Tetrahedron 73 (2017) 4227–4232

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Putative biosynthetic cycloadditions en route to the diterpenoid (+)-chatancin

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ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form
1 November 2016
Accepted 12 November 2016
Available online 14 November 2016

Keywords:
DFT
Terpenes
Cycloaddition
Pericyclic

ABSTRACT

Density functional theory calculations were carried out in order to determine the viability of putative mechanistic pathways for formation of the diterpenoid (+)-chatancin. It was found that a cycloaddition involving a pyrylium ion would have a lower energetic barrier than previously proposed cycloadditions involving a 2H-pyran or furan. All three reactions are predicted to be concerted.

1. Introduction

Terpene and terpenoid compounds constitute approximately one third of all known natural products, with over 70,000 compounds isolated to date.[1–8] The prevalence of terpenes and their derivatives, as well as their penchant for binding to human receptors, make them appealing molecules in the flavor,[2] fragrance,[9–12] and pharmaceutical[13–17] industries. Their branched, often strained, structures also have led to applications in the biofuel industry.[18–21] A large variety of terpene/terpenoid natural products have been isolated from *Sarcophyton* soft marine corals.[22] The complex structures of these have piqued the curiosity of biologists and chemists, prompting studies aimed at uncovering the mechanisms by which they may be formed in nature, and by which they may be synthesized in the laboratory.[22,23] For example, the diterpenoid (+)-chatancin (**1,** Fig. 1), which has been shown to antagonize platelet activating factor (PAF,[24] skewed levels of which have been linked to numerous diseases in the respiratory and cardiovascular systems),[25] has been the subject of considerable biosynthetic speculation and creative laboratory syntheses.[23,26,27] Here we investigate cycloadditions that may be used to form the core of chatancin during its biosynthesis and compare these to related cycloadditions proposed previously to form other complex natural products.

Work on the synthesis of (+)-chatancin was spearheaded by Deslongchamps,[26] who initially pursued a biomimetic synthesis based on a proposed biosynthetic pathway involving a transannular [4 + 2] cycloaddition of furanocembrandoid **A**, followed by "a hydride shift mediated oxygen transposition" (i.e., a dyotropic rearrangement[28–35]; Fig. 2, top). Shortly thereafter, Deslongchamps proposed an alternative, potentially biosynthetic, pathway initiated from 2*H*-pyran diene **B** (Fig. 2, middle).[27] Pyrylium ion **C** (Fig. 2, bottom) was also mentioned to be a candidate to undergo the cycloaddition, but "it was excluded based on steric arguments …"[27] Nonetheless, we set out to determine the feasibility of this cycloaddition through computations. Cycloadditions of oxidopyrylium ions related to **C** have been used in the synthesis of various terpenes and proposed as viable steps in their biosynthesis.[36–38] There have been several other reported syntheses of chatancin,[39,40] but the recent synthesis by Zhao and Maimone is the most efficient[23]; while this synthesis does make use of a cycloaddition, it is not transannular and likely not representative of chatancin biosynthesis.

Here we describe density functional theory (DFT) calculations aimed at assessing the energetic viability of transannular [4 + 2] cycloadditions of **A**, **B** and **C** (Fig. 2).

2. Computational methods

The Gaussian 09 program package was utilized for all calculations.[41] A systematic conformational search using *SPARTAN*

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http://dx.doi.org/10.1016/j.tet.2016.11.031
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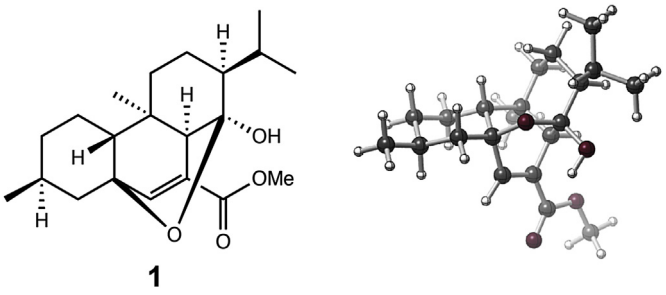

Fig. 1. Left: A two-dimensional depiction of (+)-chatancin. Right: A 3-dimensional ball-and-stick representation.

software[42] was conducted in order to determine the lowest energy conformations of reactant structures for transannular cycloaddition steps. Structures were optimized at the B3LYP/6-31G(d) level of theory.[43–45] Forward and reverse intrinsic reaction coordinate (IRC) calculations[46–48] were run on the optimized transition state structures (TSSs) to substantiate the minimum energy pathway from the TSS to its flanking minima. The structures of the products of transannular cycloadditions were found by optimizing the last point of each IRC in the product direction to a minimum. For comparison, calculations were also carried out using M06-2X[49]/6-31G(d) and B3LYP-D3[50]/6-31G(d) (to assess the magnitude of dispersion effects). The SMD continuum solvation model for water was also employed in some calculations.[51] Images of optimized structures were generated using *CYLview*.[52]

3. Results and discussion

The free energy barrier to cycloaddition of furanocembroid **A** (Fig. 2a) was found to be > 30 kcal/mol and formation of the tetracyclic product was found to be endergonic by several kcal/mol (see Supplementary Materials for details). The TSS corresponding to a dyotropic rearrangement to arrive at the final product could not be located (catalyzed and stepwise processes were not considered), but the predicted barrier to cycloaddition was significantly higher than those for the other possible starting materials (*vide infra*), so this mechanism was not pursued further.

