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Synthesis of the stereogenic triad of the halicyclamine A core

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ABSTRACT

We describe herein our progress toward the synthesis of halicyclamine A, which possesses very interesting biological activities and has never been synthesized. For this purpose, we proposed a stereoselective Diels–Alder reaction as a key step for the establishment of the stereogenic triad of the bis(piperidinyl) core of this molecule. A series of NMR studies was then conducted to establish the correct stereochemical assignment subsequent to the Diels–Alder reaction.

1. Introduction

Halicyclamine A is one member of a growing class of tetracyclic diamine alkaloids isolated from the marine sponge *Haliclona* sp. (Fig. 1). Crews and coworkers first isolated halicyclamine A and determined its structure.[1] *Haliclona* sp. inhibits inosine monophosphate dehydrogenase (IMPDH) at concentrations of 1 μg/mL. IMPDH is a major therapeutic target, and drugs that are directed at IMPDH have been approved or are currently being evaluated for antiproliferative, antiviral, and anticancer chemotherapies as well as immunosuppressive activity. Halicyclamine A is cytotoxic against P388 with an IC_{50} value of 0.45 μg/mL.[2] Besides this activity, it was recently shown that this molecule has great potential against tuberculosis with MIC values of 1.0–5.0 μg/mL for *Mycobacterium smegmatis*, *Mycobacterium bovis* BCG, and *M. tuberculosis* H37Ra growth inhibition in both active and dormant states.[3]

Although there is considerable evidence concerning its biogenetic origin, and efforts directed toward biomimetic syntheses have been recorded,[4,5] this molecule has yet to succumb to total synthesis, and its absolute configuration has yet to be determined. Noteworthy, however, is the recent synthesis of the related (±)-haliclonacyclamine C by Sulikowski and Smith, who built the core of that molecule by Stille cross-coupling of the two piperidinyl moieties followed by a non-stereoselective hydrogenation of the resulting diene, with subsequent separation of the formed diastereomers.[6] There are two fundamental challenges associated with the synthesis of halicyclamine A. The first is the establishment of the three contiguous stereocenters about the bis(piperidinyl) ring system. The second challenge is the formation of two macrocyclic ring systems in which the stereochemistry about the conjugated

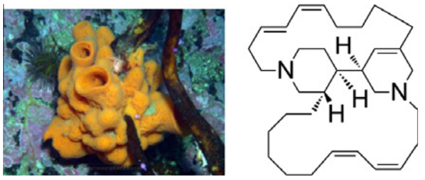
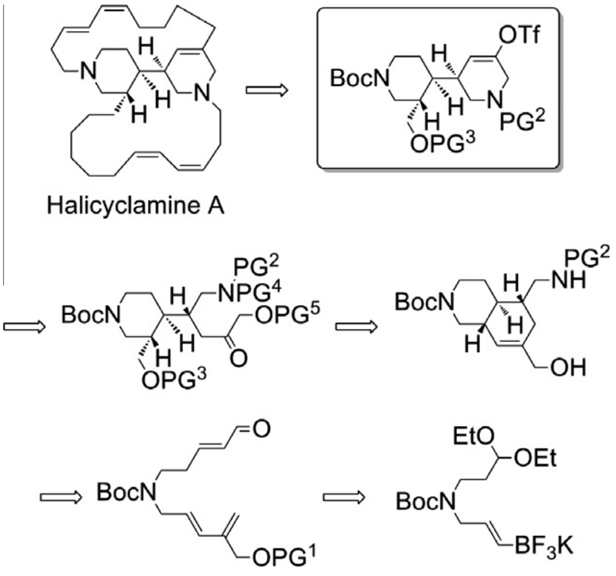


Figure 1. Sponge *Haliclona* sp. and structure of halicyclamine A.



Scheme 1. Proposed retrosynthesis.

