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Total synthesis of taxane terpenes: cyclase phase

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ABSTRACT

A full account of synthetic efforts toward a lowly oxidized taxane framework is presented. A non-natural taxane, dubbed 'taxadienone', was synthesized as our first entry into the taxane family of diterpenes. The final synthetic sequence illustrates a seven-step, gram-scale, and enantioselective route to this tricyclic compound in 18% overall yield. This product was then modified further to give (+)-taxadiene, the lowest oxidized member of the taxane family of natural products.

1. Introduction

Taxanes represent a large family of terpenes comprising over 350 natural products, of which many exhibit cytotoxic activity against various types of cancer and also display interesting neurological and antibacterial properties.[1] The most celebrated example of these diterpenoids, from both medicinal and structural standpoints, is Taxol® (**1**; Fig. 1).[1a,d,e] Its success as an anti-cancer drug, its densely functionalized and complex structure, and its unique mechanism of action involving the stabilization of microtubules[2] have fascinated medicinal chemists, synthetic chemists, and biologists alike. While chemical synthesis seems to be no longer needed to solve a supply problem for this particular drug, synthetic chemistry is able to modify biologically active structures in ways that synthetic biology cannot.[3] Coupled with the opportunity to invent new methods using a complex framework, this natural product appeared to us as an ideal target for an endeavor in organic synthesis.[4–7]

A general two-phase design for the construction of terpenes was recently formulated using eudesmane sesquiterpenes as a proof of concept.[8] In Nature, oxidized eudesmanes such as eudesmantetraol (**2**) most likely arise from C–H oxidation[9] of **3** or **4**, which in turn arise from farnesyl pyrophosphate (**5**). In a similar vein, a laboratory two-phase approach allowed for the simplification of target **2** into a lowly oxidized eudesmane framework such as dihydrojunenol (**6**), followed by retrosynthetic disconnections into simple starting materials such as methyl vinyl ketone and isovaleradehyde.[10] Our next objective is to target Taxol® (**1**) while retaining the same line of logic. Since Taxol® (**1**) is one of the most highly oxidized taxanes, a two-phase terpene synthesis strategy that targets Taxol® (**1**) would also generate other taxanes that are lower in oxidation level.[11] The ultimate goal is to divergently access as many 'pre-Taxol®' compounds as possible (both natural and unnatural) and to learn about the innate reactivity of the taxane framework through various C–H oxidation strategies.

Structurally, Taxol® (**1**) and other taxanes are highly functionalized diterpenes with a captivating 6–8–6 tricyclic skeleton and a bridgehead olefin. It is adorned with many acetyl and benzoyl groups, as well as a signature side chain at the C13 oxygen atom (see carbon numbering on **1**). For retrosynthetic analysis purposes, **1** is treated as if it was devoid of acyl groups and is substituted with oxygenated hydrocarbon **7**. Many oxidized taxanes have in common a C2-hydroxyl group and can be envisioned to arise from taxa-4(5),11(12)-dien-2-one, or 'taxadienone' (**10**; quotation marks in the text are removed hereinafter for brevity). This ketone represents a key intermediate for a comprehensive access to the taxane

