reaction is that the absolute *S* configuration of the intermediate alcohol is not racemized, and this observation was corroborated by the formation and analysis of the corresponding Mosher ester (er >95:5 in ^{1}H and ^{19}F NMR). Finally, aldehyde **16** was subjected to a Takai olefination[17] using an excess of the triiodide **7**. Pleasingly, vinyl iodide **3** was obtained stereoselectively as a single *E*-isomer in good yield (79%).

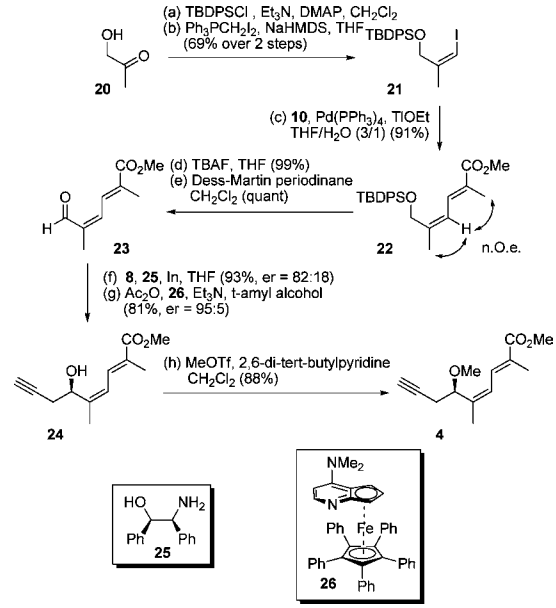
For fragment **10**, its assembly arose from the initial formation of vinyl iodide **18** from diethyl 2-methylmalonate (**17**) by a known procedure involving a reaction with iodoform followed by decarboxylation/elimination.[18] Subsequently, vinyl iodide **18** was esterified under acidic conditions and then cross-coupled with the bis(pinacolato)-diboron **19** to give boronic ester **10** in 84% yield (Scheme 5).[19]

Scheme 5. Synthesis of Boronic Ester **10**



Access to multigram quantities of vinyl iodide **21** was achieved through a silylation of hydroxyacetone **20** followed by a Wittig−Stork reaction (Scheme 6).[20] With significant amounts of fragments **21** and **10** in hand, different conditions for the key Suzuki−Miyaura coupling[21] could then be examined. As expected, the stereospecific formation of the *Z*,*E*-diene was complicated. Only when modified Kishi conditions,[22] using thallium ethoxide as a base, were employed did we obtain completely stereospecific coupling, confirmed by NOE studies, in high yield (91%) on gram scale. Several alternative less toxic bases were also investigated without success. These observations are in accord with other syntheses.[23]

Scheme 6. Synthesis of Alkyne **4**



In order to progress the synthesis, diene **22** was deprotected with TBAF and the resulting free-alcohol oxidized to the aldehyde **23** using Dess−Martin periodinane. We recognized that this aldehyde **23** would be prone to isomerization, and it was therefore used immediately in homopropargylation studies. The best conditions for this process turned out to be the use of indium as a metal source since this combines mildness and efficiency. When linked to its asymmetric version developed by Singaram,[24] excellent coupling was achieved giving homopropargylic alcohol **24** in good yield and acceptable enantiomeric ratio (er 82:18). In order to enhance this er, enzymatic methods were considered, but all required a further deprotection step. We therefore preferred a chemical process, with the method of Fu being particularly attractive.[25] The commercial availability of the required iron

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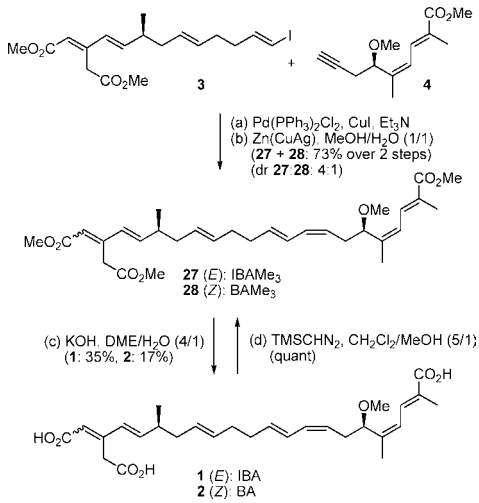
DMAP catalyst meant that we could rapidly attain an er of 95:5 for the desired enantiomer in a good yield.[26] This high enantioselectivity was sufficient to progress the synthesis. Finally, after several unsuccessful attempts, the hydroxyl group was methylated with methyl triflate and a hindered base to give the desired alkyne **4** (Scheme 6).[27]

With the two fragments **3** and **4** now available, their union via a Sonogashira coupling was investigated and successfully achieved (Scheme 7).[28] The use of triethylamine as solvent[29]

Scheme 7. Final Steps



realized the optimal conversion with the minimum dimerization of **4** resulting from the Glaser coupling.[30] At this stage, we advanced a mixture of inseparable isomers and dimers directly in the following reduction reaction. Although chemoselective hydrogenation with Lindlar catalyst failed, this regioselective *cis*-reduction of the alkyne, conjugated with an olefin, could be achieved using a large excess of copper/silver activated zinc.[31] A separable 4:1 mixture of $IBAMe_3$ (**27**) and $BAMe_3$ (**28**) was obtained in a satisfying yield of 73% over two steps. Believing that the final saponification may led inexorably to further isomerization on the polyene, the two isomers at this stage were purified only for characterization and comparison with reported data. The mixture was then forwarded to the next step. Finally, we dealt with the final and challenging tris-saponification process. After several unsuccessful attempts, we found that by using a large excess of potassium hydroxide we could obtain the two readily separable natural products IBA (**1**) and BA (**2**) (ratio 2:1). In order to prove that no racemisation occurred during this final step, IBA and BA were individually re-esterified to their corresponding $IBAMe_3$ and $BAMe_3$ and both afforded identical analytical data as the original substrates prior to their saponification.

In summary, the total synthesis of IBA and a new route to BA have been completed. The highly convergent route proved to be especially effective using only 13 steps as the longest linear path from commercially available material in a yield of 7.0% and 29 steps overall. This route therefore compares very favorably to all previous synthesis work in the area and also constitutes the shortest route so far to BA.[32] Highlights of this work include the formation of the three diene units by three different palladium cross couplings, the formation of the ether containing stereogenic center by an asymmetric homopropargylation followed by a chemical kinetic resolution, and finally access to the new building blocks **5**, **6**, and **10** and the new triiodide **7**.

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

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