

# A Racemic Synthesis of an AB-Ring System of Hexacyclenic Acid

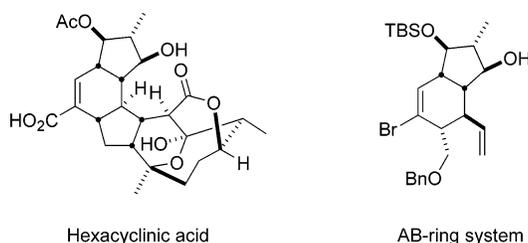
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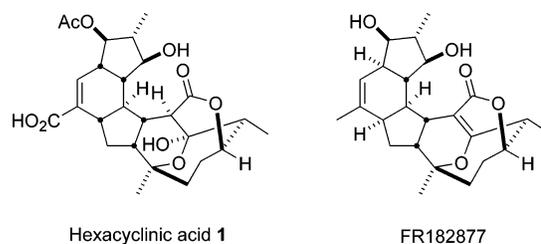
## ABSTRACT



An AB-ring system of the polyketide natural product hexacyclenic acid has been synthesized in racemic form. The key steps were an intramolecular Diels–Alder cyclization of an ester tethered 1,3-nonadiene-8-yne, which generated the B-ring, and a samarium diiodide mediated reductive annulation, which was used to form the A-ring.

Recently, the structure of hexacyclenic acid **1**, a new polyketide natural product was reported (Figure 1).<sup>1</sup> This compound was isolated from *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013) and was shown to have some cytotoxic activity when tested in three cell lines (HM02, HEPG2, and MCF7). A similar compound, also with cytotoxic activity, FR182877 (Figure 1), has also been reported.<sup>2–4</sup> FR182877 differs from hexacyclenic acid in the relative stereochemical configurations around the six-membered B-ring and that a bridgehead double bond exists where the cyclic hemiketal is in hexacyclenic acid. The B-ring of hexacyclenic acid is functionalized by a carboxylic acid residue, whereas this is a methyl group in FR182877. The main other difference is in the acylation of the C9 hydroxyl in hexacyclenic acid.

The unique structural features and challenging nature of these molecules have attracted the attention of several groups across the world. This has led to the realization of several strategies toward the FR182877 ring systems<sup>5</sup> and two total



**Figure 1.** Structures of hexacyclenic acid and FR182877.

syntheses.<sup>5a,b</sup> Despite the similarities between hexacyclenic acid and FR182877, there have been fewer reported routes toward the hexacyclenic acid ring systems.<sup>5h,6</sup>

Our strategy for the synthesis of the ABC-rings of **1** was to employ an ester tethered intramolecular Diels–Alder

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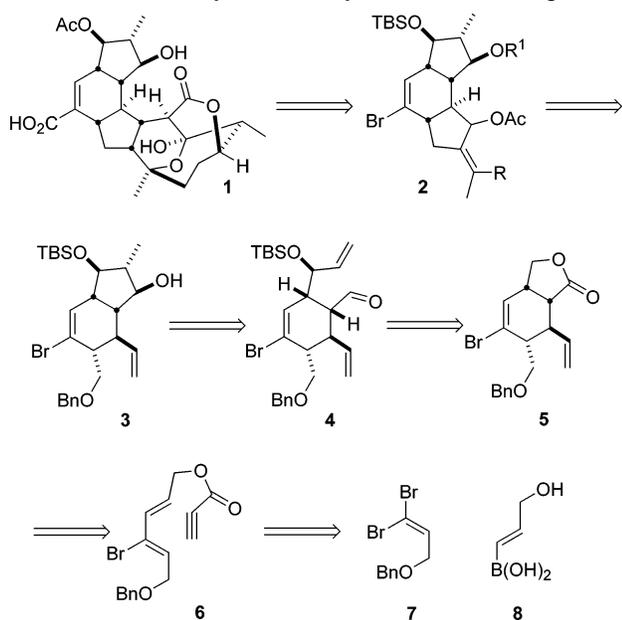
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reaction to form the B-ring **5** with control of the newly formed chiral centers. The inclusion of a bromine atom on the B-ring would enable its conversion to either the carboxylic acid group of hexacyclenic acid or the methyl group of FR182877, and thus, in theory, provide access to the B-ring of either natural product. Introduction of the appropriate functionality would then allow for the synthesis of the A- and C-rings via a reductive annulation protocol. Such a route would install the desired stereochemical triad of the A-ring **3** and form the C-ring **2** with functionality suitable to allow the homologation of a DEF-ring precursor (Scheme 1). We now wish to report the success of this strategy for

### Scheme 1. Retrosynthetic Analysis of the ABC-Rings of **1**



the construction of a functionalized AB-ring system **3** of hexacyclenic acid.

