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Structural Interrelationship between Congeners of Prattinin A: Demonstration of Biosynthetic Pathway of three Modified Diterpenes with an Unprecedented Carbon Skeleton#

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#Dedicated to loving memory of Professor M. S. Wadia

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ABSTRACT

We have studied the structural correlationship between Prattinin A (1) and its congeners. Though a cursory look may not show any relationship but keeping in mind the known molecular rearrangements clearly show how the carbon skeleton of 1 gets converted into molecules with 3-different unprecedented carbon frameworks. It reflects on the biosynthetic pathway for natural diterpene molecules 4, 6 and 7. All of them belong to 4,5-seco-Prattinin A skeleton

Keywords: *Salvia Pratti;* 4,5-Seco Rearranged Abietane; Eight Membered Cyclic Ether

Introduction

Chemical composition of the roots of *Salvia prattii* led to the isolation and identification of a new rearranged abietane diterpenoid, Pratttinin A (1) [1]. Its structure was elucidated by interpretation of the 1D and 2D NMR spectra and completed by the analysis of the HR-ESI-MS data. We have studied the structural correlationship between 1 and its congeners 4, 6 and 7. The present study revealed how Prattinin A (1) gets transformed into three previously unprecedented carbon skeletons. In-fact the genus *Salvia* has been reported to produce several rearranged abietane diterpenes [2-6]. Many of these are C4-C5 seco rearranged abiatanes. A striking feature of the present study, all the three new carbon framework (4, 6 and 7) indictes that in the C4-C5 bond gets cleaved to generate the C4-C5 seco-rearranged 6,7-dehydro-ferruginol (3). Besides the interesting structural features, the diterpenes isolated from the genus *Salvia* are known for their biological activities such as anti-oxidant, antimicrobial, cytotoxic and antihuman immunodeficiency virus activities [7-10].

Results and Discussions

In the present study, we propose the structural correlation among congeners isolated from the same source and demonstrate how these results can lead to an understanding of their biogenetic origin. Prattinin A (1), a rearranged abietane diterpenoid isolated from *Salvia pratti* (Labiatae) [1], is a blue-coloured compound. Structure 1 was established through exhaustive NMR studies. Including Prattinin A (1), there are seven congeners (Figure 1), which interestingly rep-

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resent three unprecedented carbon skeletons. Their biosynthetic origin is therefore of considerable interest. Here, we outline three interrelated biosynthetic pathways derived from Prattinin A. The first compound isolated and characterised as 10-isopropyl-2,6,6-trimethyl-2,3,4,5-tetrahydronaphtha[18-bc]oxacine-5,11-diol (4) from *Salvia prattii* Hems [11] involves C-1, C-2, C-3, C-4, C-9, C-10, C-11 and C-11 phenolic oxygen to form an eight-membered cyclic ether, based on abietane carbon numbering (Scheme 1).

