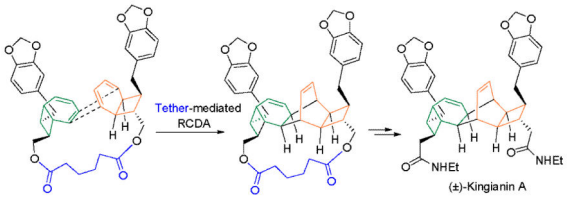
Published in final edited form as:
Org Lett. 2013 January 18; 15(2): 398–401. doi:10.1021/ol303388k.

Total Synthesis of Kingianin A

Hee Nam Lim and **Kathlyn A. Parker***
Department of Chemistry, Stony Brook University, Stony Brook, NY 11733

Abstract



A 12-step synthesis of kingianin A, an inhibitor of the antiapoptotic protein Bcl-xL, is based on a radical cation Diels Alder reaction (RCDA). This approach is thought to be biomimetic. The use of a tether in the key RCDA step controls the regiochemistry of the cycloaddition, leading to the desired core structure and a separable diastereomer.

Containing a unique pentacyclic scaffold, the kingianins (e. g. (−)-kingianin A, **1A,** Figure 1)[1] are the structurally most complex members of a class of natural products believed to arise from conjugated polyketide polyenes by one or more non-enzymatic pericyclic processes. [2] They are reported to have low- to midmicromolar binding to the antiapoptotic protein Bcl-xL.[1a] The antiapoptotic Bcl proteins are considered to be valid drug targets for the treatment of cancer, particularly lymphomas, leukemias, and small cell lung cancers.[3,4]

Each of the kingianins A-F (**1**, Figure 2) appears to be a Diels Alder adduct derived from two molecules of the purported biogenetic precursors: the enantiomers of endo[5] amide **2** and those of its exo isomer **3** (Figure 3).

The synthesis of a mixture of the two racemic bicyclooctadienes **2** and **3** by the now classical Stille coupling/electrocyclization cascade method [6, 7] and the separation of the two racemic compounds were reported by Moses et al.[8] These authors dubbed isomer **2** “prekingianin A.” (−)-Kingianin A is the homodimer of monomer **2**; kingianin D is the heterodimer of monomer **2** and monomer **ent 2** (see Table 1).

Not surprisingly, Moses and coworkers could not induce cyclohexadiene **2** or **3** (or a mixture of isomers **2** and **3**) to provide kingianins under thermal conditions. The Diels Alder dimerization of unactivated cyclohexadienes does not take place at ambient temperatures and therefore does not occur in nonenzymatic transformations in plants.

*kparker@notes.cc.sunysb.edu.

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

We suggest that the biogenetic Diels Alder addition proceeds by a cation radical-mediated reaction (perhaps initiated photochemically).[9] In support of this premise, we have pursued what we believe to be a biomimetic synthesis of kingianin A. Although the radical cation Diels Alder reaction (RCDA) has been known for 30 years, it has not previously been applied in the synthesis of complex natural product structures.[10]

The RCDA reaction of pre-kingianin A (**2**) is expected to be subject to certain regio- and steroselective influences. We know, for example, that the RCDA reaction prefers to proceed through an endo transition state[11] and we would expect the monomers to approach each other from the less hindered face of each diene. Indeed, all of the naturally occurring kingianins have stereochemistry that is derived from an endo transition state corresponding to this direction of approach.

Furthermore, each of the natural products isolated corresponds to a cycloaddition in which the dienophilic olefinic bond is the one proximal to the exo substituent on the cyclobutane ring (see Figure 3). Consequently, in all of the kingianins, the C-8 substituent is exo with respect to the adjacent bicyclic system and the C-1 substituent is endo to this system (see Figure 2). We believe that this pathway selection follows from a second steric factor that develops in the endo transition state when the dienophilic olefin is proximal to the endo substitutent (see interaction in Figure 4a). Thus, the cyclobutane ring prevents addition to the dienophile from the endo (hindered) face and the endo substituent prevents addition to the double bond nearer to it from the exo face. Consequently the reaction proceeds through a transition state resembling that shown in Figure 4b.

Because the RCDA of pre-kingianin A is subject to the stereochemical limitations described above, a single enantiomer is expected to undergo the RCDA dimerization to give a single enantiomer of kingianin A (i.e. enantiomer **2** as shown in Figure 2 should give (−)-kingianin A, **1A** as shown in Figure 1). However, racemic pre-kingianin A (**2**) should give two products, racemic kingianin A (**1A**) and racemic kingianin D (**1D**). Therefore the isolation of kingianin A at the end of the synthesis requires either an asymmetric synthesis of prekingianin A (or a synthetic equivalent)[12] or a practical method for the separation of kingianins A and D (or their synthetic equivalents).