To this end, vinyl dibromide **7**<sup>7</sup> and boronic acid **8**<sup>8</sup> were coupled by use of a Suzuki reaction, under conditions previously reported to generate the desired diene geometry.<sup>5b,9</sup> This furnished diene **9** in 77% yield (Scheme 2). As we have recently shown that intramolecular Diels–Alder cyclizations of 6-fumaryl-1,3,8-nonatrienes generate cyclohexene products in which the major diastereomer formed is the one required for the synthesis of FR182877,<sup>5i</sup> we opted to investigate the intramolecular Diels–Alder cyclization of 6-propiolyl-1,3-nonadiene-8-yne **6**. We rationalized that conjugate addition of an appropriate nucleophile would generate the diastereomer required for the synthesis of the

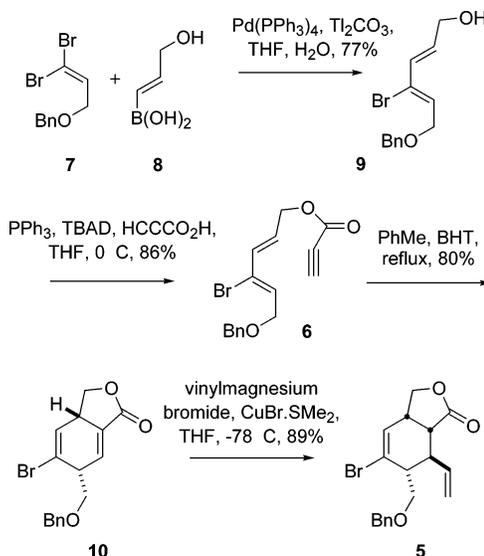
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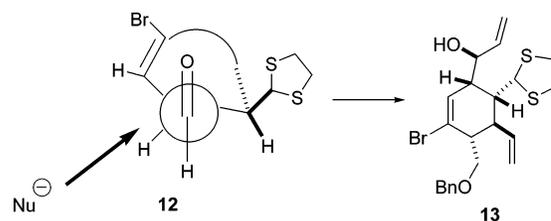
### Scheme 2. Synthesis of Lactone **5**



AB-rings of hexacyclenic acid.<sup>6b</sup> With this in mind **9** was subjected to a Mitsunobu esterification, which generated **6** in 86% yield. Heating 6-propiolyl-1,3-nonadiene-8-yne **6** under reflux in toluene provided the Diels–Alder adduct **10** in good yield (80%). Copper(I) bromide catalyzed conjugate addition of vinylmagnesium bromide to the unsaturated  $\gamma$ -lactone yielded **5** in 89% yield (Scheme 2). The relative stereochemistry of **5** was confirmed by <sup>1</sup>H NMR coupling constants and gradient nOe experiments.

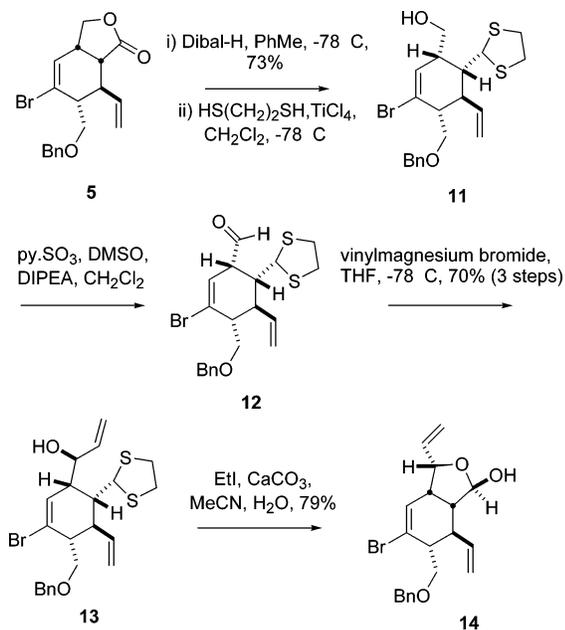
Installation of the second vinyl group, which was required for formation of the A-ring via a reductive annulation protocol, was achieved by the series of transformations detailed in Scheme 3.

Reduction of lactone **5** to the corresponding lactol with Dibal-H (73% yield) was followed by formation of the dithiolane **11**. Oxidation of the primary alcohol to aldehyde **12** allowed for the addition of vinylmagnesium bromide to yield allylic alcohol **13** as a 30:1 mixture of diastereomers. We postulated that the major diastereomer would be the one needed for continuation of the synthesis of the A-ring, as the desired diastereomeric product would result from a Felkin–Ahn controlled addition to the least hindered face of the carbonyl group (Figure 2).