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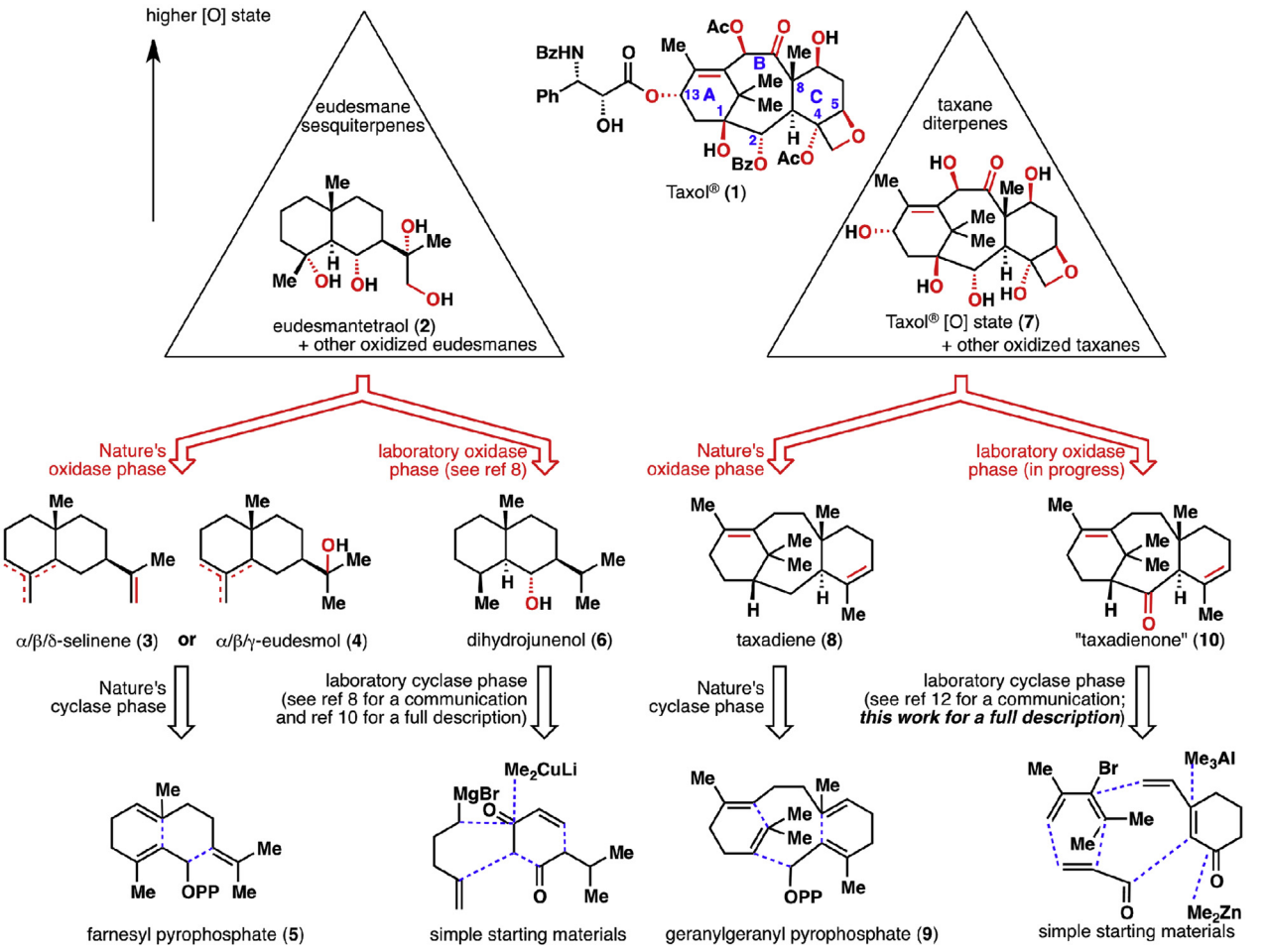

Fig. 1. A two-phase biosynthesis versus terpene synthesis in the eudesmane and taxane families of natural products. [O]=oxidation.

family because it would allow for both the natural C2α-alcohol series and the unnatural C2β-alcohol series. Furthermore, if taxadiene (**8**), the least oxidized natural product[1c] in the taxane family, was to be desired, one could simply deoxygenate **10**. Thus, taxadienone (**10**) became the target of our cyclase phase endpoint, which would serve as the diverging starting point toward polyhydroxylated taxanes. The synthesis of both taxadienone (**10**) and taxadiene (**8**) has been reported in an earlier communication[12] and is described herein as a full account.

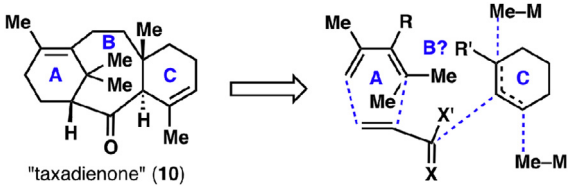

Fig. 2. Early retrosynthetic disconnections for taxadienone (**10**).

2. Results and discussion

2.1. Initial strategies and failed approaches

Considering the wealth of chemical knowledge surrounding the synthesis of the taxane framework,[4–7] there were so many retrosynthetic routes that could be followed toward the synthesis of taxadienone (**10**). While each synthesis has its strengths and weaknesses, we were particularly drawn to Nicolaou's route,[4c] which involved a Diels–Alder reaction to set the A-ring (see ring numbering on **1** in Fig. 1). For the C-ring, judging from the absence of functional groups in **10**, a simple cyclohexane-based starting material was deemed best. Numerous experimental explorations and strategy revisions then came from the synthesis of the B-ring (Fig. 2).

Many other previous attempts at making the taxane skeleton employed a Diels–Alder route for the A-ring,[6,7] possibly because of its isohypsic and atom-economical nature. These studies, as well as Nicolaou's A-ring synthesis,[4c] employed a trimethylated butadiene component for their Diels–Alder reactions. The most commonly used diene fragments, along with the number of steps it takes to make them, are shown in Fig 3A. Regarding the taxane C-ring, cyclohexane starting materials[13] that were deemed useful are listed in Fig. 3B.

With a collection of A-ring precursors and C-ring frameworks ready to use, potentially useful A-ring/C-ring coupled compounds were synthesized (Fig. 4). Many of these were generated as a mixture of inseparable diastereomers (**38**, **40**, **41**, **45**–**48**, **50**), presenting early problems in the designed routes. Furthermore, many of these steps were only feasible in low yields and were not scalable.

Despite the drawbacks in yield and diastereoselectivity in forming many of the compounds presented in Fig. 4, these intermediates were used in a number of approaches toward the B-ring, and a snapshot of many of the evaluated strategies toward taxadienone (**10**) is illustrated in Fig. 5. For example, the known