Here we report a solution to the construction problems described above: (1) the successful application of the RCDA to the synthesis of the kingianin core, and (2) the development of an intramolecular RCDA that affords separable diastereomers of the homodimeric and heterodimeric RCDA products. In addition, we describe the conversion of one of these diastereomers to kingianin A.

Our plan was to test the RCDA dimerization of a derivative of alcohol **13**. Therefore we set out to obtain a mixture of the [4.2.0]-bicyclooctadiene **13** and its isomer **14** by the proven coupling / tandem electrocyclization strategy (Scheme 1) and then to remove the undesired **14** by selective iodoetherification [13] and simple chromatography. Because of the toxicity issues that accompany working with tin reagents, we sought an alternative to the Stille reaction which has generally been used in the coupling electrocyclization cascade. We are

pleased to report that the Suzuki reaction of the known pinacolborane **9**[14] is actually superior in this context.

The 5-step, easy-to-run synthesis of the desired alcohol **13** is shown in Scheme 1. Cross metathesis of safrole (**4**) with acrolein gave the known aldehyde **5**. Stork-Zhao olefination provided the (E, Z)-iododiene **6**. The required vinyl boronic ester **9** was prepared in two steps as described in the literature[14] and coupled with iododiene **6** under Suzuki conditions. The expected mixture of bicyclo octadienes **11** and **12** was isolated from this reaction. Deprotection of the TBDPS ethers gave a mixture of alcohols; only the undesired **14** underwent iodoetherification. Thus unreacted alcohol **13** could be recovered from the product mixture by simple column chromatography.

We were aware of the heroic efforts required to separate kingianin A from other kingianins during the isolation procedure. [15] Therefore, as a strategy for obtaining easily separable isomers from the dimerization step, we considered an intramolecular RCDA approach. We imagined linking two molecules of alcohol **13** by a removable tether and we hoped that we could find a pair of diastereomers in which the transition state geometry for endo cycloaddition could be reached only by the C-2 symmetric dimer. We thought that perhaps the racemic dimer would be recovered and easily separated from the expected pentacyclic product.

Several dimeric diesters were prepared from alcohol **13** and subjected to the RCDA conditions. Contrary to our expectation, in the case of each diastereomeric pair, both isomers appeared to have undergone the intramolecular cycloaddition reaction. Noteworthy in any case was the fact that the product mixture from the adipic acid-tethered substrate (**16** and **17**) consisted of two compounds, formed in approximately equal amounts and easily separated by chromatography. The more polar product displayed a ^{1}H NMR spectrum that contained signals expected from a compound in the kingianin A series (see the Supporting Information for tabulated data). The identity of this product was firmly established as **18** by X-ray crystallography (see the Supporting Information).

The less polar product had a ^{1}H NMR spectrum that differed in noticeable ways from those of compounds in the kingianin family. Furthermore, the absence of characteristic patterns in the spectrum was not the result of the presence of the tether; removal of the tether gave a diol, the NMR spectrum of which differed in important respects from that of kingianin D (Table 1 in the Supporting Information).

A series of coupling and NOE experiments allowed us to identify the second RCDA product as **19**, the unanticipated but not surprising exo Diels Alder product. Complete data for this compound and data for the corresponding diol, along with the argument for the structure assignment, are presented in the Supporting Information.

With some confidence that we had a significant intermediate in hand, we released the diol **20** from its tether in diester **18** and applied a double homologation procedure (Scheme 3). Mesylation and displacement by cyanide were followed by peroxide-promoted hydrolysis[16] and the reductive N-alkylation procedure of Dube[17] (as recently highlighted by Moses et al

in the synthesis of prekingianin A).[8] The 5-step sequence converted diol **18** to (±)-kingianin A (**1A**) in 26 % yield.

The total synthesis of (±)-kingianin A required 12 steps (longest linear sequence from commercially available materials and 14 steps total) and two silica gel chromatographic separations (of alcohol **13** and iodoether **15** and of tethered dimers **18** and **19**). It demonstrates the use of the RCDA methodology in the synthesis of a complex natural product. Other homodimeric and also heterodimeric kingianins should be available by modification of the same overall strategy and we foresee the elaboration of the key diol **20** to other members of the kingianin family.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of Health (GM 74776) and to Stony Brook University for financial support of this work. In addition, we thank Te-Jung Hsu and Joseph Lauher (Stony Brook University) for the X-ray crystallographic structure determination and Francis Picart (Stony Brook University) for expert assistance with NMR studies.