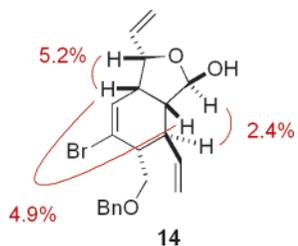


**Figure 2.** Rationale for the diastereoselectivity in the addition of vinylmagnesium bromide to aldehyde **12**.

**Scheme 3. Synthesis of Lactol 14**



As it was not possible to determine which major diastereomer had resulted from the addition reaction, the crude reaction mixture was subjected to dithiolane removal by the action of ethyl iodide and calcium carbonate in aqueous acetonitrile. This resulted in the formation of two lactol diastereomers, which were separated by flash column chromatography. The major one was shown to be **14** by  $^1\text{H}$  NMR and gradient nOe experiments (Figure 3).

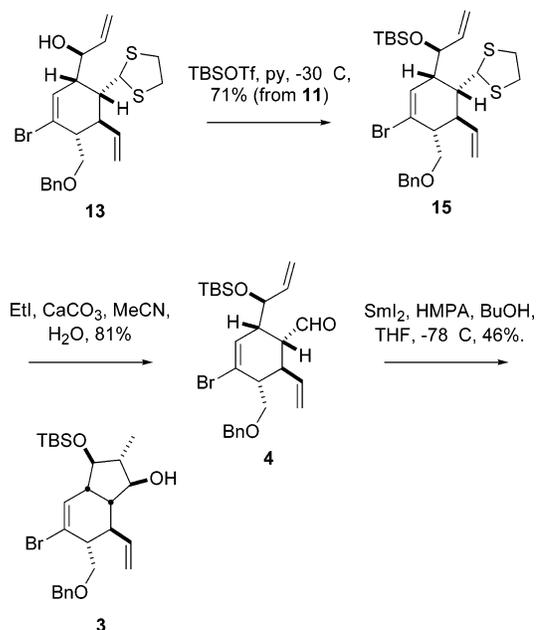


**Figure 3.** Diagnostic nOe data for lactol **14**.

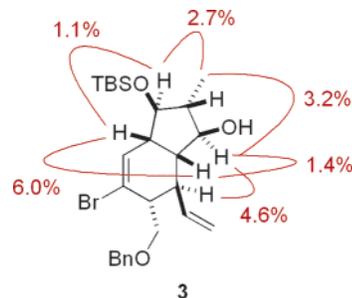
Knowing that we had synthesized the desired diastereomer of **13**, we continued our synthesis of the AB-ring system **3** by silylating the allylic alcohol in **13** with TBSOTf in pyridine to obtain silyl ether **15** in 71% yield. Reductive annulation precursor **4** was revealed (81% yield) by removal of the dithiolane with ethyl iodide and calcium carbonate in aqueous acetonitrile. Formation of the AB-ring system **3** was achieved in 46% yield when **4** was treated with samarium diiodide in THF/HMPA, with butanol as an external proton source (Scheme 4).<sup>10</sup> The AB-ring

system **3** was the only isolable product obtained from this reaction.

**Scheme 4. Synthesis of AB-Rings 3**



The *anti* arrangement of the two newly formed stereocenters was predicted due to the repulsion of the anionic oxygen and carbon atoms in the transition state. The stereochemical relationship of the newly formed stereotriad with the preexisting stereocenters was determined by  $^1\text{H}$  NMR and nOe experiments (Figure 4).



**Figure 4.** Diagnostic nOe data for AB-ring **3**.

In summary, we have executed a stereocontrolled racemic synthesis of an AB-ring system of hexacyclic acid. The key steps were a Diels–Alder cyclization of a 6-propiolyl-1,3-nonadiene-8-yne and a reductive annulation reaction promoted by samarium diiodide. Currently, we are attempting to use Diels–Alder chemistry presented in a recent report by Sherburn to develop an enantio-

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selective synthesis<sup>11</sup> of the AB-ring system. In addition we are also focusing on a way to annulate the C-ring onto the AB-ring system in such a manner as to allow for the formation of the DEF-rings via our iodocyclization protocol.<sup>6a</sup>

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AstraZeneca for unrestricted funding (P.A.C.), and the EPSRC National Mass Spectrometry Service, Swansea for accurate mass determination.

**Supporting Information Available:** Experimental procedures for the preparation of and spectroscopic data for all new compounds is available as well as copies of nOe spectroscopic data for **14** and **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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