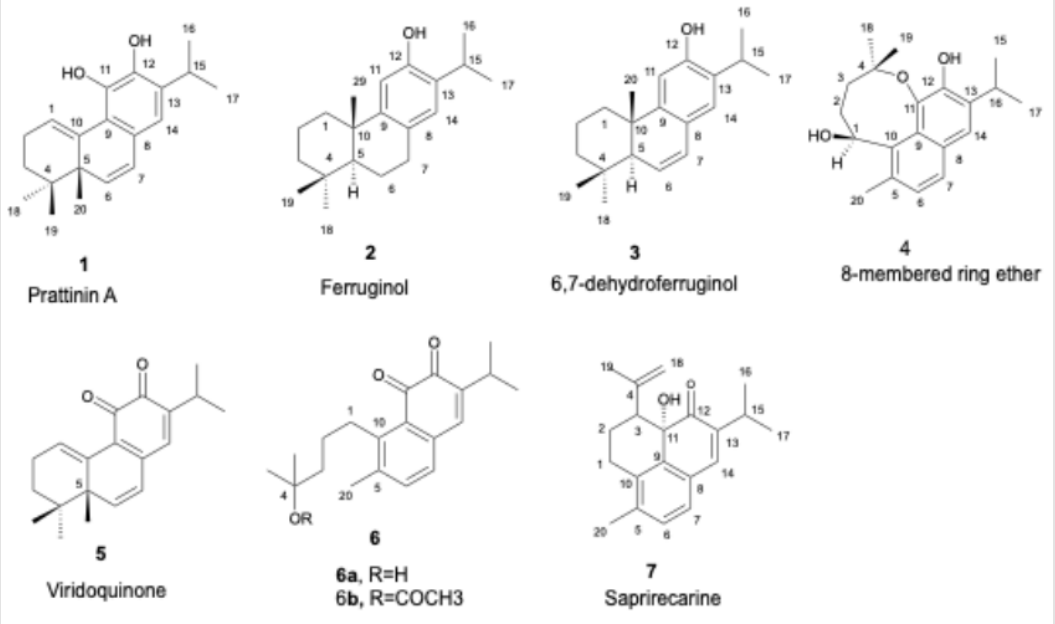
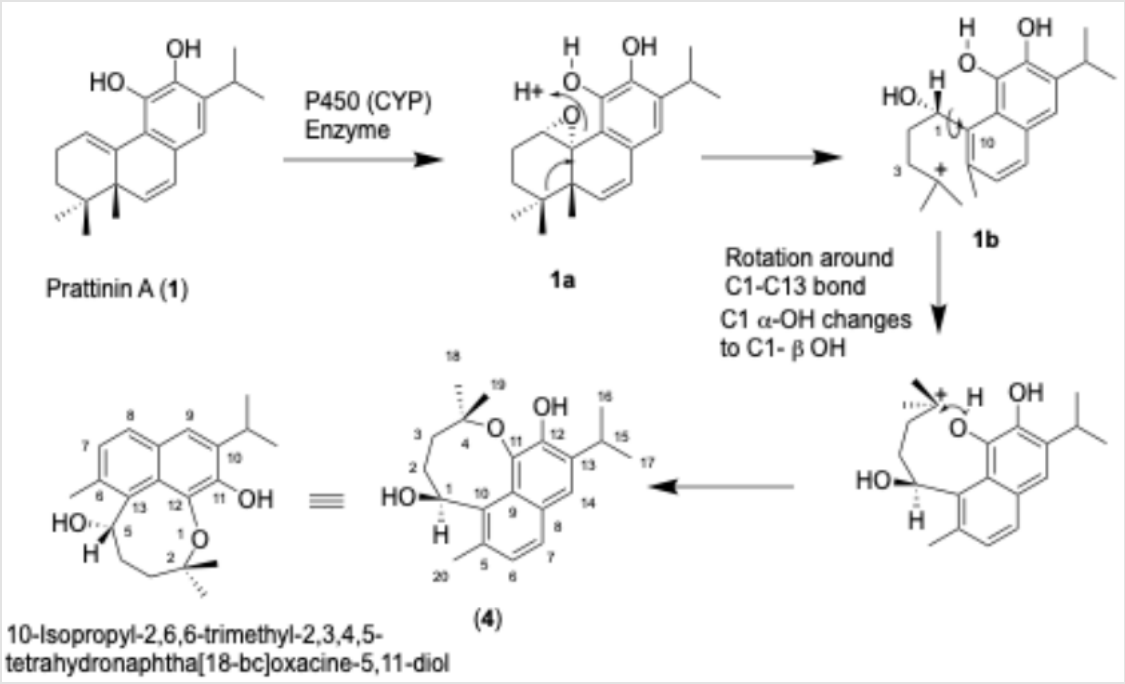


Figure 1: Prattinin A (1) and its congeners 4, 6 and 7.