References

(1) (a). Leverrier A, Awang K, Gueritte F, Litaudon M. Phytochemistry. 2011; 72:1443–1452. [PubMed: 21550092] (b) Leverrier A, Dau METH, Retailleau P, Awang K, Gueritte F, Litaudon M. Org. Lett. 2010; 12:3638–3641. [PubMed: 20704409]

(2). For representative examples, see Lim HN, Parker KA. J. Am. Chem. Soc. 2011; 133:20149–20151. [PubMed: 22085260] erratum at J. Am. Chem. Soc. 2012; 134:4449. Sharma P, Powell KJ, Burnley J, Awaad AS, Moses JE. Synthesis. 2011:2865–2892. Beaudry CM, Malerich JP, Trauner D. Chem. Rev. 2005; 105:4757–4778. [PubMed: 16351061] and references therein.

(3). Selected recent, informative reviews: Kilbride SM, Prehn JHM. Oncogene. Bodur C, Basaga H. Curr. Med. Chem. 2012; 19:1804–1820. [PubMed: 22414090] Bajwa N, Liao C, Nikolovska-Coleska Z. Expert Opin. Ther. Pat. 2012; 22:37–55. [PubMed: 22195752] Czabotar PE, Lessene G. Curr. Pharm. Des. 2010; 16:3132–3148. [PubMed: 20687882]

(4). Navitoclax, Abbott's drug candidate ABT-263, currently in phase II clinical trials for lymphomas, leukemias, and small cell lung carcinoma, inhibits Bcl-xL and Bcl-2. See http://clinicaltrials.gov/ct2/results/refine?term=navitoclax

(5). The endo/exo terminology for the bicyclooctadiene natural products is derived from the relationship of the aryl-substituted sidechain to the cyclohexadiene ring. See Parker KA, Lim Y–H. Org. Lett. 2004; 6:161–164. [PubMed: 14723518]

(6). Since its introduction for this purpose (see Beaudry CM, Trauner D. Org. Lett. 2002; 4:2221–2224. [PubMed: 12074672] the Stille coupling / electrocyclization cascade method has been used consistently to access [4.2.0]-bicyclooctadienes.

(7). Kim K, Lauher JW, Parker KA. Org. Lett. 2012; 14:138–141. See. and references therein. [PubMed: 22146007]

(8). Sharma P, Ritson DJ, Burnley J, Moses JE. Chem. Comm. 2011; 47:10605–10607. [PubMed: 21863194]

(9) (a). Ischay MA, Yoon TP. Eur. J. Org. Chem. 2012:3359–3372.(b) Lin S, Padilla CE, Ischay MA, Yoon TP. Tetrahedron Lett. 2012; 53:3073–3076. [PubMed: 22711942] (c) Lin S, Ischay MA, Fry CG, Yoon TP. J. Am. Chem. Soc. 2011; 133:19350–19353. [PubMed: 22032252] (d) Gieseler A, Steckhan E, Wiest O, Knoch F. J. Org. Chem. 1991; 56:1405–1411.

(10). An elegant demonstration of the properties of the RCDA was provided early on by Bauld in a total synthesis of the bicyclic sesquiterpene (−)-selinene; see Harirchian B, Bauld NL. J. Am. Chem. Soc. 1989; 111:1826–8. See also reference 9c.

(11). Bellville DJ, Bauld NL. J. Am. Chem. Soc. 1982; 10:2665–2667.

(12). For approaches to the asymmetric synthesis of [4.2.0] bicyclootadienes, see reference 7 and Parker KA, Wang Z. Org. Lett. 2006; 8:3553–3556. [PubMed: 16869658]

(13). Nicolaou KC, Petasis NA, Zipkin RE, Uenishi J. J. Am. Chem. Soc. 1982; 104:5555–5557.

(14). Robles O, McDonald FE. Org. Lett. 2009; 11:5498–5501. [PubMed: 19902969]

(15). During the isolation procedure, kingianin A was separated from other kingianins by a series of flash chromatographies followed by a preparative HPLC experiment (reference 1).

(16). For a study of effective media for this reaction, see Brinchi L, Chiavini L, Goracci L, Di Profio P, Germani R. Lett. Org. Chem. 2009; 6:175–179.

(17). Dube D, Scholte AA. Tetrahedron Lett. 1999; 40:2295–2298.