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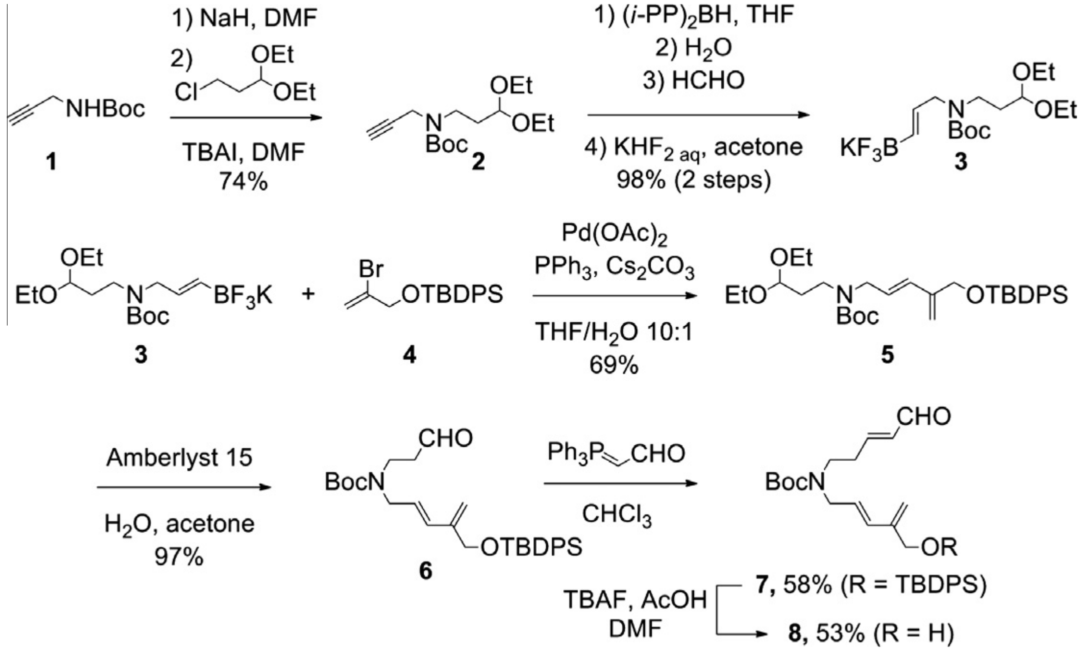
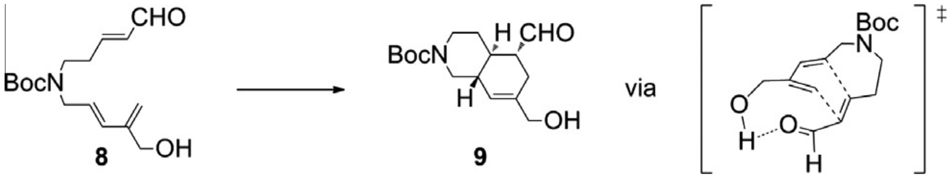
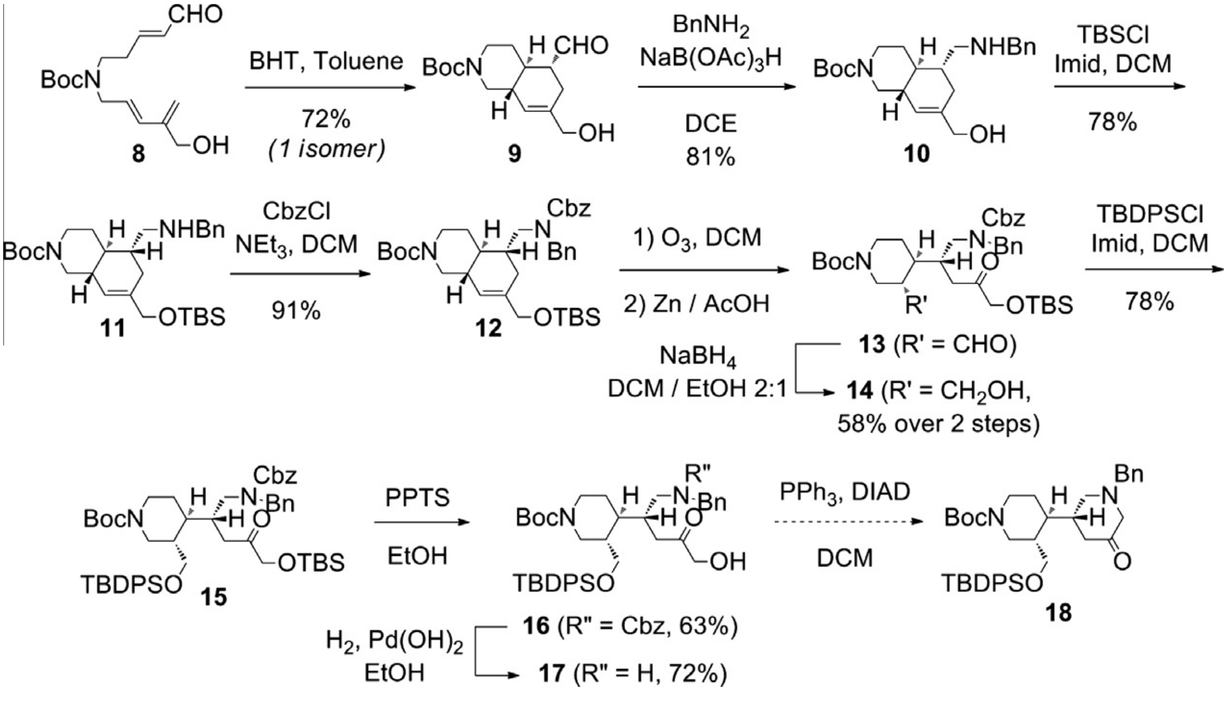


Scheme 2. Synthesis of the Diels–Alder substrate.



Scheme 3. Stereochemistry of the Diels–Alder reaction.



Scheme 4. Diels–Alder reaction and oxidative cleavage.