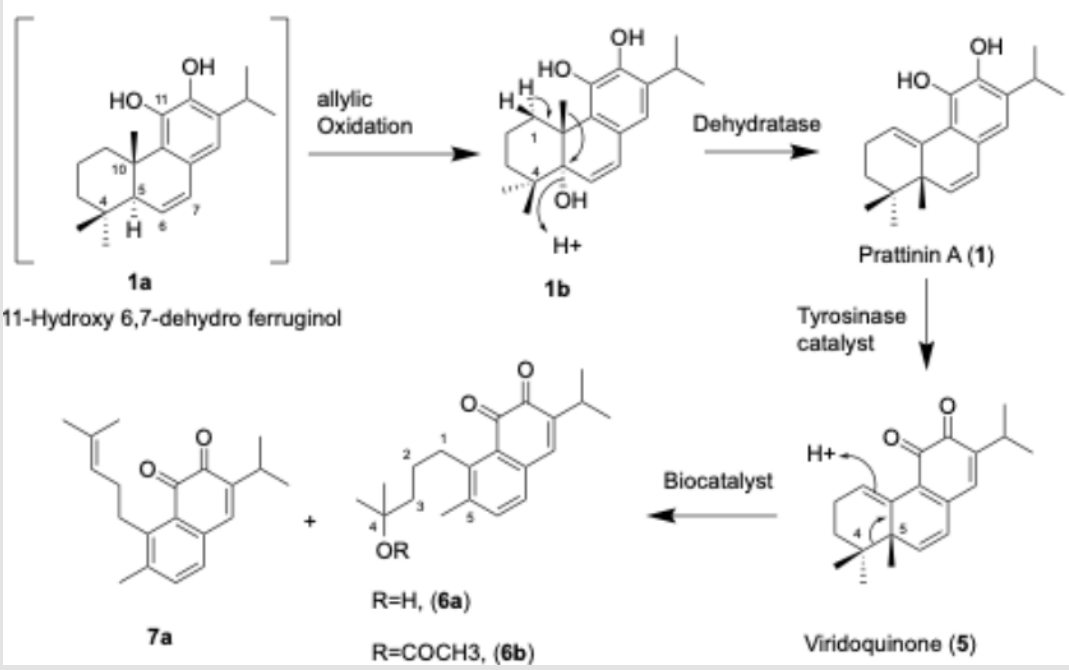


Note: Structural correlation of Prattinin A (1) with 8-membered oxide 4.
Scheme 1: Proposed biosynthetic pathway for 4 from Prattinin A (1).

Prattinin A (1) undergoes monooxygenation with enzyme P450 (CYP) to give epoxide intermediate 1a [12]. Under acid-catalysed conditions, 1a is converted *via* a tertiary cationic intermediate, 1b, which undergoes free rotation of the C-1—C-10 bond, as shown in Scheme-1, to reach the bond-closing distance of the C-11 phenolic oxygen. This affords the eight-membered cyclic ether 4. Due to free rotation, the C5-α OH changes to the C5-β OH configuration. Independently, Zhang et.al. isolated the same compound from *Nardostachys chinensis* [13] and, besides exhaustive spectral analysis, established the structure unambiguously by single-crystal analysis, as shown in Scheme 1. The carbon numbering differs from 4 because the oxygen of the eight-membered cyclic ether is used in numbering the molecule. In addition, the molecule is viewed differently. Examination of molecular models, however, established its equality with 4. A literature search showed that, among sesquiterpenes, heliannuols A-D possess an eight-membered cyclic ether ring [14,15].

Furthermore, biological activity studies revealed that these eight-membered cyclic ethers may serve as potential therapeutic candidates with diverse biological activities. Compound 6 isolated from *Salvia prionitis* [16] possesses an unprecedented carbon skeleton, a rearranged abietane-type diterpene in which the methyl group at C-10 in abietane is shifted to the C-5 position. A plausible biogenetic pathway is shown in Scheme 2, with an assumption that 6a and 6b derived from an abietane-type diterpenoid *via* Prattinin A (1). Structural correlation of Prattinin A (1) with 4,5-seco compounds 6a and 6b and the transitory intermediate 7a, occurs *via* viridoquinone (5). It is of interest to note that viridoquinone (5) has been isolated as a natural product from *Salvia pratti* (Labiatae) [1] and also *Salvia viridis* [17]. The 1,2-catechol group of Prattinin A (1) is oxidised to the ortho-quinone group of viridoquinone (5), a congener of 1. This oxidation is common and is known to occur with a tyrosinase catalyst [18]. Under the acidic medium of a biocatalyst, the ring A olefinic linkage is protonated, with simultaneous cleavage of the C4—C5 bond, to generate the C4—C5 seco-abietane skeleton.

The tertiary cation generated at C4 is neutralised with water and acetic acid to give 6a and 6b (Scheme 2). The proposed biosynthetic pathway for naturally occurring saprirecarine (7) [1,16,19] from Pratinin A (1) may be envisaged *via* viridiquinone (5) which can lose an adjacent proton to form 7a, which under the acidic medium of a biocatalyst, produces saprirecarine (7) as the end product (Scheme 3). The structural correlation between Prattinin A (1) and its congeners convincingly demonstrates the pathways involved in the biosynthesis of 4, 6a, 6b, and 7 from 1, (Schemes 1, 2 & 3). However, one important question remains: what is the biosynthetic pathway for Prattinin A (1)? The isolation of ferruginol (2) and 6,7-dehydroferruginol (3) also from *Salvia pratti* (Labiatae) [1] suggests their involvement, along with a missing link, namely 11-hydroxy-6,7-dehydroferruginol (8). These steps are shown in Scheme 4.



Note: Structural correlation of Prattinin A (1) with 4,5-secoproducts 6a and 6b via Viridiquinone (5).

Scheme 2: Proposed biosynthetic pathway for 4,5-seco-orthoquinononones 6a and 6b from 11-hydroxy-6,7-dehydro ferruginol (1a) via Prattinin A (1).