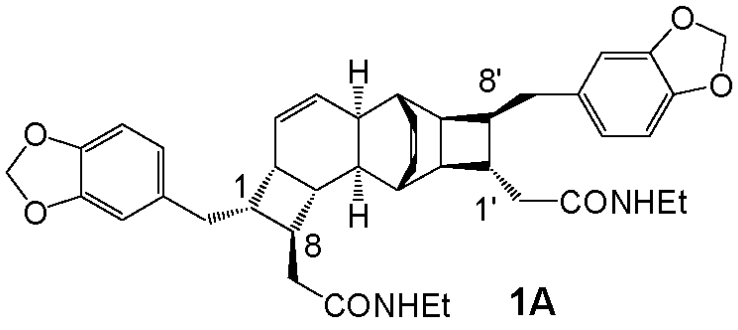


Figure 1.
(−)-Kingianin A

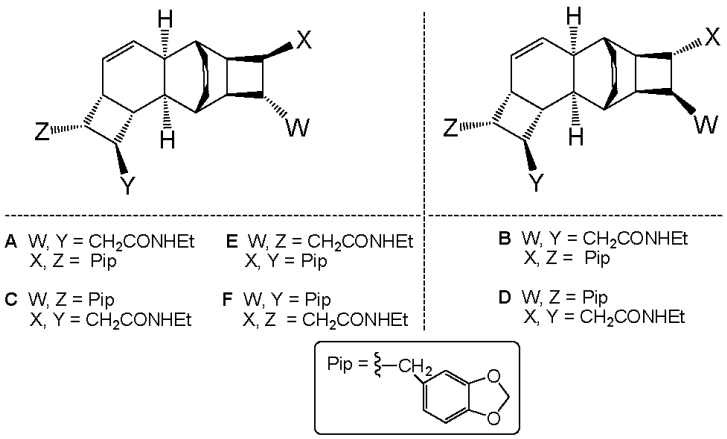


Figure 2.
Kingianins A-F

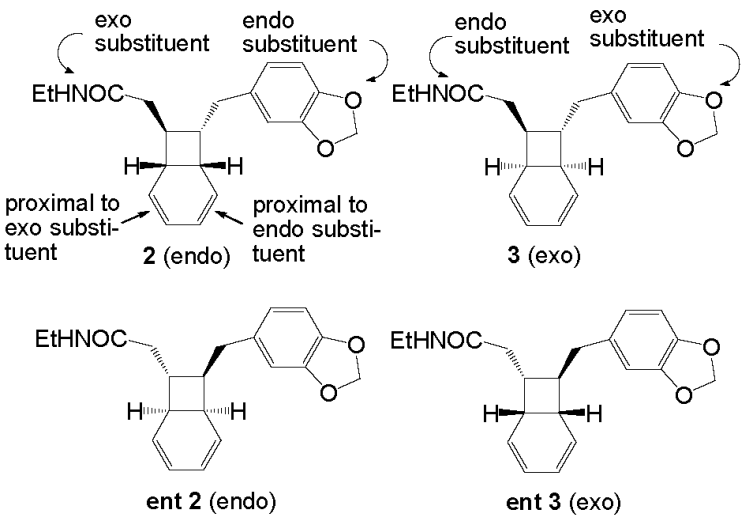


Figure 3.
Pre-kingianin A and its exo isomer

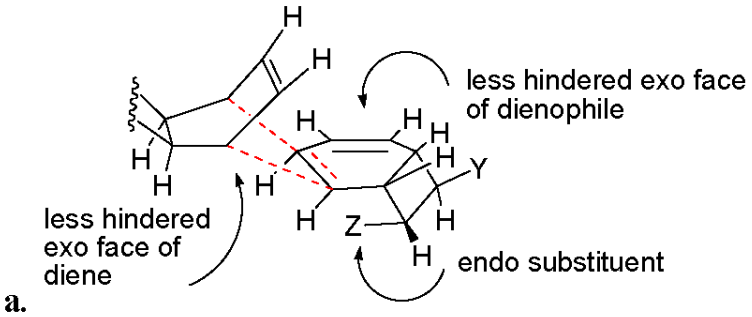
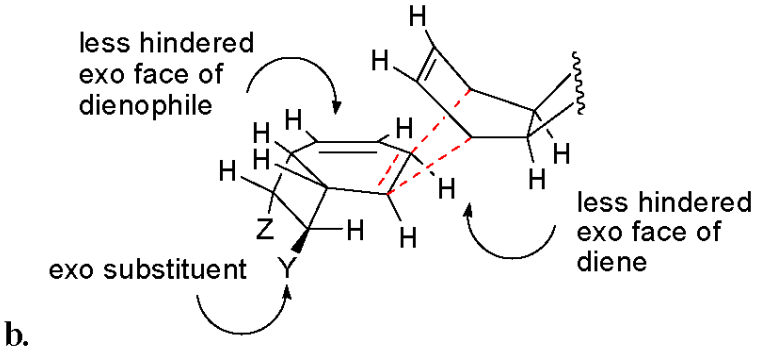


Figure 4.