At every level of theory investigated, it was found that the barrier for transannular cycloaddition (Fig. 3) of pyrylium ion **C** (Fig. 2c) was lower (by 4–9 kcal/mol) than that of neutral diene **B** (Fig. 2b). The barriers calculated at the three levels of theory utilizing B3LYP tended to be higher than those calculated using M06-2X. Additionally, the exergonicities at the B3LYP levels of theory were lower (i.e. the energy of the product relative to the reactant was predicted to be higher at the B3LYP levels of theory than M06-2X would predict). Both of these trends are typical for these levels of theory.[53,54] The predicted barriers for transannular cycloaddition of **B** are low enough that this reaction could occur biosynthetically without direct enzyme intervention, but if **B** expels hydroxide (likely in the form of a water molecule), cycloaddition is predicted to be much more rapid. While enzymatic barrier lowering appears not to be needed for these cycloadditions to occur in a biological setting, in that their predicted barriers are all approximately 20 kcal/mol or less, an enzyme would likely be needed to generate the immediate precursors to cycloaddition. A similar scenario has

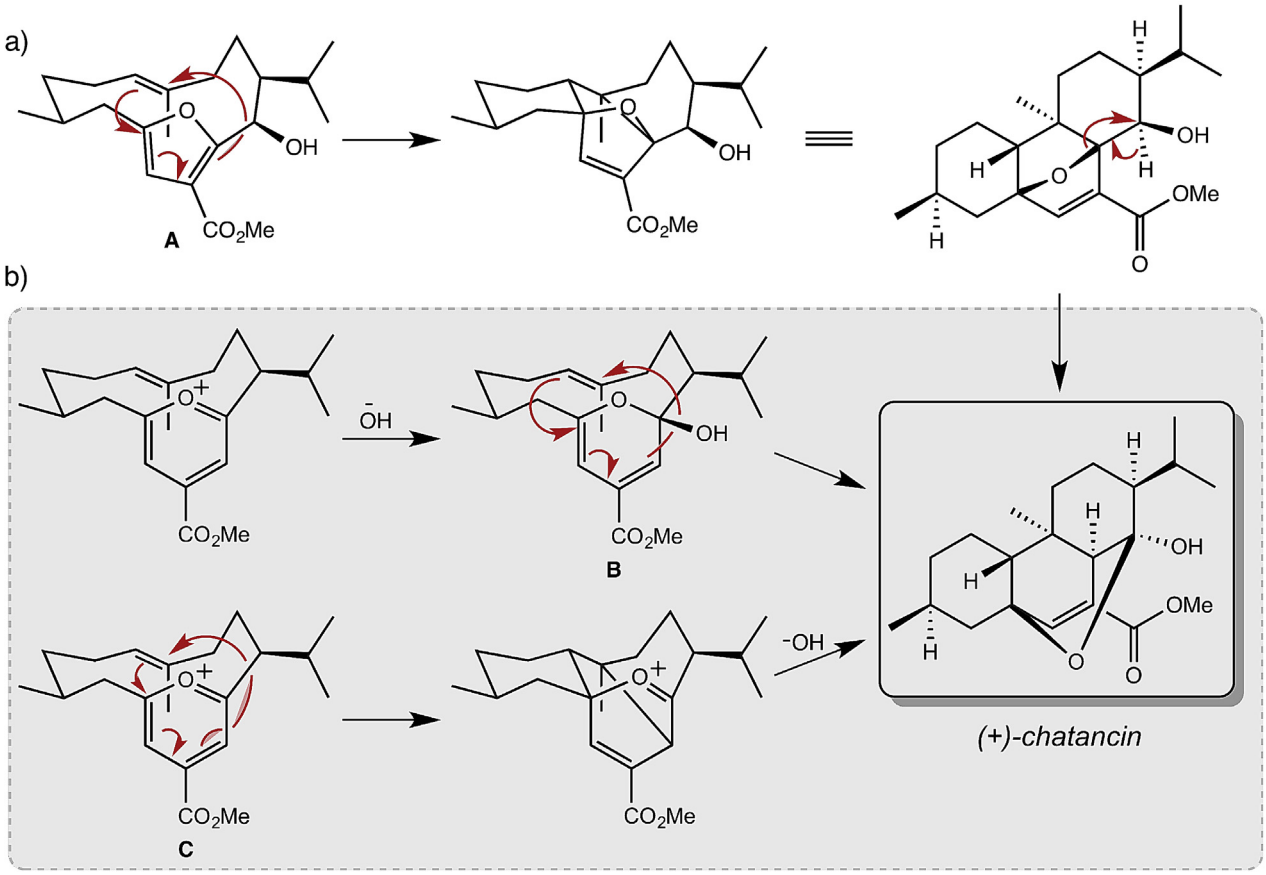

Fig. 2. a) The first proposal for the transannular cycloaddition step in the biosynthesis of (+)-chatancin by Deslongchamps,[26] b) Two alternative pathways explored computationally in this work.[27,39]