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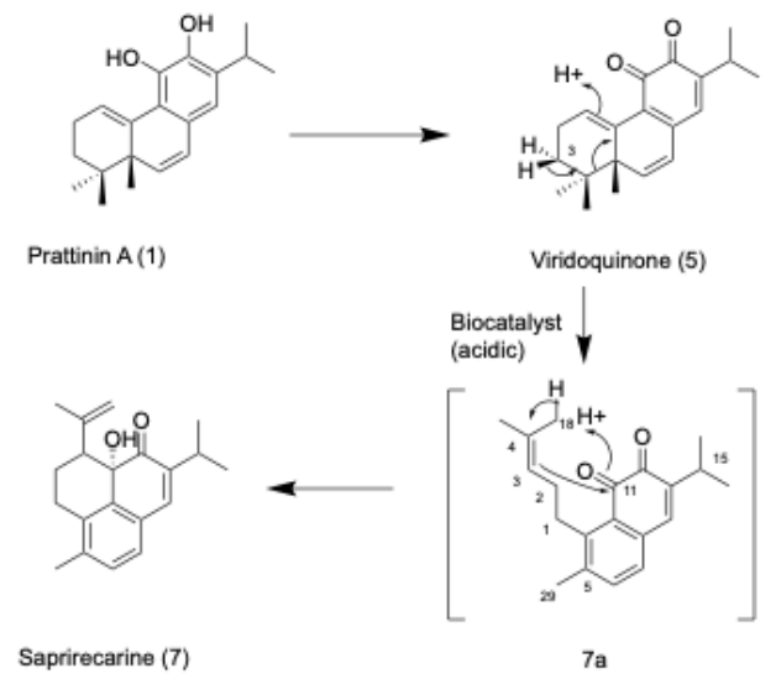
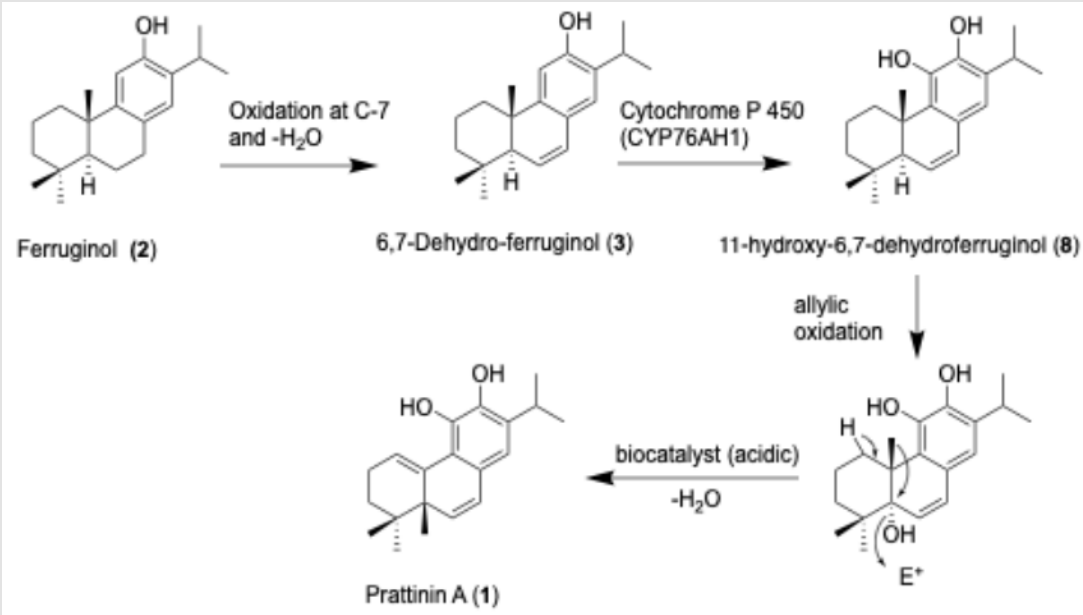


Note: Structural correlationship between Prattinin A (1) with Saprirecarine (7) via 7a.
Scheme 3: Proposed biosynthetic pathway for Saprirecarine (7) from Prattinin A (1).



Note: Role of Ferruginol and its derivatives in tracing genetic pathway for Prattinin A.
Scheme 4: Plausible biosynthesis of Prattinin A (1).

Conclusion

We have presented the simplicity and utility of structural correlation among congeners of Prattinin A (1) to derive a biosynthetic link between 1 and 4, 6a, 6b, and 7. The role of ferruginol (2) and 6,7-dehydroferruginol (3) in proposing a plausible biosynthetic pathway is presented (Scheme 4). All three unprecedented carbon skeletons are proposed to arise after the C10 angular methyl group undergoes a stereospecific 1,2-methyl shift to C5, generating a tertiary cation at C10. This transformation provides the basis for the formation of C4–C5 seco-abietanes. In the present study, these new carbon skeletons may be designated as C4–C5 seco-prattinanes.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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