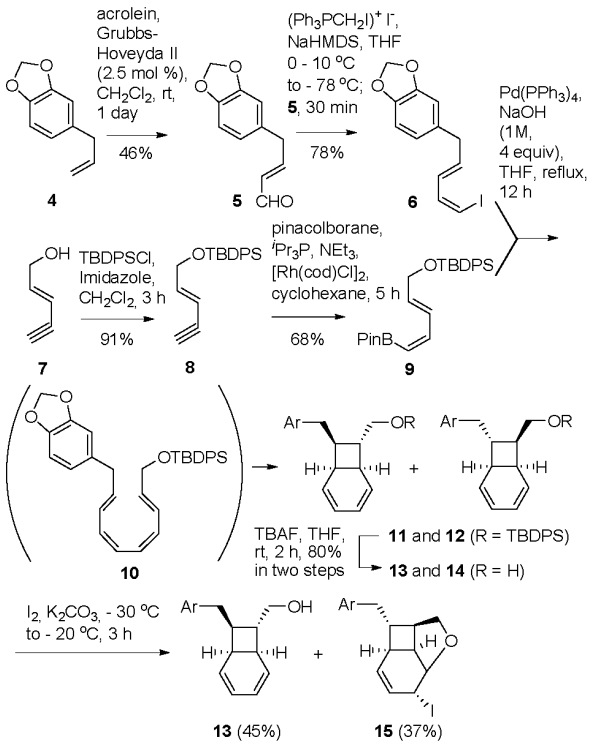
a. Disfavored endo transition state for RCDA. The approach is from the less hindered face of the diene to the less hindered face of the dienophile. The dienophilic olefin is proximal to the endo substituent.



b.

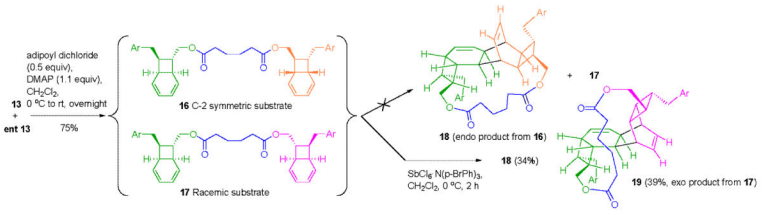
Figure 4.

b. Favored endo transition state for RCDA. The approach is from the less hindered face of the diene to the less hindered face of the dienophile. The dienophilic olefin is proximal to the exo substituent.



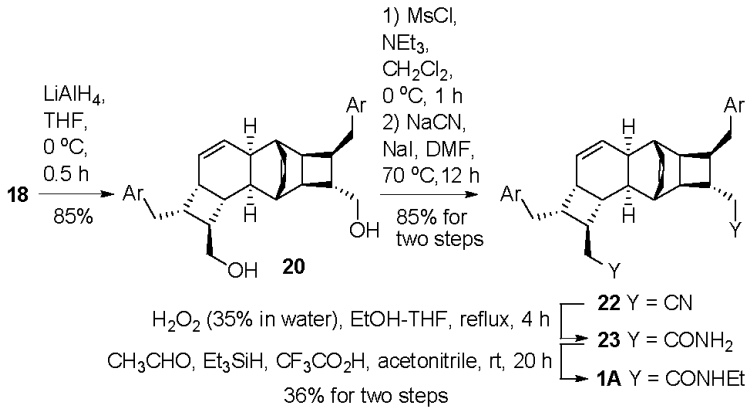
Scheme 1.

Tandem Suzuki-Coupling, 8π, 6π Electrocyclization Cascade



Scheme 2.

Preparation of the Tethered Substrates **16**, **17**, Postulated RCDA Product Mixture, and Actual RCDA Products



Scheme 3.

Removal of Tether and Double Homologation; Completion of the Total Synthesis of Kingianin A.

Table 1

Derivation of Kingianins A-F from Pre-kingianin A **2** and its exo isomer **3**

kingianin	dienophile	diene
A	**2**	**2**
B	**2**	**ent 3**
C	**2**	**3**
D	**2**	**ent 2**
E	**3**	**2**
F	**3**	**3**